# PRECISION HEALTHCARE: GENOMICS-INFORMED NURSING

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# ACCESSING AND USING PERSONALIZED HEALTH IN NURSING: GENOMICS-INFORMED PRACTICE

## Welcome to Personalized Health in Nursing: Genomics-Informed Practice

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# Attribution & References

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# ACKNOWLEDGEMENTS

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Jen Booth, Faculty Librarian, Georgian College

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## Source Authors

This book is primarily a curation of open access materials on genetics and genomics. I would like to express my sincere gratitude to the original source authors for creating this important and timely content and for making it openly accessible.

## Book Cover

- Cover created by Andrea Gretchev, using Canva (https://www.canva.com/)

I am grateful to Georgian College, Dr. Sara Lankshear, Associate Dean – Nursing programs, and the faculty in the Honours Bachelor of Science – Nursing (HBSN) Program for having the foresight to include genomics in their undergraduate nursing curriculum. Their innovation in curriculum development and the creation of open access resources is leading the way for increasing nursing genomic literacy in Canada and globally.

## Copyright & Open Licensing

This OER was first published on **January 10, 2024**

This OER, *Personalized Health in Nursing: Genomics-Informed Practice*, is a collection of resources adapted by Andrea Gretchev to meet the needs of students enrolled in the Georgian College Honours Bachelor of Science – Nursing (HBSN) Program, NURS 4001: Precision Healthcare: Genomics-Informed Nursing course. In most sections of this OER, updates have been made to the existing content to improve usability and accessibility, incorporate interactive elements and improve the overall student experience. This collection reuses content from the following key resources:

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# Attribution & References

# INTRODUCTION

## About the Book

*Precision Healthcare: Genomics-Informed Nursing* was developed for Georgian College as course material for NURS 4001.

Genomics is changing the healthcare landscape and providing opportunities to personalize patient care. With the widespread integration of genomics, nurses will increasingly need to incorporate genomic knowledge into their practice to provide safe, equitable, timely, and accessible care. This book will provide nursing professionals with the foundational genomic knowledge to navigate this rapidly evolving field.

Readers will explore genomics integration in personalized healthcare and how it relates to nursing practice. Genomic literacy is vital to understanding how genetic variations and environmental and lifestyle factors contribute to disease susceptibility and progression. Nurses with a strong foundation in genomics will be better equipped to assess genetic risk factors, interpret genetic and genomic data, and communicate with patients about their genomic health.

The chapters in this book will allow readers to explore the many factors that influence gene expression and lead to disease development, such as obesity, cancer, diabetes, cardiovascular disease and mental health disorders. Nurses will gain insight into modifiable and non-modifiable risk factors to develop evidence-based interventions that promote health and improve patient outcomes. By applying genomics-informed practices, nurses can advocate for personalized healthcare strategies that meet the needs of individual patients and populations. Nurses will also consider their role as part of an interdisciplinary team delivering genomic services and future nursing practice initiatives.

## Navigation

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The content of this book is divided into thirteen units. Students are expected to work through the materials in a unit for each week of study. This course was designed for an asynchronous course. The 28-hours of course time is to be used reviewing materials. Additional time will be spent on reviewing and completing assignments in further depth. Units 7 and 11 provide time to apply learning. The intent of these two weeks is to give students time to work on discussion posts, case studies, and

scholarly posters. Additional case studies and learning activities are provided for optional independent practice.

Each chapter begins with an overview of the content covered and learning outcomes for the unit. Canada has not developed genomic competencies for nurses. Therefore, the NHS competencies from the UK and the ANA competencies from the US will be used. It should be noted that the competencies are meant to be demonstrated in practice. Each chapter aims to provide foundational theoretical knowledge that nurses need to be able to demonstrate these competencies in practice. However, this course does not include a practical component, so the competencies should be interpreted with this in mind. The competency documents should be consulted for clinical performance indicators.

The National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI) talking glossary, and other sources provide definitions of key terminology in the unit. For pronunciation of terminology and audiovisual resources to enhance understanding of the term, visit the NHGRI talking glossary website. Select terms are listed at the start of each chapter and are highlighted as they appear in the body of the text. The subsequent sections of each unit contain the course content, learning activities, external resources, additional required reading, and related media. Key takeaways and additional optional readings are in the final chapter of each unit.

# Overview

## Unit 1: Introduction to Personalized Healthcare and the Role of the Nurse

- Genetics and genomics introduction
- The contributions of nursing professionals in genomics healthcare

## Unit 2: Molecular Genetics Review

- DNA structure and function
- The genome and the cell cycle
- Cancer and the cell cycle
- The cellular basis of inheritance
- Patterns of inheritance

## Unit 3: The Exposome

- Nature vs nurture

- Epigenetics
- Developmental origins of health and disease
- The exposome
- Adverse early childhood experiences
- Epigenetics in practice

## Unit 4: Genetic Disorders

- Gene variants
- Genetic disorders
- Single gene disorders
- Polygenic disorders
- Chromosomal disorders
- Mitochondrial disorders

## Unit 5: Genomics Nursing Research

- Genomic research in nursing
- Human genetic research in Canada and Internationally
- Research priorities and funding
- Knowledge translation and mobilization
- Scholarly posters

## Unit 6: Assessing Genetic Risk

- Family history
- Constructing a pedigree chart
- Pedigree analysis and modes of inheritance
- Calculating probabilities using pedigree charts
- Polygenic risk scores

## Unit 7: Application of Theory in Practice Part 1

- There is no new reading material for this unit.
- Some case studies and exercises are presented for optional additional independent review and practice.
- Students are given time to complete the discussion post group assignment and begin work on the case study assignment.

## Unit 8: Genetic Testing

- Genetic testing overview
- Types of Genetic tests
- Interpreting genetic test results

## Unit 9: Pharmacogenomics

- Pharmacogenomics overview
- Genomic variation in drug response
- Personalized drug therapy
- Limitations of pharmacogenomic testing

## Unit 10: Ethical, Legal, and Social Issues Arising from Genomics

- Genetic discrimination
- Eugenics and scientific racism
- Use of population descriptors in genomics
- Nursing implications

## Unit 11: Application of Theory in Practice Part 2

- There is no new reading material for this unit.
- Some case studies and exercises are presented for optional additional independent review and practice.
- Students are given time to complete the discussion post group assignment and complete work on the case study assignment.

## Unit 12: Special Topics in Genomics

- Genomics and global health
- Cancer genomics
- Genomics application by specialty

## Unit 13: The Future of Genomics and Nursing

- Gene editing
- Other genomic technologies

- Health system readiness for the genomic era

## Attribution

# FOR EDUCATORS

## About Precision Healthcare: Genomics-Informed Nursing

This book introduces nurses and nursing students to the applications of genomics in practice and research. It is designed to be engaging, promote self-directed learning, and remain accessible, with content presented in a clear and reader-friendly format. The text is tailored for a single-semester, 28-hour online asynchronous undergraduate course. However, it can also benefit practicing nurses seeking to enhance their genomic literacy.

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Supplementary course materials for instructors are available upon request and with confirmation of educator status. These include a sample syllabus, quiz question bank, case studies with instructor keys, assignment guidelines for a scholarly poster project, and a comprehensive reading list.

Journal articles have been assigned as required reading throughout the book, in addition to textbook content, for the purposes of the 28-hour course.

At the end of each unit there is a list of recommended additional readings and resources. For in-person courses, educators may elect to present the textbook contents, or reduce some of the journal articles. For a 40-hour course, see the optional additional readings. The citations below are recommended first-choice additions from the additional optional readings for expanded course content.

### Chapter 1

Although this is an older article, it has an excellent summary table. Review p.171, Table 1 – Standards in Genetics and Genomics for General Nursing Practice.

Kerber, A. S., & Ledbetter, N. J. (2017). Standards of practice: Applying genetics and genomics resources to oncology. *Clinical Journal of Oncology Nursing*, *21*(2), 169–173. https://doi.org/10.1188/17.CJON.169-173

### Chapter 3

Focus on definitions and distinctions between terms:

Harden, K.P. (2023). Genetic determinism, essentialism and reductionism: semantic clarity for contested science. *Nature Reviews Genetics, 24*, 197–204. https://doi.org/10.1038/s41576-022-00537-x

## Chapter 5

Caron, N. R., Adam, W., Anderson, K., Boswell, B. T., Chongo, M., Deineko, V., Dick, A., Hall, S. E., Hatcher, J. T., Howard, P., Hunt, M., Linn, K., & O'Neill, A. (2023). Partnering with First Nations in Northern British Columbia Canada to reduce inequity in access to genomic research. *International Journal of Environmental Research and Public Health, 20*(10), 5783-. https://doi.org/10.3390/ijerph20105783

Hickey, K. T., Bakken, S., Byrne, M. W., Bailey, D. E., Demiris, G., Docherty, S. L., Dorsey, S. G., Guthrie, B. J., Heitkemper, M. M., Jacelon, C. S., Kelechi, T. J., Moore, S. M., Redeker, N. S., Renn, C. L., Resnick, B., Starkweather, A., Thompson, H., Ward, T. M., McCloskey, D. J., Austin, J. K., & Grady, P. A. Precision health: Advancing symptom and self-management science. (2019). *Nursing Outlook, 67*(4), 462-475. https://doi.org/10.1016/j.outlook.2019.01.003

## Chapter 8

Miller, D. T., Lee, K., Abul-Husn, N. S., Amendola, L. M., Brothers, K., Chung, W. K., Gollob, M. H., Gordon, A. S., Harrison, S. M., Hershberger, R. E., Klein, T. E., Richards, C. S., Stewart, D. R., Martin, C. L., & ACMG Secondary Findings Working Group. Electronic address: documents@acmg.net (2023). ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine*, *25*(8), 100866. https://doi.org/10.1016/j.gim.2023.100866

## Chapter 10

The full article that the news brief is based on is available here:

Fernando, A., Kondrup, E., Cheung, K., Uberoi, D., & Joly, Y. (2024). Still using genetic data? A comparative review of Canadian life insurance application forms before and after the GNDA. *FACETS, 9,* 1-10. https://doi.org/10.1139/facets-2023-0101

Thomas, G. M. & Katz Rothman, B. (2016). Keeping the backdoor of eugenics ajar: Disability and future prenatal screening. *AMA Journal of Ethics, 18*(4), 406-415. https://journalofethics.ama-assn.org/article/keeping-backdoor-eugenics-ajar-disability-and-future-prenatal-screening/2016-04

# Peer Review and Feedback

The book has undergone expert review by professionals in nursing and genomics. Feedback is welcomed from

healthcare professionals with genomic expertise. Suggestions for additional activities, examples, video content, emerging research, or revisions can be submitted to our contact addresses below. See the acknowledgement section for a list of peer reviewers.

## Contact

Please contact us with feedback, suggestions or to request supplemental materials at:

- andrea.gretchev [at] gmail.com
- oer [at] georgiancollege.ca

Please check for updates, alternate versions, or errata on the Update & Change Log page.

## Attribution & References

# UNIT 1 - INTRODUCTION TO PRECISION HEALTHCARE AND THE ROLE OF THE NURSE

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 1 Contents


- 1.1 Unit Overview
- 1.2 Genetics and Genomics Introduction
- 1.3 The Role of the Genomic Healthcare Professional
- 1.4 Unit Summary and Review


## Attribution

# 1.1 UNIT OVERVIEW

## Learning Objectives

- Define common genomic terms.
- Establish the relevance of genomics for nursing and the need for nurses to become literate in this emerging knowledge form.
- Describe nurses' distinct and overlapping contributions to the interdisciplinary team delivering genomics-informed care.
- Identify policies to guide genomics-informed nursing practice.
- Explore professional organizations for nurses interested in genomics.

## Outline

Topics covered in this chapter include:

- Genetics and genomics introduction
- The contributions of nursing professionals in genomics healthcare

## Competencies Nurses will Develop in this Chapter

### ANA (2023):

#### Nursing assessment: Applying/integrating genomic knowledge:

- Demonstrates an understanding of the relationship of genomics to health, prevention, screening, diagnostics, prognostics, selection of treatment, and monitoring of treatment effectiveness.

### Provision of education, care, and support:

- Advocates for autonomous, informed genomic-related decision-making.
- Provides genomic health care in collaboration with interdisciplinary professionals and when possible clients and their families.

## NHS (2023):

### Examine your own competency of practice on a regular basis:

- recognizing areas where professional development related to genomics would be beneficial;
- maintaining awareness of clinical developments in genomics that are likely to be of most relevance to your area of practice, seeking further information on a case-by case basis; and
- based on an understanding of the boundaries of your professional role in delivering genomic healthcare, including referral, provision, or follow-up of genomic services.

### Provide ongoing nursing care and support to patients, caregivers, families and communities with genomic healthcare needs:

- working in partnership with family members, multidisciplinary teams, and other agencies in the management of conditions.

## Key terminology

### Family history

A family health history is a record of the diseases and health conditions of an individual and that person's biological family members, both living and deceased. A family history can help determine whether someone has an increased genetic risk of having or developing certain diseases, disorders or conditions. It is often recorded by drawing a pedigree  (a family tree) that illustrates the relationships among individuals.

### Gene

The gene is considered the basic unit of inheritance. Genes are passed from parents to offspring and contain the information needed to specify physical and biological traits. Most genes code for specific proteins, or segments of proteins, which have differing functions within the body. Humans have approximately 20,000 protein-coding genes.

## Genetics

Genetics is the branch of biology concerned with the study of inheritance, including the interplay of genes, DNA variation and their interactions with environmental factors.

## Genome

The genome is the entire set of DNA instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes located in the cell's nucleus, as well as a small chromosome in the cell's mitochondria. A genome contains all the information needed for an individual to develop and function.

## Genomics

Genomics is a field of biology focused on studying all the DNA of an organism — that is, its genome. Such work includes identifying and characterizing all the genes and functional elements in an organism's genome as well as how they interact.

## Human Genome Project

The Human Genome Project was a large international, collaborative effort that mapped and sequenced the human genome for the first time. Conducted from 1990 to 2003, the project was historic in its scope and scale as well as its groundbreaking approach for the free release of genomic data well ahead of publication, leading to a new ethos for data sharing in biomedical research.

## Inherited

Inherited, as related to genetics, refers to a trait or variants encoded in DNA and passed from parent to offspring during reproduction. Inheritance is determined by the rules of Mendelian genetics.

## Precision medicine (also referred to as precision healthcare/ medicine or personalized medicine)

Precision medicine (generally considered analogous to personalized medicine or individualized medicine) is an innovative approach that uses information about an individual's genomic, environmental and lifestyle information to guide decisions related to their medical management. The goal of precision medicine is to provide more a precise approach for the prevention, diagnosis and treatment of disease.

### Protein

Proteins are large, complex molecules that play many important roles in the body. They are critical to most of the work done by cells and are required for the structure, function and regulation of the body's tissues and organs. A protein is made up of one or more long, folded chains of amino acids (each called a polypeptide), whose sequences are determined by the DNA sequence of the protein-encoding gene.

## Attribution & References



Except where otherwise noted, this page is adapted from:

- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.

## References

American Nurses Association (ANA). (2023). *Essentials of genomic nursing: Competencies and outcome indicators* (3rd ed.). https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/

National Health Service (NHS). (2023). *The 2023 genomic competency framework for UK nurses*. https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2023/12/2023-Genomic-Competency-Framework-for-UK-Nurses.pdf

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# 1.2 GENETICS AND GENOMICS INTRODUCTION

## Understanding Genomics

### Genetics and Genomics – What's the Difference?

Genetics and genomics both play roles in health and disease. **Genetics** refers to the study of genes and the way that certain traits or conditions are passed down from one generation to another. **Genomics** describes the study of all of a person's genes (the **genome**).

Genetics is a term that refers to the study of genes and their roles in inheritance – in other words, the way that certain traits or conditions are passed down from one generation to another. Genetics involves scientific studies of genes and their effects. **Genes** (units of heredity) carry the instructions for making **proteins**, which direct the activities of cells and functions of the body. Examples of genetic or **inherited** disorders include cystic fibrosis (See: Learning About Cystic Fibrosis (https://www.genome.gov/10001213/learning-about-cystic-fibrosis/)), Huntington's disease (Learning About Huntington's Disease (https://www.genome.gov/10001215/learning-about-huntingtons-disease/)), and phenylketonuria (PKU) (Learning About Phenylketonuria (https://www.genome.gov/25020037/learning-about-phenylketonuria/)).

Genomics is a more recent term that describes the study of a person's genes (the genome), including interactions of those genes with each other and the person's environment. Genomics includes the scientific study of complex diseases such as heart disease, asthma, diabetes, and cancer because these diseases are typically caused more by a combination of genetic and environmental factors than by individual genes. Genomics offers new possibilities for therapies and treatments for some complex diseases and new diagnostic methods.

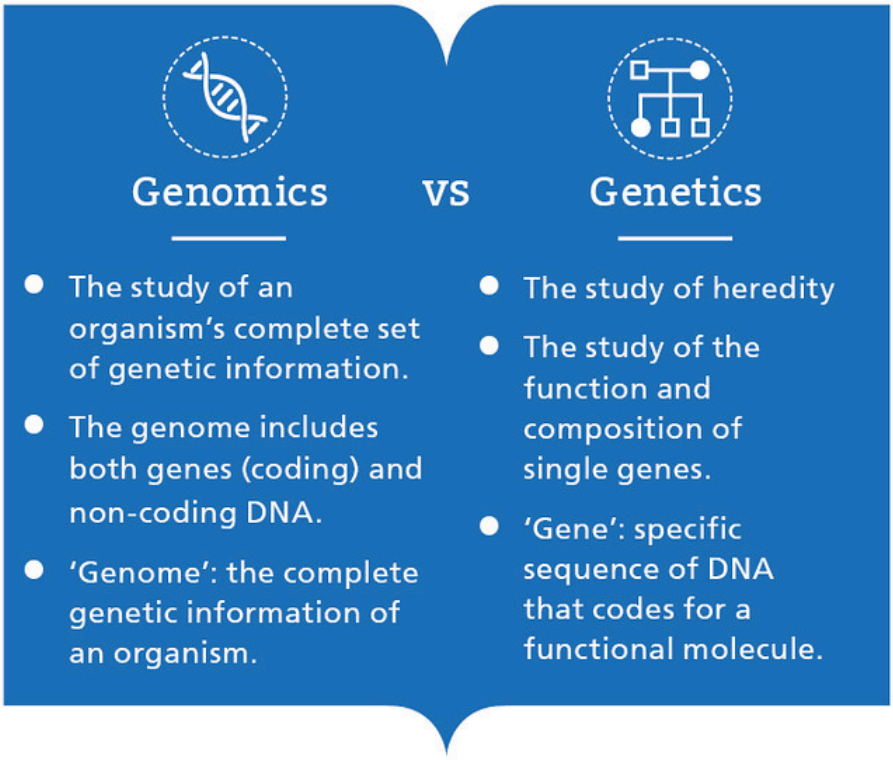


**Figure 1.1.** Genomics vs. Genetics: Genomics is the study of an organism's complete set of genetic information. The genome includes both genes (coding) and non-coding DNA. 'Genome': the complete genetic information of an organism. Genetics is the study of heredity, the function and composition of single genes. 'Gene': specific sequence of DNA that codes for a functional molecule. **Source:** What is Genomics? by Genomics Education Programme (GEP), CC BY-NC 4.0

Personalized medicine (or healthcare) is an emerging practice that uses an individual's genetic profile to guide decisions made regarding disease prevention, diagnosis, and treatment. Knowing a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the appropriate dose or regimen. Personalized medicine is being advanced through data from the Human Genome Project.

Personalized medicine is a fantastic opportunity to take a "one size fits all" approach to diagnostics, drug therapy, and prevention and turn it into an individualized approach. We all are similar, of course, but we are also different. The idea that medicine would be applied in a fashion that ignores those differences can't be any more correct than going to the shoe store and buying any old pair of shoes without checking the size. Genomics plays a significant role in the emergence of personalized medicine as it gives us a window in a particular molecular way into those differences between us and allows the opportunity for making individual predictions about disease risk that can help somebody choose a prevention plan that is right for them. It also allows the possibility, in some instances, of picking the right drug at the right dose for the right person instead of the "one size fits all" approach to drug therapy. And ultimately, it will be hard to see how any kind of medicine will not be affected by this as we learn more and more about the individual and as many of us find

our complete genomes being sequenced and placed into our medical records to empower that kind of personalized approach. Lots of work to do here, but it may be the biggest revolution in medicine in a very long time.

**Precision medicine** is a newer term with a similar meaning to the often analogously used "personalized medicine or healthcare." The shift away from the word personalized was in response to concerns over misinterpretation of the word "personalized" to imply that each individual could have uniquely tailored care and treatment. Precision medicine/healthcare takes advantage of large data sets of individuals such as their genome or their entire electronic health record to tailor their healthcare to their unique attributes. "Precision medicine consists of identifying which approaches/treatment will be effective for which patients according to the group to which they belong based on their biological characteristics. In this sense, it is more stratified medicine than personalized medicine" (Delpierre & Lefèvre, 2023). It is common sense that no two individuals are the same, so they should not get the same healthcare. Precision healthcare embodies that simple idea.

**Personalized Medicine (text version)**
**Watch the video Personalized Medicine (5 mins) at BC Campus Media (https://media.bccampus.ca/media/0_78tjylkd)**

Pause the video at 4:25 to answer the following question:

True or false? How drugs interact with your unique genetic makeup is a part of personalized medicine.

**Check your answer in footnote**[1]

**Activity source:** Concepts of Biology – 1st Canadian Edition, CC BY 4.0

## The Human Genome Project

**The Human Genome Project** (HGP) is one of the most remarkable scientific feats in history. The project was a voyage of biological discovery led by an international group of researchers looking to comprehensively study all of the DNA (known as a genome) of a select set of organisms. Launched in October 1990 and completed in April 2003, the Human Genome Project's signature accomplishment – generating the first sequence of the human genome – provided fundamental information about the human blueprint, which has since accelerated the study of human biology and improved the practice of medicine.

1. True

Checkout this Human Genome Project timeline of events (https://www.genome.gov/human-genome-project/timeline) from the NHGRI

Visit NHGRI (https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genome-project) to learn more about the Human Genome Project.


**Figure 1.2.** Francis Collins, M.D., Ph.D., announces the successful completion of the Human Genome Project. **Source:** Photo by Ernie Branson, NIH, PDM.

## Facts About the Human Genome

- Humans have approximately 20,000 genes
- DNA contains 6 billion nucleotides, which amounts to 3 billion base pairs.
- There is a 99.9% similarity in the DNA sequences of humans.
- A human gene may have 1-3 letters that differ from person to person.
- Humans have 23 pairs of chromosomes

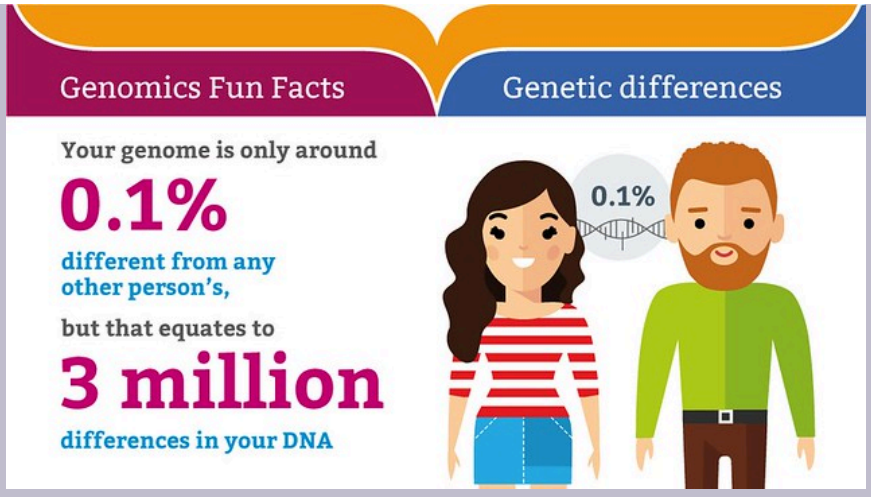


**Figure 1.3. Source:** Genomics Fun Facts: Genetic Differences by Genomics Education Programme (GEP), CC BY-NC 4.0

**Watch History – Making Sense of the Human Genome (4 mins) on YouTube (https://youtu.be/iHuUkb-Mvz8)**

# Genomics Applications

## Why Are Genetics and Genomics Important to Health?

Genetics and genomics both play roles in health and disease. Genetics helps individuals and families learn about how conditions such as sickle cell anemia and cystic fibrosis are inherited in families, what screening and testing options are available, and, for some genetic conditions, what treatments are available.

Genomics is helping researchers discover why some people get sick from certain infections, environmental factors, and behaviours while others do not. For example, some people exercise their whole lives, eat a healthy diet, have regular medical checkups, and die of a heart attack at age 40. Some people smoke, never exercise, eat unhealthy foods and live to be 100. Genomics may hold the key to understanding these differences.

Apart from accidents (such as falls, motor vehicle accidents or poisoning), genomic factors play a role in nine of the ten leading causes of death in the United States (for example, heart disease, cancer and diabetes. See: Leading Causes of Death (http://www.cdc.gov/nchs/FASTATS/lcod.htm)). All human beings are 99.9 percent identical in their genetic makeup. Differences in the remaining 0.1 percent hold important clues about the causes of diseases. Gaining a better understanding of the interactions between genes and the environment using genomics is helping researchers find better ways to improve health and prevent disease,

such as modifying diet and exercise plans to prevent or delay the onset of type 2 diabetes in people who carry genetic predispositions to developing this disease.

## Why Are Genetics and Genomics Important to the Health of Families?

Understanding more about diseases caused by a single gene (using genetics) and complex diseases caused by multiple genes and environmental factors (using genomics) can lead to earlier diagnoses, interventions, and targeted treatments. A person's health is influenced by their family history and shared environmental factors. This makes family history an important, personalized tool that can help identify many of the causative factors for conditions with a genetic component. The **family history** can serve as the cornerstone for learning about genetic and genomic conditions in a family and for developing individualized approaches to disease prevention, intervention, and treatment.

### Concept in Action

**Watch My Genomics Journey: three perspectives (5 mins) on Vimeo (https://vimeo.com/888710908)**

### 15 ways genomics influences our world:

1. DNA sequencing – Advances in genomics are reducing the cost of genome sequencing by a million-fold.
2. Human genomic variation – Genomics is helping us understand what makes each of us different and what makes us the same.
3. Cancer genomics – Genomics transforms how we study, diagnose and treat cancer.
4. Human origins and ancestry – Genomics is illuminating human and family origins at a

previously impossible level.

5. Agriculture – Genomics is empowering farmers to improve the food supply.
6. Genomes at work – We are learning how our genomes serve as blueprints for life.
7. Rare genetic diseases – Genomics is ending diagnostic odysseys for patients with rare diseases.
8. Pharmacogenomics – Genomics is helping us choose the right medication at the right dose for each patient.
9. Noninvasive prenatal genetic testing – Genomics is revolutionizing health assessments before birth.
10. Enhanced forensics – Genomics establishes more robust methods for DNA-based forensic analyses.
11. Microbes and microbiomes – Genomics is advancing the study of individual and communities of microbes.
12. Direct-to-consumer genomic testing – Genomics is helping you access information about your genome from your home.
13. The natural world – Genomics helps us understand evolution and protect our biological ecosystems.
14. Genome editing – Genomics alters a genome with unparalleled efficiency and precision.
15. Social context – Genomics fosters an appreciation of what our DNA means for our health, identities and culture.

To view this source and for more details on these applications, visit NHGRI. (https://www.genome.gov/dna-day/15-ways)

## Genomic Literacy

What exactly is meant by "genomic literacy?"

**Watch the short animation Canadian Nursing and Genomics: Whiteboard Video 1 (1 minute) on YouTube (https://youtu.be/4yYfMNE39JE)**

## Evidence Informing the Definition of Genomic Literacy

Boerwinkel et al. (2017) conducted a Delphi study to achieve expert consensus on the essential knowledge required for informed decision-making in genomics. Genomic literacy is necessary not only for healthcare professionals delivering genomic services but also for patients receiving them. The authors classified this knowledge into three categories:

> Conceptual knowledge: knowledge of genetic concepts;
>
> Sociocultural knowledge: knowledge of how applications of genetic technologies are used in societal activities and in what ways they influence human lives;
>
> Epistemic knowledge: knowledge of the meaning of genetic information. This concerns the knowledge needed to interpret genetic information from different sources and how to use these in argument and decision-making. This knowledge includes Nature of Science aspects such as the certainty and uncertainty of genetic information and how genetic concepts have evolved (Boerwinkel et al., 2017, p.1106).

## How Can Genomic Literacy Assist Nurses in Addressing the Social, Ethical, and Equity Issues Associated with Nursing?

**Watch this short animation: Canadian Nursing and Genomics Whiteboard Video 4 (2 mins) from YouTube (https://youtu.be/IFo8IgltQDY)**

## Attribution & References

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- Precision Medicine, Courtesy of: National Human Genome Research Institute, Public Domain with attribution
- 15 Ways Genomics Influences Our World, Courtesy of: National Human Genome Research Institute, Public Domain with attribution
- H5P/video from 10.3 Genomics and Proteomics In *Concepts of Biology – 1st Canadian Edition* by Charles Molnar and Jane Gair, CC BY 4.0

Adaptations include combining sources, minor grammatical changes, and addition of quotes, videos and commentary to improve student understanding.

## References

Boerwinkel, D.J., Yarden, A. & Waarlo, A.J. (2017). Reaching a consensus on the definition of genetic literacy that is required from a twenty-first-century citizen. *Science & Education, 26*, 1087–1114. https://doi.org/10.1007/s11191-017-9934-y

Delpierre, C., & Lefèvre, T. (2023). Precision and personalized medicine: What their current definition says and silences about the model of health they promote. Implication for the development of personalized health. *Frontiers in Sociology*, *8*, 1112159. https://doi.org/10.3389/fsoc.2023.1112159

# 1.3 THE CONTRIBUTIONS OF NURSING PROFESSIONALS IN GENOMICS HEALTHCARE

There is a wide variety of ways that healthcare professionals can contribute to providing genomic services. As technologies advance and genomics becomes increasingly integrated into routine practices, new roles will emerge.

Visit the NHS Genomics Education Programme website (from the United Kingdom) – Careers in Genomics (https://www.genomicseducation.hee.nhs.uk/careers/), to learn more about some of the interdisciplinary team members that nurses will work with.

To learn more about different practice contexts and medical specialties, visit the Genomics Education Programme website's section on Genomics in Healthcare.

## Nurses' Contributions to Genomics

Watch this short video on the relevance of genomics to nursing practice. This video briefly overviews some critical takeaways nurses will gain from reading this book.

**Watch Nursing in the Genomic Era (3 mins) on YouTube (https://youtu.be/LaHSMJGUco8)**

## Why should nurses understand basic genomic principles?

Genomics plays a role in every aspect of nursing, which includes providing one-on-one care, treating entire populations, teaching the next generation of nurses, or making discoveries in the lab.

### Genomic principles form the foundation for disease pathophysiology

- Genomics underlies all diseases
- Genomics contributes to our understanding of the mechanisms of disease

### Genomics principles influence clinical actions

- Genomics knowledge supports clinical practice and potential interventions (e.g., newborn screening tests).

- Obtaining genomic information about a patient can change recommendations for prevention and screening (e.g., recommendations for annual MRI with elevated breast cancer risk).
- Genomics affects pharmacokinetics and pharmacodynamics, affecting drug selection and dose (e.g., antidepressants, anticoagulants).

## Understanding genomic principles facilitates communication with patients and family members and supports genomics-informed care

- Patients often need help understanding how genomics influences their health and the health of their family members.
- Effective patient and family education requires foundational knowledge of genomics.
- Nurses can help patients understand how genomics affects disease risk.
- Ethical nursing care includes understanding the ethical considerations of genomic healthcare (e.g., right not to know).


**Figure 1.4** Nursing in the Genomic Era. Nurses communicate by explaining processes and tests, listening for clinical clues, advising and signposting. Nurses are hands on: Taking samples, administering drugs, managing infection control. Nurses collaborate: Leading and guiding others, escalating concerns, representing patients at meetings. **Source:** Nursing in the Genomic Era by Genomics Education Programme, CC BY 2.0.

## In What Settings Can Genomics be Used?

Genomics is used in all practice settings across all aspects of nursing care, including educating patients and families, administering medications, advocating for health promotion and disease prevention and interpreting family histories.

While all nurses will encounter genomics at some point in their practice, there are particular areas where genomics is highly relevant, such as oncology, pediatrics, and maternity. As new genomics applications are developed, these areas are likely to increase.

## Rare disease

Nurses who care for patients with rare diseases support these families and help them through the health and social care system. Some nurses specialize in a particular rare condition, such as:

- Familial hypercholesterolemia: These roles usually involve identifying and supporting affected families. You can read more about this work here: North East and Cumbria [PDF]. (http://www.ahsn-nenc.org.uk/wp-content/uploads/2018/07/The-role-of-the-FH-Nurse-.pdf)
- Monogenic diabetes: Specialist genetic diabetes nurses (https://www.genomicseducation.hee.nhs.uk/about-us/training-a-network-of-genetic-diabetes-nurses/) support patients with this rare form of diabetes and their families and increase recognition and diagnosis of monogenic diabetes among healthcare professionals. More information can be found on the Diabetes Genes website. (https://www.diabetesgenes.org/training/genetic-diabetes-nurses/)

## Advanced practice settings

Nurses working as experts in a particular clinical area, such as oncology, cardiology or pediatrics, will increasingly be trained to manage patients with inherited genetic conditions and targeted treatments. Keeping abreast of rapid developments in genomics is a vital part of the role of many specialisms. Here is an example of the work that a clinical nurse specialist with expertise in genomics may do [PDF] (https://www.thinkkidneys.nhs.uk/kquip/wp-content/uploads/sites/5/2017/12/FamilyHistoryOfGeneticRenalDiseases.pdf), with a special focus on renal medicine.

As new initiatives are developed, it is often appropriate for advanced practice and specialist nurses to become involved with service development to help meet patient needs and address patient demands, aiming to improve patient outcomes. Advanced practice and specialist nurses are uniquely situated to provide these services.

## Research

Although advances in genomics have been rapid and impressive, we still have a long way to go. Ongoing research is vital to ensure that all patients can benefit. There are many opportunities to be involved with research projects as a nurse, and you may choose to specialize in this area. The work may include developing hypotheses, recruiting patients to research projects, training other staff members, collecting and analyzing data, and caring for and communicating with those involved. Nursing research in genomics will be explored further in a subsequent unit.

### How Can Nurses Apply Genomics to Practice?

- Record and interpret a comprehensive family history to identify risk for heritable genetic conditions.
- Understand the genomic basis for specific health conditions and the associated prognosis.
- Recognize newborn risk for morbidity and mortality based on identified genetic conditions.
- Identify risk for asymptomatic individuals with high risk for hereditary cancers.
- Advocate for interventions based on individual genetic needs.
- Facilitate screening and follow-up for individuals with known genetic conditions.
- Encourage genetic testing for at-risk family members.
- Obtain and verify informed consent.
- Ensure understanding of all risks, benefits, and limitations of genetic testing and research.
- Use current credible information to answer questions about genomic information or services and assess for understanding.
- Identify at-risk populations.
- Form empathetic relationships to support individuals and families at risk for or affected by genetic conditions.
- Educate individuals, families, and communities about the role of genomics in medication response.
- Discuss and educate about the function of the new genomics-based vaccine.

## How Are Nurses Prepared and Positioned to Provide Genomics-Informed Care?

**Nurses practice from a holistic viewpoint**. Nurses consider patients, families and communities within their contexts.

- Genomics must be considered in context, including patients' genomic information, clinical presentation and the environments in which they live.
- Nurses consider ethical, legal and social issues for individuals and families.

**Nurses have a central position in the healthcare team and interact the most with patients.**

- Nurses are central to interdisciplinary communication and coordination.
- Nurses translate and relay the concerns of patients and family members to the healthcare team.

**Nurses have an optimal skill set for applying genomics in all practice settings and roles.** Nurses apply genomics principles at the bedside, in the community, in policy and research.

- Nurses are skilled at obtaining individual and family histories to provide critical information for genomics-informed care.
- Nurses obtain and analyze data from physical assessments, individual and family histories, laboratory tests and other sources.
- Nurses plan and implement interventions central to genomics-informed care.
- Nurses champion patient education and translate complex topics into lay terms.
- Nurses are ethical practitioners prepared to advocate for patient needs.

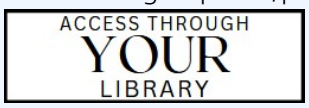
## Concept in Action

This podcast (https://www.genomicseducation.hee.nhs.uk/education/podcasts/genomics-conversation-genomics-in-nursing-with-dr-christine-patch/)(approx 5min) features Dr Christine Patch, Clinical Lead for Genetic Counselling at Genomics England and the new Chair of the Global Genomics Nursing Alliance, also known as 'G2NA'. Christine talks about the influence of genomics on nursing practice and how nurses need to be aware of its potential in patient care. She also talks about the work of the G2NA and other international collaborations to raise the genomics profile. She discusses the need for genomics to become an established part of nursing training.

**Source:** Health Education England's Genomics Education Programme (GEP)

## Read

Dewell, S., Benzies, K., & Ginn, C. (2020). Precision health and nursing: Seeing the familiar in the foreign. *The Canadian Journal of Nursing Research*, *52*(3), 199–208. https://doi.org/10.1177/0844562120945159

(https://georgian.primo.exlibrisgroup.com/permalink/01OCLS_GEORG/21p491/cdi_proquest_miscellaneous_2440663648) 


Fu, M. R., Kurnat-Thoma, E., Starkweather, A., Henderson, W. A., Cashion, A. K., Williams, J. K., Katapodi, M. C., Reuter-Rice, K., Hickey, K. T., Barcelona de Mendoza, V., Calzone, K., Conley, Y. P., Anderson, C. M., Lyon, D. E., Weaver, M. T., Shiao, P. K., Constantino, E. E., Wung, S., Hammer, M. J., Voss, J. G., Coleman, B. (2020). Precision health: A nursing perspective, International Journal of Nursing Sciences, 7(1), 5-12. https://doi.org/10.1016/j.ijnss.2019.12.008.

(https://doi.org/10.1016/j.ijnss.2019.12.008)

## Genomics-Informed Nursing Policies

Nurses typically rely on policy to guide practice. Examples of nursing policies include professional or practice standards, scope of practice, competencies, practice guidelines, and educational frameworks. Currently, in Canada, there are no policies to guide genomics-informed nursing (Puddester et al., 2023). The United States and the UK have modelled the way about interdisciplinary genomics integration. These countries have developed evidence-based competencies for nurses delivering genomic services. One aspect of preparing the health system for genomics integration is developing policies for healthcare professionals, including nurses, to delineate roles and responsibilities and foster the development of genomic literacy.

Briefly review the following documents. As you progress through each chapter in this book, consider the competencies you are beginning to develop. The unit overview sections will list the competencies developed in each unit.

- NHS. (2023). Genomic competency framework for UK nurses (https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2023/12/2023-Genomic-Competency-Framework-for-UK-Nurses.pdf).
- ANA. (2023). Essentials of genomic nursing: Competencies and outcome indicators (https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/) (3rd ed.).

*Note: the ANA website will request some personal information, including an email address, to distribute the competency document.*

## Genomics Organizations for Nurses and Other Healthcare Professionals

The following organizations offer member benefits, including continuing professional development, practice resources, conferences, journals, scholarships, grants, and more. These organizations also offer opportunities to provide policy input or for nurses to get involved in governance.

Most of them offer **student discounts** for membership and conference attendance.

- The International Society of Nurses in Genetics (ISONG (https://www.isong.org/))
- Global Genomics Nursing Alliance (G2NA (https://g2na.org/))
- The Canadian College of Medical Genetics (CCMG (https://cihr-irsc.gc.ca/e/13147.html))
- The American College of Medical Genetics (ACMG (https://www.acmg.net/))
- The American Society of Human Genetics (ASHG (https://www.ashg.org/))
- Oncology Nursing Society (ONS (https://www.ons.org/)) – not specific to genomics but has excellent education resources on cancer genetics.

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- Genomics in Nursing: Roles for Nurses by Genomics Education Programme, CC BY-NC 4.0

Adaptations include combining content from the 3 pages, minor edits and addition of links to improve student understanding.

## References

Puddester, R., Limoges, J., Dewell, S., Maddigan, J., Carlsson, L., & Pike, A. (2023). The Canadian landscape of genetics and genomics in nursing: A policy document analysis. *The Canadian Journal of Nursing Research*, *55*(4), 494–509. https://doi.org/10.1177/08445621231159164

# 1.4 UNIT SUMMARY AND REVIEW

## Key Takeaways

This chapter introduced genomics as a field of study with a related yet distinct focus from genetics. Some key terminology was provided that will be utilized throughout the book. The completion of the Human Genome Project in 2003 provided fundamental information about the human blueprint and was a launching point for the acceleration of genomic sciences. As the use of genomic technologies becomes more commonplace in healthcare settings, nurses need genomic literacy to be able to provide safe and equitable care. While all nurses will encounter genomics at some point in their practice, certain roles require more specialized knowledge. It is also likely that as genomics is advanced in healthcare system, new roles for nurses will be created to meet workforce demands. The Canadian healthcare system has more work to do to be ready for the complete adoption of genomics. One area where nurses can advocate for change relates to developing policy infrastructure to guide genomics-informed nursing practice, education, and research. Finally, nurses are encouraged to get involved in genomics organizations in order to have a voice in how genomics is integrated into the nursing profession and the healthcare system to benefit patient care.

## Additional Optional Readings:

Although this is an older article, it has an excellent summary table. Review p.171, Table 1 – Standards in Genetics and Genomics for General Nursing Practice.

1. Kerber, A. S., & Ledbetter, N. J. (2017). Standards of practice: Applying genetics and genomics resources to oncology. *Clinical Journal of Oncology Nursing*, *21*(2), 169–173. https://doi.org/10.1188/17.CJON.169-173

Discover how nurses and nursing leaders across Canada are working to accelerate the integration of genomics in practice, education, and research.

1. Carlsson, L. & Limoges, J. (2022). Canadian nursing and genomics: An engagement initiative. *Canadian Oncology Nursing Journal, 32*(4), 559–564. https://canadianoncologynursingjournal.com/index.php/conj/article/view/1318
2. Limoges, J., Pike, A., Dewell, S., Meyer, A., Puddester, R., & Carlsson, L. (2022). Leading Canadian nurses into the genomic era of healthcare. *Nursing Leadership, 35*(2), 79–95. https://doi.org/10.12927/cjnl.2022.26869
3. Canadian Nurses Association. (2020). *Nurses poised to play key role in advancing precision care through genetics and genomics*. https://community.cna-aiic.ca/blogs/cn-content/2020/10/26/nurses-poised-to-play-key-role-in-advancing-precis

## Attribution and References

# UNIT 2 - MOLECULAR GENETICS REVIEW

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 2 Contents


- 2.1 Unit Overview
- 2.2 DNA Structure and Function
- 2.3 The Genome and the Cell Cycle
- 2.4 Cancer and the Cell Cycle
- 2.5 The Cellular Basis of Inheritance
- 2.5 Patterns of Inheritance
- 2.7 Unit Summary and Review


## Attribution

# 2.1 UNIT OVERVIEW

## Learning Objectives

- Review DNA structure and function.
- Describe the process of cellular reproduction.
- Explain the central dogma and how DNA encodes protein.
- Identify factors that influence gene expression.
- Explain inheritance at the cellular level.
- Calculate expected outcomes for monohybrid crosses involving different patterns of inheritance.

*In most chapters of this textbook, the learning outcomes are listed solely in the chapter overview. This chapter is longer than the others to provide a comprehensive review of foundational biology concepts that students will need to progress in this course. As such, learning objectives will be provided at the beginning of each chapter in this unit as an exception.

***Note:*** this chapter is intended to provide a review of these concepts, which would have been covered in previous biology courses. Many of these principles and core concepts are presented here as an overview but will be revisited in greater detail in subsequent units. Cancer is covered briefly in this unit from a cellular perspective for a complete understanding of replication and division. Cancer genomics will be reviewed in greater detail in unit 12.

Students who are well-versed in this content can move through this chapter quickly. For students who need a deeper review, additional learning resources will be recommended in the chapter summary. It is recommended to start with the final summary and the review questions at the end of each chapter to identify learning needs.

# Outline

Topics covered in this chapter include:

- DNA structure and function
- The genome and the life cycle
- Cancer and the cell cycle
- The cellular basis of inheritance
- Patterns of inheritance

## Competencies Nurses will Develop in this Chapter

### NHS, 2023:

#### Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice.

- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

## Key terminology

*This unit will summarize additional key terminology at the end of each chapter.

### Adenine

Adenine (A) is one of the four nucleotide bases in DNA, with the other three being cytosine (C), guanine (G) and thymine (T). Within a double-stranded DNA molecule, adenine bases on one strand pair with thymine bases on the opposite strand. The sequence of the four nucleotide bases encodes DNA's information.

### Allele

An allele is one of two or more versions of DNA sequence (a single base or a segment of bases) at a given genomic location. An individual inherits two alleles, one from each parent, for any given genomic location where such variation exists. If the two alleles are the same, the individual is homozygous for

that allele. If the alleles are different, the individual is heterozygous.

## Amino Acid

An amino acid is the fundamental molecule that is the building block for proteins. There are 20 different amino acids. A protein consists of one or more chains of amino acids (called polypeptides) whose sequence is encoded in a gene. Some amino acids can be synthesized in the body, but others (essential amino acids) cannot and must be obtained from a person's diet.

## Aneuploidy

Aneuploidy is an abnormality in the number of chromosomes in a cell due to loss or duplication. Aneuploidy would be any number of chromosomes other than the usual 46 in humans.

## Autosomal Dominant Disorder

Autosomal dominant is a pattern of inheritance characteristic of some genetic disorders. "Autosomal" means that the gene in question is located on one of the numbered, or non-sex, chromosomes. "Dominant" means that a single copy of the gene variant (from one parent) is enough to cause the disorder. A child of a person affected by an autosomal dominant condition has a 50% chance of being affected by that condition via inheritance of a dominant allele. By contrast, an autosomal recessive disorder requires two copies of the gene variant (one from each parent) to cause the disorder. Huntington's disease is an example of an autosomal dominant genetic disorder.

## Autosomal Recessive Disorder

Autosomal recessive is a pattern of inheritance characteristic of some genetic disorders. "Autosomal" means that the gene in question is located on one of the numbered, or non-sex, chromosomes. "Recessive" means that two copies of the gene variant (one from each parent) are required to cause the disorder. In a family where both parents are carriers and do not have the disease, roughly a quarter of their children will inherit two disease-causing alleles and have the disease. By contrast, an autosomal dominant disorder requires only a single copy of the gene variant from one parent to cause the disorder. Sickle cell anemia is an example of an autosomal recessive genetic disorder.

## Autosome

An autosome is one of the numbered chromosomes, as opposed to the sex chromosomes. Humans have 22 pairs of autosomes and one pair of sex chromosomes (XX or XY). Autosomes are numbered

roughly in relation to their sizes. The largest autosome — chromosome 1 — has approximately 2,800 genes; the smallest autosome — chromosome 22 — has approximately 750 genes.

## Base Pair

A base pair consists of two complementary DNA nucleotide bases that pair together to form a "rung of the DNA ladder." DNA is made of two linked strands that wind around each other to resemble a twisted ladder — a shape known as a double helix. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases: adenine (A), cytosine (C), guanine (G) or thymine (T). The two strands are held together by hydrogen bonds between pairs of bases: adenine pairs with thymine, and cytosine pairs with guanine.

## Cancer

Cancer is a disease in which some of the body's cells grow uncontrollably. There are many different types of cancer, and each begins when a single cell acquires a genomic change (or mutation) that allows the cell to divide and multiply unchecked. Additional variants can cause the cancer to spread to other sites. Such variants can be caused by errors during DNA replication or result from DNA damage due to environmental exposures (such as tobacco smoke or the sun's ultraviolet rays). In certain cases, variants in cancer genes are inherited, which increases a person's risk of developing cancer.

## Carrier

A carrier, as related to genetics, is an individual who "carries" and can pass on to its offspring a genomic variant (allele) associated with a disease (or trait) that is inherited in an autosomal recessive or sex-linked manner, and who does not show symptoms of that disease (or features of that trait). The carrier has inherited the variant allele from one parent and a normal allele from the other parent. Any offspring of carriers is at risk of inheriting a variant allele from their parents, which would result in that child having the disease (or trait).

## Central Dogma

The central dogma of molecular biology is a theory first proposed by Francis Crick in 1958. It states that genetic information flows only in one direction, from DNA to RNA to protein. Scientists have since discovered several exceptions to the theory.

## Chromosome

Chromosomes are threadlike structures made of protein and a single molecule of DNA that serve to carry the genomic information from cell to cell. In plants and animals (including humans), chromosomes reside in the nucleus of cells. Humans have 22 pairs of numbered chromosomes (autosomes) and one pair of sex chromosomes (XX or XY), for a total of 46. Each pair contains two chromosomes, one coming from each parent, which means that children inherit half of their chromosomes from their mother and half from their father. Chromosomes can be seen through a microscope when the nucleus dissolves during cell division.

## Codon

A codon is a DNA or RNA sequence of three nucleotides (a trinucleotide) that forms a unit of genomic information encoding a particular amino acid or signaling the termination of protein synthesis (stop signals). There are 64 different codons: 61 specify amino acids and 3 are used as stop signals.

## Codominance

Codominance, as it relates to genetics, refers to a type of inheritance in which two versions (alleles) of the same gene are expressed separately to yield different traits in an individual. That is, instead of one trait being dominant over the other, both traits appear, such as in a plant or animal that has more than one pigment color.

Learn more about Codominance (https://www.genome.gov/genetics-glossary/Codominance)

## Cytosine

Cytosine (C) is one of the four nucleotide bases in DNA, with the other three being adenine (A), guanine (G) and thymine (T). Within a double-stranded DNA molecule, cytosine bases on one strand pair with guanine bases on the opposite strand. The sequence of the four nucleotide bases encodes DNA's information.

## Deoxyribonucleic Acid (DNA)

Deoxyribonucleic acid (abbreviated DNA) is the molecule that carries genetic information for the development and functioning of an organism. DNA is made of two linked strands that wind around each other to resemble a twisted ladder — a shape known as a double helix. Each strand has a

backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases: adenine (A), cytosine (C), guanine (G) or thymine (T). The two strands are connected by chemical bonds between the bases: adenine bonds with thymine, and cytosine bonds with guanine. The sequence of the bases along DNA's backbone encodes biological information, such as the instructions for making a protein or RNA molecule.

## Diploid

Diploid is a term that refers to the presence of two complete sets of chromosomes in an organism's cells, with each parent contributing a chromosome to each pair. Humans are diploid, and most of the body's cells contain 23 chromosomes pairs. Human gametes (egg and sperm cells), however, contain a single set of chromosomes and are said to be haploid.

## DNA Replication

DNA replication is the process by which the genome's DNA is copied in cells. Before a cell divides, it must first copy (or replicate) its entire genome so that each resulting daughter cell ends up with its own complete genome.

## Dominant Traits and Alleles

Dominant, as related to genetics, refers to the relationship between an observed trait and the two inherited versions of a gene related to that trait. Individuals inherit two versions of each gene, known as alleles, from each parent. In the case of a dominant trait, only one copy of the dominant allele is required to express the trait. The effect of the other allele (the recessive allele) is masked by the dominant allele. Typically, an individual who carries two copies of a dominant allele exhibits the same trait as those who carry only one copy. This contrasts to a recessive trait, which requires that both alleles be present to express the trait.

## Epistasis

Epistasis is a circumstance where the expression of one gene is modified (e.g., masked, inhibited or suppressed) by the expression of one or more other genes.

## Exome

An exome is the sequence of all the exons in a genome, reflecting the protein-coding portion of a genome. In humans, the exome is about 1.5% of the genome.

## Exon

An exon is a region of the genome that ends up within an mRNA molecule. Some exons are coding, in that they contain information for making a protein, whereas others are non-coding. Genes in the genome consist of exons and introns.

## Gamete

A gamete is a reproductive cell of an animal or plant. In animals, female gametes are called ova or egg cells, and male gametes are called sperm. Ova and sperm are haploid cells, with each cell carrying only one copy of each chromosome. During fertilization, a sperm and ovum unite to form a new diploid organism.

## Genetic code

Genetic code refers to the instructions contained in a gene that tell a cell how to make a specific protein. Each gene's code uses the four nucleotide bases of DNA: adenine (A), cytosine (C), guanine (G) and thymine (T) — in various ways to spell out three-letter "codons" that specify which amino acid is needed at each position within a protein.

## Gene Regulation

Gene regulation is the process used to control the timing, location and amount in which genes are expressed. The process can be complicated and is carried out by a variety of mechanisms, including through regulatory proteins and chemical modification of DNA. Gene regulation is key to the ability of an organism to respond to environmental changes.

## Genomic Variation

Genomic variation refers to DNA sequence differences among individuals or populations. A variant is a change in the DNA sequence of an organism. Some variants influence biological function (such as a mutation that causes a genetic disease), while others have no biological effects. Variants can result from errors in DNA replication during cell division, exposure to mutagens or a viral infection. Germline variants (that occur in eggs and sperm) can be passed on to offspring, while somatic variants (that occur in body cells) are not passed on.

## Genotype

A genotype is a scoring of the type of variant present at a given location (i.e., a locus) in the genome. It can be represented by symbols. For example, BB, Bb, bb could be used to represent a given variant in a gene. Genotypes can also be represented by the actual DNA sequence at a specific location, such as CC, CT, TT. DNA sequencing and other methods can be used to determine the genotypes at millions of locations in a genome in a single experiment. Some genotypes contribute to an individual's observable traits, called the phenotype.

## Germ Line

Germ line refers to the sex cells (eggs and sperm) that sexually reproducing organisms use to pass on their genomes from one generation to the next (parents to offspring). Egg and sperm cells are called germ cells, in contrast to the other cells of the body, which are called somatic cells.

## Guanine

Guanine (G) is one of the four nucleotide bases in DNA, with the other three being adenine (A), cytosine (C) and thymine (T). Within a double-stranded DNA molecule, guanine bases on one strand pair with cytosine bases on the opposite strand. The sequence of the four nucleotide bases encodes DNA's information.

## Haploid

Haploid refers to the presence of a single set of chromosomes in an organism's cells. Sexually reproducing organisms are diploid (having two sets of chromosomes, one from each parent). In humans, only the egg and sperm cells are haploid.

## Heterozygous

Heterozygous, as related to genetics, refers to having inherited different versions (alleles) of a genomic marker from each biological parent. Thus, an individual who is heterozygous for a genomic marker has two different versions of that marker. By contrast, an individual who is homozygous for a marker has identical versions of that marker.

## Histone

A histone is a protein that provides structural support for a chromosome. Each chromosome contains a long molecule of DNA, which must fit into the cell nucleus. To do that, the DNA wraps around complexes of histone proteins, giving the chromosome a more compact shape. Histones also play a role in the regulation of gene expression.

## Homologous Recombination

Homologous recombination is a type of genetic recombination in which nucleotide sequences are exchanged between two similar or identical molecules of DNA. During the formation of egg and sperm cells (meiosis), paired chromosomes from the male and female parents align so that similar DNA sequences can cross over, or be exchanged, from one chromosome to the other. This exchanging of DNA is an important source of the genomic variation seen among offspring.

## Homozygous

Homozygous, as related to genetics, refers to having inherited the same versions (alleles) of a genomic marker from each biological parent. Thus, an individual who is homozygous for a genomic marker has two identical versions of that marker. By contrast, an individual who is heterozygous for a marker has two different versions of that marker.

## Inherited

Inherited, as related to genetics, refers to a trait or variants encoded in DNA and passed from parent to offspring during reproduction. Inheritance is determined by the rules of Mendelian genetics.

## Intron

An intron is a region that resides within a gene but does not remain in the final mature mRNA molecule following transcription of that gene and does not code for amino acids that make up the protein encoded by that gene. Most protein-coding genes in the human genome consist of exons and introns.

## Linkage

Linkage, as related to genetics and genomics, refers to the closeness of genes or other DNA sequences

to one another on the same chromosome. The closer two genes or sequences are to each other on a chromosome, the greater the probability that they will be inherited together.

## Locus

A locus, as related to genomics, is a physical site or location within a genome (such as a gene or another DNA segment of interest), somewhat like a street address. The plural of locus is loci.

## Lyonization

Lyonization (also called X-inactivation) refers to the normal phenomenon in which one of the two X chromosomes in every cell of a female individual is inactivated during embryonic development. This inactivation prevents females from having twice as many X chromosome gene products as males, who possess only a single copy of the X chromosome. Lyonization is named after Mary F. Lyon, the British geneticist who discovered the phenomenon.

## Meiosis

Meiosis is a type of cell division in sexually reproducing organisms that reduces the number of chromosomes in gametes (the sex cells, or egg and sperm). In humans, body (or somatic) cells are diploid, containing two sets of chromosomes (one from each parent). To maintain this state, the egg and sperm that unite during fertilization must be haploid, with a single set of chromosomes. During meiosis, each diploid cell undergoes two rounds of division to yield four haploid daughter cells — the gametes.""Mendel, Johann (Gregor)""Gregor Mendel was an Austrian monk in the 19th century who worked out the basic laws of inheritance through experiments with pea plants. In his monastery garden, Mendel performed thousands of crosses with pea plants, discovering how characteristics are passed down from one generation to the next — namely, dominant and recessive traits. Mendel's early experiments provided the basis of modern genetics.

## Mendelian Inheritance

Mendelian inheritance refers to certain patterns of how traits are passed from parents to offspring. These general patterns were established by the Austrian monk Gregor Mendel, who performed thousands of experiments with pea plants in the 19th century. Mendel's discoveries of how traits (such as color and shape) are passed down from one generation to the next introduced the concept of dominant and recessive modes of inheritance.

## Messenger RNA (mRNA)

Messenger RNA (abbreviated mRNA) is a type of single-stranded RNA involved in protein synthesis. mRNA is made from a DNA template during the process of transcription. The role of mRNA is to carry protein information from the DNA in a cell's nucleus to the cell's cytoplasm (watery interior), where the protein-making machinery reads the mRNA sequence and translates each three-base codon into its corresponding amino acid in a growing protein chain.

## Mitosis

Mitosis is the process by which a cell replicates its chromosomes and then segregates them, producing two identical nuclei in preparation for cell division. Mitosis is generally followed by equal division of the cell's content into two daughter cells that have identical genomes.

## Mutagen

A mutagen is a chemical or physical agent capable of inducing changes in DNA, formerly called mutations, now termed variants. Examples of mutagens include tobacco products, radioactive substances, x-rays, ultraviolet radiation and a wide variety of chemicals. Exposure to a mutagen can produce DNA changes that cause or contribute to certain diseases.

## Non-Coding DNA

Non-coding DNA corresponds to the portions of an organism's genome that do not code for amino acids, the building blocks of proteins. Some non-coding DNA sequences are known to serve functional roles, such as in the regulation of gene expression, while other areas of non-coding DNA have no known function.

## Nucleic Acids

Nucleic acids are large biomolecules that play essential roles in all cells and viruses. A major function of nucleic acids involves the storage and expression of genomic information. Deoxyribonucleic acid, or DNA, encodes the information cells need to make proteins. A related type of nucleic acid, called ribonucleic acid (RNA), comes in different molecular forms that play multiple cellular roles, including protein synthesis.

## Nucleosome

A nucleosome is the basic repeating subunit of chromatin packaged inside the cell's nucleus. In humans, about six feet of DNA must be packaged into a nucleus with a diameter less than a human hair, and nucleosomes play a key role in that process. A single nucleosome consists of about 150 base pairs of DNA sequence wrapped around a core of histone proteins. In forming a chromosome, the nucleosomes repeatedly fold in on themselves to tighten and condense the packaged DNA.

## Oncogene

An oncogene is a gene variant that has the potential to cause cancer. Before an oncogene becomes altered, it is called a proto-oncogene, and it plays a role in regulating normal cell division. Cancer can arise when a proto-oncogene is altered, changing it into an oncogene and causing the cell to divide and multiply uncontrollably. Some oncogenes work like an accelerator pedal in a car, pushing a cell to divide again and again. Others work like a faulty brake in a car parked on a hill, also causing the cell to divide unchecked.

## Phenotype

Phenotype refers to an individual's observable traits, such as height, eye color and blood type. A person's phenotype is determined by both their genomic makeup (genotype) and environmental factors.

## Proto-oncogene:

A normal gene that controls cell division by regulating the cell cycle that becomes an oncogene if it is altered.

## Ribonucleic Acid (RNA)

Ribonucleic acid (abbreviated RNA) is a nucleic acid present in all living cells that has structural similarities to DNA. Unlike DNA, however, RNA is most often single-stranded. An RNA molecule has a backbone made of alternating phosphate groups and the sugar ribose, rather than the deoxyribose found in DNA. Attached to each sugar is one of four bases: adenine (A), uracil (U), cytosine (C) or guanine (G). Different types of RNA exist in cells: messenger RNA (mRNA), ribosomal RNA (rRNA) and transfer RNA (tRNA). In addition, some RNAs are involved in regulating gene expression. Certain viruses use RNA as their genomic material.

## Sex Chromosome

A sex chromosome is a type of chromosome involved in sex determination. Humans and most other mammals have two sex chromosomes, X and Y, that in combination determine the sex of an individual. Females have two X chromosomes in their cells, while males have one X and one Y.

## Somatic Cells

Somatic cells are the cells in the body other than sperm and egg cells (which are called germ cells). In humans, somatic cells are diploid, meaning they contain two sets of chromosomes, one inherited from each parent. DNA mutations in somatic cells can affect an individual, but they cannot be passed on to their offspring.

## Stop Codon

A stop codon is a sequence of three nucleotides (a trinucleotide) in DNA or messenger RNA (mRNA) that signals a halt to protein synthesis in the cell. There are 64 different trinucleotide codons: 61 specify amino acids and 3 are stop codons (i.e., UAA, UAG and UGA).

## Trait

A trait, as related to genetics, is a specific characteristic of an individual. Traits can be determined by genes, environmental factors or by a combination of both. Traits can be qualitative (such as eye color) or quantitative (such as height or blood pressure). A given trait is part of an individual's overall phenotype.

## Telomere

A telomere is a region of repetitive DNA sequences at the end of a chromosome. Telomeres protect the ends of chromosomes from becoming frayed or tangled. Each time a cell divides, the telomeres become slightly shorter. Eventually, they become so short that the cell can no longer divide successfully, and the cell dies.

## Thymine

Thymine (T) is one of the four nucleotide bases in DNA, with the other three being adenine (A), cytosine (C) and guanine (G). Within a double-stranded DNA molecule, thymine bases on one strand

pair with adenine bases on the opposite strand. The sequence of the four nucleotide bases encodes DNA's information.

## Transcription

Transcription is the process of making an RNA copy of a gene sequence. This copy, called a messenger RNA (mRNA) molecule, leaves the cell nucleus and enters the cytoplasm, where it directs the synthesis of the protein, which it encodes.

## Translation

Translation is the process of translating the sequence of a messenger RNA (mRNA) molecule to a sequence of amino acids during protein synthesis. The genetic code describes the relationship between the sequence of base pairs in a gene and the corresponding amino acid sequence that it encodes. In the cell cytoplasm, the ribosome reads the sequence of the mRNA in groups of three bases to assemble the protein

## Tumor Suppressor Gene

A tumor suppressor gene encodes a protein that acts to regulate cell division, keeping it in check. When a tumor suppressor gene is inactivated by a variant, the protein it encodes is not produced or does not function properly, and as a result, uncontrolled cell division may occur. Such variants may contribute to the development of a cancer.

## Uracil

Uracil (U) is one of the four nucleotide bases in RNA, with the other three being adenine (A), cytosine (C) and guanine (G). In RNA, uracil pairs with adenine. In a DNA molecule, the nucleotide thymine (T) is used in place of uracil.

## X Chromosome

The X chromosome is one of the two sex chromosomes that are involved in sex determination. Humans and most other mammals have two sex chromosomes (X and Y) that in combination determine the sex of an individual. Females have two X chromosomes in their cells, while males have one X and one Y.

### Y Chromosome

The Y chromosome is one of the two sex chromosomes that are involved in sex determination. Humans and most other mammals have two sex chromosomes (X and Y) that in combination determine the sex of an individual. Females have two X chromosomes in their cells, while males have one X and one Y.

## Attribution & References

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- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.

## References

National Health Service (NHS). (2023). *The 2023 genomic competency framework for UK nurses*. https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2023/12/2023-Genomic-Competency-Framework-for-UK-Nurses.pdf

# 2.2 DNA STRUCTURE AND FUNCTION

## Learning Objectives

- Describe the structure of DNA.
- Explain the process of DNA replication.
- Describe mechanisms of DNA repair.
- Explain the central dogma.
- Explain the main steps of transcription.
- Discuss why every cell does not express all of its genes.
- Identify how eukaryotic gene expression occurs at the epigenetic, transcriptional, post-transcriptional, translational, and post-translational levels.
- Describe the different steps in protein synthesis.
- Describe the genetic code and how the nucleotide sequence determines the amino acid and the protein sequence.

Let's begin with a review the structure of the two types of nucleic acids, **deoxyribonucleic acid (DNA)** and **ribonucleic acid (RNA).** The building blocks of DNA are **nucleotides**, which are made up of three parts: a **deoxyribose** (5-carbon sugar), a phosphate group, and a **nitrogenous base** (Figure 2.1). There are four types of nitrogenous bases in DNA. **Adenine (A)** and **guanine (G)** are **double-ringed purines**, and **cytosine (C)** and **thymine (T)** are smaller, single-ringed pyrimidines. The nucleotide is named according to the nitrogenous base it contains.

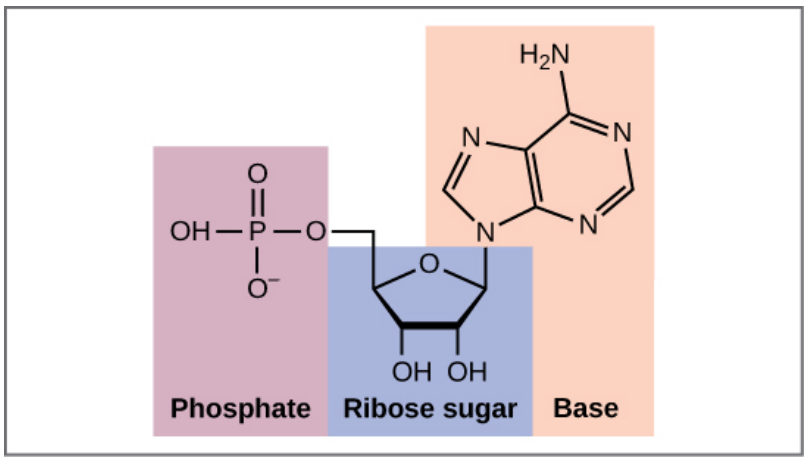



**Figure 2.1** Each DNA nucleotide is made up of a sugar, a phosphate group, and a base. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0).

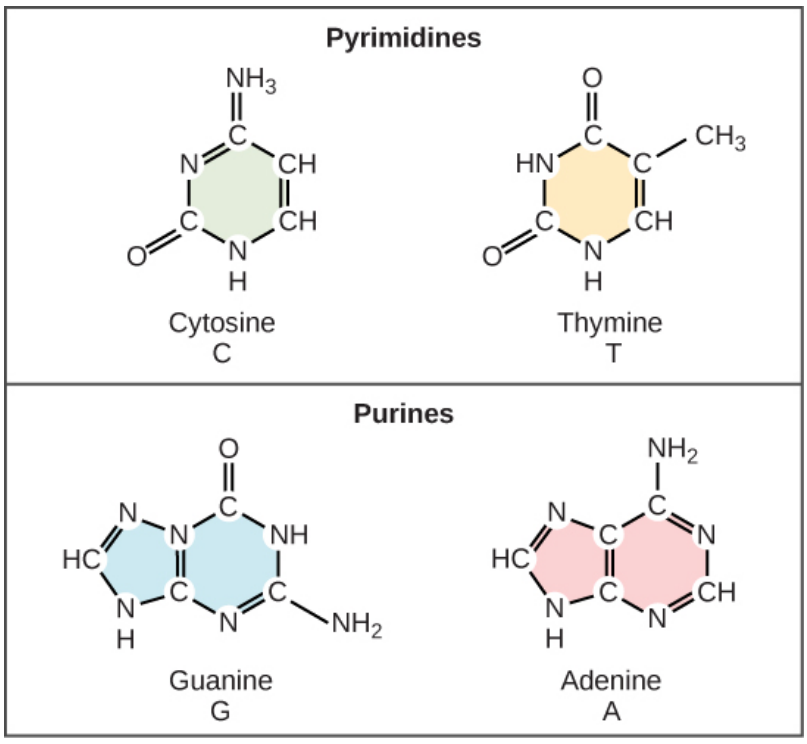



**Figure 2.2** Cytosine and thymine are pyrimidines. Guanine and adenine are purines. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0).

The phosphate group of one nucleotide bonds covalently with the sugar molecule of the next nucleotide, and so on, forming a long polymer of nucleotide monomers. The sugar–phosphate groups line up in a "backbone" for each single strand of DNA, and the nucleotide bases stick out from this backbone. The carbon atoms of the five-carbon sugar are numbered clockwise from the oxygen as 1′, 2′, 3′, 4′, and 5′ (1′ is

read as "one prime"). The phosphate group is attached to the 5′ carbon of one nucleotide and the 3′ carbon of the next nucleotide. In its natural state, each DNA molecule is actually composed of two single strands held together along their length with hydrogen bonds between the bases.

DNA is made up of two strands that are twisted around each other to form a right-handed helix, called a **double helix**. Base pairing occurs between a purine and pyrimidine: A pairs with T, and G pairs with C. In other words, adenine and thymine are complementary base pairs, and cytosine and guanine are complementary base pairs. This is the basis for Chargaff's rule; because of their complementarity, there is as much adenine as thymine in a DNA molecule and as much guanine as cytosine. Two hydrogen bonds, connect adenine and thymine and cytosine and guanine are connected by three hydrogen bonds. The two strands are anti-parallel; one strand will have the 3′ carbon of the sugar in the "upward" position, whereas the other strand will have the 5′ carbon in the upward position. The diameter of the DNA double helix is uniform throughout because a purine (two rings) always pairs with a pyrimidine (one ring), and their combined lengths are always equal. (Figure 2.3).

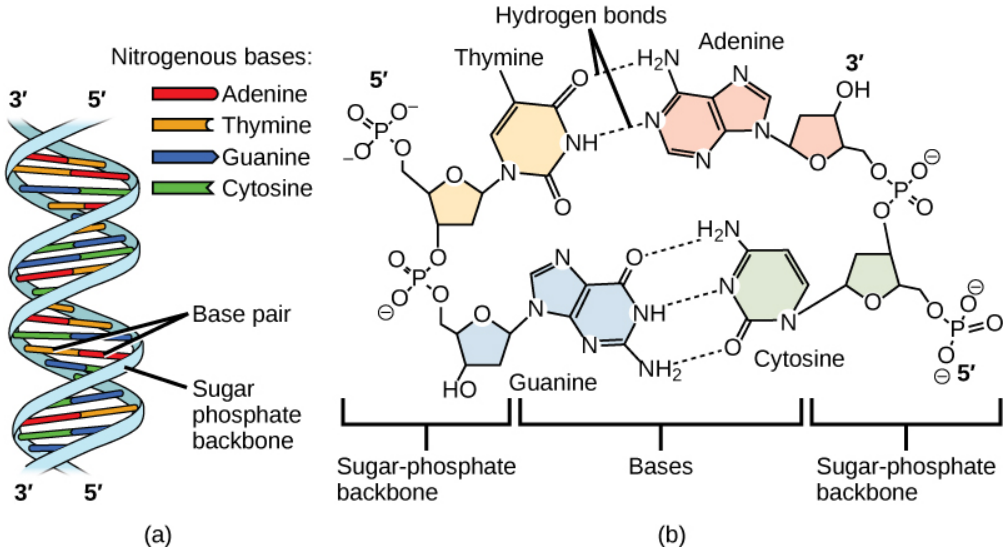



**Figure 2.3** DNA (a) forms a double-stranded helix, and (b) adenine pairs with thymine and cytosine with guanine. **Source:** modification of work by Jerome Walker, Dennis Myts, *Concepts of Biology* (OpenStax), CC BY 4.0)

## The Structure of RNA

A second nucleic acid in all cells is called **ribonucleic acid, or RNA**. Like DNA, RNA is a polymer of nucleotides. Each of the nucleotides in RNA is made up of a nitrogenous base, a five-carbon sugar, and a phosphate group. In the case of RNA, the **five-carbon sugar is ribose, not deoxyribose**. Ribose has a hydroxyl group at the 2′ carbon, unlike deoxyribose, which has only a hydrogen atom (Figure 2.4).

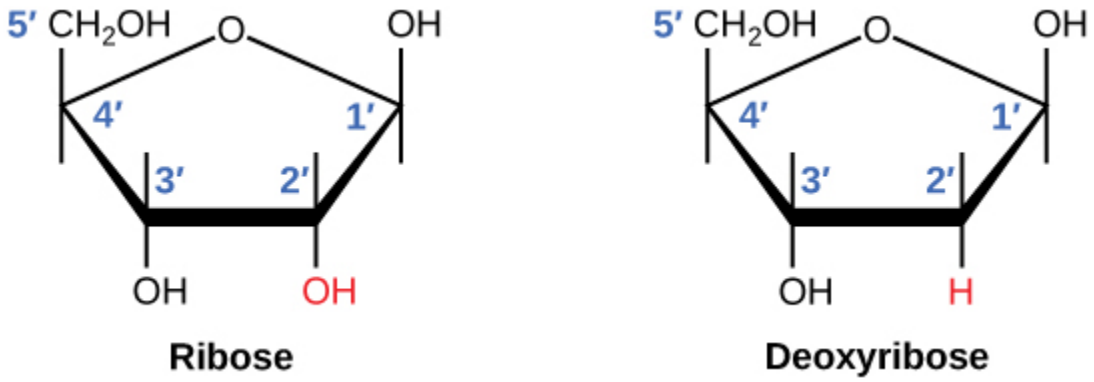



**Figure 2.4** The difference between the ribose found in RNA and the deoxyribose found in DNA is that ribose has a hydroxyl group at the 2' carbon. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0).

RNA nucleotides contain the nitrogenous bases adenine, cytosine, and guanine. However, they d**o not contain thymine, which is replaced by uracil,** symbolized by a "U." RNA exists as a single-stranded molecule rather than a double-stranded helix. Molecular biologists have named several kinds of RNA based on their function. These include messenger RNA (mRNA), transfer RNA (**tRNA**), and ribosomal RNA (**rRNA**)—molecules that are involved in the production of proteins from the DNA code.

## How DNA Is Arranged in the Cell

DNA is a working molecule; it must be replicated when a cell is ready to divide, and it must be "read" to produce the molecules, such as proteins, to carry out the functions of the cell. For this reason, the DNA is protected and packaged in particular ways. In addition, DNA molecules can be very long. Stretched end-to-end, the DNA molecules in a single human cell would come to a length of about 2 meters. Thus, the DNA for a cell must be packaged in a very ordered way to fit and function within a structure (the cell) that is not visible to the naked eye.

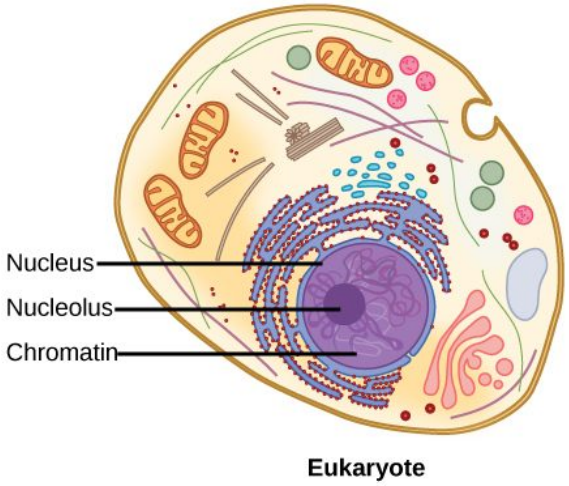



**Figure 2.5** A eukaryotic cell**. Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

Eukaryotes, whose chromosomes each consist of a linear DNA molecule, have a specific packing strategy to fit their DNA inside the nucleus. At the most basic level, DNA is wrapped around proteins known as histones to form structures called nucleosomes. The DNA is wrapped tightly around the histone core. This nucleosome is linked to the next one by a short strand of DNA that is free of histones. This is also known as the "beads on a string" structure; the nucleosomes are the "beads," and the short lengths of DNA between them are the "string." With their DNA coiled around them, the nucleosomes stack compactly onto each other to form a 30-nm–wide fiber. This fibre is further coiled into a thicker and more compact structure. At the metaphase stage of mitosis, when the chromosomes are lined up in the center of the cell, the chromosomes are at their most compacted. They are approximately 700 nm in width, and are associated with scaffold proteins.

In interphase, the phase of the cell cycle between mitoses at which the chromosomes are decondensed, eukaryotic chromosomes have two distinct regions that can be distinguished by staining. There is a tightly packaged region that stains darkly and a less dense region. The darkly staining regions usually contain genes that are not active and are found in the centromere and telomere regions. The lightly staining regions usually contain active genes, with DNA packaged around nucleosomes but not further compacted.

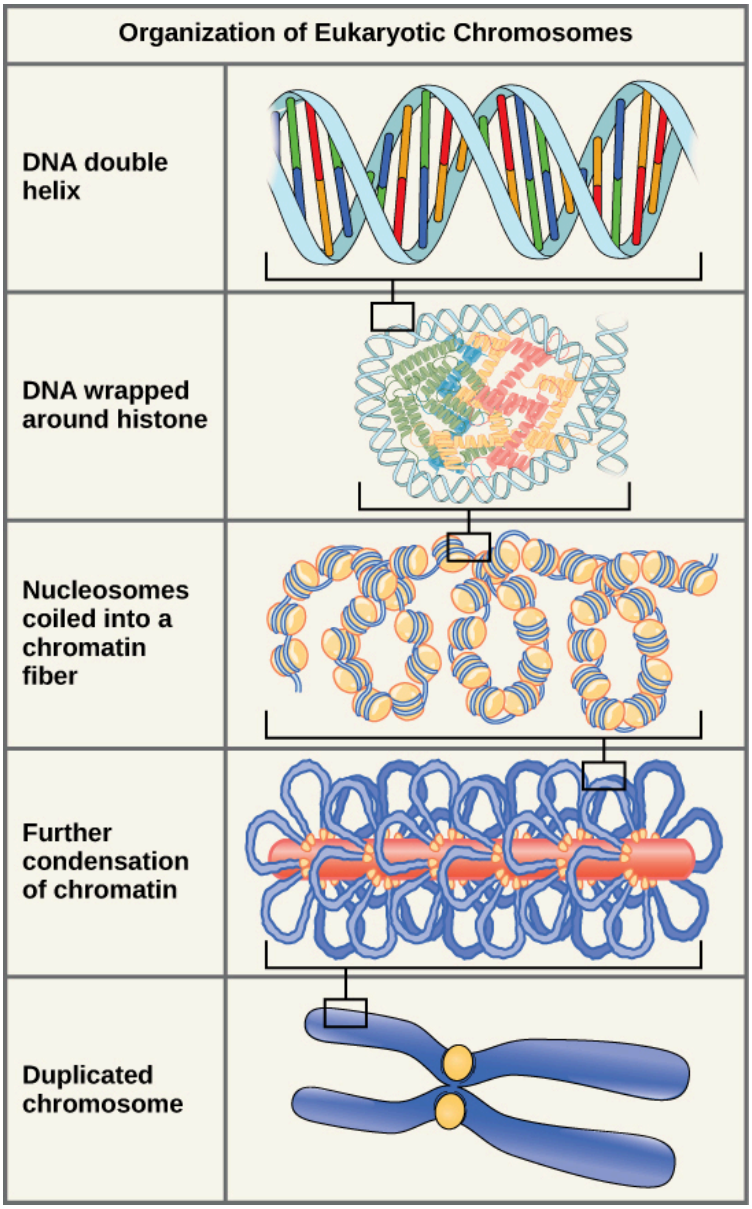



**Figure 2.6** These figures illustrate the compaction of the eukaryotic chromosome. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Concept in Action – DNA

Use the interactive slideshow to review this concept in action, or access the videos and questions using the text version.

**Concept in Action – DNA (text version)**

Watch How DNA is Packaged (Advanced) (2 mins) on YouTube (https://youtu.be/gbSIBhFwQ4s)

Watch the video DNA is the Genetic Material (4 mins) on BCCampus (https://media.bccampus.ca/media/DNA+as+Genetic+Material/0_ajd2anyl) and try the following knowledge check:

Pause the video at 1:55 and match the terms to the correct blanks for this statement:

**Terms:** copied, changes, encode

Genetic material must be able to [Blank A] information. Genetic material must be [Blank B] when cells divide. Mutations are [Blank C] to a DNA sequence.

**Check your answer in footnote**[1]



When a cell divides, each daughter cell must receive an identical copy of the DNA. The process of DNA replication accomplishes this. DNA replication occurs during the synthesis phase, or S phase, of the cell cycle before the cell enters mitosis or meiosis.

The elucidation of the structure of the double helix provided a hint as to how DNA is copied. Recall that adenine nucleotides pair with thymine nucleotides and cytosine with guanine. This means that the two strands are complementary to each other. For example, a strand of DNA with a nucleotide sequence of AGTCATGA will have a complementary strand with the sequence TCAGTACT (Figure 2.7).

1. A – encode, B – copied, C – changes

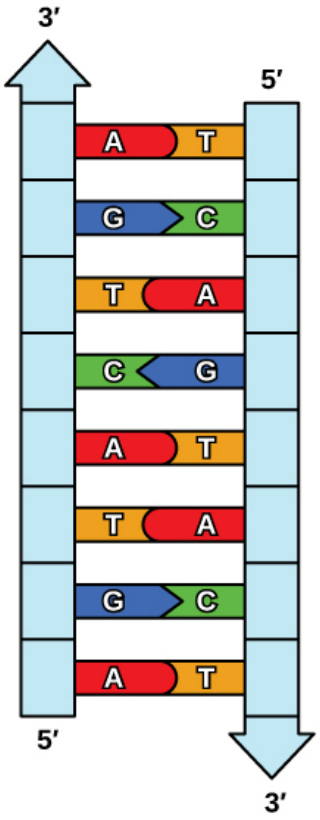



**Figure 2.7** The two strands of DNA are complementary, meaning the sequence of bases in one strand can be used to create the correct sequence of bases in the other strand.
**Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

Because of the complementarity of the two strands, having one strand makes it possible to recreate the other strand. This model for replication suggests that the two strands of the double helix separate during replication, and each strand serves as a template from which the new complementary strand is copied (Figure 2.8).

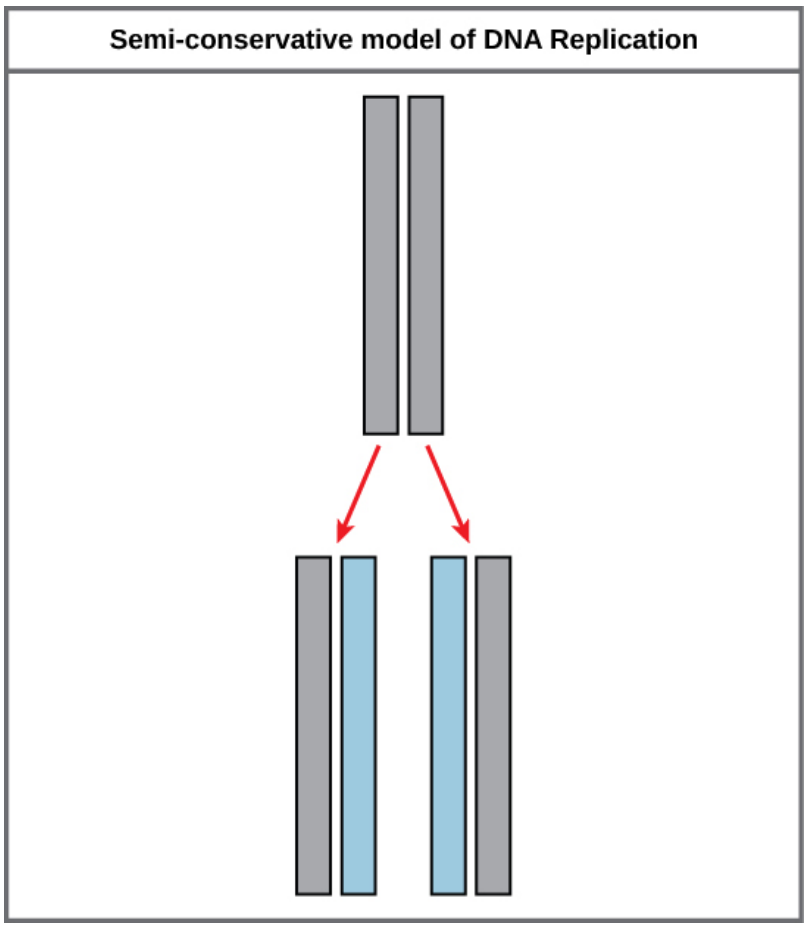



**Figure 2.8** The semiconservative model of DNA replication is shown. Gray indicates the original DNA strands, and blue indicates newly synthesized DNA**. Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

During DNA replication, each of the two strands that make up the double helix serves as a **template** from which new strands are copied. The new strand will be **complementary** to the parental or "old" strand. Each new double strand consists of one parental strand and one new daughter strand. This is known as **semiconservative replication**. When two DNA copies are formed, they have an identical sequence of nucleotide bases and are divided equally into two daughter cells.

## DNA Replication in Eukaryotes

Because eukaryotic genomes are very complex, DNA replication is a very complicated process that involves several enzymes and other proteins. It occurs in three main stages: **i**nitiation, elongation, and termination.

Recall that eukaryotic DNA is bound to proteins known as histones to form structures called nucleosomes. During **initiation**, the DNA is made accessible to the proteins and enzymes involved in the replication process. How does the replication machinery know where on the DNA double helix to begin? It

turns out that there are specific nucleotide sequences called **origins of replication** at which replication begins. Certain proteins bind to the origin of replication while an enzyme called **helicase** unwinds and opens up the DNA helix. As the DNA opens up, Y-shaped structures called **replication forks** are formed (Figure 2.9). Two replication forks are formed at the origin of replication, which are extended in both directions as replication proceeds. There are multiple origins of replication on the eukaryotic chromosome, such that replication can occur simultaneously from several places in the genome.

During elongation, an enzyme called **DNA polymerase** adds DNA nucleotides to the 3′ end of the template. Because DNA polymerase can only add new nucleotides at the end of a backbone, a primer sequence, which provides this starting point, is added with complementary RNA nucleotides. This primer is removed later, and the nucleotides are replaced with DNA nucleotides. One strand, which is complementary to the parental DNA strand, is synthesized continuously toward the replication fork so the polymerase can add nucleotides in this direction. This continuously synthesized strand is known as the **leading strand**. Because DNA polymerase can only synthesize DNA in a 5′ to 3′ direction, the other new strand is put together in short pieces called Okazaki fragments. The Okazaki fragments each require a primer made of RNA to start the synthesis. The strand with the Okazaki fragments is known as the **lagging strand**. As synthesis proceeds, an enzyme removes the RNA primer, which is then replaced with DNA nucleotides, and the gaps between fragments are sealed by an enzyme called **DNA ligase**.

The process of DNA replication can be summarized as follows:

1. DNA unwinds at the origin of replication.
2. New bases are added to the complementary parental strands. One new strand is made continuously, while the other strand is made in pieces.
3. Primers are removed, new DNA nucleotides are put in place of the primers and the backbone is sealed by DNA ligase.

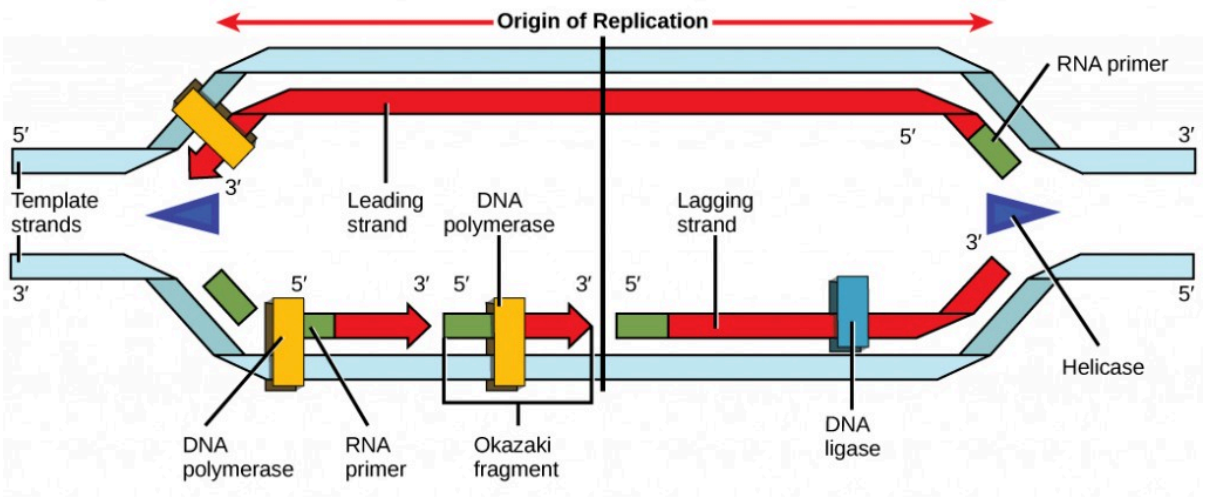



**Figure 2.9** A replication fork is formed by the opening of the origin of replication, and helicase separates the DNA strands. An RNA primer is synthesized and is elongated by the DNA polymerase. DNA is synthesized continuously on the leading strand, whereas on the lagging strand, DNA is synthesized in short stretches. The DNA fragments are joined by DNA ligase (not shown)**. Source:** *Concepts of Biology* (OpenStax), CC BY 4.0).

## Telomere Replication

Because eukaryotic chromosomes are linear, DNA replication comes to the end of a line in eukaryotic chromosomes. As you have learned, the DNA polymerase enzyme can add nucleotides in only one direction. In the leading strand, synthesis continues until the end of the chromosome is reached; however, on the lagging strand, there is no place for a primer to be made for the DNA fragment to be copied at the end of the chromosome. This presents a problem for the cell because the ends remain unpaired; over time, these ends get progressively shorter as cells continue to divide. The ends of the linear chromosomes are known as **telomeres**, which have **repetitive sequences** that do not code for a particular gene. As a consequence, it is telomeres that are shortened with each round of DNA replication instead of genes. For example, in humans, a six base-pair sequence, TTAGGG, is repeated 100 to 1000 times. The discovery of the enzyme **telomerase** (Figure 2.10) helped in the understanding of how chromosome ends are maintained. The telomerase attaches to the end of the chromosome, and complementary bases to the RNA template are added on the end of the DNA strand. Once the lagging strand template is sufficiently elongated, DNA polymerase can add nucleotides complementary to the ends of the chromosomes. Thus, the ends of the chromosomes are replicated.

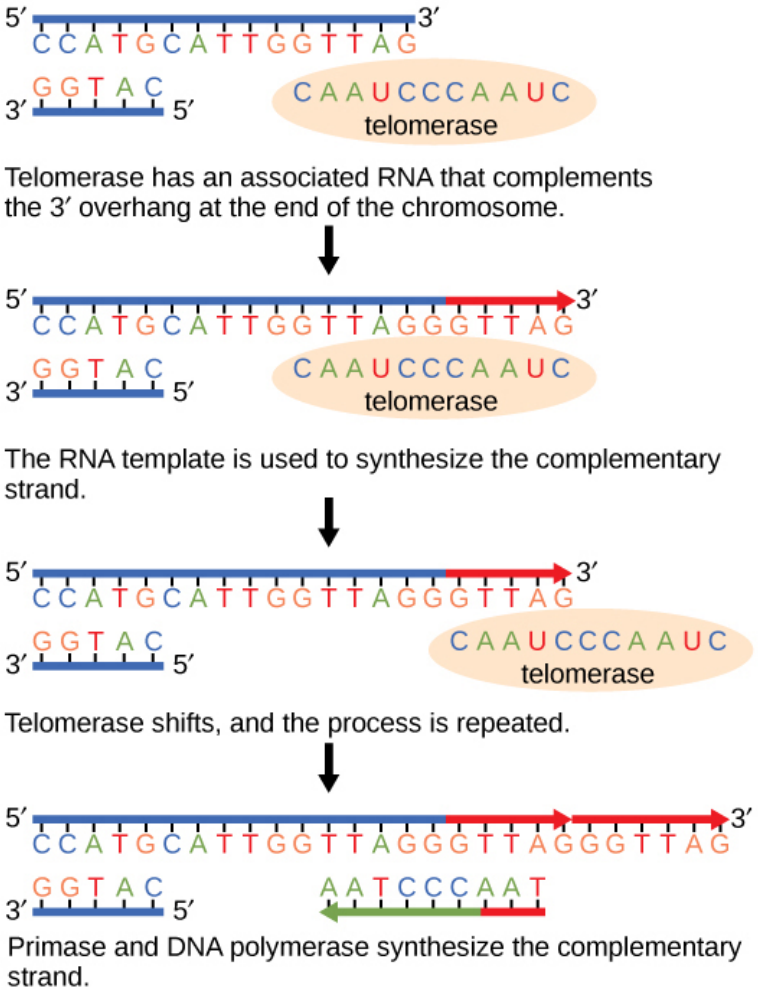



**Figure 2.10** The ends of linear chromosomes are maintained by the action of the telomerase enzyme. **Source**: *Biology (OpenStax)*, CC BY 4.0.

Telomerase is typically found to be active in germ cells, adult stem cells, and some cancer cells. Elizabeth Blackburn (Figure 2.11) received the Nobel Prize for Medicine and Physiology in 2009 for her discovery of telomerase and its action.

**Figure 2.11** Elizabeth Blackburn, 2009 Nobel Laureate, was the scientist who discovered how telomerase works. **Source:** Image by U.S. Embassy, Stockholm, Sweden, CC BY 2.0.

Telomerase is not active in adult somatic cells. Adult somatic cells that undergo cell division continue to have their telomeres shortened. This essentially means that telomere shortening is associated with aging. In 2010, scientists found that telomerase can reverse some age-related conditions in mice, which may have potential in regenerative medicine.[2] Telomerase-deficient mice were used in these studies; these mice have tissue atrophy, stem-cell depletion, organ system failure, and impaired tissue injury responses. Telomerase reactivation in these mice caused extension of telomeres, reduced DNA damage, reversed neurodegeneration, and improved functioning of the testes, spleen, and intestines. Thus, telomere reactivation may have the potential to treat age-related diseases in humans.

## Concept in Action – DNA Replication

**Watch DNA replication animation by interact Medical (1 min) on YouTube (https://youtu.be/zdDkiRw1PdU)**

2. Mariella Jaskelioff, et al., "Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice," *Nature, 469* (2011):102–

## DNA Repair

DNA polymerase can make mistakes while adding nucleotides. It edits the DNA by **proofreading** every newly added base. Incorrect bases are removed and replaced by the correct base, then polymerization continues (Figure 2.12 **a**). Most mistakes are corrected during replication, although the mismatch repair mechanism is employed when this does not happen. **Mismatch repair** enzymes recognize the wrongly incorporated base and excise it from the DNA, replacing it with the correct base (Figure 2.12 b). In yet another type of repair, **nucleotide excision repair**, the DNA double-strand is unwound and separated, the incorrect bases are removed along with a few bases on the 5′ and 3′ end, and these are replaced by copying the template with the help of DNA polymerase (Figure 2.12 c). Nucleotide excision repair is particularly important in correcting thymine dimers, which are primarily caused by ultraviolet light. In a thymine dimer, two thymine nucleotides adjacent to each other on one strand are covalently bonded to each other rather than their complementary bases. If the dimer is not removed and repaired, it will become a variant. Individuals with flaws in their nucleotide excision repair genes show extreme sensitivity to sunlight and develop skin cancers early in life.

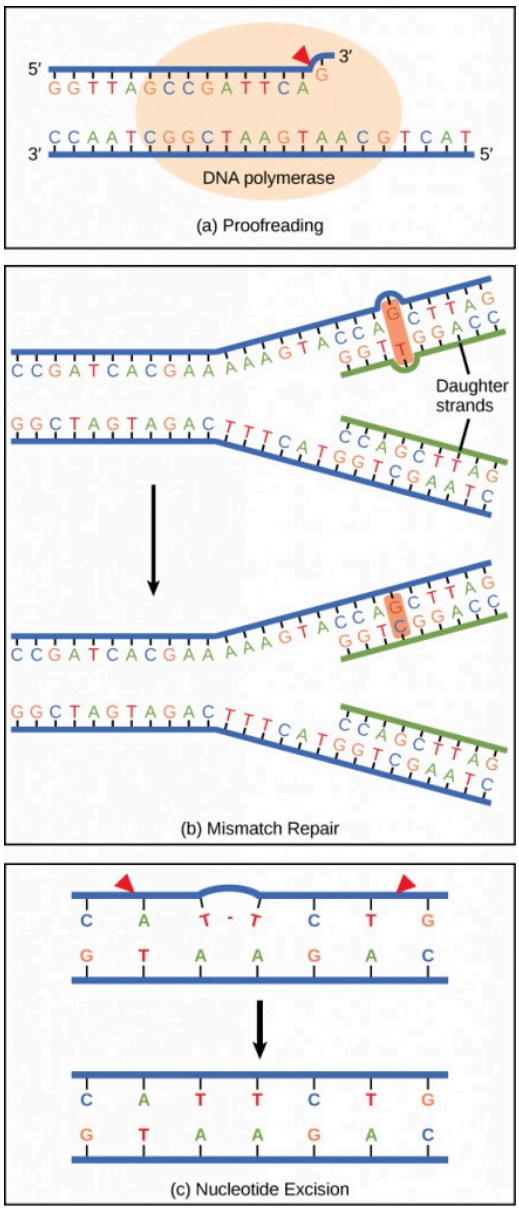



**Figure 2.12** Proofreading by DNA polymerase (a) corrects errors during replication. In mismatch repair (b), the incorrectly added base is detected after replication. The mismatch repair proteins detect and remove this base from the newly synthesized strand by nuclease action. The gap is now filled with the correctly paired base. Nucleotide excision (c) repairs thymine dimers. When exposed to UV, thymines lying adjacent can form thymine dimers. In normal cells, they are excised and replaced. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

Most mistakes are corrected; if not, they may result in a **variant**—defined as a permanent change in the DNA sequence. Variants in repair genes may lead to serious consequences like cancer.

The second function of DNA (the first was replication) is to **provide the information needed to construct the proteins** necessary so that the cell can perform all of its functions. To do this, the DNA is "read" or transcribed into an mRNA molecule. The mRNA then provides the code to form a protein by a process called translation. Through the processes of transcription and translation, a protein is built with a specific sequence of amino acids that was originally encoded in the DNA. This module discusses the details of transcription.

## The Central Dogma: DNA Encodes RNA; RNA Encodes Protein

The central dogma describes the flow of genetic information in cells from DNA to mRNA to protein (Figure 2.13), which states that genes specify the sequences of mRNAs, which in turn specify the sequences of proteins.

Copying DNA to mRNA is relatively straightforward, with one nucleotide being added to the mRNA strand for every complementary nucleotide read in the DNA strand. The translation to protein is more complex because groups of three mRNA nucleotides correspond to one amino acid of the protein sequence. However, as we shall see in the next module, the translation to protein is still systematic, such that nucleotides 1 to 3 correspond to amino acid 1, nucleotides 4 to 6 correspond to amino acid 2, and so on.

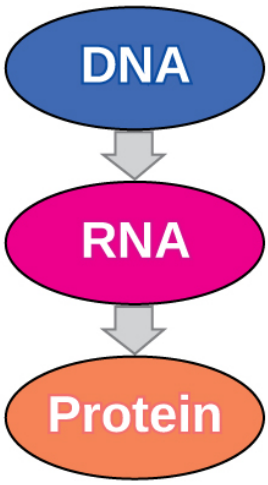



**Figure 2.13** The central dogma states that DNA encodes RNA, which encodes protein. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Transcription: from DNA to mRNA

In eukaryotes, the genes are bound in the nucleus, so transcription occurs in the nucleus of the cell and the mRNA transcript must be transported to the cytoplasm. Transcription occurs in three main stages: initiation, elongation, and termination.

## Initiation

Transcription requires the DNA double helix to partially unwind in the region of mRNA synthesis. The region of unwinding is called a transcription bubble. The DNA sequence onto which the proteins and enzymes involved in transcription bind to initiate the process is called a **promoter**. In most cases, promoters exist **upstream** of the genes they regulate. The specific sequence of a promoter is very important because it determines whether the corresponding gene is transcribed all of the time, some of the time, or hardly at all (Figure 2.14).

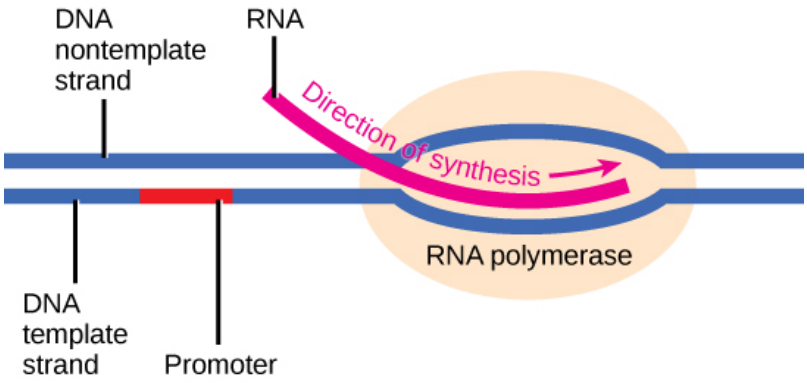



**Figure 2.14** The initiation of transcription begins when DNA is unwound, forming a transcription bubble. Enzymes and other proteins involved in transcription bind at the promoter. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0).

## Elongation

Transcription always proceeds from one of the two DNA strands, which is called the template strand. The mRNA product is complementary to the **template strand** and is almost identical to the other DNA strand, called the **non-template strand**, except that RNA contains a uracil (U) in place of the thymine (T) found in DNA. During elongation, an enzyme called RNA polymerase proceeds along the DNA template adding nucleotides by base pairing with the DNA template in a manner similar to DNA replication, with the difference that an RNA strand is being synthesized that does not remain bound to the DNA template. As elongation proceeds, the DNA is continuously unwound ahead of the core enzyme and rewound behind it (Figure 2.15).

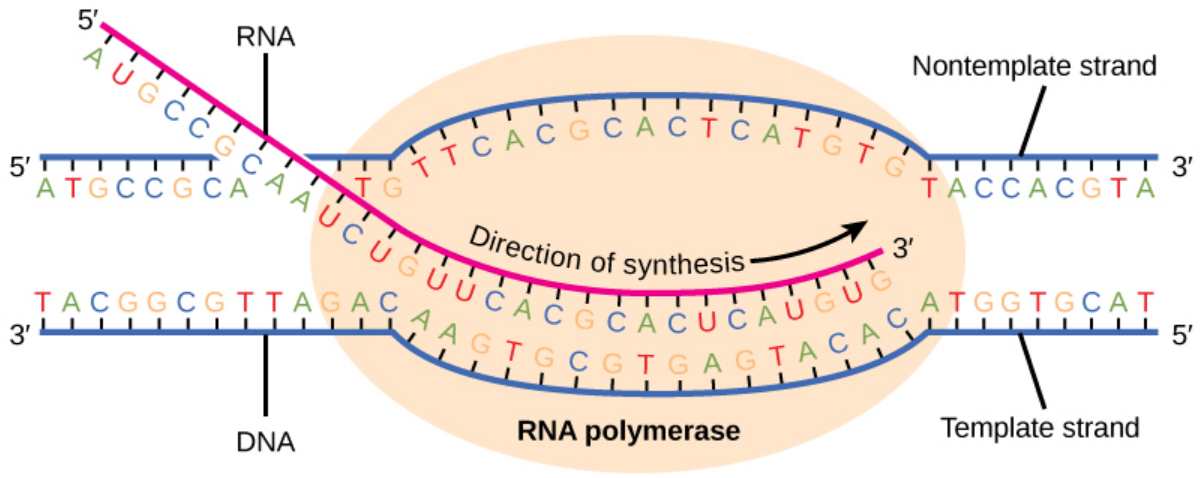



**Figure 2.15** During elongation, RNA polymerase tracks along the DNA template, synthesizes mRNA in the 5' to 3' direction, and unwinds then rewinds the DNA as it is read. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Termination

Depending on the gene being transcribed, there are two kinds of termination signals, but both involve repeated nucleotide sequences in the DNA template that result in RNA polymerase stalling, leaving the DNA template, and freeing the mRNA transcript. On termination, the process of transcription is complete.

# Eukaryotic RNA Processing

The newly transcribed eukaryotic mRNAs must undergo several processing steps before they can be transferred from the nucleus to the cytoplasm and translated into a protein. The mRNA transcript is first coated in RNA-stabilizing proteins to prevent it from degrading while it is processed and exported out of the nucleus. This occurs while the pre-mRNA is still being synthesized by adding a special nucleotide "cap" to the 5′ end of the growing transcript. In addition to preventing degradation, factors involved in protein synthesis recognize the cap to help initiate translation by ribosomes.

Once elongation is complete, an enzyme then adds a string of approximately 200 adenine residues to the 3′ end, called the **poly-A tail**. This modification further protects the pre-mRNA from degradation and signals to cellular factors that the transcript needs to be exported to the cytoplasm.

Eukaryotic genes are composed of protein-coding sequences called **exons** (*ex*-on signifies that they are *ex*pressed) and *int*ervening sequences called **introns** (*int*-ron denotes their *int*ervening role). Introns are removed from the pre-mRNA during processing. Intron sequences in mRNA do not encode functional proteins. It is essential that all of a pre-mRNA's introns be completely and precisely removed before protein synthesis so that the exons join together to code for the correct amino acids. If the process errs by even a single

nucleotide, the sequence of the rejoined exons would be shifted, and the resulting protein would be nonfunctional. The process of removing introns and reconnecting exons is called splicing (Figure 2.16). Introns are removed and degraded while the pre-mRNA is still in the nucleus.

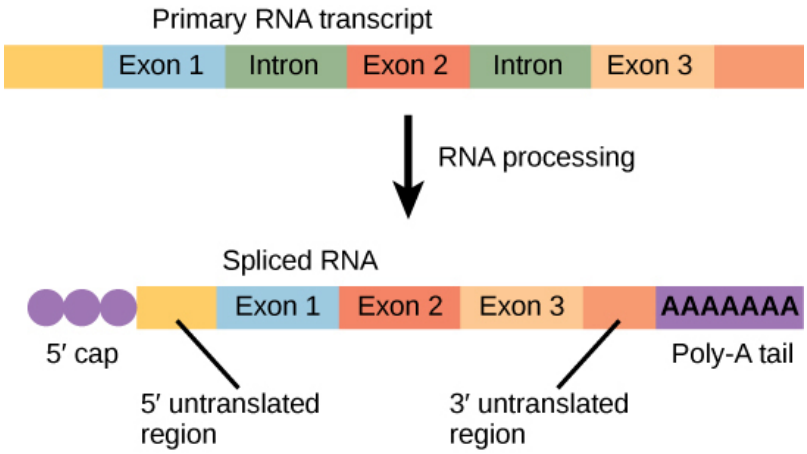



**Figure 2.16** Eukaryotic mRNA contains introns that must be spliced out. A 5' cap and 3' tail are also added. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

The synthesis of proteins is one of a cell's most energy-consuming metabolic processes. In turn, proteins account for more mass than any other component of living organisms (with the exception of water), and proteins perform a wide variety of the functions of a cell. Translation, or protein synthesis, involves decoding an mRNA message into a polypeptide product. Amino acids are covalently strung together in lengths ranging from approximately 50 amino acids to more than 1,000.

## The Protein Synthesis Machinery

In addition to the mRNA template, many other molecules contribute to the process of translation. The composition of each component may vary across species; for instance, ribosomes may consist of different numbers of ribosomal RNAs (rRNA) and polypeptides, depending on the organism. However, the general structures and functions of the protein synthesis machinery are comparable to those of bacteria and human cells. Translation requires the input of an mRNA template, ribosomes, tRNAs, and various enzymatic factors (Figure 2.17).

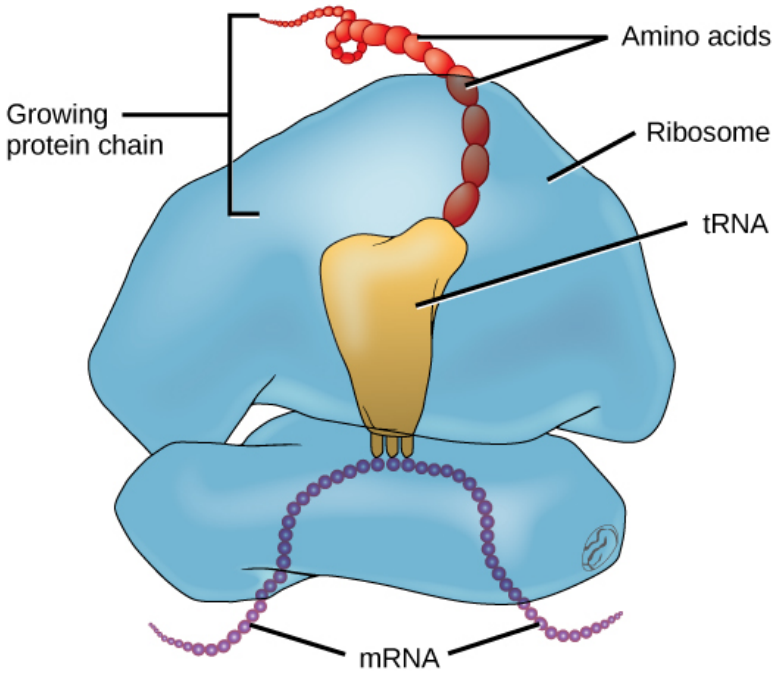



**Figure 2.17** The protein synthesis machinery includes the large and small subunits of the ribosome, mRNA, and tRNA. **Source:** modification of work by NIGMS, NIH, *Concepts of Biology* (OpenStax), CC BY 4.0.

In *E. coli*, there are 200,000 ribosomes present in every cell at any given time. A ribosome is a complex macromolecule composed of structural and catalytic rRNAs, and many distinct polypeptides. In eukaryotes, the nucleolus is completely specialized for the synthesis and assembly of rRNAs.

Ribosomes are located in the cytoplasm and endoplasmic reticulum of eukaryotes. Ribosomes are made up of a large and a small subunit that come together for translation. The small subunit is responsible for binding the mRNA template, whereas the large subunit sequentially binds tRNAs, a type of RNA molecule that brings amino acids to the growing chain of the polypeptide. Each mRNA molecule is simultaneously translated by many ribosomes, all synthesizing protein in the same direction.

Depending on the species, 40 to 60 types of tRNA exist in the cytoplasm. Serving as adaptors, specific tRNAs bind to sequences on the mRNA template and add the corresponding amino acid to the polypeptide chain. Therefore, tRNAs are the molecules that actually "translate" the language of RNA into the language of proteins. For each tRNA to function, it must have its specific amino acid bonded to it. In the process of tRNA "charging," each tRNA molecule is bonded to its correct amino acid.

# The Genetic Code

Use the interactive slides to watch two videos and check your knowledge, or access the text version of the activity below.

**The Genetic Code (text version)**
**Watch the video:** Universality of the Genetic Code (5 mins) on BCCampus (https://media.bccampus.ca/media/Universality+of+the+Genetic+Code/0_gw00p3jq).

1. After watching the first video fill in the missing words in the following statement:
   There are [Blank A] different ways to arrange 4 bases of DNA i groups of [Blank B].
   Since there are 20 amino acids there are more than one codon for each amino acid. This makes the genetic code [Blank C].

**Watch the video:** Mutations (5 mins) on BCCampus

2. Pause at 2:01. True or false? DNA can have mutations occur spontaneously.
3. Pause at 3:33. True or false? Agents that cause mutations are rarely cancer causing as well.

**Check your answers in footnote**[3]

**Activity source:** *Concepts of Biology – 1st Canadian Edition*, CC BY 4.0

To summarize what we know to this point, the cellular process of transcription generates messenger RNA (mRNA), a mobile molecular copy of one or more genes with an alphabet of A, C, G, and uracil (U). Translation of the mRNA template converts nucleotide-based genetic information into a protein product. Protein sequences consist of 20 commonly occurring amino acids; therefore, it can be said that the protein alphabet consists of 20 letters. Each amino acid is defined by a three-nucleotide sequence called the **triplet codon**. The relationship between a nucleotide codon and its corresponding amino acid is called the **genetic code**.

Given the different numbers of "letters" in the mRNA and protein "alphabets," combinations of nucleotides corresponded to single amino acids. Using a three-nucleotide code means that there are a total of 64 (4 × 4 × 4) possible combinations; therefore, a given amino acid is encoded by more than one nucleotide triplet (Figure 2.18).

3. 1. A – 64, B – 3, C – redundant. 2. True. 3. False.

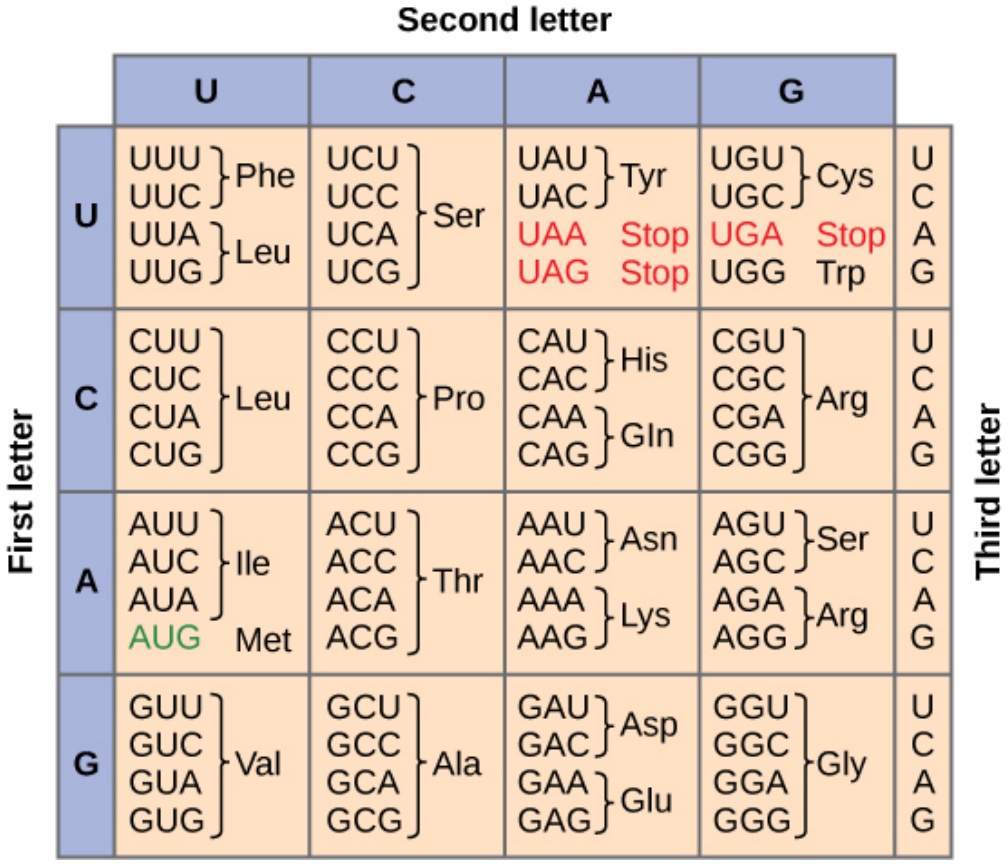
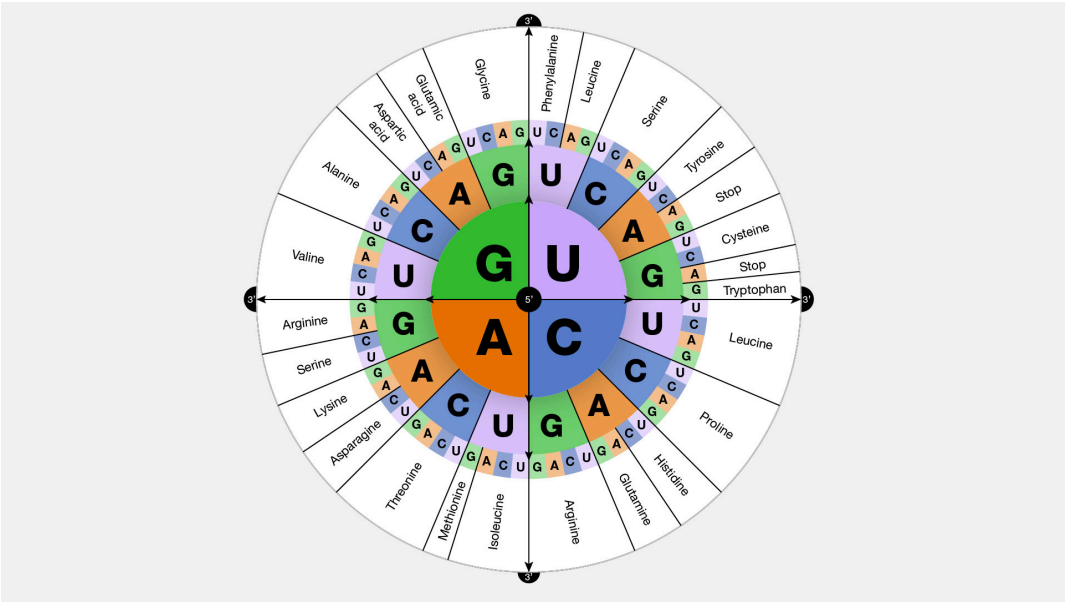



**Figure 2.18** This figure shows the genetic code for translating each nucleotide triplet, or codon, in mRNA into an amino acid or a termination signal in a nascent protein. **Source**: modification of work by NIH, *Concepts of Biology* (OpenStax), CC BY 4.0.




Genetic code refers to the instructions contained in a gene that tell a cell how to make a specific protein. Each gene's code uses the four nucleotide bases of DNA: adenine (A), cytosine (C), guanine (G) and thymine (T) — in various ways to spell out three-letter "codons" that specify which amino acid is needed at each position within a protein. **Source:** Genetic Code Courtesy: National Human Genome Research Institute, PDM with attribution.

Three of the 64 codons terminate protein synthesis and release the polypeptide from the translation machinery. These triplets are called **stop codons**. Another codon, AUG, also has a special function. In addition to specifying the amino acid methionine, it also serves as the **start codon** to initiate translation. The reading frame for translation is set by the AUG start codon near the 5′ end of the mRNA. *The genetic code is universal*. With a few exceptions, virtually all species use the same genetic code for protein synthesis, which is powerful evidence that all life on Earth shares a common origin.

## The Mechanism of Protein Synthesis

Just as with mRNA synthesis, protein synthesis can be divided into three phases: initiation, elongation, and termination. Here we will explore how translation occurs in *E. coli*, a representative prokaryote, and specify any differences between prokaryotic and eukaryotic translation.

Protein synthesis begins with the formation of an initiation complex. In *E. coli*, this complex involves the small ribosome subunit, the mRNA template, three initiation factors, and a special initiator tRNA. The

initiator tRNA interacts with the AUG start codon, and links to a special form of the amino acid methionine that is typically removed from the polypeptide after translation is complete.

In prokaryotes and eukaryotes, the basics of polypeptide elongation are the same, so we will review elongation from the perspective of *E. coli*. The large ribosomal subunit of *E. coli* consists of three compartments: the A site binds incoming charged tRNAs (tRNAs with their attached specific amino acids). The P site binds charged tRNAs carrying amino acids that have formed bonds with the growing polypeptide chain but have not yet dissociated from their corresponding tRNA. The E site releases dissociated tRNAs so they can be recharged with free amino acids. The ribosome shifts one codon at a time, catalyzing each process that occurs in the three sites. With each step, a charged tRNA enters the complex, the polypeptide becomes one amino acid longer, and an uncharged tRNA departs. The energy for each bond between amino acids is derived from GTP, a molecule similar to ATP (Figure 2.19). Amazingly, the *E. coli* translation apparatus takes only 0.05 seconds to add each amino acid, meaning that a 200-amino acid polypeptide could be translated in just 10 seconds.

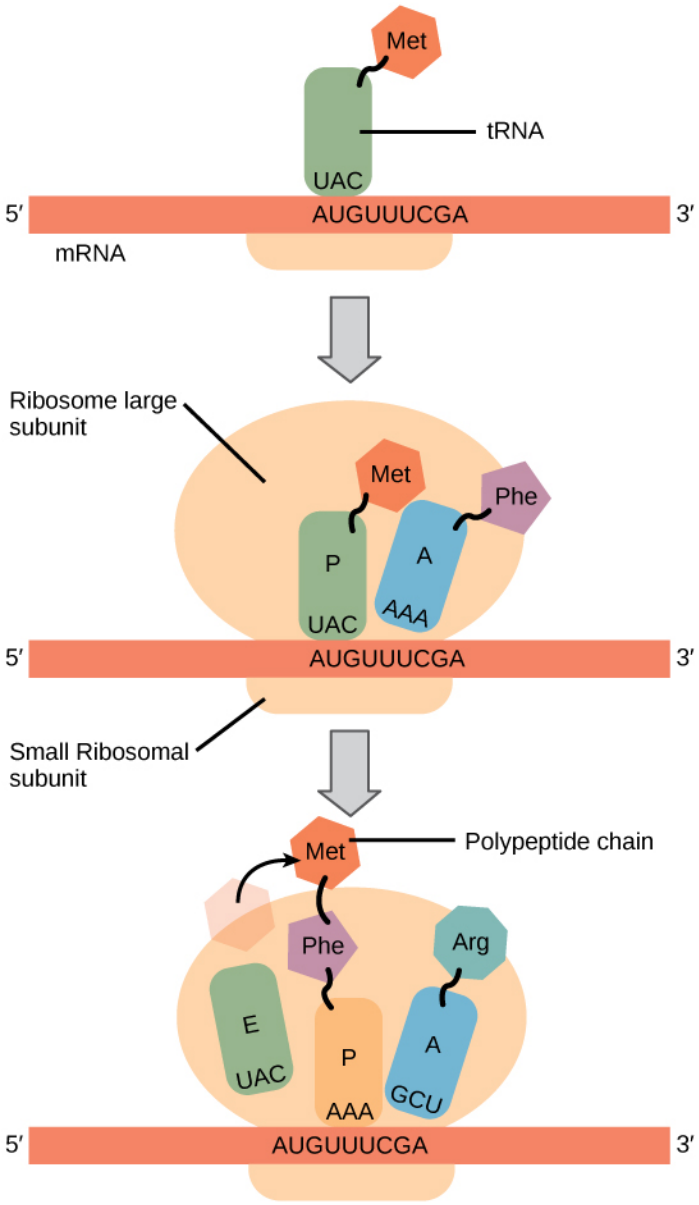



**Figure 2.19** Translation begins when a tRNA anticodon recognizes a codon on the mRNA. The large ribosomal subunit joins the small subunit, and a second tRNA is recruited. As the mRNA moves relative to the ribosome, the polypeptide chain is formed. Entry of a release factor into the A site terminates translation and the components dissociate. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

Termination of translation occurs when a stop codon (UAA, UAG, or UGA) is encountered. When the ribosome encounters the stop codon, the growing polypeptide is released and the ribosome subunits dissociate and leave the mRNA. After many ribosomes have completed translation, the mRNA is degraded so the nucleotides can be reused in another transcription reaction.

### Concept in Action – Transcribe a gene

Visit the Learn Genetics website to transcribe a gene and translate it to protein using complementary pairing and the genetic code .

For a cell to function properly, necessary proteins must be synthesized at the proper time. All organisms and cells control or regulate the transcription and translation of their DNA into protein. The process of turning on a gene to produce RNA and protein is called **gene expression**. Whether in a simple unicellular organism or in a complex multicellular organism, each cell controls when and how its genes are expressed. For this to occur, there must be a mechanism to control when a gene is expressed to make RNA and protein, how much of the protein is made, and when it is time to stop making that protein because it is no longer needed.

Cells in multicellular organisms are specialized; cells in different tissues look very different and perform different functions. For example, a muscle cell is very different from a liver cell, which is very different from a skin cell. These differences are a consequence of the expression of different sets of genes in each of these cells. All cells have certain basic functions they must perform for themselves, such as converting the energy in sugar molecules into energy in ATP. Each cell also has many genes that are not expressed, and expresses many that are not expressed by other cells, such that it can carry out its specialized functions. In addition, cells will turn on or off certain genes at different times in response to changes in the environment or at different times during the development of the organism. Unicellular organisms, also turn on and off genes in response to the demands of their environment so that they can respond to special conditions.

The control of gene expression is extremely complex. Malfunctions in this process are detrimental to the cell and can lead to the development of many diseases, including cancer.

## Eukaryotic Gene Expression

To understand how gene expression is regulated, we must first understand how a gene becomes a functional protein in a cell. Eukaryotic cells have intracellular organelles and are complex. Recall that in eukaryotic cells, the DNA is contained inside the cell's nucleus and it is transcribed into mRNA there. The newly synthesized mRNA is then transported out of the nucleus into the cytoplasm, where ribosomes translate the mRNA into protein. The processes of transcription and translation are physically separated by the nuclear membrane; transcription occurs only within the nucleus, and translation only occurs outside the nucleus in the cytoplasm. The regulation of gene expression can occur at all stages of the process (Figure 2.20). Regulation may occur when the DNA is uncoiled and loosened from nucleosomes to bind transcription factors (**epigenetic** level), when the RNA is transcribed (transcriptional level), when RNA is processed and exported

to the cytoplasm after it is transcribed (post-transcriptional level), when the RNA is translated into protein (translational level), or after the protein has been made (post-translational level).

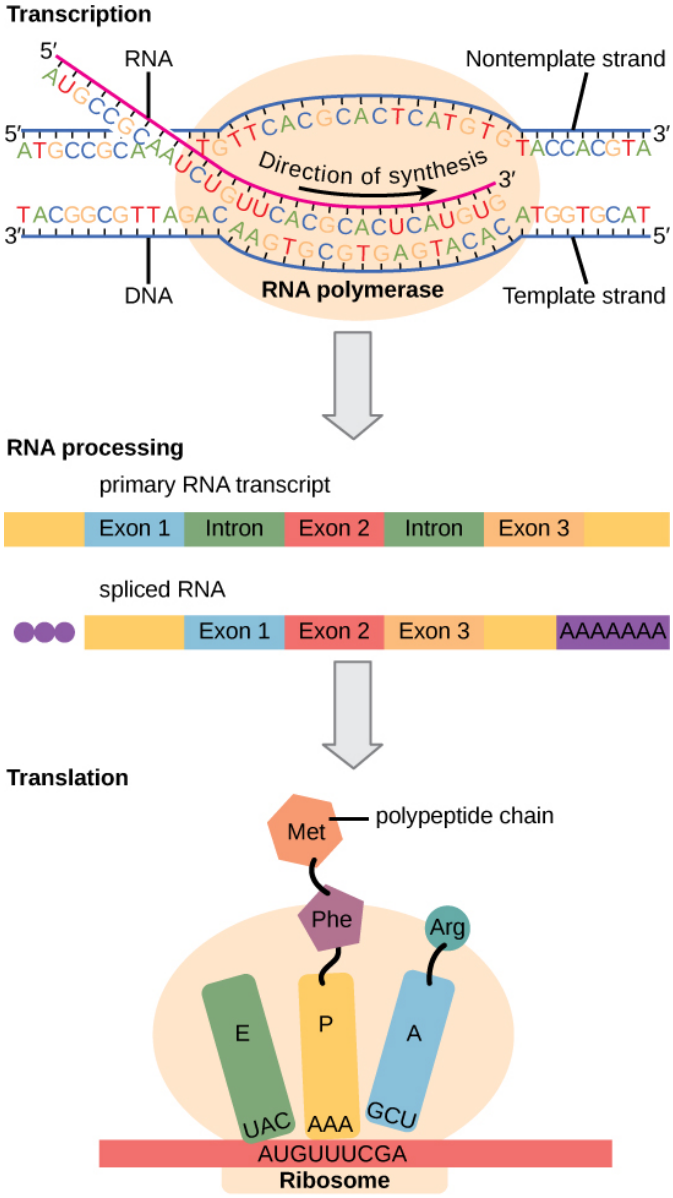



**Figure 2.20** Eukaryotic gene expression is regulated during transcription and RNA processing, which take place in the nucleus, as well as during protein translation, which takes place in the cytoplasm. Further regulation may occur through post-translational modifications of proteins. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Alternative RNA Splicing

In the 1970s, genes were first observed that exhibited **alternative RNA splicing**. Alternative RNA splicing

is a mechanism that allows different protein products to be produced from one gene when different combinations of introns (and sometimes exons) are removed from the transcript (Figure 2.21). This alternative splicing can be haphazard, but more often it is controlled and acts as a mechanism of gene regulation, with the frequency of different splicing alternatives controlled by the cell as a way to control the production of different protein products in different cells, or at different stages of development. Alternative splicing is now understood to be a common mechanism of gene regulation in eukaryotes; according to one estimate, 70% of genes in humans are expressed as multiple proteins through alternative splicing.

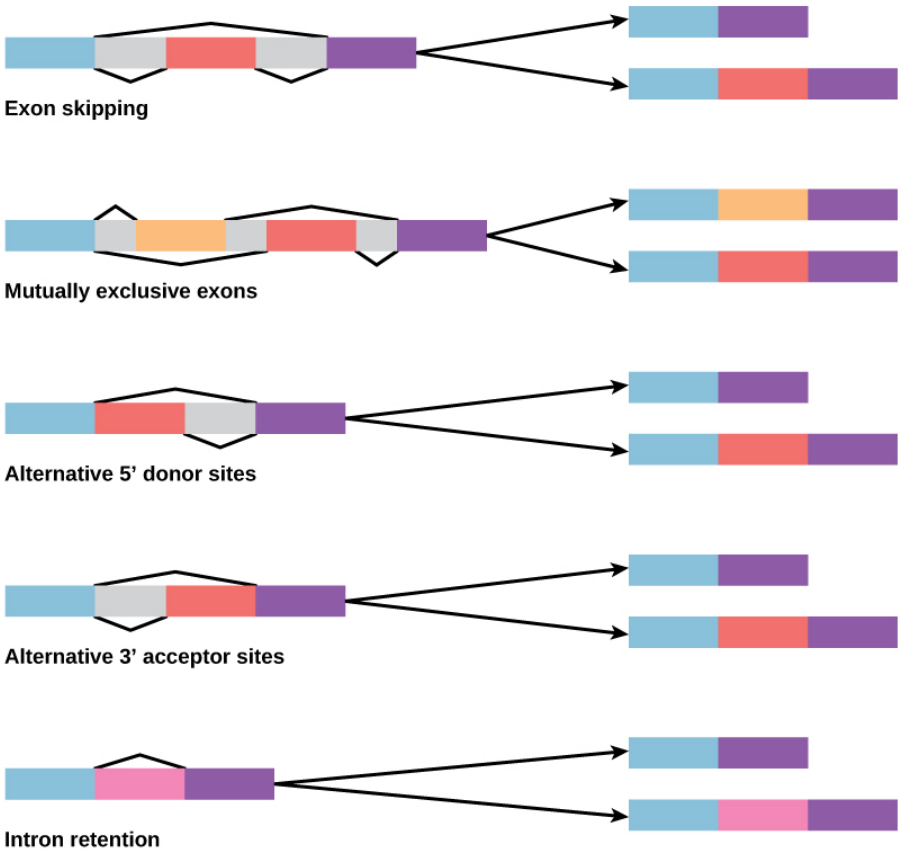



**Figure 2.21** There are five basic modes of alternative splicing. Segments of pre-mRNA with exons shown in blue, red, orange, and pink can be spliced to produce a variety of new mature mRNA segments. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

How could alternative splicing evolve? Introns have a beginning and ending recognition sequence, and it is easy to imagine the failure of the splicing mechanism to identify the end of an intron and find the end of the next intron, thus removing two introns and the intervening exon. In fact, there are mechanisms in place to prevent such exon skipping, but variants are likely to lead to their failure. Such "mistakes" would more than likely produce a nonfunctional protein. Indeed, the cause of many genetic diseases is alternative splicing rather than variants in a sequence. However, alternative splicing would create a protein variant without the loss of the original protein, opening up possibilities for adaptation of the new variant to new functions. Gene

duplication has played an important role in the evolution of new functions in a similar way—by providing genes that may evolve without eliminating the original functional protein.

## Exercises

**Exercises (text version)**

1. True or false? Nucleotides are made up of three parts: a base, ribose sugar, and phosphate.
2. Fill in the blanks in the following statements:
    a. a. The letters of the 4 nucleotides are [Blank 1] and [Blank 2] and [Blank 3] and [Blank 4].
    b. b. The base pairing rules are the A always pairs with [Blank 1] and [Blank 2] always pairs with [Blank 3].
    c. DNA replication is said to be [Blank 1]- conservative.
    d. The enzyme that is crucial in copying DNA strands is called [Blank 1].
    e. The central dogma of molecular biology is:
    DNA——1——— arrow to mRNA—2—- arrow to Protein.
    The number that represents Translation is [Blank 1]. The number that represents Transcription is [Blank 2].
    f. Since (with a few exceptions) all organisms use the same genetic code, it is said to be [Blank 1].
    g. DNA functions to provide the information needed to construct [Blank 1]*Protein/Proteins/protein/Protein*.
3. Which of the following does cytosine pair with?
    a. guanine
    b. thymine
    c. adenine
    d. a pyrimidine
4. How are chromosomes arranged and packaged in a eukaryotic cell (select all that apply)?
    a. double-stranded, linear
    b. single-stranded, circular

c. wrapped around histones
d. wrapped around nucleosomes

5. Match the words to the correct blank to describe the organization of the eukaryotic chromosome.
   **Words:** histones, interphase, fibre, euchromatin, metaphase, heterochromatin
   The DNA is wound around proteins called [Blank A]. These proteins then stack together in a compact form that creates a [Blank B]*fiber* 30-nm thick that is further coiled for greater compactness. During [Blank C] of mitosis, the *chromosome* is at its most compact to facilitate *chromosome* movement. During [Blank D]*interphase*, there are denser areas of chromatin, called [Blank E]*heterochromatin*, that contain DNA that is not expressed, and less dense [Blank F]*euchromatin* that contains DNA that is expressed.
6. Match the words to the correct blank to describe the structure and complementary base pairing of DNA.
   **Words:** double helix, adenine/thymine, two strands, cytosine/guanine, phosphate group, cytosine/guanine, nucleic acids, nitrogenous, covalently, deoxyribose sugar, hydrogen
   A single strand of DNA is a polymer of [Blank A] joined [Blank B] between the [Blank C] of one and the [Blank D] of the next to form a "backbone" from which the [Blank E] bases stick out. In its natural state, DNA has [Blank F] wound around each other in a [Blank G]. The bases on each strand are bonded to each other with [Blank H] bonds. Only specific bases bond with each other; [Blank i] bonds with [Blank J], and [Blank K] bonds with [Blank L].
7. Fill in the missing word to complete the statement.
   You isolate a cell strain in which the joining together of Okazaki fragments is impaired and suspect that a mutation has occurred in an enzyme found at the replication fork. The enzyme most likely to be altered is [Blank A], as this enzyme joins together Okazaki fragments.
8. DNA replicates by which of the following models?

   a. conservative
   b. semiconservative
   c. dispersive
   d. none of the above

9. What is the initial mechanism for repairing nucleotide errors in DNA?

   a. mismatch repair
   b. DNA polymerase proofreading
   c. nucleotide excision repair

d. thymine dimers

10. True or false? The linear chromosomes in eukaryotes ensure that its ends are replicated completely because telomerase has an inbuilt RNA template that extends the 3' end, so a primer is synthesized and extended, and the ends are protected.
11. What is a promoter?

    a. a specific sequence of DNA nucleotides
    b. a protein that binds to DNA
    c. an enzyme that synthesizes RNA
    d. a specific sequence of RNA nucleotides

12. What is the term for the portions of eukaryotic mRNA sequence that are removed during RNA processing?

    a. exons
    b. caps
    c. poly-A tails
    d. introns

13. Where are the RNA components of ribosomes synthesized?

    a. cytoplasm
    b. nucleus
    c. nucleolus
    d. endoplasmic reticulum

14. How long would the peptide be that is translated from this mRNA sequence: 5'-AUGGGCUACCGA-3'?

    a. 0
    b. 2
    c. 3
    d. 4

15. At what level(s) does the control of gene expression occur in eukaryotic cells?

    a. only the transcriptional level
    b. epigenetic and transcriptional levels
    c. epigenetic, transcriptional, and translational levels

d. epigenetic, transcriptional, post-transcriptional, translational, and post-translational levels

16. What does post-translational control refer to?

    a. the regulation of gene expression after transcription
    b. the regulation of gene expression after translation
    c. the control of epigenetic activation
    d. the period between transcription and translation

17. Match the words into the correct blanks to describe how controlling gene expression will alter the overall protein levels in the cell.
    **Words:** decrease, stages, Prokaryotic, Eukaryotic, translation, lifespan, Eukaryotic, increase, amount, Prokaryotic,
    The cell controls which protein is expressed, and to what level that protein is expressed, in the cell. [Blank A] cells alter the transcription rate to turn genes on or off. This method will [Blank B] or [Blank C] protein levels in response to what is needed by the cell. [Blank D] cells change the accessibility (epigenetic), transcription, or translation of a gene. This will alter the [Blank E] and [Blank F] of RNA, to alter how much protein exists. These cells also change the protein's [Blank G] to increase or decrease its overall levels. [Blank H] organisms are much more complex than [Blank i] organisms and can manipulate protein levels by changing many [Blank J] in the process.

**Check your answers in footnote**[4]

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4.
1. True. .
2. a. 1: A/G/T/C/a/t/g/c; 2: A/G/T/C/a/t/g/c; 3: A/G/T/C/a/t/g/c; 4: A/G/T/C/a/t/g/c.
   b. 1: T/t; 2: G/g; 3: C/c
   c. 1. semi
   d. 1. DNA polymerase/DNA Polymerase/dna polymerase*.
   e. 1: 2, 2: 1.
   f. 1. universal
   g. Protein/Proteins/protein/Protein
3. a) guanine
4. a) double-stranded, linear
5. A – histones, B – Fiber, C – metaphase, D – interphase, E – heterochromatin, F – euchromatin
6. A – nucleic acids, B – covalently, C – phosphate group, D – deoxyribose sugar, E – nitrogenous, F – two strands, G – double helix, H – hydrogen, i – adenine/thymine, J – adenine/thymine, K – cytosine/guanine, L – cytosine/guanine.

## Attribution & References



7. a. Ligase/ligase
8. b. semiconservative
9. b. DNA polymerase proofreading
10. True.
11. a. a specific sequence of DNA nucleotides
12. d. introns
13. c. nucleolus
14. d. 4
15. epigenetic, transcriptional, post-transcriptional, translational, and post-translational levels
16. b. the regulation of gene expression after translation
17. A – Prokaryotic, B – increase, C – decrease, D – Eukaryotic, E – amount, F – lifespan, G – translation, H – Eukaryotic, i – Prokaryotic, J – stages

# 2.3 THE GENOME AND THE CELL CYCLE

## Learning Objectives

- Describe the eukaryotic genome.
- Distinguish between chromosomes, genes, traits, and phenotype.
- Describe the three stages of interphase.
- Discuss the behaviour of chromosomes during mitosis and how the cytoplasmic content divides during cytokinesis.
- Define the quiescent $G_0$ phase.
- Explain how the three internal control checkpoints occur at the end of $G_1$, at the $G_2$–M transition, and during metaphase.

## Genomic DNA

Before discussing the steps a cell undertakes to replicate, a deeper understanding of the structure and function of a cell's genetic information is necessary. A cell's complete complement of DNA is called its genome. In eukaryotes, the genome comprises several double-stranded, linear DNA molecules (Figure 2.22) bound with proteins to form complexes called chromosomes. Each eukaryote species has a characteristic number of chromosomes in the nuclei of its cells. Human body cells (somatic cells) have **46 chromosomes,** including **44 autosomes** and **2 sex chromosomes**. A somatic cell contains two matched sets of chromosomes, a configuration known as **diploid**. The letter *n* represents a single set of chromosomes; therefore, a diploid organism is designated 2*n*. Human cells that contain one set of **23 chromosomes** are called **gametes,** or sex cells; these eggs and sperm are designated ***n***, or **haploid**.

The matched pairs of chromosomes in a diploid organism are called homologous chromosomes. **Homologous** chromosomes are the same length and have specific nucleotide segments called genes in exactly the same location, or **locus**. Genes, the functional units of chromosomes, determine specific **characteristics** by coding for specific proteins. An individual's **genotype** refers to the set of genes an organism carries for a

specific trait. **Traits** are the different forms of a characteristic. For example, the shape of earlobes is a characteristic with traits of free or attached. A **phenotype** is the observable physical and physiological traits of an individual resulting from the interaction of its genotype with the environment. The phenotype encompasses all traits, visible or otherwise. Subsequent chapters will discuss how to track phenotypes (specifically diseases) through multiple generations using a pedigree chart.

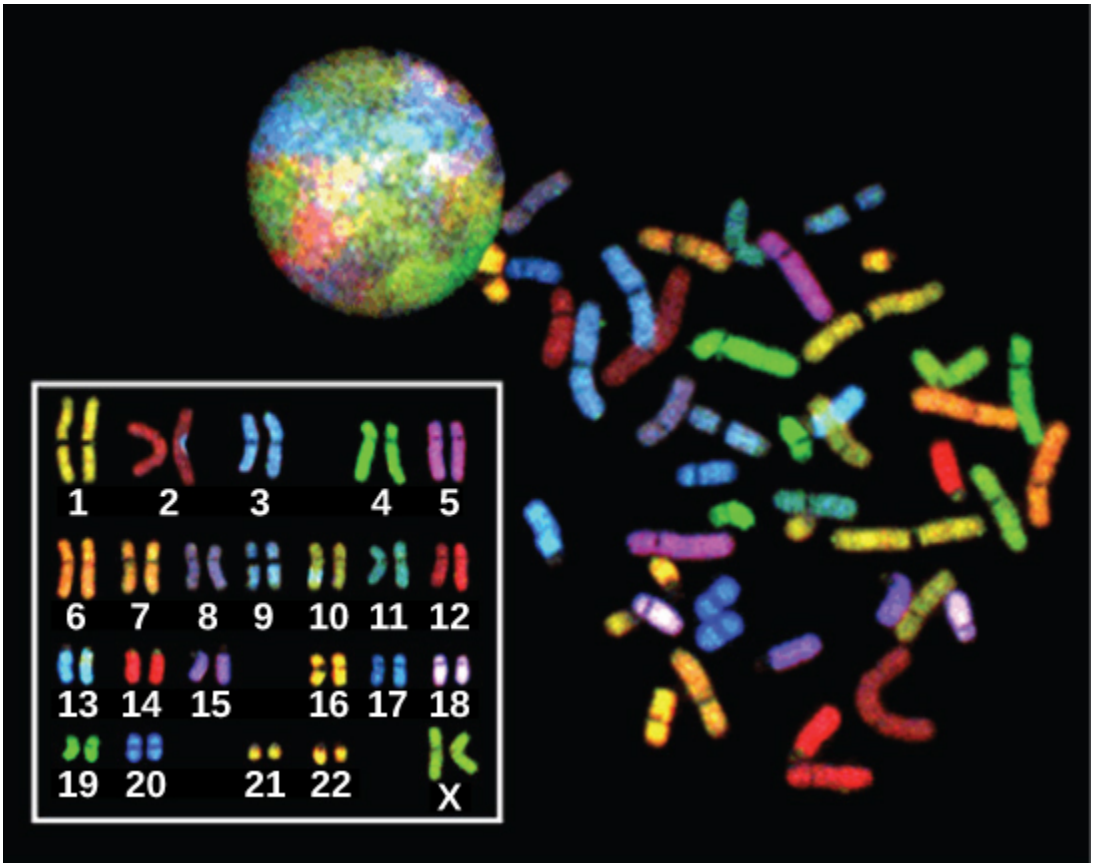



**Figure 2.22** There are 23 pairs of homologous chromosomes in a female human somatic cell. These chromosomes are viewed within the nucleus (top), removed from a cell in mitosis (right), and arranged according to length (left) in an arrangement called a karyotype. In this image, the chromosomes were exposed to fluorescent stains to distinguish them. **Source:** Image Courtesy: National Human Genome Research, PDM

Each copy of the homologous pair of chromosomes originates from a different parent; therefore, the copies of each of the genes themselves may not be identical. The **variation** of individuals within a species is caused by the specific combination of the genes inherited from both parents. For example, there are three possible gene sequences on the human chromosome that codes for blood type: sequence A, sequence B, and sequence O. Because all diploid human cells have two copies of the chromosome that determines blood type, the blood type (the trait) is determined by which two versions of the marker gene are inherited. It is possible to have two copies of the same gene sequence, one on each homologous chromosome (for example, AA, BB, or OO), or

two different sequences, such as AB. This is due to incomplete dominance or codominance. Subsequent chapters will discuss these concepts of patterns of inheritance.

Minor variations in traits such as those for blood type, eye color, and height contribute to the natural variation found within a species. However, if the entire DNA sequence from any pair of human homologous chromosomes is compared, the *difference is much less than one percent*. The sex chromosomes, X and Y, are the single exception to the rule of homologous chromosomes; other than a small amount of homology that is necessary to reliably produce gametes, the genes found on the X and Y chromosomes are not the same.

The continuity of life from one cell to another has its foundation in the reproduction of cells by way of the **cell cycle**. The cell cycle is an orderly sequence of events in the life of a cell, from the division of a single parent cell to produce two new daughter cells to the subsequent division of those daughter cells. The mechanisms involved in the cell cycle are highly conserved across eukaryotes.

## The Cell Cycle

The cell cycle is an ordered series of events involving cell growth and cell division that produces two new daughter cells. Cells on the path to cell division proceed through a series of precisely timed and carefully regulated stages of growth, DNA replication, and division that produce two genetically identical cells. The cell cycle has two major phases: **interphase** and the **mitotic phase** (Figure 2.24). During interphase, the cell grows and DNA is replicated. During the mitotic phase, the replicated DNA and cytoplasmic contents are separated and the cell divides.

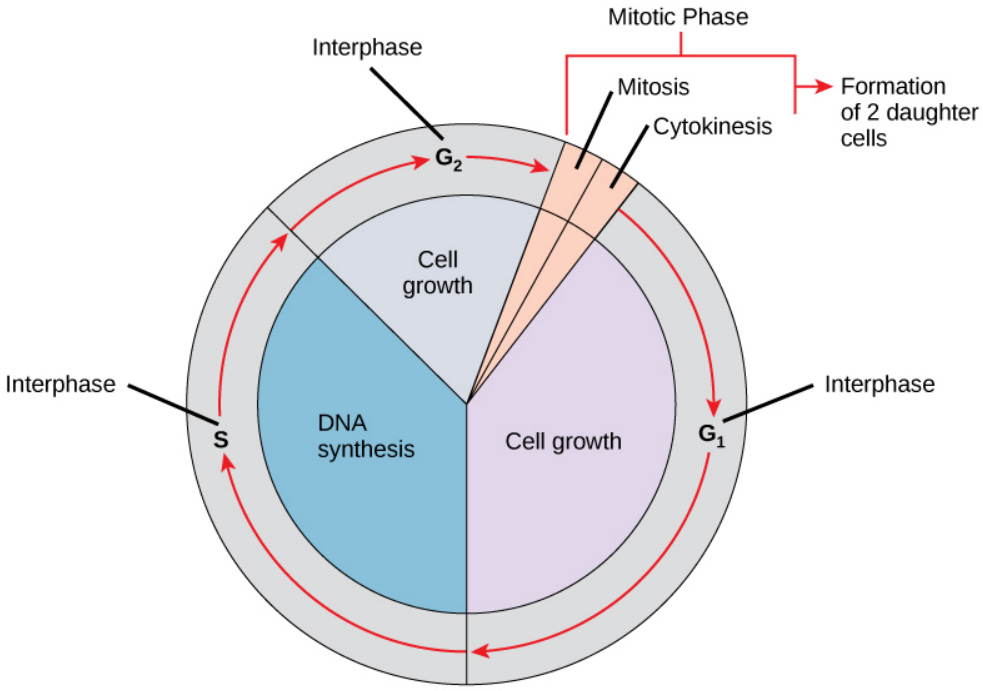



**Figure 2.24** A cell moves through a series of phases in an orderly manner. During interphase, G1 involves cell growth and protein synthesis, the S phase involves DNA replication and the replication of the centrosome, and G2 involves further growth and protein synthesis. The mitotic phase follows interphase. Mitosis is nuclear division during which duplicated chromosomes are segregated and distributed into daughter nuclei. Usually the cell will divide after mitosis in a process called cytokinesis in which the cytoplasm is divided and two daughter cells are formed. **Source:** *Concepts of Biology (OpenStax)*, caption edited by *Biology 2e (OpenStax)*, CC BY 4.0.

# Interphase

During interphase, the cell undergoes normal processes while also preparing for cell division. For a cell to move from interphase to the mitotic phase, many internal and external conditions must be met. The three stages of interphase are called $G_1$, S, and $G_2$.

## $G_1$ Phase

The first stage of interphase is called the **$G_1$ phase**, or first gap, because little change is visible. However, during the $G_1$ stage, the cell is quite active at the biochemical level. The cell is accumulating the building blocks of chromosomal DNA and the associated proteins, as well as accumulating enough energy reserves to complete the task of replicating each chromosome in the nucleus.

## S Phase

Throughout interphase, nuclear DNA remains in a semi-condensed chromatin configuration. In the **S phase** (synthesis phase), **DNA replication** results in the formation of two identical copies of each chromosome—sister chromatids—that are firmly attached at the centromere region. At this stage, each chromosome is made of two sister chromatids and is a duplicated chromosome. The centrosome is duplicated during the S phase. The two centrosomes will give rise to the **mitotic spindle**, the apparatus that orchestrates the movement of chromosomes during mitosis. The centrosome consists of a pair of rod-like **centrioles** at right angles to each other. Centrioles help organize cell division. Centrioles are not present in the centrosomes of many eukaryotic species, such as plants and most fungi.

## $G_2$ Phase

In the **$G_2$ phase**, or second gap, the cell replenishes its energy stores and synthesizes the proteins necessary for chromosome manipulation. Some cell organelles are duplicated, and the cytoskeleton is dismantled to provide resources for the mitotic spindle. There may be additional cell growth during $G_2$. The final preparations for the mitotic phase must be completed before the cell is able to enter the first stage of mitosis.

# The Mitotic Phase

To make two daughter cells, the contents of the nucleus and the cytoplasm must be divided. The mitotic phase is a multistep process during which the duplicated chromosomes are aligned, separated, and moved to opposite poles of the cell, and then the cell is divided into two new identical daughter cells. The first portion of the mitotic phase, **mitosis**, is composed of five stages, which accomplish nuclear division. The second portion of the mitotic phase, called **cytokinesis**, is the physical separation of the cytoplasmic components into two daughter cells.

## Mitosis

**Mitosis** is divided into a series of phases— prophase, prometaphase, metaphase, anaphase, and telophase—that result in the division of the cell nucleus (Figure 2.25).

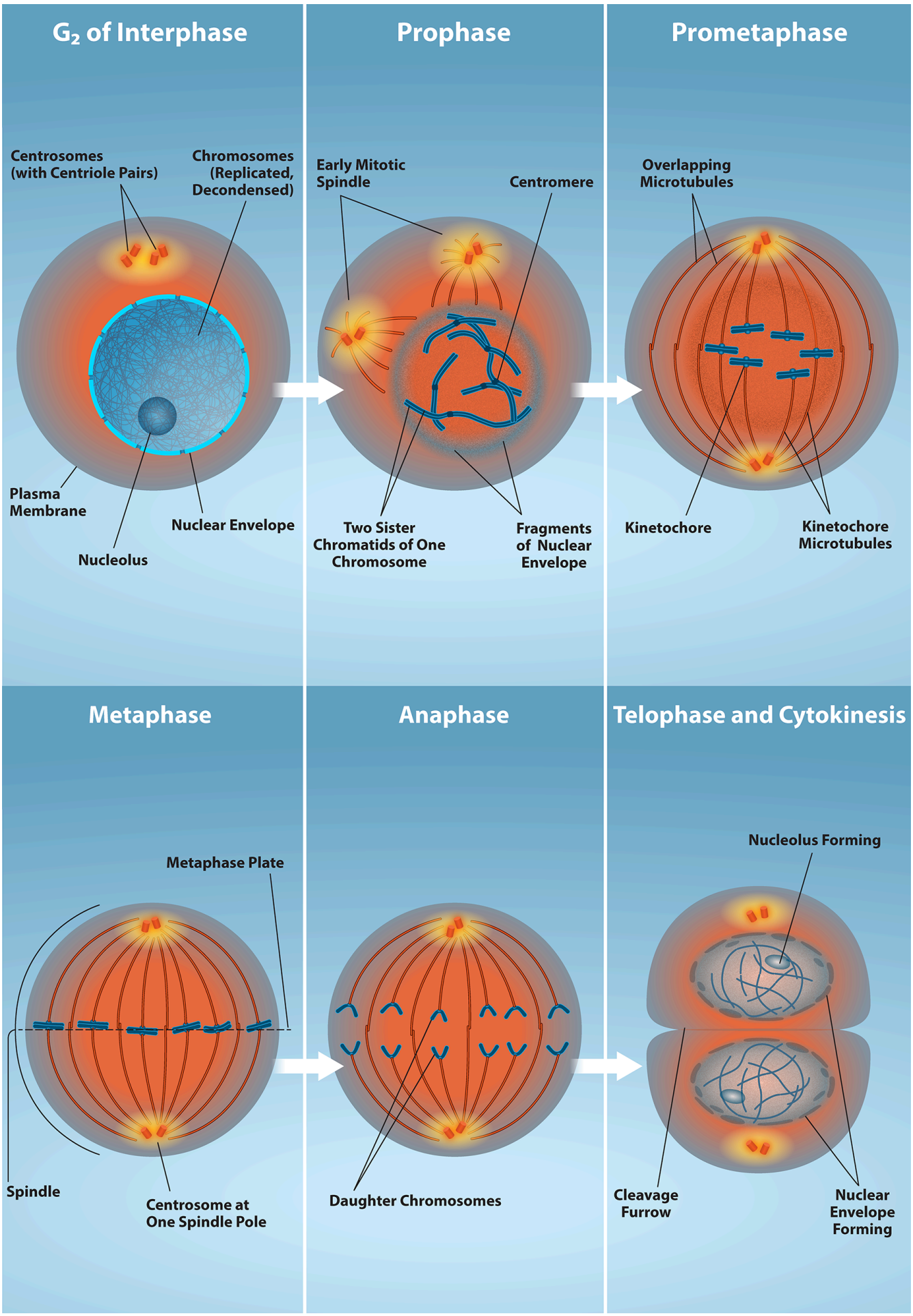

G2 of Interphase
Centrosomes (with Centriole Pairs)
Chromosomes (Replicated, Decondensed)
Plasma Membrane
Nucleolus
Nuclear Envelope
Prophase
Early Mitotic Spindle
Centromere
Two Sister Chromatids of One Chromosome
Fragments of Nuclear Envelope
Prometaphase
Overlapping Microtubules
Kinetochore
Kinetochore Microtubules
Metaphase
Metaphase Plate
Spindle
Centrosome at One Spindle Pole
Anaphase
Daughter Chromosomes
Telophase and Cytokinesis
Nucleolus Forming
Cleavage Furrow
Nuclear Envelope Forming

**Figure 2.25** G2 of Interphase – The last stage of interphase is the second gap period, G2. During this stage, cells grow, replenish energy and synthesize needed macromolecules, such as proteins and lipids. Mitosis – When G2 is complete, the cell will enter mitosis. Although there are 5 phases in mitosis, with the exception of the metaphase to anaphase transition, these phases are not discrete and happen as a continuous process. Prophase is the first stage in mitosis. The nuclear envelope begins to break down and chromosomes condense and are now visible. Spindle fibers start to appear and centrosomes begin to move towards opposite poles. Prometaphase – Chromosomes continue to condense and are more visible. Kinetochores appear at the centromere and kinetochore microtubules attach. Centrosomes continue to move towards opposite poles. Metaphase – The mitotic spindle is fully developed and centrosomes are at opposite poles. Chromosomes are aligned at the "equatorial plate", and each sister chromatid rests on one side of the plate, with spindle fibers attached to them. Anaphase – Sister chromatids are pulled apart by spindle fibers and are separated from each other. Each chromatid is now a chromosome. Telophase and Cytokinesis – Chromosomes arrive at opposite poles and start to decondense and become less visible. The nuclear envelope reassembles and begins to surround each new set of chromosomes. The mitotic spindle assembly breaks down and the division of the cytoplasm begins via cytokinesis. This physical separation into two cells are remarkably different processes in plant and animal cells. **Source:** Rao, A., Hawkins, A. and Fletcher, S. Department of Biology, Texas A&M University, *Biology 2e (OpenStax)*, CC BY 4.0.

During **prophase**, the "first phase," several events must occur to provide access to the chromosomes in the nucleus. The nuclear envelope starts to break into small vesicles, and the Golgi apparatus and endoplasmic reticulum fragment and disperse to the periphery of the cell. The nucleolus disappears. The centrosomes begin to move to opposite poles of the cell. The microtubules that form the basis of the mitotic spindle extend between the centrosomes, pushing them farther apart as the microtubule fibers lengthen. The sister chromatids begin to coil more tightly and become visible under a light microscope.

During **prometaphase**, many processes that were begun in prophase continue to advance and culminate in the formation of a connection between the chromosomes and cytoskeleton. The remnants of the nuclear envelope disappear. The mitotic spindle continues to develop as more microtubules assemble and stretch across the length of the former nuclear area. Chromosomes become more condensed and visually discrete. Each sister chromatid attaches to spindle microtubules at the centromere via a protein complex called the kinetochore.

During **metaphase**, all of the chromosomes are aligned in a plane called the **metaphase plate**, or the equatorial plane, midway between the two poles of the cell. The sister chromatids are still tightly attached to each other. At this time, the chromosomes are maximally condensed.

During **anaphase**, the sister chromatids at the equatorial plane are split apart at the centromere. Each chromatid, now called a chromosome, is pulled rapidly toward the centrosome to which its microtubule was attached. The cell becomes visibly elongated as the non-kinetochore microtubules slide against each other at the metaphase plate where they overlap.

During **telophase**, all of the events that set up the duplicated chromosomes for mitosis during the first three phases are reversed. The chromosomes reach the opposite poles and begin to decondense (unravel). The mitotic spindles are broken down into monomers that will be used to assemble cytoskeleton components for each daughter cell. Nuclear envelopes form around chromosomes.

### Concept in Action – Mitosis

**Watch Mitosis: The Amazing Cell Process that Uses Division to Multiply! (Updated) (6 mins) on YouTube (https://youtu.be/gcz1FOWw0Cg)**

## Cytokinesis

Cytokinesis is the second part of the mitotic phase during which cell division is completed by the physical separation of the cytoplasmic components into two daughter cells. Although the stages of mitosis are similar for most eukaryotes, the process of cytokinesis is quite different for eukaryotes that have cell walls, such as plant cells.

In cells such as animal cells that lack cell walls, cytokinesis begins following the onset of anaphase. A contractile ring composed of actin filaments forms just inside the plasma membrane at the former metaphase plate. The actin filaments pull the equator of the cell inward, forming a fissure. This fissure, or "crack," is called the **cleavage furrow**. The furrow deepens as the actin ring contracts, and eventually the membrane and cell are cleaved in two (Figure 2.25).

In plant cells, a cleavage furrow is not possible because of the rigid cell walls surrounding the plasma membrane. A new cell wall must form between the daughter cells. During interphase, the Golgi apparatus accumulates enzymes, structural proteins, and glucose molecules prior to breaking up into vesicles and dispersing throughout the dividing cell. During telophase, these Golgi vesicles move on microtubules to collect at the metaphase plate. There, the vesicles fuse from the center toward the cell walls; this structure is called a cell plate. As more vesicles fuse, the cell plate enlarges until it merges with the cell wall at the periphery of the cell. Enzymes use the glucose that has accumulated between the membrane layers to build a new cell wall of cellulose. The Golgi membranes become the plasma membrane on either side of the new cell wall (Figure 2.26).

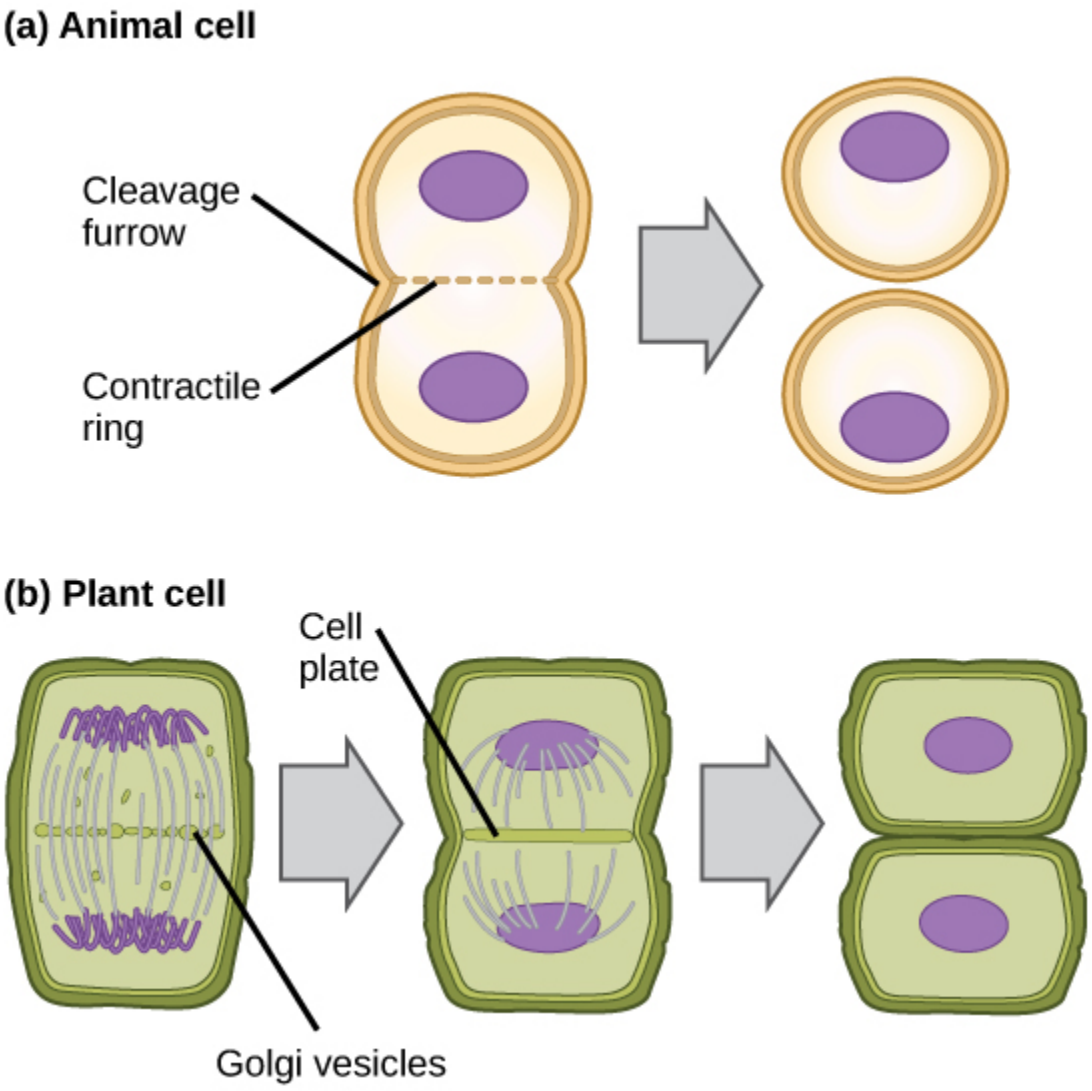



**Figure 2.26** In part (a), a cleavage furrow forms at the former metaphase plate in the animal cell. The plasma membrane is drawn in by a ring of actin fibers contracting just inside the membrane. The cleavage furrow deepens until the cells are pinched in two. In part (b), Golgi vesicles coalesce at the former metaphase plate in a plant cell. The vesicles fuse and form the cell plate. The cell plate grows from the center toward the cell walls. New cell walls are made from the vesicle contents. **Source:** *Concepts of Biology (OpenStax)*, CC BY 4.0.

### Concept in Action – Cell Cycle

Watch The Cell Cycle by Nucleus Biology (4 mins) on YouTube (https://youtu.be/e6N9_RhD10Q?si=_5hAiWQtpuVCdgQL)

## Go Phase

Not all cells adhere to the classic cell-cycle pattern in which a newly formed daughter cell immediately enters interphase, closely followed by the mitotic phase. Cells in the **$G_0$ phase** are *not actively preparing to divide.* The cell is in a **quiescent (inactive) stage**, having exited the cell cycle. Some cells enter $G_0$ temporarily until an external signal triggers the onset of $G_1$. Other cells that never or rarely divide, such as mature cardiac muscle and nerve cells, remain in $G_0$ permanently (Figure 2.27).

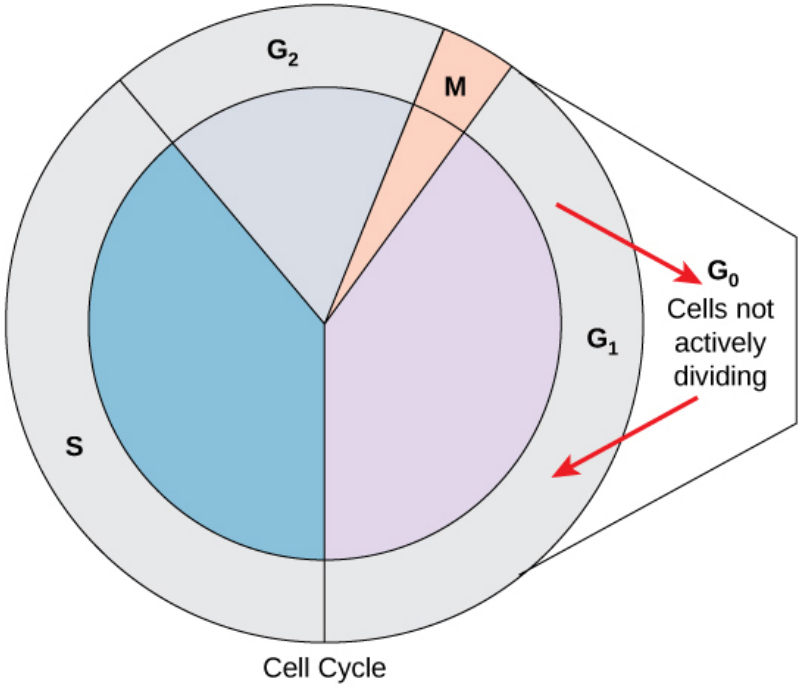



**Figure 2.27** Cells that are not actively preparing to divide enter an alternate phase called G0. In some cases, this is a temporary condition until triggered to enter G1. In other cases, the cell will remain in G0 permanently. **Source:** Concepts of Biology (OpenStax), CC BY 4.0.

## Control of the Cell Cycle

The length of the cell cycle is highly variable even within the cells of an individual organism. In humans, the frequency of cell turnover ranges from a few hours in early embryonic development to an average of two to five days for epithelial cells, or to an entire human lifetime spent in $G_0$ by specialized cells such as cortical neurons or cardiac muscle cells. There is also variation in the time that a cell spends in each phase of the cell cycle. When fast-dividing mammalian cells are grown in culture (outside the body under optimal growing conditions), the length of the cycle is approximately 24 hours. In rapidly dividing human cells with a 24-hour cell cycle, the $G_1$ phase lasts approximately 11 hours. The timing of events in the cell cycle is controlled by mechanisms that are both internal and external to the cell.

# Regulation at Internal Checkpoints

It is essential that daughter cells be exact duplicates of the parent cell. Mistakes in the duplication or distribution of the chromosomes lead to gene **variants** (mutations) that may be passed forward to every new cell produced from the abnormal cell. To prevent a compromised cell from continuing to divide, there are internal control mechanisms that operate at three main **cell cycle checkpoints** at which the cell cycle can be stopped until conditions are favorable. These checkpoints occur near the end of $G_1$, at the **$G_2$–M transition**, and during metaphase (Figure 2.28).

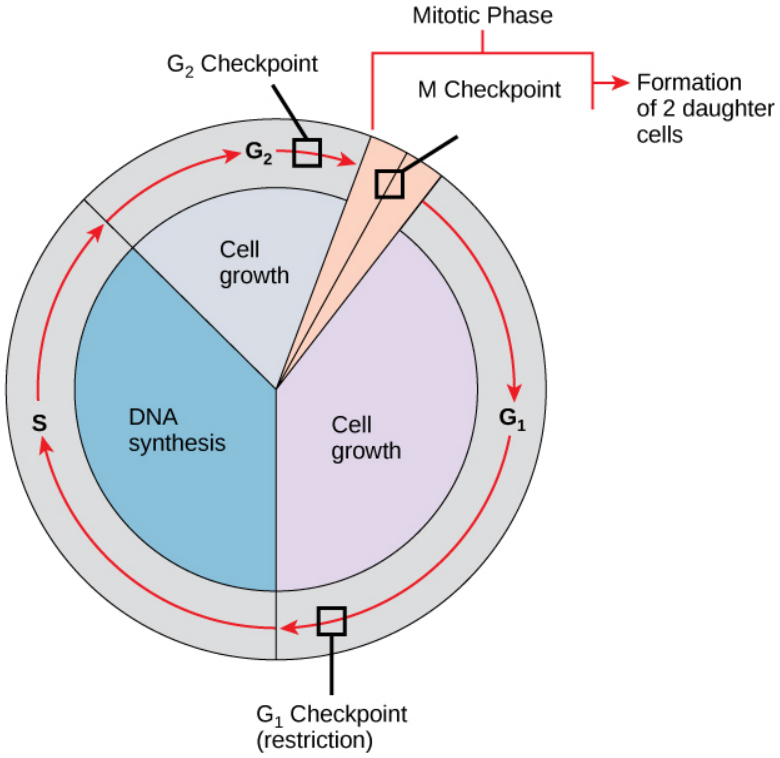



**Figure 2.28** The cell cycle is controlled at three checkpoints. Integrity of the DNA is assessed at the G1 checkpoint. Proper chromosome duplication is assessed at the G2 checkpoint. Attachment of each kinetochore to a spindle fiber is assessed at the M checkpoint**. Source:** *Concepts of Biology (OpenStax)*, CC BY 4.0.

## The $G_1$ Checkpoint

The **$G_1$ checkpoint** determines whether all conditions are favorable for cell division to proceed. The $G_1$ checkpoint, also called the restriction point, is the point at which the cell irreversibly commits to the cell-division process. In addition to adequate reserves and cell size, there is a check for damage to the genomic DNA at the $G_1$ checkpoint. A cell that does not meet all the requirements will not be released into the S phase.

## The $G_2$ Checkpoint

The **$G_2$ checkpoint** bars the entry to the mitotic phase if certain conditions are not met. As in the $G_1$ checkpoint, cell size and protein reserves are assessed. However, the most important role of the $G_2$ checkpoint is to ensure that all of the chromosomes have been replicated and that the replicated DNA is not damaged.

## The M Checkpoint

The **M checkpoint** occurs near the end of the metaphase stage of mitosis. The M checkpoint is also known as the spindle checkpoint because it determines if all the sister chromatids are correctly attached to the spindle microtubules. Because the separation of the sister chromatids during anaphase is an irreversible step, the cycle will not proceed until the kinetochores of each pair of sister chromatids are firmly anchored to spindle fibers arising from opposite poles of the cell.

### Concept in Action – Eukaryotic Cell Cycle

Check out this interactive content that explains these concepts by visiting The Eukaryotic Cell Cycle and Cancer (https://media.hhmi.org/biointeractive/click/cellcycle/?_ga=2.198047532.225804613.1546808178-1471355355.1522416214).

## Exercises

**Exercises (text version)**

1. True or false? The longest phase in the cell cycle is the M or Mitosis phase.
2. Fill in the blanks to complete the statement:
   Matched pairs of chromosomes are called [Blank A] chromosomes. These chromosomes have the same [Blank B] at the same locations. They may have differing [Blank C] , which are differing versions of the same gene.
   The number of chromosomes Humans have is [Blank D].

The term [Blank E] or 2n applies to body cells that have matched pairs of chromosomes. Gametes like sperm and eggs are called [Blank F] or n as they have only one copy of each chromosome.
The process called [Blank G] results in the creation of identical cells. In bacterial (prokaryotic cells) the process of making identical cells is called [Blank H].
The process of [Blank i] occurs in S-phase of interphase.
In the [Blank J] stage of mitosis chromosomes become visible when viewed down the microscope.

3. How many chromosomes does a diploid cell have compared a haploid cell?

    a. one-fourth
    b. one-half
    c. twice
    d. four times

4. What specific combination is inherited that determines an organism's traits?

    a. cells
    b. genes
    c. proteins
    d. chromatids

5. Match the words into the correct blanks to compare the characteristics of a human somatic cell to a human gamete.
   **Words:** haploid/n, one, forty-six, twenty-three, n/haploid, 2n/diploid, non-homologous, homologous, twenty-two, diploid/2n
   Human somatic cells have [Blank A] chromosomes, including [Blank B] [Blank C] pairs and [Blank D] pair of [Blank E] sex chromosomes. This is the [Blank F], or [Blank G], condition.
   Human gametes have one each of [Blank H] unique chromosomes. This is the [Blank i], or [Blank J] condition.
6. Which of the following statements describes the correct order of events in mitosis?

    a. Sister chromatids line up at the metaphase plate. The kinetochore becomes attached to the mitotic spindle. The nucleus re-forms and the cell divides. The sister chromatids separate.
    b. The kinetochore becomes attached to the mitotic spindle. The sister chromatids separate. Sister chromatids line up at the metaphase plate. The nucleus re-forms and the cell divides.

c. The kinetochore becomes attached to metaphase plate. Sister chromatids line up at the metaphase plate. The kinetochore breaks down and the sister chromatids separate. The nucleus re-forms and the cell divides.
d. The kinetochore becomes attached to the mitotic spindle. Sister chromatids line up at the metaphase plate. The kinetochore breaks apart and the sister chromatids separate. The nucleus re-forms and the cell divides.

7. In what portion of the cell cycle are chromosomes duplicated?

a. $G_1$ phase
b. S phase
c. prophase
d. prometaphase

8. In what stage of mitosis is the separation of the sister chromatids characteristic?

a. prometaphase
b. metaphase
c. anaphase
d. telophase

9. In what stage of mitosis do the individual chromosomes become visible with a light microscope?

a. prophase
b. prometaphase
c. metaphase
d. anaphase

10. What condition is necessary for a cell to pass the $G_2$ checkpoint?

a. cell has reached a sufficient size
b. an adequate stockpile of nucleotides
c. accurate and complete DNA replication
d. proper attachment of mitotic spindle fibers to kinetochores

**Check your answers in footnote**[1]



## Attribution & References

Except where otherwise noted, this page is adapted from

- 6.1 The Genome and 6.2 The Cell Cycle In *Concepts of Biology – 1st Canadian Edition* by by Charles Molnar and Jane Gair, CC BY 4.0. / A derivative of *Concepts of Biology (OpenStax),* CC BY 4.0. Access *Biology 2e* for free at OpenStax (https://openstax.org/books/biology-2e/pages/1-introduction)

Individual sections have been combined and streamlined, including minor edits to improve student understanding and provide context.

1. 1. False.
   2. A – homologous, B – genes, C – alleles, D – 46, E -diploid, F – haploid – G – mitosis, H – binary fission, i – replication/DNA replication, J – prophase
   3. c) twice
   4. b) genes
   5. A – forty-six, B – twenty-two, C – homologous, D – one, E – non-homologous, F – 2n/diploid, G – diploid/2n, H – twenty-three, i – n/haploid, J – haploid/n
   6. d) The kinetochore becomes attached to the mitotic spindle. Sister chromatids line up at the metaphase plate. The kinetochore breaks apart and the sister chromatids separate. The nucleus re-forms and the cell divides.
   7. b) S phase
   8. c) anaphase
   9. a) prophase
   10. c) accurate and complete DNA replication

# 2.4 CANCER AND THE CELL CYCLE

## Learning Objectives

- Explain how cancer is caused by uncontrolled cell division.
- Identify how proto-oncogenes become oncogenes.
- Describe how tumor suppressors function to stop the cell cycle until certain events are completed.
- Explain how tumor suppressor variants cause cancer.

This chapter examines cancer from cellular perspective to provide a foundation for further discussion of the polygenic nature of diseases such as cancer (ch. 4.5), and cancer genomics (ch. 12.3).

Cancer is a collective name for many different diseases caused by a common mechanism: uncontrolled cell division. Despite the redundancy and overlapping levels of cell-cycle control, errors occur. One of the critical processes monitored by the cell-cycle checkpoint surveillance mechanism is the proper **replication of DNA** during the S phase. Even when all of the cell-cycle controls are fully functional, a small percentage of replication errors (variants) will be passed on to the daughter cells. If one of these changes to the DNA nucleotide sequence occurs within a gene, a gene variant results. All cancers begin when a gene variant gives rise to a faulty protein that participates in the process of cell reproduction. The change in the cell that results from the malformed protein may be minor. Even minor mistakes, however, may allow subsequent mistakes to occur more readily. Over and over, small, uncorrected errors are passed from parent cell to daughter cells and accumulate as each generation of cells produces more non-functional proteins from uncorrected DNA damage. Eventually, the pace of the cell cycle speeds up as the effectiveness of the control and repair mechanisms decreases. Uncontrolled growth of the altered cells outpaces the growth of normal cells in the area, and a tumor can result.

## Proto-oncogenes

The genes that code for the **positive cell-cycle regulators** are called **proto-oncogenes**. Proto-oncogenes are normal genes that, when altered, become **oncogenes**—genes that cause a cell to become cancerous. Consider what might happen to the cell cycle in a cell with a recently acquired oncogene. In most instances, the alteration of the DNA sequence will result in a less functional (or non-functional) protein. The result is detrimental to the cell and will likely prevent the cell from completing the cell cycle; however, the organism is not harmed because the variant will not be carried forward. If a cell cannot reproduce, the variant is not propagated and the damage is minimal. Occasionally, however, a gene variant causes a change that increases the activity of a positive regulator. For example, a variant that allows Cdk, a protein involved in cell-cycle regulation, to be activated before it should be could push the cell cycle past a checkpoint before all of the required conditions are met. If the resulting daughter cells are too damaged to undertake further cell divisions, the variant would not be propagated and no harm comes to the organism. However, if the atypical daughter cells are able to divide further, the subsequent generation of cells will likely accumulate even more variants, some possibly in additional genes that regulate the cell cycle.

The Cdk example is only one of many genes that are considered proto-oncogenes. In addition to the cell-cycle regulatory proteins, any protein that influences the cycle can be altered in such a way as to override cell-cycle checkpoints. **Once a proto-oncogene has been altered such that there is an increase in the rate of the cell cycle, it is then called an oncogene**.

## Tumor Suppressor Genes

Like proto-oncogenes, many of the **negative cell-cycle regulatory proteins** were discovered in cells that had become cancerous. **Tumor suppressor genes** are genes that code for the **negative regulator proteins**, the type of regulator that—when activated—can prevent the cell from undergoing uncontrolled division. The collective function of the best-understood tumor suppressor gene proteins, retinoblastoma protein (RB1), p53, and p21, is to put up a roadblock to cell-cycle progress until certain events are completed. A cell that carries a varied form of a negative regulator might not be able to halt the cell cycle if there is a problem.

Altered p53 genes have been identified in more than half of all human tumor cells. This discovery is not surprising in light of the multiple roles that the p53 protein plays at the $G_1$ checkpoint. The p53 protein activates other genes whose products halt the cell cycle (allowing time for DNA repair), activates genes whose products participate in DNA repair, or activates genes that initiate cell death when DNA damage cannot be repaired. A damaged p53 gene can result in the cell behaving as if there are no variants (Figure 2.29). This allows cells to divide, propagating the variant in daughter cells and allowing the accumulation of new variants. In addition, the damaged version of p53 found in cancer cells cannot trigger cell death.

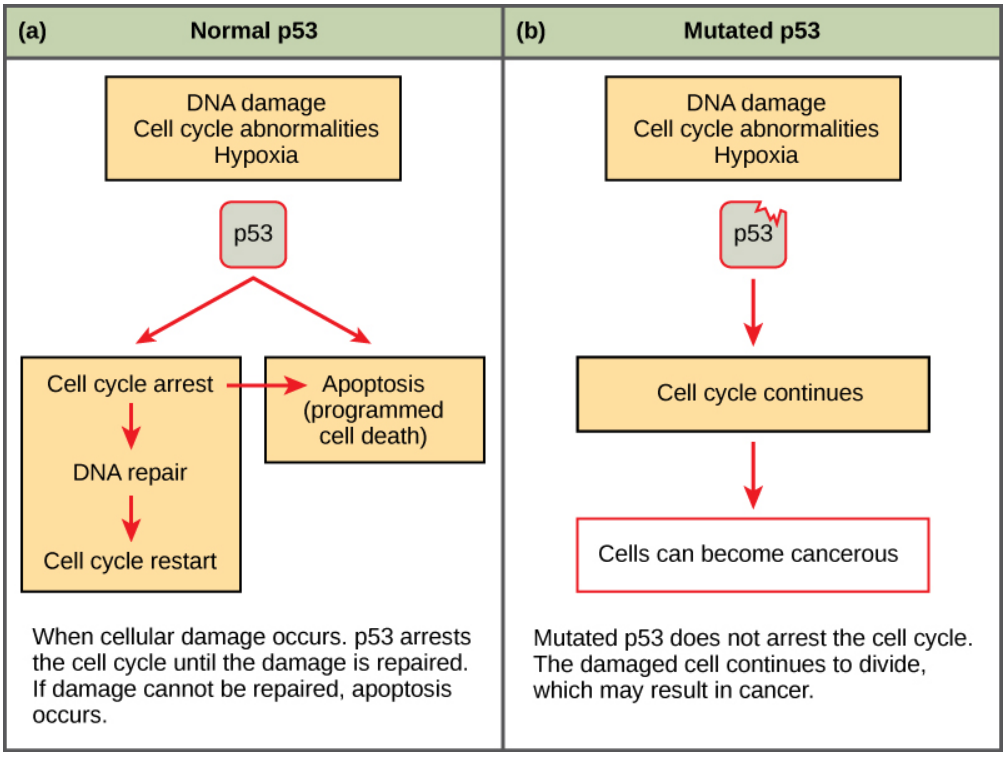



**Figure 2.29** (a) The role of p53 is to monitor DNA. If damage is detected, p53 triggers repair mechanisms. If repairs are unsuccessful, p53 signals apoptosis. (b) A cell with an abnormal p53 protein cannot repair damaged DNA and cannot signal apoptosis. Cells with abnormal p53 can become cancerous. **Source:** modification of work by Thierry Soussi from *Concepts of Biology* (OpenStax), CC BY 4.0.

## Concept in Action

**Watch The Cell Cycle (and cancer) [Updated] (9 mins) on YouTube (https://youtu.be/QVCjdNxJreE)**

## Exercises

**Exercises (text version)**

1. What are changes to the nucleotides called in a segment of DNA that codes for a protein?

    a. proto-oncogenes
    b. tumor suppressor genes
    c. gene variants
    d. negative regulators

2. What is a gene called that codes for a positive cell cycle regulator?

    a. kinase inhibitor
    b. tumor suppressor gene
    c. proto-oncogene
    d. oncogene

3. Match the words to the correct blanks to describe the steps that lead to a cell becoming cancerous.
   **Words:** proteins, un-repaired, regulator, altered, cell-cycle
   The steps that lead to a cell becoming cancerous occur when one of the genes that produce [Blank A] proteins becomes [Blank B], and produces a malformed, possibly non-functional, [Blank C] regulator. This increases the chance that more variants will be left [Blank D] in the cell. Each subsequent generation of cells sustains more damage. The cell cycle can speed up as a result of loss of functional checkpoint [Blank E]. The cells can lose the ability to self-destruct.
4. Match the words to the correct blanks to describe the steps that lead to a cell becoming cancerous.
   **Words: overactive, negative, underactive, positive, oncogene**
   The difference between a proto-oncogene and a tumor suppressor gene is a proto-oncogene is the segment of DNA that codes for one of the [Blank A] cell-cycle regulators. If that gene becomes altered to a form that is [Blank B], it is considered an [Blank C]. A tumor suppressor gene is a segment of DNA that codes for one of the [Blank D] cell-cycle regulators. If that gene becomes altered to a form that is [Blank E], the cell cycle will run unchecked.

**Check your answers in footnote**[1]

1. a. c) gene variants
   b. c) proto-oncogene

## Attribution & References



c. A – regulator, B – altered, C – cell-cycle, D – un-repaired, E – proteins
d. A – positive, B – overactive, C – oncogene, D – negative, E – underactive

# 2.5 THE CELLULAR BASIS OF INHERITANCE

## Learning Objectives

- Explain why variation among offspring is a potential evolutionary advantage resulting from sexual reproduction.
- Identify why a gamete can not be identical to either of the parent gametes.
- Examine cellular events and chromosomal behavior during meiosis.
- Distinguish the differences between meiosis and mitosis.

**Watch Sexual Reproduction (4 mins) from BCCampus (https://media.bccampus.ca/media/Sexual+Reproduction/0_25x7u748) and answer the question when prompted to check your learning.**

**Sexual reproduction (text version)**

Watch Sexual Reproduction (4 mins) from BCCampus (https://media.bccampus.ca/media/Sexual+Reproduction/0_25x7u748)

1. Pause the video at 3:20. True or false? The processes that create variation in meiosis include both crossing over and independent assortment.
2. Pause the video at 4:20. True or false? Meiosis makes each human genetically unique.

**Check your answer in footnote**[1]

**Activity source:** *Concepts of Biology – 1st Canadian Edition*, CC BY 4.0.

1. 1. True. 2. True.

# Life Cycles of Sexually Reproducing Organisms

Sexual reproduction requires **fertilization**, a union of two cells from two individual organisms. Fertilization occurs with the fusion of two gametes, usually from different individuals, restoring the diploid state. If those two cells each contain one set of chromosomes, then the resulting cell contains two sets of chromosomes. The number of sets of chromosomes in a cell is called its ploidy level. Haploid cells contain one set of chromosomes. Cells containing two sets of chromosomes are called diploid. If the reproductive cycle is to continue, the diploid cell must somehow reduce its number of chromosome sets before fertilization can occur again, or there will be a continual doubling in the number of chromosome sets in every generation. So, in addition to fertilization, sexual reproduction includes a nuclear division, known as meiosis, that reduces the number of chromosome sets. The variation that sexual reproduction creates among offspring is very important to the survival and reproduction of those offspring. In addition, variants are continually reshuffled from one generation to the next when different parents combine their unique genomes, and the genes are mixed into different combinations by the process of meiosis. Meiosis is the division of the contents of the nucleus that divides the chromosomes among gametes. Variation is introduced during meiosis, as well as when the gametes combine in fertilization.

Most animals and plants are diploid, containing two sets of chromosomes; in each **somatic** cell (the nonreproductive cells of a multicellular organism), the nucleus contains two copies of each chromosome that are referred to as homologous chromosomes. Somatic cells are sometimes referred to as "body" cells. Homologous chromosomes are matched pairs containing genes for the same traits in identical locations along their length. Diploid organisms inherit one copy of each homologous chromosome from each parent; all together, they are considered a full set of chromosomes. In animals, haploid cells containing a single copy of each homologous chromosome are found only within **gametes**. Gametes fuse with another haploid gamete to produce a diploid cell.

The nuclear division that forms haploid cells (meiosis) is related to mitosis. As you have learned, mitosis is part of a cell reproduction cycle that results in identical daughter nuclei that are also genetically identical to the original parent nucleus. In mitosis, both the parent and the daughter nuclei contain the same number of chromosome sets—diploid for most plants and animals. Meiosis employs many of the same mechanisms as mitosis. However, the starting nucleus is always diploid and the nuclei that result at the end of a meiotic cell division are haploid. To achieve the reduction in chromosome number, meiosis consists of one round of chromosome duplication and two rounds of nuclear division. Because the events that occur during each of the division stages are analogous to the events of mitosis, the same stage names are assigned. However, because there are two rounds of division, the stages are designated with a "I" or "II." Thus, meiosis I is the first round of meiotic division and consists of prophase I, prometaphase I, and so on. Meiosis I reduces the number of chromosome sets from two to one. The genetic information is also mixed during this division to create unique **recombinant** chromosomes. Meiosis II, in which the second round of meiotic division takes place in a way that is similar to mitosis, includes prophase II, prometaphase II, and so on.

## Interphase

Meiosis is preceded by an interphase consisting of the $G_1$, S, and $G_2$ phases, which are nearly identical to the phases preceding mitosis. The $G_1$ phase is the first phase of interphase and is focused on cell growth. In the S phase, the DNA of the chromosomes is replicated. Finally, in the $G_2$ phase, the cell undergoes the final preparations for meiosis.

During DNA duplication of the S phase, each chromosome becomes composed of two identical copies (called sister chromatids) that are held together at the centromere until they are pulled apart during meiosis II. In an animal cell, the centrosomes that organize the microtubules of the meiotic spindle also replicate. This prepares the cell for the first meiotic phase.

## Meiosis I

Early in prophase I, the chromosomes can be seen clearly microscopically. As the nuclear envelope begins to break down, the proteins associated with homologous chromosomes bring the pair close to each other. The tight pairing of the homologous chromosomes is called **synapsis**. In synapsis, the genes on the chromatids of the homologous chromosomes are precisely aligned with each other. An exchange of chromosome segments between non-sister homologous chromatids occurs and is called **crossing over**. This process is revealed visually after the exchange as **chiasmata (singular = *chiasma*)** (Figure 2.30).

As prophase I progresses, the close association between homologous chromosomes begins to break down, and the chromosomes continue to condense, although the homologous chromosomes remain attached to each other at chiasmata. The number of chiasmata varies with the species and the length of the chromosome. At the end of prophase I, the pairs are held together only at chiasmata (Figure 2.30) and are called **tetrads** because the four sister chromatids of each pair of homologous chromosomes are now visible.

The crossover events are the first source of genetic variation produced by meiosis. A single crossover event between homologous non-sister chromatids leads to a reciprocal exchange of equivalent DNA between a maternal chromosome and a paternal chromosome. Now, when that sister chromatid is moved into a gamete, it will carry some DNA from one parent of the individual and some DNA from the other parent. The recombinant sister chromatid has a combination of maternal and paternal genes that did not exist before the crossover.

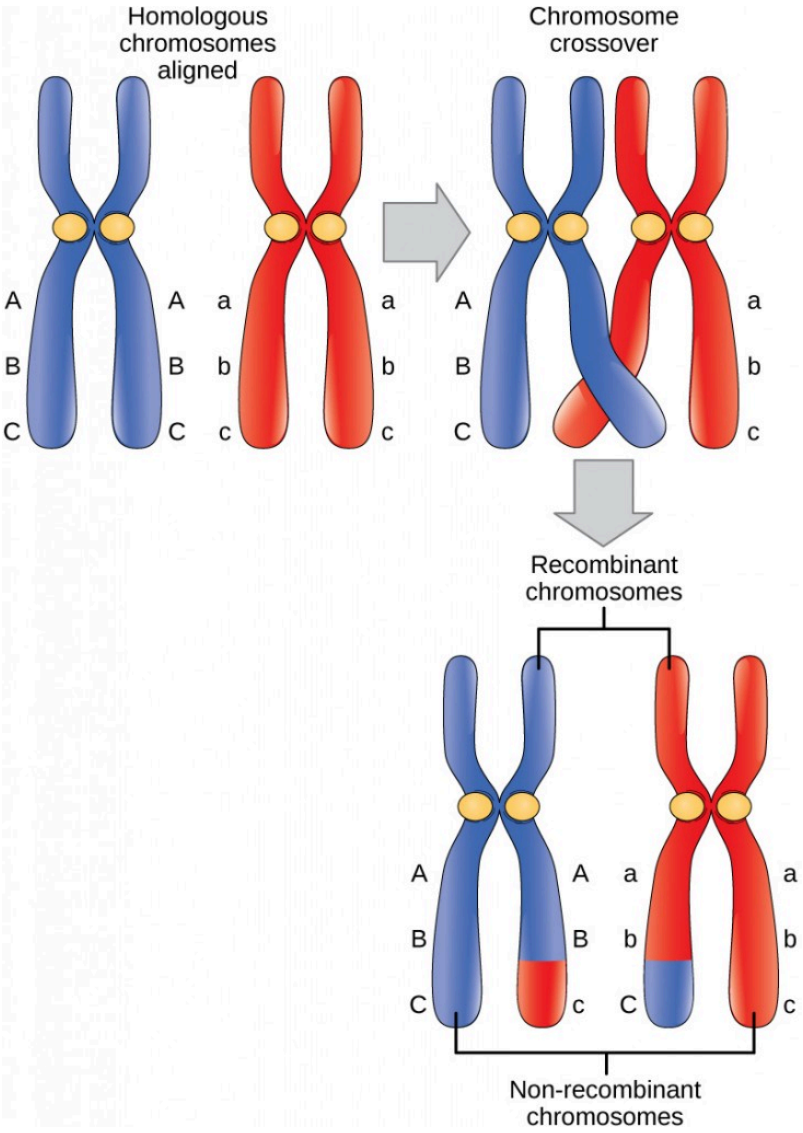



**Figure 2.30** In this illustration of the effects of crossing over, the blue chromosome came from the individual's father and the red chromosome came from the individual's mother. Crossover occurs between non-sister chromatids of homologous chromosomes. The result is an exchange of genetic material between homologous chromosomes. The chromosomes that have a mixture of maternal and paternal sequence are called recombinant and the chromosomes that are completely paternal or maternal are called non-recombinant. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

The key event in prometaphase I is the attachment of the spindle fiber microtubules to the kinetochore proteins at the centromeres. The microtubules assembled from centrosomes at opposite poles of the cell grow toward the middle of the cell. At the end of prometaphase I, each tetrad is attached to microtubules from both poles, with one homologous chromosome attached at one pole and the other homologous chromosome

attached to the other pole. The homologous chromosomes are still held together at chiasmata. In addition, the nuclear membrane has broken down entirely.

During metaphase I, the homologous chromosomes are arranged in the center of the cell with the **kinetochores** facing opposite poles. The orientation of each pair of homologous chromosomes at the center of the cell is random.

This randomness, called **independent assortment**, is the physical basis for the generation of the second form of genetic variation in offspring. Consider that the homologous chromosomes of a sexually reproducing organism are originally inherited as two separate sets, one from each parent. Using humans as an example, one set of 23 chromosomes is present in the egg donated by the mother. The father provides the other set of 23 chromosomes in the sperm that fertilizes the egg. In metaphase I, these pairs line up at the midway point between the two poles of the cell. Because there is an equal chance that a microtubule fiber will encounter a maternally or paternally inherited chromosome, the arrangement of the tetrads at the metaphase plate is random. Any maternally inherited chromosome may face either pole. Any paternally inherited chromosome may also face either pole. The orientation of each tetrad is independent of the orientation of the other 22 tetrads.

In each cell that undergoes meiosis, the arrangement of the tetrads is different. The number of variations depends on the number of chromosomes making up a set. There are two possibilities for orientation (for each tetrad); thus, the possible number of alignments equals $2^n$ where $n$ is the number of chromosomes per set. Humans have 23 chromosome pairs, which results in over eight million ($2^{23}$) possibilities. This number does not include the variability previously created in the sister chromatids by crossover. Given these two mechanisms, it is highly unlikely that any two haploid cells resulting from meiosis will have the same genetic composition (Figure 2.31).

To summarize the genetic consequences of meiosis I: the maternal and paternal genes are recombined by crossover events occurring on each homologous pair during prophase I; in addition, the random assortment of tetrads at metaphase produces a unique combination of maternal and paternal chromosomes that will make their way into the gametes.

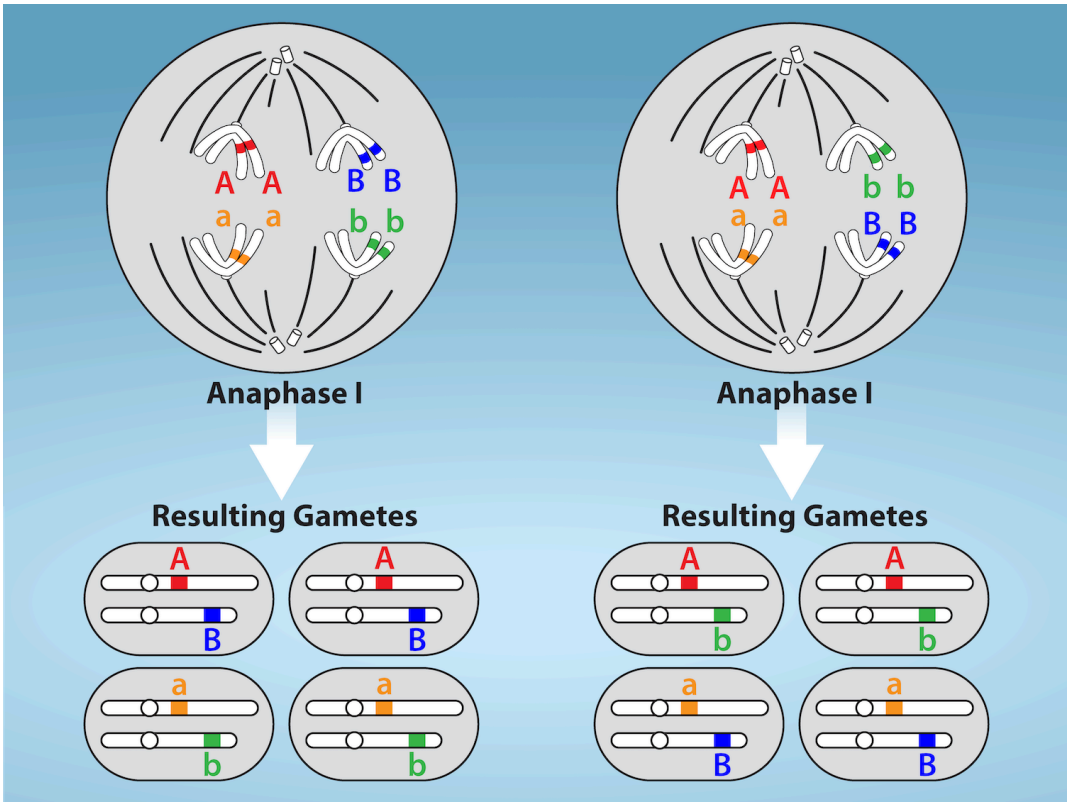



**Figure 2.31** To demonstrate random, independent assortment at metaphase I, consider a cell with n = 2. In this case, there are two possible arrangements at the equatorial plane in metaphase I, as shown in the upper cell of each panel. These two possible orientations lead to the production of genetically different gametes. With more chromosomes, the number of possible arrangements increases dramatically. **Source:** *Biology 2e* (OpenStax), a derivative of *Concepts of Biology* (OpenStax), CC BY 4.0.

In anaphase I, the spindle fibers pull the linked chromosomes apart. The sister chromatids remain tightly bound together at the centromere. It is the chiasma connections that are broken in anaphase I as the fibers attached to the fused kinetochores pull the homologous chromosomes apart.

In telophase I, the separated chromosomes arrive at opposite poles. The remainder of the typical telophase events may or may not occur depending on the species. In some organisms, the chromosomes decondense and nuclear envelopes form around the chromatids in telophase I.

Cytokinesis, the physical separation of the cytoplasmic components into two daughter cells, occurs without reformation of the nuclei in other organisms. In nearly all species, cytokinesis separates the cell contents by either a cleavage furrow (in animals and some fungi), or a cell plate that will ultimately lead to formation of cell walls that separate the two daughter cells (in plants). At each pole, there is just one member

of each pair of the homologous chromosomes, so only one full set of the chromosomes is present. This is why the cells are considered haploid—there is only one chromosome set, even though there are duplicate copies of the set because each homolog still consists of two sister chromatids that are still attached to each other. However, although the sister chromatids were once duplicates of the same chromosome, they are no longer identical at this stage because of crossovers.

## Meiosis II

In meiosis II, the connected sister chromatids remaining in the haploid cells from meiosis I will be split to form four haploid cells. In some species, cells enter a brief interphase, or **interkinesis**, that lacks an S phase, before entering meiosis II. Chromosomes are not duplicated during interkinesis. The two cells produced in meiosis I go through the events of meiosis II in synchrony. Overall, meiosis II resembles the mitotic division of a haploid cell.

In prophase II, if the chromosomes decondensed in telophase I, they condense again. If nuclear envelopes were formed, they fragment into vesicles. The centrosomes duplicated during interkinesis move away from each other toward opposite poles, and new spindles are formed. In prometaphase II, the nuclear envelopes are completely broken down, and the spindle is fully formed. Each sister chromatid forms an individual kinetochore that attaches to microtubules from opposite poles. In metaphase II, the sister chromatids are maximally condensed and aligned at the center of the cell. In anaphase II, the sister chromatids are pulled apart by the spindle fibers and move toward opposite poles.

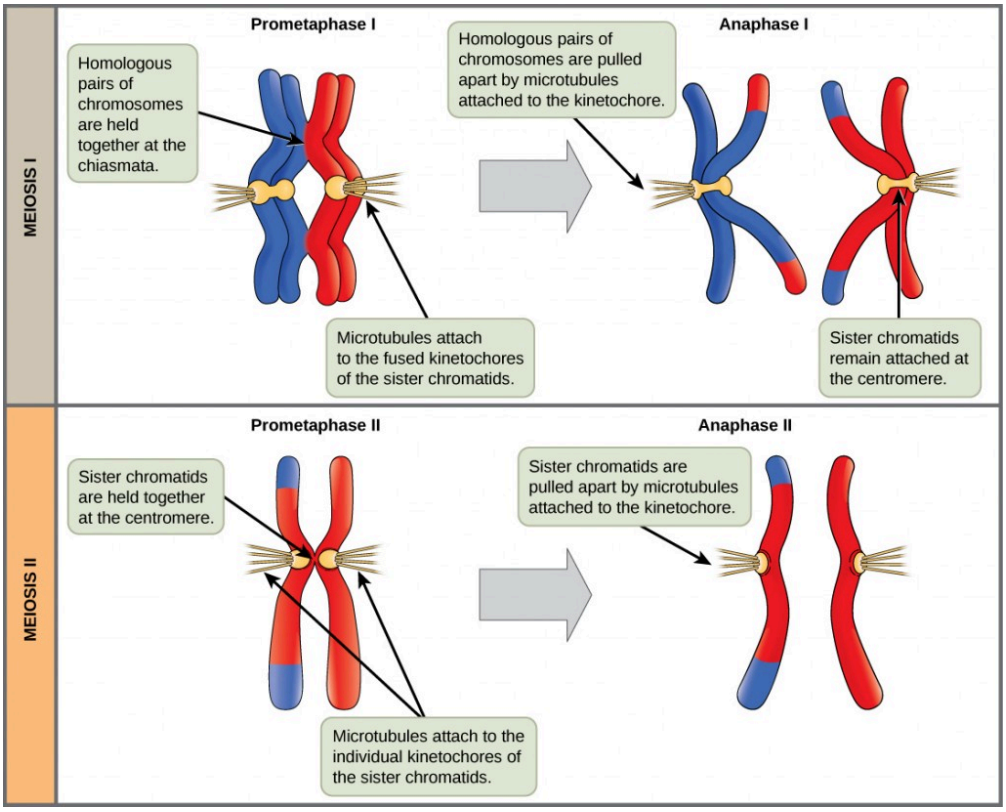



**Figure 2.32** In prometaphase I, microtubules attach to the fused kinetochores of homologous chromosomes. In anaphase I, the homologous chromosomes are separated. In prometaphase II, microtubules attach to individual kinetochores of sister chromatids. In anaphase II, the sister chromatids are separated. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

In telophase II, the chromosomes arrive at opposite poles and begin to decondense. Nuclear envelopes form around the chromosomes. Cytokinesis separates the two cells into four genetically unique haploid cells. At this point, the nuclei in the newly produced cells are both haploid and have only one copy of the single set of chromosomes. The cells produced are genetically unique because of the random assortment of paternal and maternal homologs and because of the recombination of maternal and paternal segments of chromosomes—with their sets of genes—that occurs during crossover.

## Concept in Action – Meiosis

**Watch Meiosis 3D Animation (7 mins) on YouTube (https://youtu.be/GoJCer_acIQ)**

# Comparing Meiosis and Mitosis

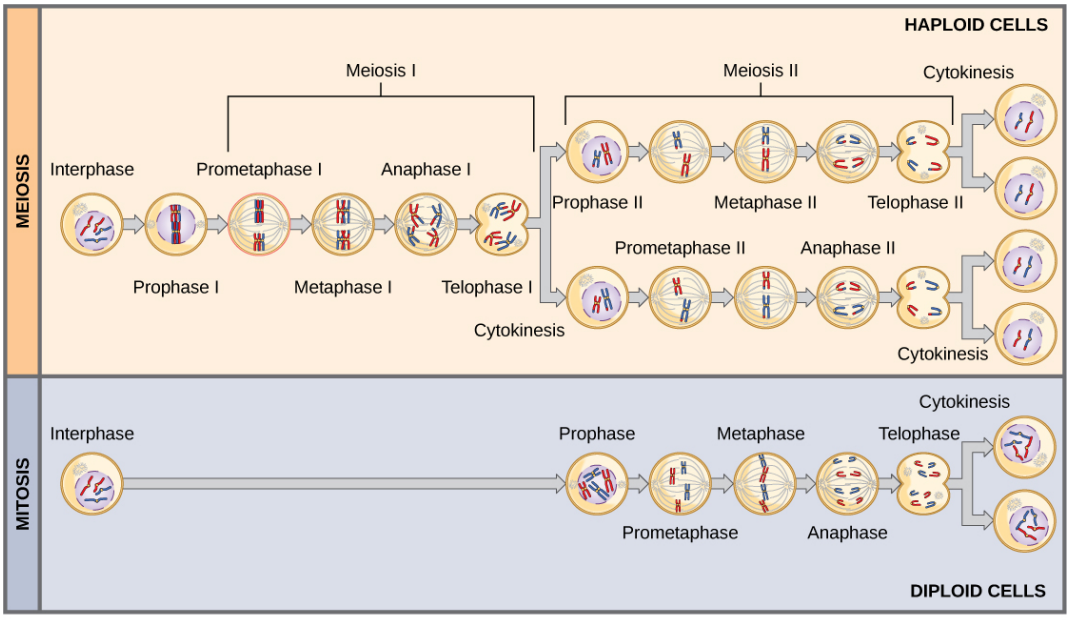
Mitosis and meiosis, which are both forms of division of the nucleus in eukaryotic cells, share some similarities, but also exhibit distinct differences that lead to their very different outcomes. Mitosis is a single nuclear division that results in two nuclei, usually partitioned into two new cells. The nuclei resulting from a mitotic division are genetically identical to the original. They have the same number of sets of chromosomes: one in the case of haploid cells, and two in the case of diploid cells. On the other hand, meiosis is two nuclear divisions that result in four nuclei, usually partitioned into four new cells. The nuclei resulting from meiosis are never genetically identical, and they contain one chromosome set only—this is half the number of the original cell, which was diploid.

The differences in the outcomes of meiosis and mitosis occur because of differences in the behavior of the chromosomes during each process. Most of these differences in the processes occur in meiosis I, which is a very different nuclear division than mitosis. In meiosis I, the homologous chromosome pairs become associated with each other, are bound together, experience chiasmata and crossover between sister chromatids, and line up along the metaphase plate in tetrads with spindle fibers from opposite spindle poles attached to each kinetochore of a homolog in a tetrad. All of these events occur only in meiosis I, never in mitosis.

Homologous chromosomes move to opposite poles during meiosis I so the number of sets of chromosomes in each nucleus-to-be is reduced from two to one. For this reason, meiosis I is referred to as a reduction division. There is no such reduction in ploidy level in mitosis.

Meiosis II is much more analogous to a mitotic division. In this case, duplicated chromosomes (only one set of them) line up at the center of the cell with divided kinetochores attached to spindle fibers from opposite poles. During anaphase II, as in mitotic anaphase, the kinetochores divide and one sister chromatid is pulled to one pole and the other sister chromatid is pulled to the other pole. If it were not for the fact that there had been crossovers, the two products of each meiosis II division would be identical as in mitosis; instead, they are different because there has always been at least one crossover per chromosome. Meiosis II is not a reduction division because, although there are fewer copies of the genome in the resulting cells, there is still one set of chromosomes, as there was at the end of meiosis I.

Cells produced by mitosis will function in different parts of the body as a part of growth or replacing dead or damaged cells. Cells produced by meiosis in a diploid-dominant organism such as an animal will only participate in sexual reproduction.




| | | | | | | OUTCOME |
|---|---|---|---|---|---|---|
| PROCESS | DNA synthesis | Synapsis of homologous chromosomes | Crossover | Homologous chromosomes line up at metaphase plate | Sister chromatids line up at metaphase plate | Number and genetic composition of daughter cells |
| MEIOSIS | Occurs in S phase of interphase | During prophase I | During prophase I | During metaphase I | During metaphase II | Four haploid cells at the end of meiosis II |
| MITOSIS | Occurs in S phase of interphase | Does not occur in mitosis | Does not occur in mitosis | Does not occur in mitosis | During metaphase | Two diploid cells at the end of mitosis |

**Figure 2.33** Meiosis and mitosis are both preceded by one round of DNA replication; however, meiosis includes two nuclear divisions. The four daughter cells resulting from meiosis are haploid and genetically distinct. The daughter cells resulting from mitosis are diploid and identical to the parent cell. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0

## Concept in Action – Mitosis & Meiosis

For an animation comparing mitosis and meiosis, go to How Cells Divide: Mitosis vs. Meiosis (https://www.pbs.org/wgbh/nova/baby/divi_text.html)

# Exercises

**Exercises (text version)**

1. True or false? Sexual reproduction is so common because it creates uniformity in its offspring.
2. Fill in the missing words to complete the statement:
   Mitosis has only one division but meiosis has [Blank A] divisions. The first of these divisions is called [Blank B] and is said to be reductional because in humans the chromosome number is reduced from 46 to [Blank C].
   Humans have a [Blank D] dominant lifecycle.
   The tight pairing of homolous chromosomes in Prophase 1 is called [Blank E].
   Independent assortment of homologous pairs in Meiosis 1 produces 2 to the 23rd power of possible combinations. That is over [Blank F] million combinations.
   Two processes create unique gametes in Meiosis. In prophase 1 the homologous chromosomes pair and [Blank G] mixes the genetic material. In Metaphase 1 the process of Independent [Blank H] occurs.
3. Which event leads to a diploid cell in a life cycle?

   a. meiosis
   b. fertilization
   c. alternation of generations
   d. mutation

4. Match the words to the correct blanks to describe the two events that are common to all sexually reproducing organisms, and how they fit into the different life cycles of those organisms.
   **Words:** mitosis, fertilization, meiosis
   The two events common to all sexually reproducing organisms are [Blank A] and [Blank B]. In [Blank C] the diploid cell is reduced to a haploid state. The haploid cell may divide through [Blank D] to produce an organism, some of whose cells will combine during [Blank E], or the haploid cells produced by [Blank F] may immediately combine in [Blank G] to produce a diploid cell that divides to produce an organism.
5. At which stage of meiosis are sister chromatids separated from each other?

   a. prophase I
   b. prophase II
   c. anaphase I
   d. anaphase II

6. How many daughter cells does meiosis produce?

   a. two haploid

b. two diploid
c. four haploid
d. four diploid

7. What is the part of meiosis that is similar to mitosis?

   a. meiosis I
   b. anaphase I
   c. meiosis II
   d. interkinesis

8. If a muscle cell of a typical organism has 32 chromosomes, how many chromosomes will be in a gamete of that same organism?

   a. 8
   b. 16
   c. 32
   d. 64

9. Match the words to the correct blanks to explain how the random alignment of homologous chromosomes during metaphase I contributes to variation in gametes produced by meiosis.
   **Words:** random, anaphase I, center, orientation, differently, unique, equal, metaphase I, sperm, egg
   Random alignment leads to new combinations of traits. The chromosomes that were originally inherited by the gamete-producing individual came equally from the [Blank A] and the [Blank B]. In [Blank C], the duplicated copies of these maternal and paternal homologous chromosomes line up across the [Blank D] of the cell to form a tetrad. The [Blank E] of each tetrad is [Blank F] There is an [Blank G] chance that the maternally derived chromosomes will be facing either pole. The same is true of the paternally derived chromosomes. The alignment should occur [Blank H] in almost every meiosis. As the homologous chromosomes are pulled apart in [Blank i], any combination of maternal and paternal chromosomes will move toward each pole. The gametes formed from these two groups of chromosomes will have a mixture of traits from the individual's parents. Each gamete is [Blank J].
10. Match the words to the correct blanks to describe the ways meiosis II is similar to and different from mitosis of a diploid cell.
    **Words: two, meiosis I, half, chromatids, individually,**
    The two divisions are similar in that the chromosomes line up along the metaphase plate [Blank A], meaning unpaired with other chromosomes (as in meiosis I). In addition, each

chromosome consists of [Blank B] sister [Blank C] that will be pulled apart. The two divisions are different because in meiosis II there are [Blank D] the number of chromosomes that are present in a diploid cell of the same species undergoing mitosis. This is because [Blank E] reduced the number of chromosomes to a haploid state.

**Check your answers in footnote**[2]



## Glossary

**Summary of additional key terms introduced in this chapter:**

**Alternation of generations:** a life-cycle type in which the diploid and haploid stages alternate

**Life cycle:** the sequence of events in the development of an organism and the production of cells that produce offspring

2.

1. False. Sexual reproduction is so common because it creates variation in its offspring.
2. A – 2/two, B – meiosis 1, C – 23, D – 2n/diploid, E – synapsis, F – 8/eight, G – crossing over, H – assortment
3. c) fertilization
4. A – meiosis, B – fertilization, C – meiosis, D – mitosis, E – fertilization, F – meiosis, G – fertilization
5. d) anaphase II
6. c) four haploid
7. c) meiosis II
8. b) 16
9. A – egg, B – sperm, C – metaphase I, D – center, E – orientation, F – random, G – equal, H – differently, i – anaphase I, J – unique
10. A – individually, B – two, C – chromatids, D – half, E – meiosis I

# Attribution & References

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Adaptations: Individual sections have been combined and streamlined, including minor edits to improve student understanding and provide context.

# 2.6 PATTERNS OF INHERITANCE

## Learning Objectives

- Describe the expected outcomes of monohybrid crosses involving dominant and recessive alleles.
- Explain the relationship between genotypes and phenotypes in dominant and recessive gene systems.
- Use a Punnett square to calculate the expected proportions of genotypes and phenotypes in a monohybrid cross.
- Explain Mendel's law of segregation and independent assortment in terms of genetics and the events of meiosis.
- Identify non-Mendelian inheritance patterns such as incomplete dominance, codominance, multiple alleles, and sex linkage from the results of crosses.
- Explain the effect of linkage and recombination on gamete genotypes.
- Explain the phenotypic outcomes of epistatic effects among genes.
- Explain polygenic inheritance.

**Watch the interactive video on the history of Johann Gregor Mendel and his experiments (4 mins) on BCCampus (https://media.bccampus.ca/media/0_sexo3iqx)**, which paved the way for the discipline we now know as Genetics.

*An interactive H5P element has been excluded from this version of the text. You can view it online here: https://ecampusontario.pressbooks.pub/personalizedhealthnursing/?p=765#h5p-12*

**Mendel and the Gene Idea (text version)**

Watch Johann Gregor Mendel and his experiments (4 mins) on BCCampus (https://media.bccampus.ca/media/0_sexo3iqx)

Pause the video at 0:38 and answer the following question:

True or false? Mendel used garden peas as his experimental organism.

**Check your answer in footnote**[1]

**Activity source:** *Concepts of Biology – 1st Canadian Edition*, CC BY 4.0

Johann Gregor Mendel (1822–1884) was a lifelong learner, teacher, scientist, and man of faith. As a young adult, he joined the Augustinian Abbey of St. Thomas in Brno in what is now the Czech Republic. Supported by the monastery, he taught physics, botany, and natural science courses at the secondary and university levels. In 1856, he began a decade-long research pursuit involving inheritance patterns in honeybees and plants, ultimately settling on pea plants as his primary **model system** (a system with convenient characteristics that is used to study a specific biological phenomenon to gain understanding to be applied to other systems). In 1865, Mendel presented the results of his experiments with nearly 30,000 pea plants to the local natural history society. He demonstrated that traits are transmitted faithfully from parents to offspring in specific patterns. In 1866, he published his work, *Experiments in Plant Hybridization,*[2] in the Natural History Society of Brünn proceedings.

Mendel's work went virtually unnoticed by the scientific community, which incorrectly believed that the inheritance process involved a blending of parental traits that produced an intermediate physical appearance in offspring. This hypothetical process appeared to be correct because of what we know now as **continuous variation**. Continuous variation is the range of small differences we see among individuals in a characteristic like human height. It does appear that offspring are a "blend" of their parents' traits when we look at characteristics that exhibit continuous variation. Mendel worked instead with traits that show **discontinuous variation**. Discontinuous variation is the variation seen among individuals when each individual shows one of two—or a very few—easily distinguishable traits, such as violet or white flowers. Mendel's choice of these kinds of traits allowed him to see experimentally that the traits were not blended in the offspring as would have been expected at the time, but that they were inherited as distinct traits. In 1868, Mendel became abbot of the monastery and exchanged his scientific pursuits for his pastoral duties. He was not recognized for his

1. True.

2. Johann Gregor Mendel, "Versuche über Pflanzenhybriden." *Verhandlungen des naturforschenden Vereines in Brünn*, Bd. IV für das Jahr, 1865 Abhandlungen (1866):3–47. [for English translation, see http://www.mendelweb.org/Mendel.plain.html]; Sumiti Vinayak et al., "Origin and Evolution of Sulfadoxine Resistant *Plasmodium falciparum," PLoS Pathogens* 6 (2010): e1000830.

extraordinary scientific contributions during his lifetime; in fact, it was not until 1900 that his work was rediscovered, reproduced, and revitalized by scientists on the brink of discovering the chromosomal basis of heredity.

## Mendel's Crosses

Mendel's seminal work was accomplished using the garden pea, *Pisum sativum*, to study inheritance. This species naturally self-fertilizes, meaning that pollen encounters ova within the same flower. The flower petals remain sealed tightly until pollination is completed to prevent the pollination of other plants. The result is highly inbred, or "true-breeding," pea plants. These are plants that always produce offspring that look like the parent. By experimenting with true-breeding pea plants, Mendel avoided the appearance of unexpected traits in offspring that might occur if the plants were not true breeding. The garden pea also grows to maturity within one season, meaning that several generations could be evaluated over a relatively short time. Finally, large quantities of garden peas could be cultivated simultaneously, allowing Mendel to conclude that his results did not come about simply by chance.

Mendel performed **hybridizations**, which involve mating two true-breeding individuals that have different traits. In the pea, which is naturally self-pollinating, this is done by manually transferring pollen from the anther of a mature pea plant of one variety to the stigma of a separate mature pea plant of the second variety.

Plants used in first-generation crosses were called P, or parental generation, plants (Figure 2.34). Mendel collected the seeds produced by the P plants that resulted from each cross and grew them the following season. These offspring were called the **$F_1$, or the first filial** (filial = daughter or son), generation. Once Mendel examined the characteristics in the $F_1$ generation of plants, he allowed them to self-fertilize naturally. He then collected and grew the seeds from the $F_1$ plants to produce the **$F_2$, or second filial, generation**. Mendel's experiments extended beyond the $F_2$ generation to the $F_3$ generation, $F_4$ generation, and so on, but it was the ratio of characteristics in the P, $F_1$, and $F_2$ generations that were the most intriguing and became the basis of Mendel's postulates.

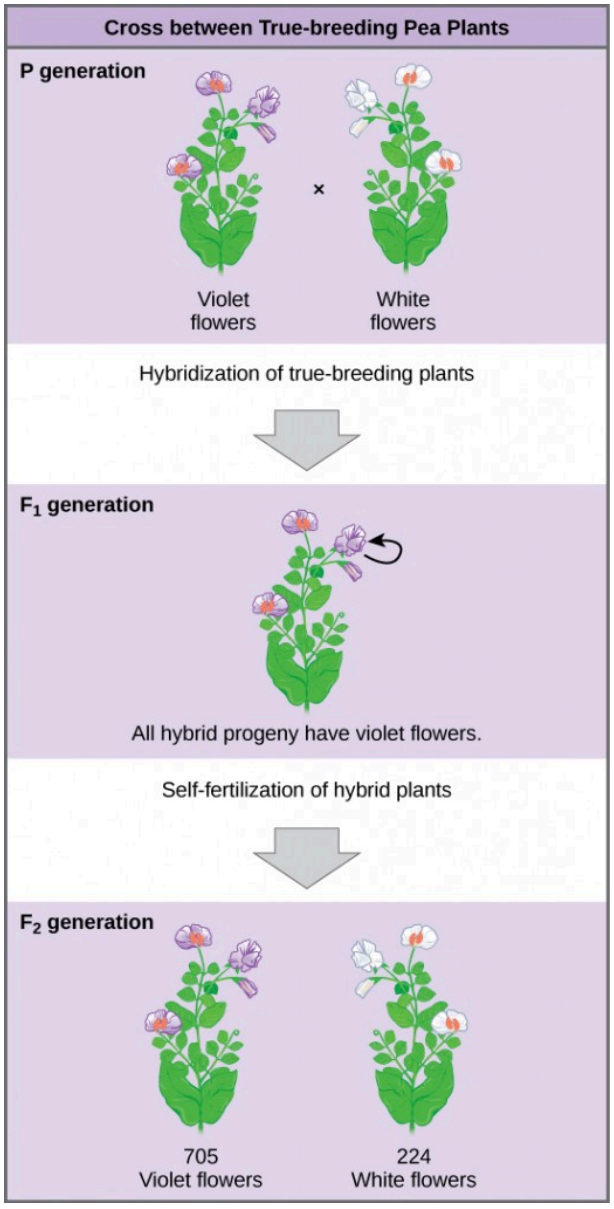


**Figure 2.34** Mendel's process for performing crosses included examining flower color. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Garden Pea Characteristics Revealed the Basics of Heredity

In his 1865 publication, Mendel reported the results of his crosses involving seven different characteristics, each with two contrasting traits. A trait is defined as a variation in the physical appearance of a heritable characteristic. The characteristics included plant height, seed texture, seed color, flower color, pea-pod size, pea-pod color, and flower position. For the characteristic of flower color, for example, the two contrasting

traits were white versus violet. To fully examine each characteristic, Mendel generated large numbers of $F_1$ and $F_2$ plants and reported results from thousands of $F_2$ plants.

What results did Mendel find in his crosses for flower color? First, Mendel confirmed that he was using plants that bred true for white or violet flower color. Irrespective of the number of generations that Mendel examined, all self-crossed offspring of parents with white flowers had white flowers, and all self-crossed offspring of parents with violet flowers had violet flowers. In addition, Mendel confirmed that, other than flower color, the pea plants were physically identical. This was an important check to make sure that the two varieties of pea plants only differed with respect to one trait, flower color.

Once these validations were complete, Mendel applied the pollen from a plant with violet flowers to the stigma of a plant with white flowers. After gathering and sowing the seeds that resulted from this cross, Mendel found that 100 percent of the $F_1$ hybrid generation had violet flowers. Conventional wisdom at that time would have predicted the hybrid flowers to be pale violet or for hybrid plants to have equal numbers of white and violet flowers. In other words, the contrasting parental traits were expected to blend in the offspring. Instead, Mendel's results demonstrated that the white flower trait had completely disappeared in the $F_1$ generation.

Importantly, Mendel did not stop his experimentation there. He allowed the $F_1$ plants to self-fertilize and found that 705 plants in the $F_2$generation had violet flowers and 224 had white flowers. This was a ratio of 3.15 violet flowers to one white flower, or approximately 3:1. When Mendel transferred pollen from a plant with violet flowers to the stigma of a plant with white flowers and vice versa, he obtained approximately the same ratio irrespective of which parent—male or female—contributed which trait. This is called a **reciprocal cross**—a paired cross in which the respective traits of the male and female in one cross become the respective traits of the female and male in the other cross. For the other six characteristics that Mendel examined, the $F_1$ and $F_2$ generations behaved in the same way that they behaved for flower color. One of the two traits would disappear completely from the $F_1$ generation, only to reappear in the $F_2$ generation at a ratio of roughly 3:1 (Figure 2.35).

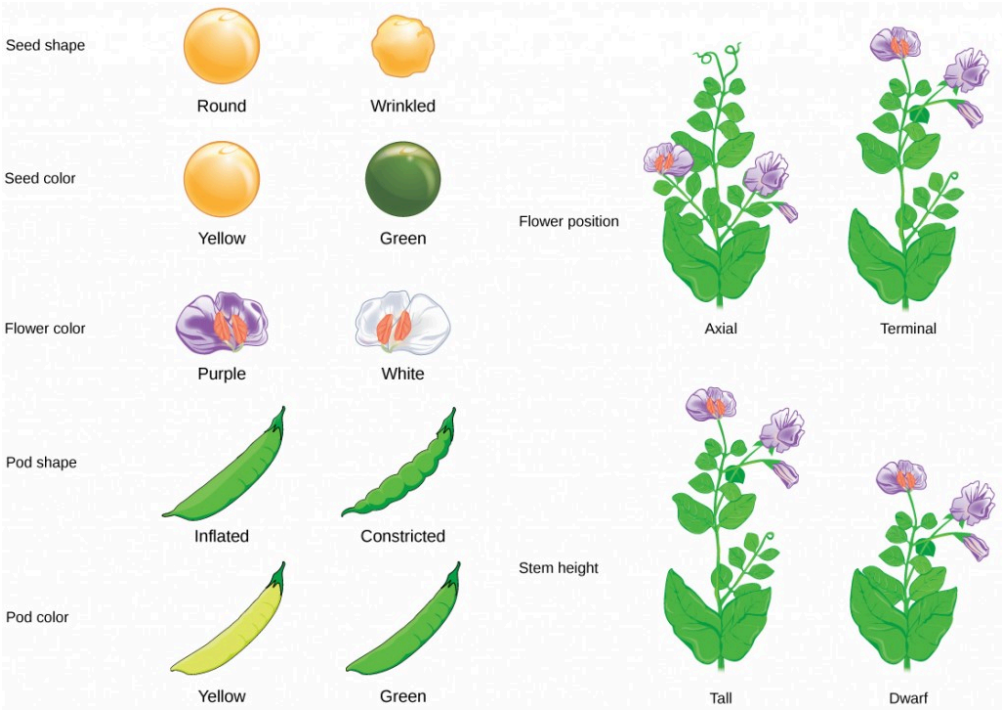


**Figure 2.35** Mendel identified seven pea plant characteristics. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0

Upon compiling his results for many thousands of plants, Mendel concluded that the characteristics could be divided into expressed and latent traits. He called these dominant and recessive traits, respectively. Dominant traits are those that are inherited unchanged in a hybridization. Recessive traits become latent, or disappear in the offspring of a hybridization. The recessive trait does, however, reappear in the progeny of the hybrid offspring. An example of a dominant trait is the violet-colored flower trait. For this same characteristic (flower color), white-colored flowers are a recessive trait. The fact that the recessive trait reappeared in the $F_2$ generation meant that the traits remained separate (and were not blended) in the plants of the $F_1$ generation. Mendel proposed that this was because the *plants possessed two copies of the trait for the flower-color characteristic*, and that each parent transmitted one of their two copies to their offspring, where they came together. Moreover, the physical observation of a dominant trait could mean that the genetic composition of the organism included two dominant versions of the characteristic, or that it included one dominant and one recessive version. Conversely, the observation of a recessive trait meant that the organism lacked any dominant versions of this characteristic.

The seven characteristics that Mendel evaluated in his pea plants were each expressed as one of two versions, or traits. Mendel deduced from his results that each individual had two discrete copies of the characteristic that are passed individually to offspring. We now call those two copies **genes**, which are carried on chromosomes. The reason we have two copies of each gene is that we inherit one from each parent. In fact, it is the chromosomes we inherit and the two copies of each gene are located on paired chromosomes. Recall

that in meiosis these chromosomes are separated out into haploid gametes. This **separation, or segregation**, of the homologous chromosomes means also that only one of the copies of the gene gets moved into a gamete. The offspring are formed when that gamete unites with one from another parent and the two copies of each gene (and chromosome) are restored.

For cases in which a single gene controls a single characteristic, a diploid organism has two genetic copies that may or may not encode the same version of that characteristic. For example, one individual may carry a gene that determines white flower color and a gene that determines violet flower color. Gene variants that arise by mutation and exist at the same relative locations on homologous chromosomes are called **alleles**. Mendel examined the inheritance of genes with just two allele forms, but it is common to encounter more than two alleles for any given gene in a natural population.

## Phenotypes and Genotypes

Two alleles for a given gene in a diploid organism are expressed and interact to produce physical characteristics. The observable traits expressed by an organism are referred to as its **phenotype**. An organism's underlying genetic makeup, consisting of both the physically visible and the non-expressed alleles, is called its **genotype**. Mendel's hybridization experiments demonstrate the difference between phenotype and genotype. For example, the phenotypes that Mendel observed in his crosses between pea plants with differing traits are connected to the diploid genotypes of the plants in the P, $F_1$, and $F_2$ generations. We will use a second trait that Mendel investigated, seed color, as an example. Seed color is governed by a single gene with two alleles. The yellow-seed allele is dominant and the green-seed allele is recessive. When true-breeding plants were cross-fertilized, in which one parent had yellow seeds and one had green seeds, all of the $F_1$ hybrid offspring had yellow seeds. That is, the hybrid offspring were phenotypically identical to the true-breeding parent with yellow seeds. However, we know that the allele donated by the parent with green seeds was not simply lost because it reappeared in some of the $F_2$ offspring (Figure 2.36). Therefore, the $F_1$ plants must have been genotypically different from the parent with yellow seeds.

The P plants that Mendel used in his experiments were each **homozygous** for the trait he was studying. Diploid organisms that are homozygous for a gene have two identical alleles, one on each of their homologous chromosomes. The genotype is often written as *YY* or *yy*, for which each letter represents one of the two alleles in the genotype. The dominant allele is capitalized and the recessive allele is lower case. The letter used for the gene (seed color in this case) is usually related to the dominant trait (yellow allele, in this case, or "*Y*"). Mendel's parental pea plants always bred true because both produced gametes carried the same allele. When P plants with contrasting traits were cross-fertilized, all of the offspring were **heterozygous** for the contrasting trait, meaning their genotype had different alleles for the gene being examined. For example, the $F_1$ yellow plants that received a *Y* allele from their yellow parent and a *y* allele from their green parent had the genotype *Yy*.

*Note:* though in classical Mendelian genetics the convention was to name the gene after the dominant trait, modern genetics often names genes after the mutant phenotype, since this is usually what is first observed and studied. For example, is Drosophila, a variant that causes abnormally small wings, called vestigial, is denoted *vg*. Additionally, Mendelian genetics provide a foundation for understanding these basic concepts. Traits that follow Mendelian inheritance are often associated with genetic disorders (e.g. cystic fibrosis or Huntington's disease). Please keep in mind that inheritance is not always so straight-forward and that multiple genetic and environmental factors can interact to influence gene expression.

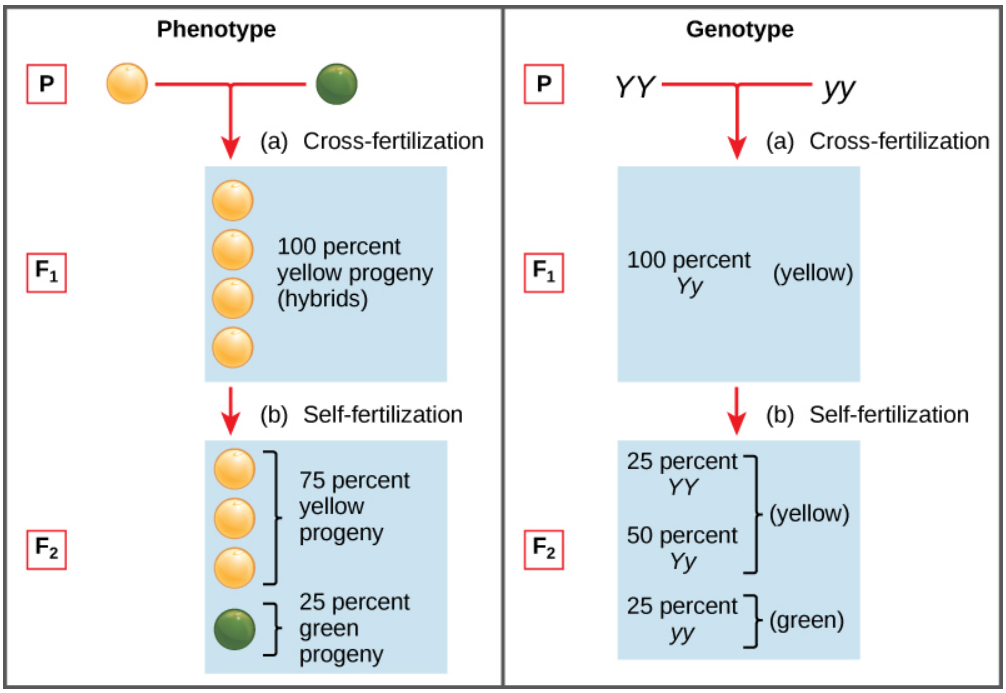


**Figure 2.36** Phenotypes are physical expressions of traits that are transmitted by alleles. Capital letters represent dominant alleles and lowercase letters represent recessive alleles. The phenotypic ratios are the ratios of visible characteristics. The genotypic ratios are the ratios of gene combinations in the offspring, and these are not always distinguishable in the phenotypes. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Law of Dominance

Our discussion of homozygous and heterozygous organisms brings us to why the $F_1$ heterozygous offspring were identical to one of the parents, rather than expressing both alleles. In all seven pea-plant characteristics, one of the two contrasting alleles was dominant, and the other was recessive. Mendel called the dominant allele the expressed unit factor; the recessive allele was referred to as the latent unit factor. We now know that these so-called unit factors are actually genes on homologous chromosomes. For a gene that is expressed in a dominant and recessive pattern, *homozygous dominant and heterozygous organisms will look identical* (that is,

they will have different genotypes but the same phenotype), and the *recessive allele will only be observed in homozygous recessive individuals*.

**Correspondence between Genotype and Phenotype for a Dominant-Recessive Characteristic.**

| Type | Homozygous | Heterozygous | Homozygous |
|---|---|---|---|
| Genotype | *YY* | *Yy* | *yy* |
| Phenotype | yellow | yellow | green |

Mendel's **law of dominance** states that in a heterozygote, one trait will conceal the presence of another trait for the same characteristic. For example, when crossing true-breeding violet-flowered plants with true-breeding white-flowered plants, all of the offspring were violet-flowered, even though they all had one allele for violet and one allele for white. Rather than both alleles contributing to a phenotype, the dominant allele will be expressed exclusively. The recessive allele will remain latent, but will be transmitted to offspring in the same manner as that by which the dominant allele is transmitted. The recessive trait will only be expressed by offspring that have two copies of this allele (Figure 2.37), and these offspring will breed true when self-crossed.

**Figure 2.37** The allele for albinism, expressed here in humans, is recessive. Both of this child's parents carried the recessive allele. **Source:** Image by Amapola89, PDM .

## Monohybrid Cross and the Punnett Square

When fertilization occurs between two true-breeding parents that differ by only the characteristic being studied, the process is called a **monohybrid cross**, and the resulting offspring are called monohybrids. Mendel performed seven types of monohybrid crosses, each involving contrasting traits for different characteristics. Out of these crosses, all of the $F_1$ offspring had the phenotype of one parent, and the $F_2$ offspring had a 3:1 phenotypic ratio. On the basis of these results, Mendel postulated that each parent in the monohybrid cross contributed one of two paired unit factors to each offspring, and every possible combination of unit factors was equally likely.

The results of Mendel's research can be explained in terms of probabilities, which are mathematical measures of likelihood. The probability of an event is calculated by the number of times the event occurs divided by the total number of opportunities for the event to occur. A probability of one (100 percent) for

some event indicates that it is guaranteed to occur, whereas a probability of zero (0 percent) indicates that it is guaranteed to not occur, and a probability of 0.5 (50 percent) means it has an equal chance of occurring or not occurring.

To demonstrate this with a monohybrid cross, consider the case of true-breeding pea plants with yellow versus green seeds. The dominant seed color is yellow; therefore, the parental genotypes were *YY* for the plants with yellow seeds and *yy* for the plants with green seeds. A Punnett square, devised by the British geneticist Reginald Punnett, is useful for determining probabilities because it is drawn to predict all possible outcomes of all possible random fertilization events and their expected frequencies. Figure 2.39 shows a Punnett square for a cross between a plant with yellow peas and one with green peas. To prepare a **Punnett square**, all possible combinations of the parental alleles (the genotypes of the gametes) are listed along the top (for one parent) and side (for the other parent) of a grid. The combinations of egg and sperm gametes are then made in the boxes in the table on the basis of which alleles are combining. Each box then represents the diploid genotype of a zygote, or fertilized egg. Because each possibility is equally likely, genotypic ratios can be determined from a Punnett square. If the pattern of inheritance (dominant and recessive) is known, the phenotypic ratios can be inferred as well. For a monohybrid cross of two true-breeding parents, each parent contributes one type of allele. In this case, only one genotype is possible in the $F_1$ offspring. All offspring are *Yy* and have yellow seeds.

When the $F_1$ offspring are crossed with each other, each has an equal probability of contributing either a *Y* or a *y* to the $F_2$ offspring. The result is a 1 in 4 (25 percent) probability of both parents contributing a *Y*, resulting in an offspring with a yellow phenotype; a 25 percent probability of parent A contributing a *Y* and parent B a *y*, resulting in offspring with a yellow phenotype; a 25 percent probability of parent A contributing a *y* and parent B a *Y*, also resulting in a yellow phenotype; and a (25 percent) probability of both parents contributing a *y*, resulting in a green phenotype. When counting all four possible outcomes, there is a 3 in 4 probability of offspring having the yellow phenotype and a 1 in 4 probability of offspring having the green phenotype. This explains why the results of Mendel's $F_2$ generation occurred in a 3:1 phenotypic ratio. Using large numbers of crosses, Mendel was able to calculate probabilities, found that they fit the model of inheritance, and use these to predict the outcomes of other crosses.

## Law of Segregation

Observing that true-breeding pea plants with contrasting traits gave rise to $F_1$ generations that all expressed the dominant trait and $F_2$ generations that expressed the dominant and recessive traits in a 3:1 ratio, Mendel proposed the **law of segregation**. This law states that paired unit factors (genes) must segregate equally into gametes such that offspring have an equal likelihood of inheriting either factor. For the $F_2$ generation of a monohybrid cross, the following three possible combinations of genotypes result: homozygous dominant, heterozygous, or homozygous recessive. Because heterozygotes could arise from two different pathways (receiving one dominant and one recessive allele from either parent), and because heterozygotes and

homozygous dominant individuals are phenotypically identical, the law supports Mendel's observed 3:1 phenotypic ratio. The equal segregation of alleles is the reason we can apply the Punnett square to accurately predict the offspring of parents with known genotypes. The physical basis of Mendel's law of segregation is the first division of meiosis in which the homologous chromosomes with their different versions of each gene are segregated into daughter nuclei. This process was not understood by the scientific community during Mendel's lifetime (Figure 2.38).

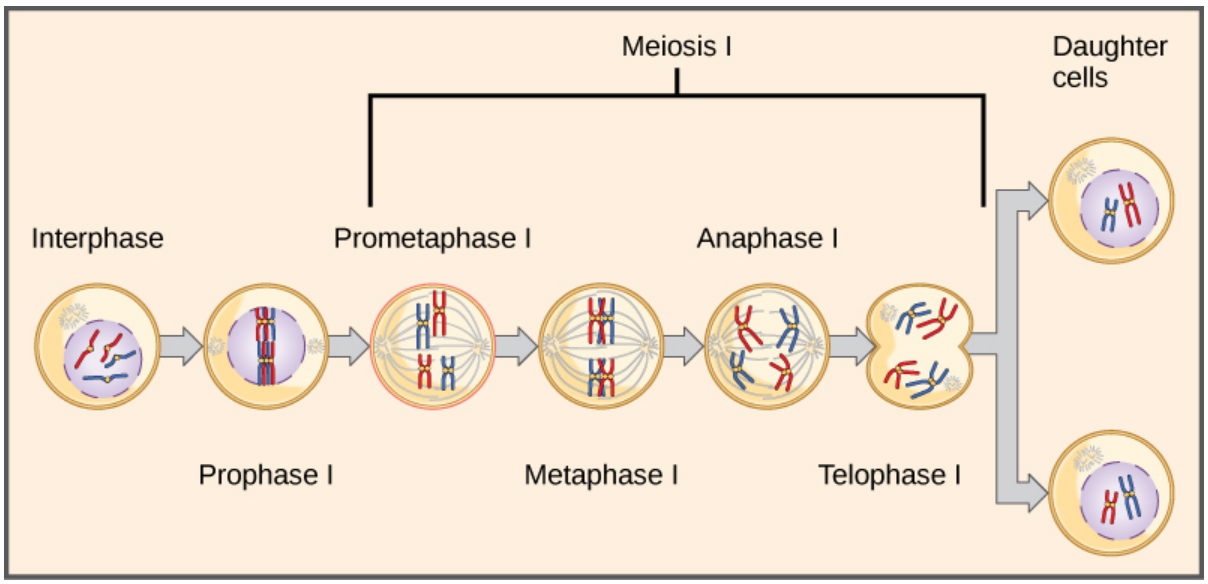


**Figure 2.38** The first division in meiosis is shown. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Test Cross

Beyond predicting the offspring of a cross between known homozygous or heterozygous parents, Mendel also developed a way to determine whether an organism that expressed a dominant trait was a heterozygote or a homozygote. Called the **test cross**, this technique is still used by plant and animal breeders. In a test cross, the **d**ominant-expressing organism is crossed with an organism that is homozygous recessive for the same characteristic. If the dominant-expressing organism is a homozygote, then all $F_1$ offspring will be heterozygotes expressing the dominant trait (Figure 2.39). Alternatively, if the dominant-expressing organism is a heterozygote, the $F_1$ offspring will exhibit a 1:1 ratio of heterozygotes and recessive homozygotes (Figure 2.40). The test cross further validates Mendel's postulate that pairs of unit factors segregate equally.

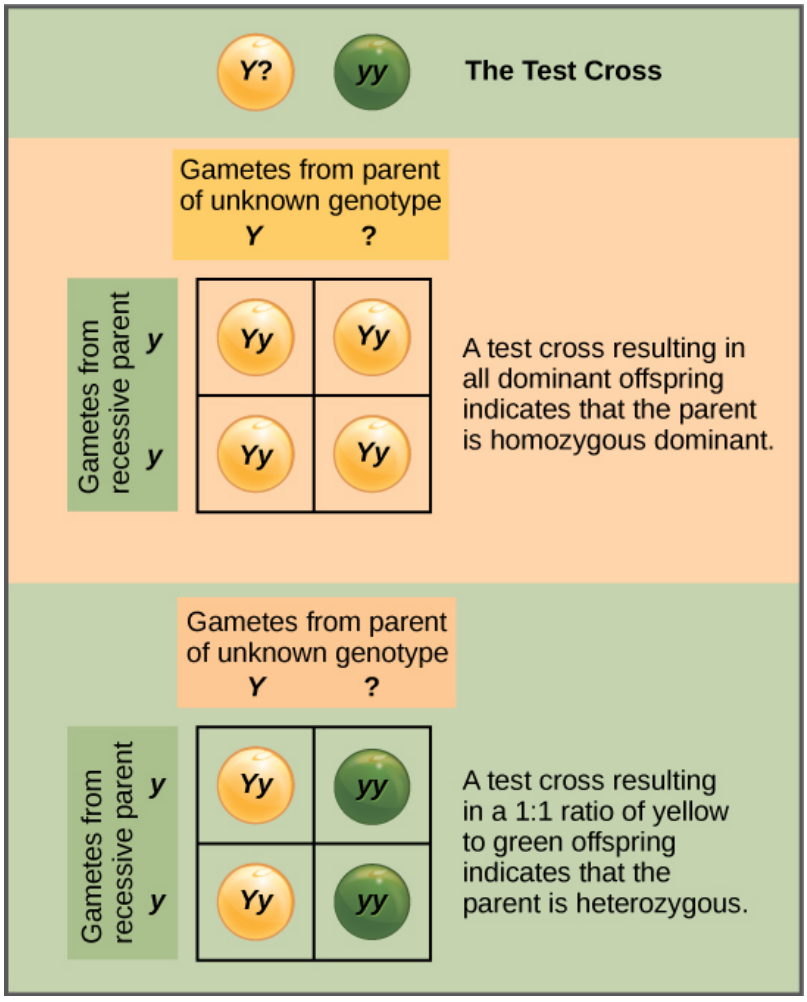


**Figure 2.39** A test cross can be performed to determine whether an organism expressing a dominant trait is a homozygote or a heterozygote. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

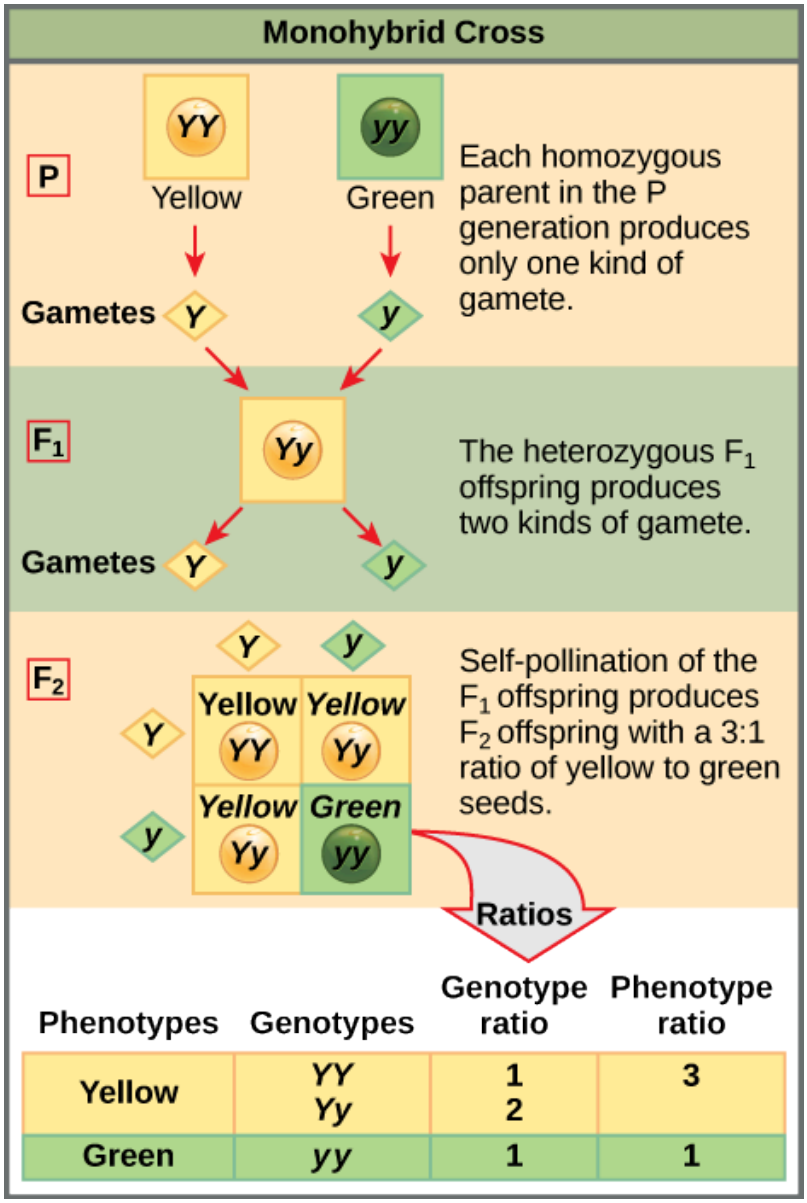


**Figure 2.40** This Punnett square shows the cross between plants with yellow seeds and green seeds. The cross between the true-breeding P plants produces F1 heterozygotes that can be self-fertilized. The self-cross of the F1 generation can be analyzed with a Punnett square to predict the genotypes of the F2 generation. Given an inheritance pattern of dominant–recessive, the genotypic and phenotypic ratios can then be determined. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

In pea plants, round peas (*R*) are dominant to wrinkled peas (*r*). You do a test cross between a pea plant with wrinkled peas (genotype *rr*) and a plant of unknown genotype that has round peas. You end up with three plants, all which have round peas. From this data, can you tell if the parent plant is homozygous dominant or heterozygous?

You cannot be sure if the plant is homozygous or heterozygous as the data set is too small: by random chance, all three plants might have acquired only the dominant gene even if the recessive one is present.

### Concept in Action – Punnett Square

**Watch How to use a Punnett Square (with genetics practice questions) (27 mins) on YouTube (https://youtu.be/uDoNTugVtCM)**

## Law of Independent Assortment

Mendel's **law of independent assortment** states that **genes do not influence each other with regard to the sorting of alleles into gametes**, and every possible combination of alleles for every gene is equally likely to occur. Independent assortment of genes can be illustrated by the **dihybrid** cross, a cross between two true-breeding parents that express different traits for two characteristics. Consider the characteristics of seed color and seed texture for two pea plants, one that has wrinkled, green seeds (*rryy*) and another that has round, yellow seeds (*RRYY*). Because each parent is homozygous, the law of segregation indicates that the gametes for the wrinkled–green plant all are *ry*, and the gametes for the round–yellow plant are all *RY*. Therefore, the $F_1$ generation of offspring all are *RrYy* (Figure 2.41).

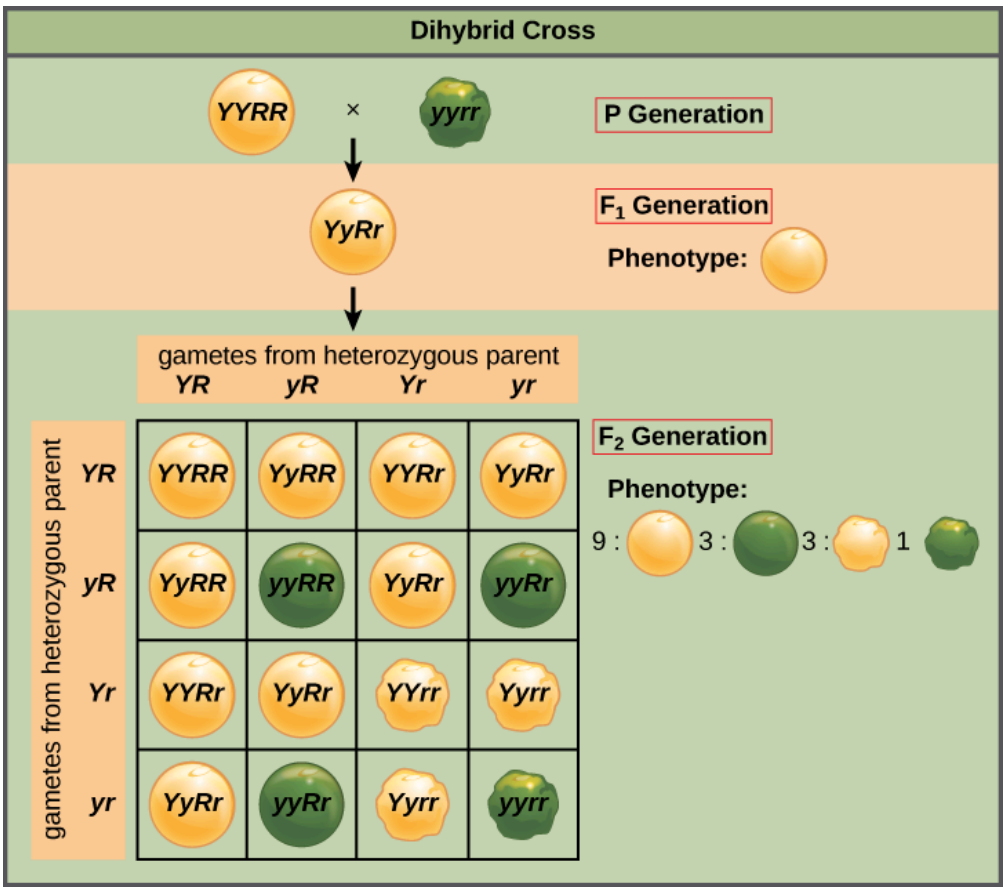


**Figure 2.41** A dihybrid cross in pea plants involves the genes for seed color and texture. The P cross produces F1 offspring that are all heterozygous for both characteristics. The resulting 9:3:3:1 F2 phenotypic ratio is obtained using a Punnett square. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

In pea plants, purple flowers (*P*) are dominant to white (*p*), and yellow peas (*Y*) are dominant to green (*y*). What are the possible genotypes and phenotypes for a cross between *PpYY* and *ppYy* pea plants? How many squares would you need to complete a Punnett square analysis of this cross?

The possible genotypes are PpYY, PpYy, ppYY, and ppYy. The former two genotypes would result in plants with purple flowers and yellow peas, while the latter two genotypes would result in plants with white flowers with yellow peas, for a 1:1 ratio of each phenotype. You only need a 2 × 2 Punnett square (four squares total) to do this analysis because two of the alleles are homozygous.

The gametes produced by the $F_1$ individuals must have one allele from each of the two genes. For example, a gamete could get an *R* allele for the seed shape gene and either a *Y* or a *y* allele for the seed color gene. It cannot get both an *R* and an *r* allele; each gamete can have only one allele per gene. The law of independent assortment states that a gamete into which an *r* allele is sorted would be equally likely to contain either a *Y* or a *y* allele. Thus, there are four equally likely gametes that can be formed when the *RrYy* heterozygote is self-crossed, as follows: *RY*, *rY*, *Ry*, and *ry*. Arranging these gametes along the top and left of a 4 × 4 Punnett

square gives us 16 equally likely genotypic combinations. From these genotypes, we find a phenotypic ratio of 9 round–yellow:3 round–green:3 wrinkled–yellow:1 wrinkled–green. These are the offspring ratios we would expect, assuming we performed the crosses with a large enough sample size.

The physical basis for the law of independent assortment also lies in meiosis I, in which the different homologous pairs line up in random orientations. Each gamete can contain any combination of paternal and maternal chromosomes (and therefore the genes on them) because the orientation of tetrads on the metaphase plane is random (Figure 2.42).

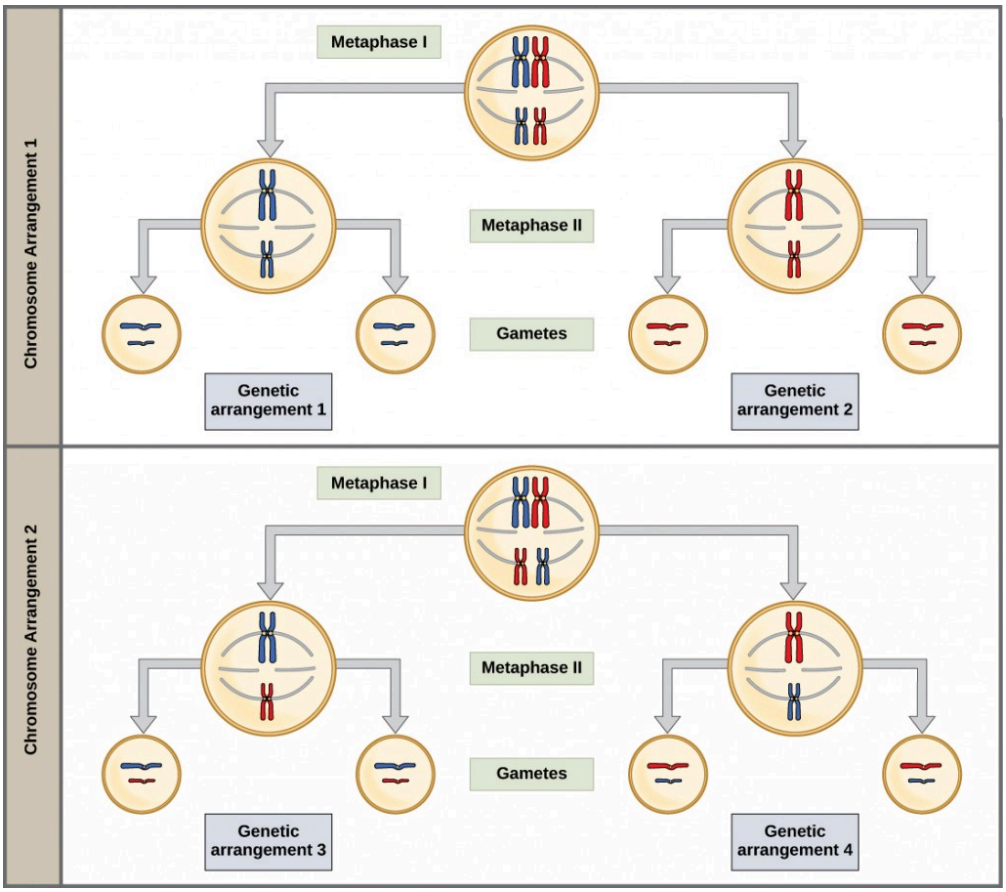


**Figure 2.42** The random segregation into daughter nuclei that happens during the first division in meiosis can lead to a variety of possible genetic arrangements. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Probability Basics

**Probabilities** are mathematical measures of likelihood. The empirical probability of an event is calculated by dividing the number of times the event occurs by the total number of opportunities for the event to occur. It is also possible to calculate theoretical probabilities by dividing the number of times that an event is expected to occur by the number of times that it could occur. Empirical probabilities come from observations, like those of Mendel. Theoretical probabilities come from knowing how the events are produced and assuming

that the probabilities of individual outcomes are equal. A probability of one for some event indicates that it is guaranteed to occur, whereas a probability of zero indicates that it is guaranteed not to occur. An example of a genetic event is a round seed produced by a pea plant. In his experiment, Mendel demonstrated that the probability of the event "round seed" occurring was one in the $F_1$ offspring of true-breeding parents, one of which has round seeds and one of which has wrinkled seeds. When the $F_1$ plants were subsequently self-crossed, the probability of any given $F_2$ offspring having round seeds was now three out of four. In other words, in a large population of $F_2$ offspring chosen at random, 75 percent were expected to have round seeds, whereas 25 percent were expected to have wrinkled seeds. Using large numbers of crosses, Mendel was able to calculate probabilities and use these to predict the outcomes of other crosses.

## The Product Rule and Sum Rule

Mendel demonstrated that the pea-plant characteristics he studied were transmitted as discrete units from parent to offspring. As will be discussed, Mendel also determined that different characteristics, like seed color and seed texture, were transmitted independently of one another and could be considered in separate probability analyses. For instance, performing a cross between a plant with green, wrinkled seeds and a plant with yellow, round seeds still produced offspring that had a 3:1 ratio of green:yellow seeds (ignoring seed texture) and a 3:1 ratio of round:wrinkled seeds (ignoring seed color). The characteristics of color and texture did not influence each other.

The **product rule of probability** can be applied to this phenomenon of the independent transmission of characteristics. The product rule states that *the probability of two independent events occurring together can be calculated by multiplying the individual probabilities of each event occurring alone*. To demonstrate the product rule, imagine that you are rolling a six-sided die (D) and flipping a penny (P) at the same time. The die may roll any number from 1–6 ($D_{\#}$), whereas the penny may turn up heads ($P_H$) or tails ($P_T$). The outcome of rolling the die has no effect on the outcome of flipping the penny and vice versa. There are 12 possible outcomes of this action, and each event is expected to occur with equal probability.

**Twelve Equally Likely Outcomes of Rolling a Die and Flipping a Penny**

| Rolling Die | Flipping Penny |
|---|---|
| $D_1$ | $P_H$ |
| $D_1$ | $P_T$ |
| $D_2$ | $P_H$ |
| $D_2$ | $P_T$ |
| $D_3$ | $P_H$ |
| $D_3$ | $P_T$ |
| $D_4$ | $P_H$ |
| $D_4$ | $P_T$ |
| $D_5$ | $P_H$ |
| $D_5$ | $P_T$ |
| $D_6$ | $P_H$ |
| $D_6$ | $P_T$ |

Of the 12 possible outcomes, the die has a 2/12 (or 1/6) probability of rolling a two, and the penny has a 6/12 (or 1/2) probability of coming up heads. By the product rule, the probability that you will obtain the combined outcome 2 and heads is: $(D_2) \times (P_H) = (1/6) \times (1/2)$ or 1/12. Notice the word "and" in the description of the probability. **The "and" is a signal to apply the product rule**. For example, consider how the product rule is applied to the dihybrid cross: the probability of having both dominant traits in the $F_2$ progeny is the product of the probabilities of having the dominant trait for each characteristic, as shown here:

$$3/4 \times 3/4 = 9/16$$

On the other hand, the **sum rule of probability** is applied when considering two mutually exclusive outcomes that can come about by more than one pathway. The sum rule states that *the probability of the occurrence of one event or the other event, of two mutually exclusive events, is the sum of their individual probabilities*. Notice the word "or" in the description of the probability. **The "or" indicates that you should apply the sum rule.** In this case, let's imagine you are flipping a penny (P) and a quarter (Q). What is the probability of one coin coming up heads and one coin coming up tails? This outcome can be achieved by two cases: the penny may be heads ($P_H$) and the quarter may be tails ($Q_T$), or the quarter may be heads ($Q_H$) and the penny may be tails ($P_T$). Either case fulfills the outcome. By the sum rule, we calculate the probability of obtaining one head and one tail as $[(P_H) \times (Q_T)] + [(Q_H) \times (P_T)] = [(1/2) \times (1/2)] + [(1/2) \times (1/2)] = 1/2$. You should also notice that we used the product rule to calculate the probability of $P_H$ and $Q_T$, and also the

probability of $P_T$ and $Q_H$, before we summed them. Again, the sum rule can be applied to show the probability of having just one dominant trait in the $F_2$ generation of a dihybrid cross:

$$3/16 + 3/4 = 15/16$$

**The Product Rule and Sum Rule**

| Product Rule | Sum Rule |
|---|---|
| For independent events A and B, the probability (P) of them both occurring (A ***and*** B) is ($P_A \times P_B$) | For mutually exclusive events A and B, the probability (P) that at least one occurs (A ***or*** B) is ($P_A + P_B$) |

To use probability laws in practice, it is necessary to work with large sample sizes because small sample sizes are prone to deviations caused by chance. The large quantities of pea plants that Mendel examined allowed him calculate the probabilities of the traits appearing in his $F_2$ generation. As you will learn, this discovery meant that when parental traits were known, the offspring's traits could be predicted accurately even before fertilization.

## Example – Pedigree chart

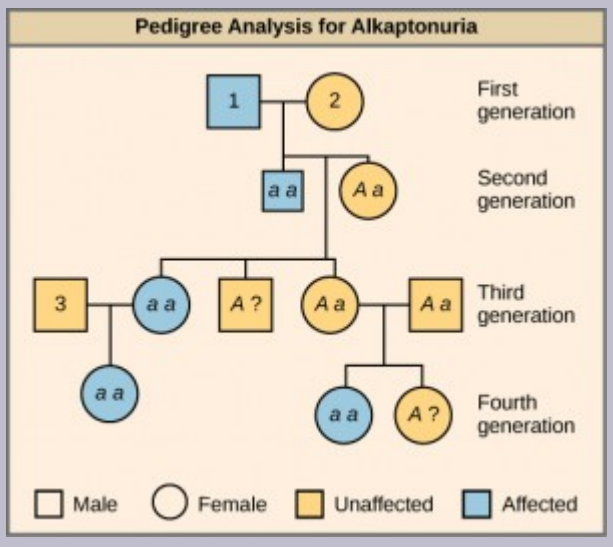


**Figure 2.43.** Pedigree chart of family with recessive disorder alkaptonuria. **Source:** *Biology 2e (OpenStax)*, CC BY 4.0.

Figure 2.43 shows a pedigree of a family that carries the recessive disorder alkaptonuria. In the second generation, an unaffected mother and an affected father have three children. One child has the disorder, so the genotype of the mother must be Aa and the genotype of the father is aa. One unaffected child goes on to have two children, one affected and one unaffected. Because her husband was not affected, she and her husband must both be heterozygous. The genotype of their unaffected child is unknown, and is designated A?. In the third generation, the other unaffected child had no offspring, and his genotype is therefore also unknown. The affected third-generation child goes on to have one child with the disorder. Her husband is unaffected and is labeled "3." The first

generation father is affected and is labeled "1." The first generation mother is unaffected and is labeled "2." The Art Connection question asks the genotype of the three numbered individuals.

Alkaptonuria is a recessive genetic disorder in which two amino acids, phenylalanine and tyrosine, are not properly metabolized. Affected individuals may have darkened skin and brown urine, and may suffer joint damage and other complications. In this pedigree, individuals with the disorder are indicated in blue and have the genotype *aa*. Unaffected individuals are indicated in yellow and have the genotype *AA* or *Aa*. Note that it is often possible to determine a person's genotype from the genotype of their offspring. For example, if neither parent has the disorder but their child does, they must be heterozygous. Two individuals on the pedigree have an unaffected phenotype but unknown genotype. Because they do not have the disorder, they must have at least one normal allele, so their genotype gets the "*A?*" designation.

What are the genotypes of the individuals labeled 1, 2 and 3?

## Alternatives to Dominance and Recessiveness

Mendel's experiments with pea plants suggested that: 1) two types of "units" or alleles exist for every gene; 2) alleles maintain their integrity in each generation (no blending); and 3) in the presence of the dominant allele, the recessive allele is hidden, with no contribution to the phenotype. Therefore, recessive alleles can be "carried" and not expressed by individuals. Such **heterozygous individuals** are sometimes referred to as "**carriers**." Since then, genetic studies in other organisms have shown that much more complexity exists, but that the fundamental principles of Mendelian genetics still hold true. In the sections to follow, we consider some of the extensions of Mendelism.

## Incomplete Dominance

**Figure 2.44** These pink flowers of a heterozygote snapdragon result from incomplete dominance. **Source:** Image by storebukkebruse, CC BY 2.0.

Mendel's results, demonstrating that traits are inherited as dominant and recessive pairs, contradicted the view at that time that offspring exhibited a blend of their parents' traits. However, the heterozygote phenotype occasionally does appear to be intermediate between the two parents. For example, in the snapdragon, *Antirrhinum majus* (Figure 2.44), a cross between a homozygous parent with white flowers ($C^{W}C^{W}$) and a homozygous parent with red flowers ($C^{R}C^{R}$) will produce offspring with pink flowers ($C^{R}C^{W}$). (Note that different genotypic abbreviations are used for Mendelian extensions to distinguish these patterns from simple dominance and recessiveness.) This pattern of inheritance is described as **incomplete dominance**, meaning that one of the alleles appears in the phenotype in the heterozygote, but not to the exclusion of the other, which can also be seen. The allele for red flowers is incompletely dominant over the allele for white flowers. However, the results of a heterozygote self-cross can still be predicted, just as with Mendelian dominant and recessive crosses. In this case, the genotypic ratio would be 1 $C^{R}C^{R}$:2 $C^{R}C^{W}$:1 $C^{W}C^{W}$, and the phenotypic ratio would be 1:2:1 for red:pink:white. The basis for the intermediate color in the heterozygote is simply that the pigment produced by the red allele (anthocyanin) is diluted in the heterozygote and therefore appears pink because of the white background of the flower petals.

## Codominance

A variation on incomplete dominance is **codominance**, in which both alleles for the same characteristic are **simultaneously expressed** in the heterozygote. An example of codominance occurs in the ABO blood groups of humans. The A and B alleles are expressed in the form of A or B molecules present on the surface of red blood cells. Homozygotes ($I^{A}I^{A}$ and $I^{B}I^{B}$) express either the A or the B phenotype, and heterozygotes ($I^{A}I^{B}$) express both phenotypes equally. The $I^{A}I^{B}$ individual has blood type AB. In a self-cross between heterozygotes expressing a codominant trait, the three possible offspring genotypes are phenotypically distinct. However, the 1:2:1 genotypic ratio characteristic of a Mendelian monohybrid cross still applies (Figure 2.45).

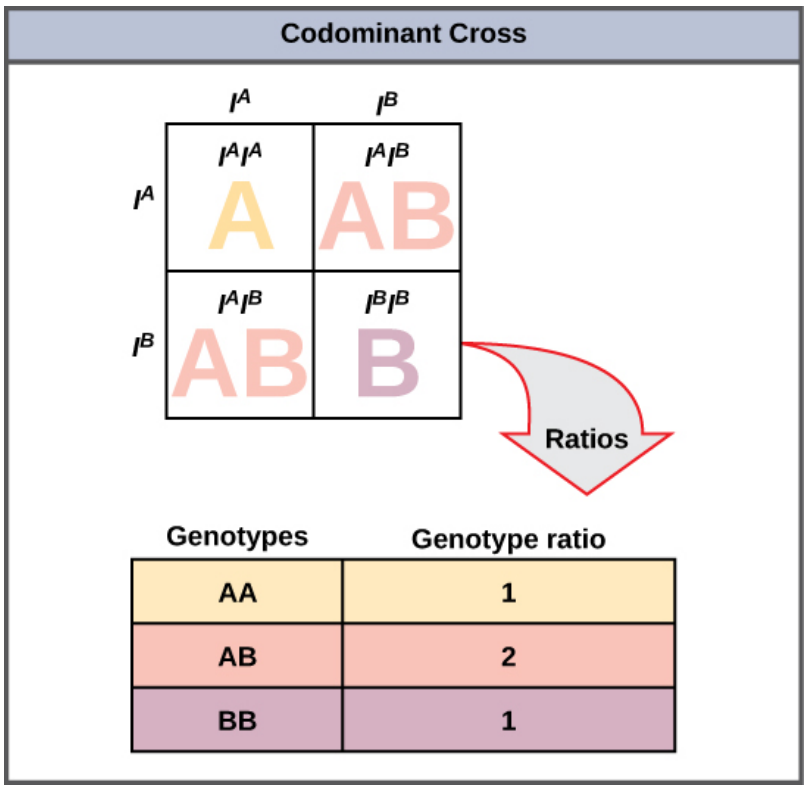


**Figure 2.45** This Punnett square shows an AB/AB blood type cross. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Multiple Alleles

Mendel implied that only two alleles, one dominant and one recessive, could exist for a given gene. We now know that this is an oversimplification. Although individual humans (and all diploid organisms) can only have two alleles for a given gene, multiple alleles may exist at the population level, such that many combinations of two alleles are observed. Note that when many alleles exist for the same gene, the convention is to denote the most common phenotype or genotype in the natural population as the **wild type** (often abbreviated "+"). All other phenotypes or genotypes are considered variants (mutants) of this typical form, meaning they deviate from the wild type. The variant may be recessive or dominant to the wild-type allele.

An example of multiple alleles is the ABO blood-type system in humans. In this case, there are three alleles circulating in the population. The $I^A$ allele codes for A molecules on the red blood cells, the $I^B$ allele codes for B molecules on the surface of red blood cells, and the $i$ allele codes for no molecules on the red blood cells. In this case, the $I^A$ and $I^B$ alleles are codominant with each other and are both dominant over the $i$ allele. Although there are three alleles present in a population, each individual only gets two of the alleles from their parents. This produces the genotypes and phenotypes shown in Figure 2.46. Notice that instead of three genotypes, there are six different genotypes when there are three alleles. The number of possible phenotypes depends on the dominance relationships between the three alleles.

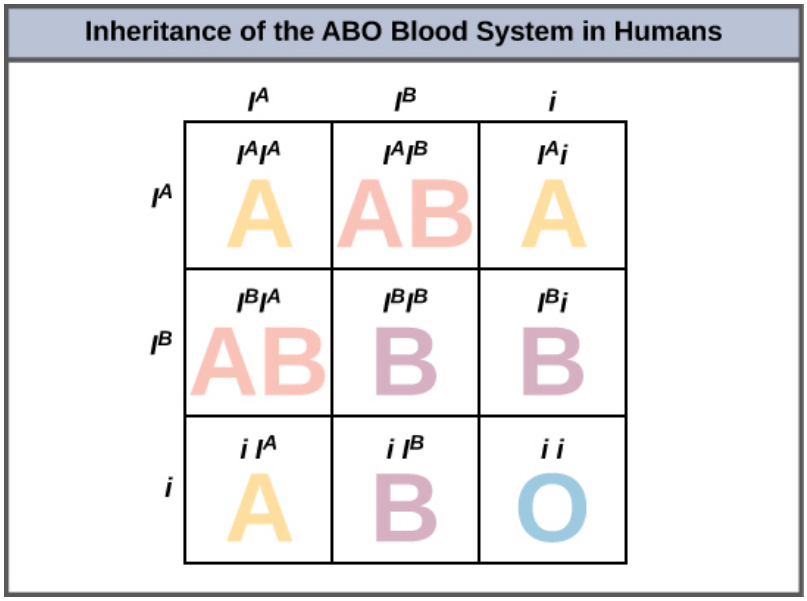


**Figure 2.46** Inheritance of the ABO blood system in humans is shown. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

## Multiple Alleles Confer Drug Resistance in the Malaria Parasite

Malaria is a parasitic disease in humans that is transmitted by infected female mosquitoes, including *Anopheles gambiae*, and is characterized by cyclic high fevers, chills, flu-like symptoms, and severe anemia. *Plasmodium falciparum* and *P. vivax* are the most common causative agents of malaria, and *P. falciparum* is the most deadly. When promptly and correctly treated, *P. falciparum* malaria has a mortality rate of 0.1 percent. However, in some parts of the world, the parasite has evolved resistance to commonly used malaria treatments, so the most effective malarial treatments can vary by geographic region.

In Southeast Asia, Africa, and South America, *P. falciparum* has developed resistance to the anti-malarial drugs chloroquine, mefloquine, and sulfadoxine-pyrimethamine. *P. falciparum*, which is haploid during the life stage in which it is infective to humans, has evolved multiple drug-resistant mutant alleles of the *dhps* gene. Varying degrees of sulfadoxine resistance are associated with each of these alleles. Being haploid, *P. falciparum* needs only one drug-resistant allele to express this trait.

In Southeast Asia, different sulfadoxine-resistant alleles of the *dhps* gene are localized to different geographic regions. This is a common evolutionary phenomenon that comes about because drug-resistant mutants arise in a population and interbreed with other *P. falciparum* isolates in close proximity. Sulfadoxine-resistant parasites cause considerable human hardship in regions in which this drug is widely used as an over-the-counter malaria remedy. As is common with pathogens that multiply to large numbers within an infection cycle, *P. falciparum* evolves relatively rapidly (over a decade or so) in response to the selective

pressure of commonly used anti-malarial drugs. For this reason, scientists must constantly work to develop new drugs or drug combinations to combat the worldwide malaria burden[3].

## Sex-Linked Traits

In humans, as well as in many other animals and some plants, the sex of the individual is determined by sex chromosomes—one pair of non-homologous chromosomes. Until now, we have only considered inheritance patterns among non-sex chromosomes, or autosomes. In addition to 22 homologous pairs of autosomes, human females have a homologous pair of X chromosomes, whereas human males have an XY chromosome pair. Although the Y chromosome contains a small region of similarity to the X chromosome so that they can pair during meiosis, the Y chromosome is much shorter and contains fewer genes. When a gene being examined is present on the X, but not the Y, chromosome, it is **X-linked**.

Eye color in *Drosophila*, the common fruit fly, was the first X-linked trait to be identified. Thomas Hunt Morgan mapped this trait to the X chromosome in 1910. Like humans, *Drosophila* males have an XY chromosome pair, and females are XX. In flies the wild-type eye color is red ($X^W$) and is dominant to white eye color ($X^w$) (Figure 2.47). Because of the location of the eye-color gene, reciprocal crosses do not produce the same offspring ratios. Males are said to be **hemizygous**, in that they have only one allele for any X-linked characteristic. Hemizygosity makes descriptions of dominance and recessiveness irrelevant for XY males. *Drosophila* males lack the white gene on the Y chromosome; that is, their genotype can only be $X^WY$ or $X^wY$. In contrast, females have two allele copies of this gene and can be $X^WX^W$, $X^WX^w$, or $X^wX^w$.

3. Sumiti Vinayak et al., "Origin and Evolution of Sulfadoxine Resistant *Plasmodium falciparum*," *PLoS Pathogens* 6 (2010): e1000830.

**Figure 2.47** In Drosophila, the gene for eye color is located on the X chromosome. Red eye color is wild-type and is dominant to white eye color. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

In an X-linked cross, the genotypes of $F_1$ and $F_2$ offspring depend on whether the recessive trait was expressed by the male or the female in the P generation. With respect to *Drosophila* eye color, when the P male expresses the white-eye phenotype and the female is homozygously red-eyed, all members of the $F_1$ generation exhibit red eyes (Figure 2.48). The $F_1$ females are heterozygous ($X^WX^w$), and the males are all $X^WY$, having received their X chromosome from the homozygous dominant P female and their Y chromosome from the P male. A subsequent cross between the $X^WX^w$ female and the $X^WY$ male would produce only red-eyed females (with $X^WX^W$ or $X^WX^w$ genotypes) and both red- and white-eyed males (with $X^WY$ or $X^wY$ genotypes). Now, consider a cross between a homozygous white-eyed female and a male with red eyes. The $F_1$ generation would exhibit only heterozygous red-eyed females ($X^WX^w$) and only white-eyed males ($X^wY$). Half of the $F_2$ females would be red-eyed ($X^WX^w$) and half would be white-eyed ($X^wX^w$). Similarly, half of the $F_2$ males would be red-eyed ($X^WY$) and half would be white-eyed ($X^wY$).

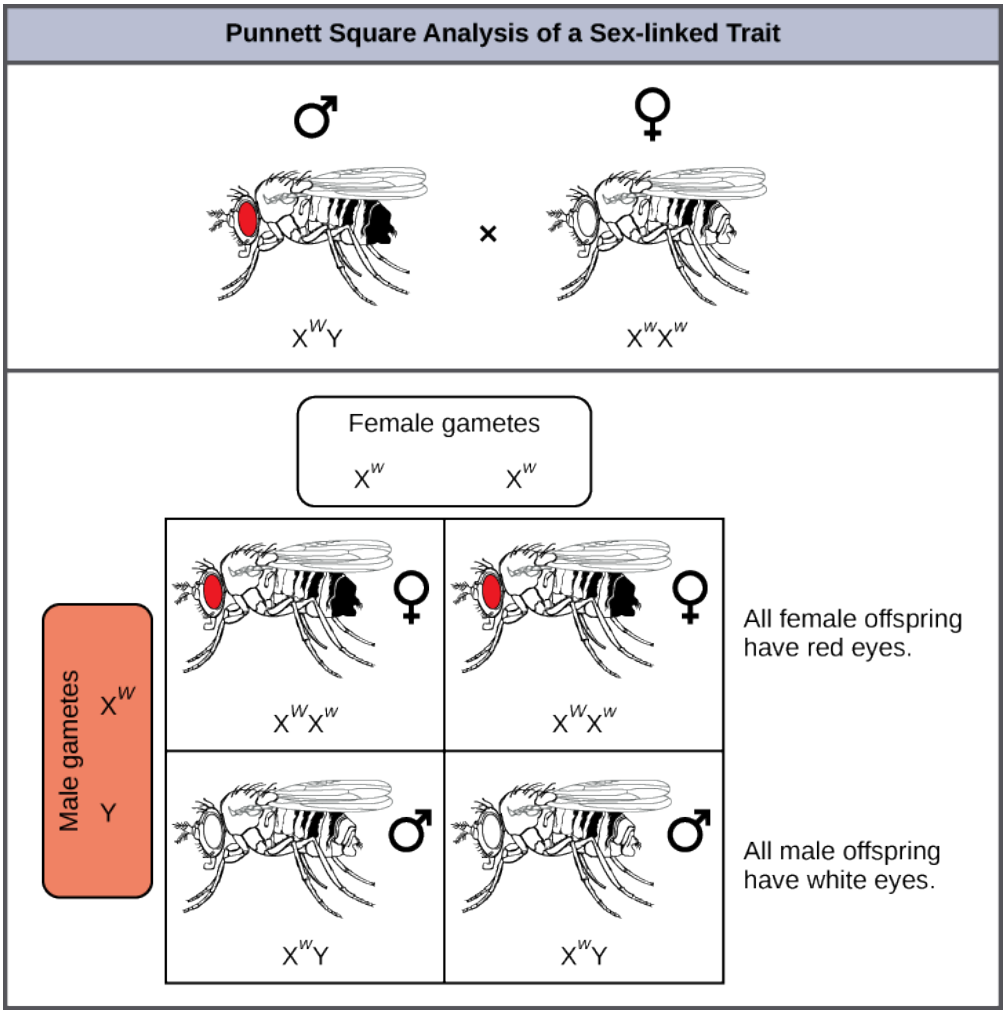


**Figure 2.48** Crosses involving sex-linked traits often give rise to different phenotypes for the different sexes of offspring, as is the case for this cross involving red and white eye color in Drosophila. In the diagram, w is the white-eye mutant allele and W is the wild-type, red-eye allele. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0).

## What ratio of offspring would result from a cross between a white-eyed male and a female that is heterozygous for red eye color?

Half of the female offspring would be heterozygous ($X^WX^w$) with red eyes, and half would be homozygous recessive ($X^wX^w$) with white eyes. Half of the male offspring would be hemizygous dominant ($X^WY$) with red eyes, and half would be hemizygous recessive ($X^wY$) with white eyes.

Discoveries in fruit fly genetics can be applied to human genetics. When a female parent is homozygous for a recessive X-linked trait, she will pass the trait on to 100 percent of her male offspring, because the males will receive the Y chromosome from the male parent. In humans, the alleles for certain conditions (some color-blindness, hemophilia, and muscular dystrophy) are X-linked. Females who are heterozygous for these diseases

are said to be carriers and may not exhibit any phenotypic effects. These females will pass the disease to half of their sons and will pass carrier status to half of their daughters; therefore, X-linked traits appear more frequently in males than females.

In some groups of organisms with sex chromosomes, the sex with the non-homologous sex chromosomes is the female rather than the male. This is the case for all birds. In this case, sex-linked traits will be more likely to appear in the female, in whom they are hemizygous.

### Concept in Action – Sex Linked Traits

**Watch Sex Linked Traits: Baldness and Hemophilia (4 mins) on YouTube (https://youtu.be/-6RGz1YM11o)**

## Linked Genes Violate the Law of Independent Assortment

Although all of Mendel's pea plant characteristics behaved according to the law of independent assortment, we now know that some allele combinations are not inherited independently of each other. Genes that are located on separate, non-homologous chromosomes will always sort independently. However, each chromosome contains hundreds or thousands of genes, organized linearly on chromosomes like beads on a string. The segregation of alleles into gametes can be influenced by linkage, in which genes that are located physically close to each other on the same chromosome are more likely to be inherited as a pair. However, because of the process of **recombination**, or "crossover," it is possible for two genes on the same chromosome to behave independently, or as if they are not linked. To understand this, let us consider the biological basis of gene linkage and recombination.

Homologous chromosomes possess the same genes in the same order, though the specific alleles of the gene can be different on each of the two chromosomes. Recall that during interphase and prophase I of meiosis, homologous chromosomes first replicate and then synapse, with like genes on the homologs aligning with each other. At this stage, segments of homologous chromosomes exchange linear segments of genetic material (Figure 2.49). This process is called recombination, or crossover, and it is a common genetic process. Because the genes are aligned during recombination, the gene order is not altered. Instead, the result of recombination is that maternal and paternal alleles are combined onto the same chromosome. Across a given chromosome, several recombination events may occur, causing extensive shuffling of alleles.

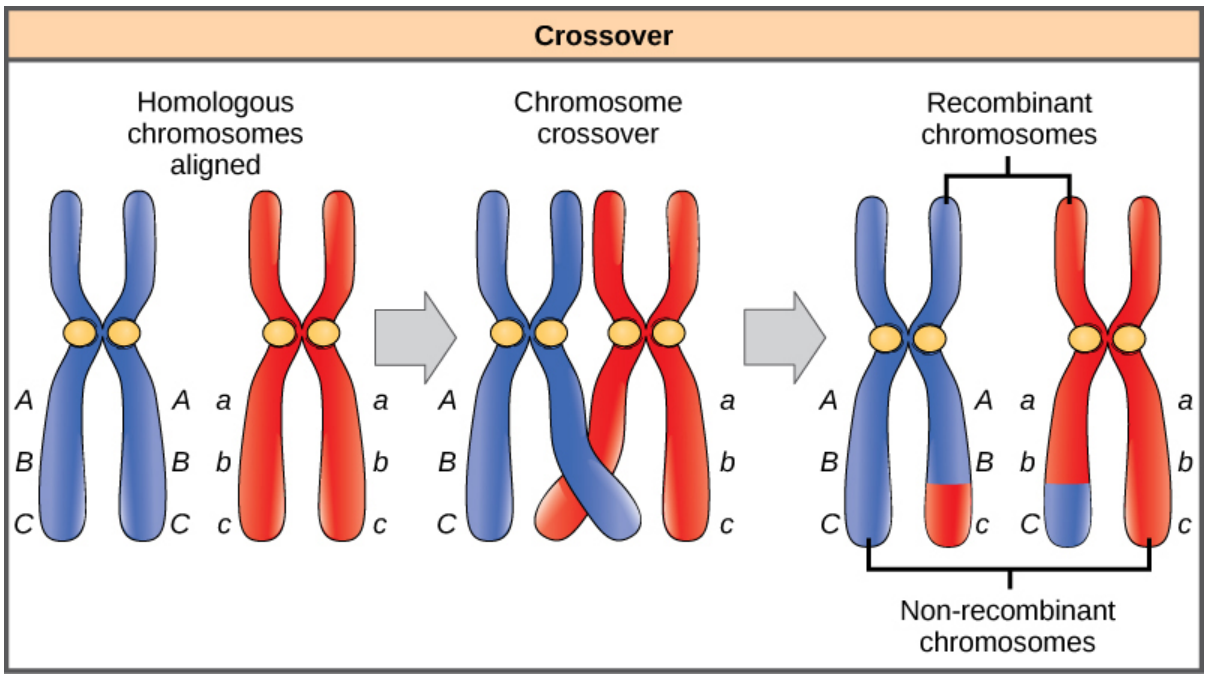


**Figure 2.49** The process of crossover, or recombination, occurs when two homologous chromosomes align and exchange a segment of genetic material. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

When two genes are located on the same chromosome, they are considered linked, and their alleles tend to be transmitted through meiosis together. To exemplify this, imagine a dihybrid cross involving flower color and plant height in which the genes are next to each other on the chromosome. If one homologous chromosome has alleles for tall plants and red flowers, and the other chromosome has genes for short plants and yellow flowers, then when the gametes are formed, the tall and red alleles will tend to go together into a gamete and the short and yellow alleles will go into other gametes. These are called the parental genotypes because they have been inherited intact from the parents of the individual producing gametes. But unlike if the genes were on different chromosomes, there will be no gametes with tall and yellow alleles and no gametes with short and red alleles. If you create a Punnett square with these gametes, you will see that the classical Mendelian prediction of a 9:3:3:1 outcome of a dihybrid cross would not apply. As the distance between two genes increases, the probability of one or more crossovers between them increases and the genes behave more like they are on separate chromosomes. Geneticists have used the proportion of recombinant gametes (the ones not like the parents) as a measure of how far apart genes are on a chromosome. Using this information, they have constructed linkage maps of genes on chromosomes for well-studied organisms, including humans.

Mendel's seminal publication makes no mention of linkage, and many researchers have questioned whether he encountered linkage but chose not to publish those crosses out of concern that they would invalidate his independent assortment postulate. The garden pea has seven chromosomes, and some have suggested that his choice of seven characteristics was not a coincidence. However, even if the genes he examined were not

located on separate chromosomes, it is possible that he simply did not observe linkage because of the extensive shuffling effects of recombination.

## Epistasis

Mendel's studies in pea plants implied that the sum of an individual's phenotype was controlled by genes (or as he called them, unit factors), such that every characteristic was distinctly and completely controlled by a single gene. In fact, single observable characteristics are almost always under the influence of multiple genes (each with two or more alleles) acting in unison. For example, at least eight genes contribute to eye color in humans.

In some cases, several genes can contribute to aspects of a common phenotype without their gene products ever directly interacting. In the case of organ development, for instance, genes may be expressed sequentially, with each gene adding to the complexity and specificity of the organ. Genes may function in complementary or synergistic fashions, such that two or more genes expressed simultaneously affect a phenotype. An apparent example of this occurs with human skin color, which appears to involve the action of at least three (and probably more) genes. Cases in which inheritance for a characteristic like skin color or human height depend on the combined effects of numerous genes are called polygenic inheritance.

Genes may also oppose each other, with one gene suppressing the expression of another. In **epistasis**, the interaction between genes is antagonistic, such that one gene masks or interferes with the expression of another. "Epistasis" is a word composed of Greek roots meaning "standing upon." The alleles that are being masked or silenced are said to be hypostatic to the epistatic alleles that are doing the masking. Often the biochemical basis of epistasis is a gene pathway in which expression of one gene is dependent on the function of a gene that precedes or follows it in the pathway.

An example of epistasis is pigmentation in mice. The wild-type coat color, agouti (AA) is dominant to solid-colored fur (aa). However, a separate gene C, when present as the recessive homozygote (cc), negates any expression of pigment from the A gene and results in an albino mouse (Figure 2.50). Therefore, the genotypes *AAcc*, *Aacc*, and *aacc* all produce the same albino phenotype. A cross between heterozygotes for both genes (*AaCc* x *AaCc*) would generate offspring with a phenotypic ratio of 9 agouti:3 black:4 albino (Figure 2.50). In this case, the *C* gene is epistatic to the *A* gene.

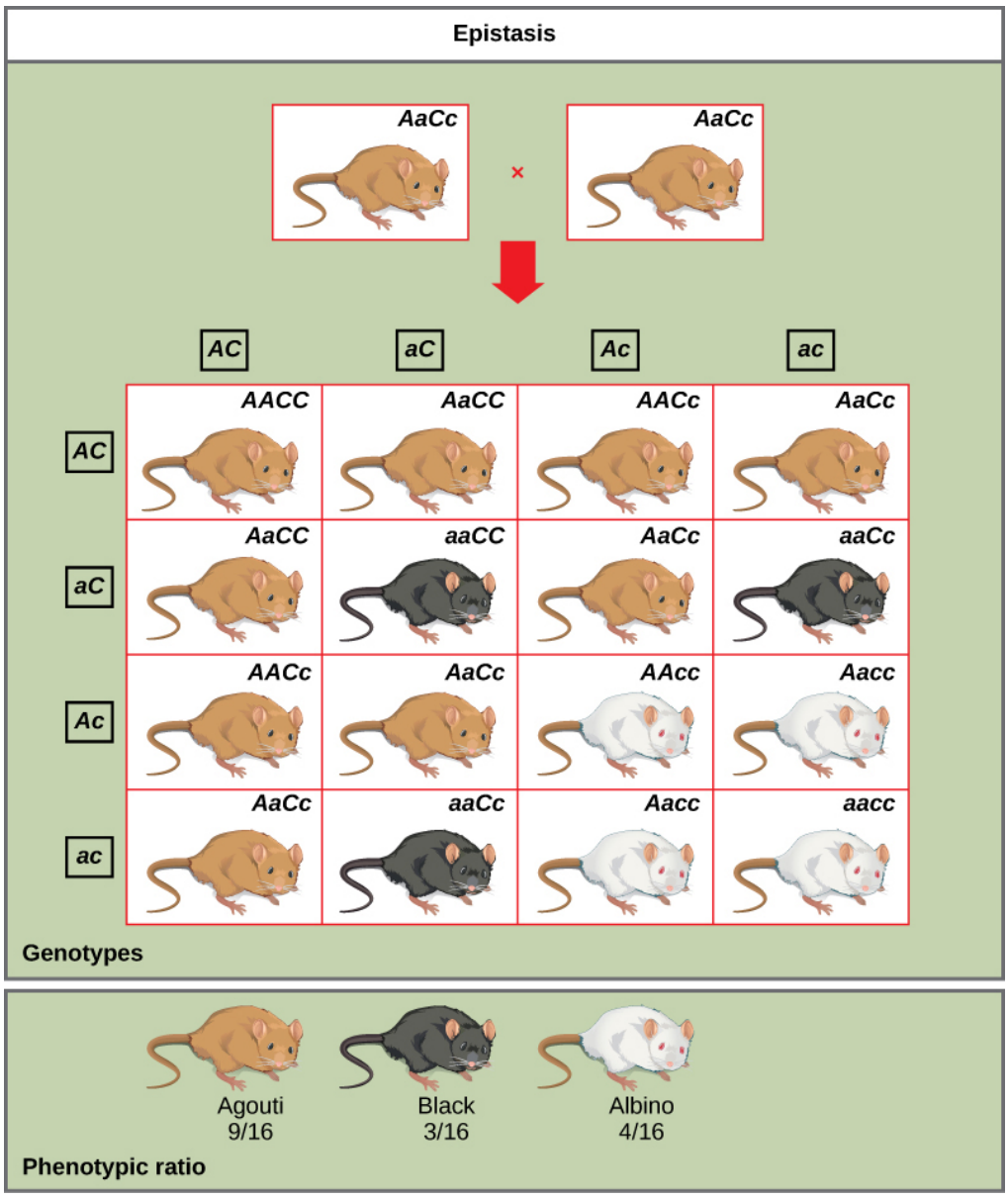


**Figure 2.50** In this example of epistasis, one gene (C) masks the expression of another (A) for coat color. When the C allele is present, coat color is expressed; when it is absent (cc), no coat color is expressed. Coat color depends on the A gene, which shows dominance, with the recessive homozygote showing a different phenotype than the heterozygote or dominant homozygote. **Source:** *Concepts of Biology* (OpenStax), CC BY 4.0.

# Exercises

**Exercises (text version)**

1. Match words into the correct blanks to complete the statements.

    A. Mendel's experiments measured quantitative traits and his analysis was of [Blank a] sample sizes.
    B. One of the incorrect ideas about inheritance prior to Mendel's experiments was that inheritance was a [Blank b] of parental traits.
    C. Mendel worked with common garden [Blank c] plants. The traits showed [Blank d] variation.
    D. The trait that masks the other recessive trait is called [Blank e].
    E. Gene variants that exist at the same chromosomal location are called [Blank f].
    F. Observable traits expressed by an organism are referred to as its [Blank g] where the underlying genetic make-up is known as the [Blank h].
    G. The P generation plants Mendel crossed had 2 alike alleles and are therefore [Blank i] the F1 plants they produced have differing alleles and are therefore [Blank j].
    H. Mendels' Law of [Blank k] refers to the separation of 2 alleles so that gametes contain only one or the other alleles.
    I. If the F1 progeny of a cross show a phenotype that is "in between" the parental phenotypes the trait is said to display [Blank l] dominance.
    J. If the F1 progeny of a cross display both traits displayed in the parents the trait is said to exhibit [Blank m]dominance.
    K. Traits on chromosomes 1-22 are said to be [Blank n] traits and genes on the X chromosome are called [Blank o] linked traits.
    L. Human eye colour is determined by [Blank p] alleles.
    M. Some genes can block or "stand upon" other genes. This is called [Blank q].

2. What traits of pea seed color would you expect to observe in F1 offspring if you cross true-breeding parents with green seeds and yellow seeds, and the yellow seed color is dominant over green?

    a. only yellow-green seeds

b. only yellow seeds
c. 1:1 yellow seeds:green seeds
d. 1:3 green seeds:yellow seeds

3. Which of the following experimental results, in terms of numbers of plants are closest to what you would expect in the F2 progeny of a cross involving seed surface texture in garden pea plants? True-breeding round and wrinkled parents were crossed to obtain F1 offspring.

   a. 810 round seeds
   b. 810 wrinkled seeds
   c. 405:395 round seeds:wrinkled seeds
   d. 610:190 round seeds:wrinkled seeds

4. True or false? One of the reasons that the garden pea was an excellent choice of model systems for studying inheritance is that the flowers close tightly during self-pollination to prevent accidental or unintentional fertilizations that could have diminished the accuracy of Mendel's data.
5. Select the correct words from the pair in bold type to answer the question.
   **Question:** Based on the following data, can you tell if the parent plant is homozygous dominant or heterozygous? In pea plants, round peas (*R*) are dominant to wrinkled peas (*r*). You do a test cross between a pea plant with wrinkled peas (genotype *rr*) and a plant of unknown genotype that has round peas. You end up with three plants, all which have round peas.
   **Answer:** You cannot be sure if the plant is homozygous or heterozygous as the data set is too **[Pair A: large or small]**: by **[Pair B: mathematical or random]** chance, all three plants might have acquired only the **[Pair C: recessive or dominant*]** gene even if the **[Pair D: recessive or dominant]** one is present.
6. Fill in the missing words to answer the questions:
   **Question:** What are the possible genotypes and phenotypes for a cross between *PpYY* and *ppYy* pea plants where purple flowered pea plants (*P*) are dominant to white flowered pea plants (*p*), and yellow peas (*Y*) are dominant to green (*y*)? How many squares would you need to complete a Punnett square analysis of this cross?
   **Answer:** The possible genotypes are [Blank A]**PpYY/PpYy**, [Blank B]**PpYY/PpYy**, [Blank C]**ppYY/ppYy**, and [Blank D]**ppYY/ppYy**. The former two genotypes would result in plants with [Blank E]*purple* flowers and [Blank F]*yellow* peas, while the latter two genotypes would result in plants with [Blank G]*white* flowers with [Blank H]*yellow* peas, for a 1:1 ratio of each phenotype. You only need a [Blank i]*2 × 2* Punnett square, [Blank J]*four*

squares total to do this analysis because two of the alleles are homozygous.

7. What are the observable traits expressed by an organism called?

    a. phenotype
    b. genotype
    c. alleles
    d. zygote

8. What is it called when a recessive trait will be observed in individuals?

    a. heterozygous
    b. homozygous or heterozygous
    c. homozygous
    d. diploid

9. What are the types of gametes that can be produced by an individual with the genotype *AaBb?*

    a. *Aa*, *Bb*
    b. *AA*, *aa*, *BB*, *bb*
    c. *AB*, *Ab*, *aB*, *ab*
    d. *AB*, *ab*

10. What is the reason for doing a test cross?

    a. to identify heterozygous individuals with the dominant phenotype
    b. to determine which allele is dominant and which is recessive
    c. to identify homozygous recessive individuals in the F2
    d. to determine if two genes assort independently

11. Match the words to the correct blanks to answer the question.
    **Question:** What is the phenotypic ratio of the offspring where a Punnett square is used to predict the offspring in a cross between a dwarf pea plant (homozygous recessive) and a tall pea plant (heterozygous)?
    **Words:** 2 × 2 , genotypes, tall, t and t, T and t, dwarf
    **Answer:** The phenotypic ratio will be 1 [Blank A]:1 [Blank B], and the Punnett square would be [Blank C] and will have [Blank D] along the top and [Blank E] along the left side. Clockwise from the top left, the [Blank F] listed within the boxes will be Tt, tt, tt, and Tt.

12. Match the words to the correct blanks to answer the question.

**Question:** Describe a Punnett square used to predict the offspring in a cross between a tall pea plant (heterozygous) and a tall pea plant (heterozygous). What is the genotypic ratio of the offspring?

**Words: 1TT,** 2 × 2, Tt, 1tt, TT, tt, 2Tt, T and t

**Answer:** The Punnett square will be [Blank A] and will have [Blank B] along the top and [Blank C] along the left side. Clockwise from the top left, the genotypes listed within the boxes will be [Blank D], [Blank E], [Blank F], and [Blank G]. The genotypic ratio will be [Blank H]: [Blank i]: [Blank J].

**Check your answers in footnote**[4]

**Activity source:** *Concepts of Biology – 1st Canadian Edition*, CC BY 4.0

# Glossary

**Summary of additional key terms introduced in this chapter:**

4.

1. a) large, b) blend, c) pea, d) discontinuous, e) dominant, f) alleles, g) phenotype, h) genotype, i) homozygous, j) heterozygous, k) segregation, l) incomplete, m) co-, n) autosomal, o) X/sex, p) multiple, q) epistasis.
2. b) only yellow seeds
3. d) 610:190 round seeds:wrinkled seeds
4. True. The garden pea has flowers that close tightly during self-pollination. This helps to prevent accidental or unintentional fertilizations that could have diminished the accuracy of Mendel's data.
5. A: small, B: random, C: dominant, D: recessive
6. A – *PpYY/PpYy*, B – *PpYY/PpYy,* C – *ppYY/ppYy,* D – *ppYY/ppYy,* E – purple, F – yellow, G – white, H – yellow, i – 2 × 2, J – four
7. a) phenotype
8. c) homozygous
9. c) *AB*, *Ab*, *aB*, *ab*
10. a) to identify heterozygous individuals with the dominant phenotype
11. A – tall, B – dwarf, C – 2 × 2, D – T and t, E – t and t, F – genotypes
12. A – 2 × 2, B – T and t, C – T and t, D – TT, E – Tt, F – Tt, G – tt, H- 1TT, i – 2Tt, J – 1tt.

**P:** the parental generation in a cross

## Attribution & References

Except where otherwise noted, content on this page is adapted from 8.1 Mendel's Experiments, 8.2 Laws of Inheritance, and 8.3 Extensions of the Laws of Inheritance, In *Concepts of Biology – 1st Canadian Edition* by Charles Molnar and Jane Gair, CC BY 4.0. A derivative of *Concepts of Biology (OpenStax),* CC BY 4.0 and *Biology 2e (OpenStax)*, CC BY 4.0. Access *Concepts of Biology* (https://openstax.org/books/concepts-biology/pages/1-introduction) and *Biology 2e* (https://openstax.org/books/biology-2e/pages/1-introduction) for free at OpenStax / Adaptations: Individual sections have been combined and streamlined, including minor edits to improve student understanding and provide context.

# 2.7 UNIT SUMMARY AND REVIEW

## Key Takeaways

### The Genome

Eukaryotes have multiple, linear chromosomes surrounded by a nuclear membrane. Human somatic cells have 46 chromosomes consisting of two sets of 22 homologous chromosomes and a pair of nonhomologous sex chromosomes. This is the 2n, or diploid, state. Human gametes have 23 chromosomes or one complete set of chromosomes. This is the n, or haploid, state. Genes are segments of DNA that code for a specific protein or RNA molecule. An individual's traits are the observable or measurable features of an organism which are determined in large part by the genes inherited from each parent, but also by the environment that they experience. An individual's phenotype encompasses all traits, including those that are visible and those that are not (such as behavior). Genes are expressed as characteristics of the organism, and each characteristic may have different variants called traits that are caused by differences in the DNA sequence for a gene, which can be the distinguishing feature between two individuals.

### The Cell Cycle

The cell cycle is an orderly sequence of events. Cells on the path to cell division proceed through a series of precisely timed and carefully regulated stages. In eukaryotes, the cell cycle consists of a long preparatory period, called interphase. Interphase is divided into G1, S, and G2 phases. Mitosis consists of five stages: prophase, prometaphase, metaphase, anaphase, and telophase. Mitosis is usually accompanied by cytokinesis, during which the cytoplasmic components of the daughter cells are separated by an actin ring (animal cells). Each step of the cell cycle is monitored by internal controls called checkpoints. There are three major checkpoints in the cell cycle: one near the end of G1, a second at the G2–M transition, and the third during metaphase.

## Cancer and the Cell Cycle

Cancer is the result of unchecked cell division caused by a breakdown of the mechanisms regulating the cell cycle. The loss of control begins with a change in the DNA sequence of a gene that codes for one of the regulatory molecules. Faulty instructions lead to a protein that does not function as it should. Any disruption of the monitoring system can allow other mistakes to be passed on to the daughter cells. Each successive cell division will give rise to daughter cells with even more accumulated damage. Eventually, all checkpoints become nonfunctional, and rapidly reproducing cells crowd out normal cells, resulting in tumorous growth.

## The Cellular Basis of Inheritance

Nearly all eukaryotes undergo sexual reproduction. The variation introduced into the reproductive cells by meiosis appears to be one of the advantages of sexual reproduction that has made it so successful. Meiosis and fertilization alternate in sexual life cycles. The process of meiosis produces genetically unique reproductive cells called gametes, which have half the number of chromosomes as the parent cell. Fertilization, the fusion of haploid gametes from two individuals, restores the diploid condition. Thus, sexually reproducing organisms alternate between haploid and diploid stages. However, the ways in which reproductive cells are produced and the timing between meiosis and fertilization vary greatly. There are three main categories of life cycles: diploid-dominant, demonstrated by most animals; haploid-dominant, demonstrated by all fungi and some algae; and alternation of generations, demonstrated by plants and some algae.

## Meiosis

Sexual reproduction requires that diploid organisms produce haploid cells that can fuse during fertilization to form diploid offspring. The process that results in haploid cells is called meiosis. Meiosis is a series of events that arrange and separate chromosomes into daughter cells. During the interphase of meiosis, each chromosome is duplicated. In meiosis, there are two rounds of nuclear division resulting in four nuclei and usually four haploid daughter cells, each with half the number of chromosomes as the parent cell. During meiosis, variation in the daughter nuclei is introduced because of crossover in prophase I and random alignment at metaphase I. The cells that are produced by meiosis are genetically unique.

Meiosis and mitosis share similarities, but have distinct outcomes. Mitotic divisions are single nuclear divisions that produce daughter nuclei that are genetically identical and have the same

number of chromosome sets as the original cell. Meiotic divisions are two nuclear divisions that produce four daughter nuclei that are genetically different and have one chromosome set rather than the two sets the parent cell had. The main differences between the processes occur in the first division of meiosis. The homologous chromosomes separate into different nuclei during meiosis I causing a reduction of ploidy level. The second division of meiosis is much more similar to a mitotic division.

## Patterns of Inheritance

Working with garden pea plants, Mendel found that crosses between parents that differed for one trait produced F1 offspring that all expressed one parent's traits. The traits that were visible in the F1 generation are referred to as dominant, and traits that disappear in the F1 generation are described as recessive. When the F1 plants in Mendel's experiment were self-crossed, the F2 offspring exhibited the dominant trait or the recessive trait in a 3:1 ratio, confirming that the recessive trait had been transmitted faithfully from the original P parent. Reciprocal crosses generated identical F1 and F2 offspring ratios. By examining sample sizes, Mendel showed that traits were inherited as independent events.

When true-breeding, or homozygous, individuals that differ for a certain trait are crossed, all of the offspring will be heterozygous for that trait. If the traits are inherited as dominant and recessive, the F1 offspring will all exhibit the same phenotype as the parent homozygous for the dominant trait. If these heterozygous offspring are self-crossed, the resulting F2 offspring will be equally likely to inherit gametes carrying the dominant or recessive trait, giving rise to offspring of which one quarter are homozygous dominant, half are heterozygous, and one quarter are homozygous recessive. Because homozygous dominant and heterozygous individuals are phenotypically identical, the observed traits in the F2 offspring will exhibit a ratio of three dominant to one recessive.

Mendel postulated that genes (characteristics) are inherited as pairs of alleles (traits) that behave in a dominant and recessive pattern. Alleles segregate into gametes such that each gamete is equally likely to receive either one of the two alleles present in a diploid individual. In addition, genes are assorted into gametes independently of one another. That is, in general, alleles are not more likely to segregate into a gamete with a particular allele of another gene.

Alleles do not always behave in dominant and recessive patterns. Incomplete dominance describes situations in which the heterozygote exhibits a phenotype that is intermediate between the homozygous phenotypes. Codominance describes the simultaneous expression of both of the alleles in the heterozygote. Although diploid organisms can only have two alleles for any given

gene, it is common for more than two alleles for a gene to exist in a population. In humans, as in many animals and some plants, females have two X chromosomes and males have one X and one Y chromosome. Genes that are present on the X but not the Y chromosome are said to be X-linked, such that males only inherit one allele for the gene, and females inherit two.

According to Mendel's law of independent assortment, genes sort independently of each other into gametes during meiosis. This occurs because chromosomes, on which the genes reside, assort independently during meiosis and crossovers cause most genes on the same chromosomes to also behave independently. When genes are located in close proximity on the same chromosome, their alleles tend to be inherited together. This results in offspring ratios that violate Mendel's law of independent assortment. However, recombination serves to exchange genetic material on homologous chromosomes such that maternal and paternal alleles may be recombined on the same chromosome. This is why alleles on a given chromosome are not always inherited together. Recombination is a random event occurring anywhere on a chromosome. Therefore, genes that are far apart on the same chromosome are likely to still assort independently because of recombination events that occurred in the intervening chromosomal space.

Whether or not they are sorting independently, genes may interact at the level of gene products, such that the expression of an allele for one gene masks or modifies the expression of an allele for a different gene. This is called epistasis.

## DNA Structure and Function

The model of the double-helix structure of DNA was proposed by Watson and Crick. The DNA molecule is a polymer of nucleotides. Each nucleotide is composed of a nitrogenous base, a five-carbon sugar (deoxyribose), and a phosphate group. There are four nitrogenous bases in DNA, two purines (adenine and guanine) and two pyrimidines (cytosine and thymine). A DNA molecule is composed of two strands. Each strand is composed of nucleotides bonded together covalently between the phosphate group of one and the deoxyribose sugar of the next. From this backbone extend the bases. The bases of one strand bond to the bases of the second strand with hydrogen bonds. Adenine always bonds with thymine, and cytosine always bonds with guanine. The bonding causes the two strands to spiral around each other in a shape called a double helix. Ribonucleic acid (RNA) is a second nucleic acid found in cells. RNA is a single-stranded polymer of nucleotides. It also differs from DNA in that it contains the sugar ribose, rather than deoxyribose, and the nucleotide uracil rather than thymine. Various RNA molecules function in the process of forming proteins from the genetic code in DNA.

Prokaryotes contain a single, double-stranded circular chromosome. Eukaryotes contain double-

stranded linear DNA molecules packaged into chromosomes. The DNA helix is wrapped around proteins to form nucleosomes. The protein coils are further coiled, and during mitosis and meiosis, the chromosomes become even more greatly coiled to facilitate their movement. Chromosomes have two distinct regions which can be distinguished by staining, reflecting different degrees of packaging and determined by whether the DNA in a region is being expressed (euchromatin) or not (heterochromatin).

DNA replicates by a semi-conservative method in which each of the two parental DNA strands act as a template for new DNA to be synthesized. After replication, each DNA has one parental or "old" strand, and one daughter or "new" strand.

Replication in eukaryotes starts at multiple origins of replication, while replication in prokaryotes starts from a single origin of replication. The DNA is opened with enzymes, resulting in the formation of the replication fork. Primase synthesizes an RNA primer to initiate synthesis by DNA polymerase, which can add nucleotides in only one direction. One strand is synthesized continuously in the direction of the replication fork; this is called the leading strand. The other strand is synthesized in a direction away from the replication fork, in short stretches of DNA known as Okazaki fragments. This strand is known as the lagging strand. Once replication is completed, the RNA primers are replaced by DNA nucleotides and the DNA is sealed with DNA ligase.

The ends of eukaryotic chromosomes pose a problem, as polymerase is unable to extend them without a primer. Telomerase, an enzyme with an inbuilt RNA template, extends the ends by copying the RNA template and extending one end of the chromosome. DNA polymerase can then extend the DNA using the primer. In this way, the ends of the chromosomes are protected. Cells have mechanisms for repairing DNA when it becomes damaged or errors are made in replication. These mechanisms include mismatch repair to replace nucleotides that are paired with a non-complementary base and nucleotide excision repair, which removes bases that are damaged such as thymine dimers.

In prokaryotes, mRNA synthesis is initiated at a promoter sequence on the DNA template. Elongation synthesizes new mRNA. Termination liberates the mRNA and occurs by mechanisms that stall the RNA polymerase and cause it to fall off the DNA template. Newly transcribed eukaryotic mRNAs are modified with a cap and a poly-A tail. These structures protect the mature mRNA from degradation and help export it from the nucleus. Eukaryotic mRNAs also undergo splicing, in which introns are removed and exons are reconnected with single-nucleotide accuracy. Only finished mRNAs are exported from the nucleus to the cytoplasm.

The central dogma describes the flow of genetic information in the cell from genes to mRNA to proteins. Genes are used to make mRNA by the process of transcription; mRNA is used to synthesize proteins by the process of translation. The genetic code is the correspondence between

the three-nucleotide mRNA codon and an amino acid. The genetic code is "translated" by the tRNA molecules, which associate a specific codon with a specific amino acid. The genetic code is degenerate because 64 triplet codons in mRNA specify only 20 amino acids and three stop codons. This means that more than one codon corresponds to an amino acid. Almost every species on the planet uses the same genetic code.

The players in translation include the mRNA template, ribosomes, tRNAs, and various enzymatic factors. The small ribosomal subunit binds to the mRNA template. Translation begins at the initiating AUG on the mRNA. The formation of bonds occurs between sequential amino acids specified by the mRNA template according to the genetic code. The ribosome accepts charged tRNAs, and as it steps along the mRNA, it catalyzes bonding between the new amino acid and the end of the growing polypeptide. The entire mRNA is translated in three-nucleotide "steps" of the ribosome. When a stop codon is encountered, a release factor binds and dissociates the components and frees the new protein.

While all somatic cells within an organism contain the same DNA, not all cells within that organism express the same proteins. Prokaryotic organisms express the entire DNA they encode in every cell, but not necessarily all at the same time. Proteins are expressed only when they are needed. Eukaryotic organisms express a subset of the DNA that is encoded in any given cell. In each cell type, the type and amount of protein is regulated by controlling gene expression. To express a protein, the DNA is first transcribed into RNA, which is then translated into proteins. In prokaryotic cells, these processes occur almost simultaneously. In eukaryotic cells, transcription occurs in the nucleus and is separate from the translation that occurs in the cytoplasm. Gene expression in prokaryotes is regulated only at the transcriptional level, whereas in eukaryotic cells, gene expression is regulated at the epigenetic, transcriptional, post-transcriptional, translational, and post-translational levels.

## Additional Optional Reading:

1. Aiello, L. B., & Chiatti, B. D. (2017). Primer in Genetics and Genomics, Article 4-Inheritance Patterns. *Biological research for nursing*, *19*(4), 465–472. https://doi.org/10.1177/1099800417708616

## Attribution & References

been combined and streamlined, including minor edits to improve student understanding and provide context.

# UNIT 3 - THE EXPOSOME

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 3 Contents


- 3.1 Unit Overview
- 3.2 Nature vs. Nurture
- 3.3 Epigenetics
- 3.4 Developmental Origins of Health and Disease
- 3.5 The Exposome
- 3.6 Adverse Early Childhood Experiences
- 3.7 Epigenetics in Practice
- 3.8 Unit Summary and Review


## Attribution

# 3.1 UNIT OVERVIEW

## Learning Objectives

- Explore whether the nature–nurture debate is still relevant.
- Examine the research designs that can be used to study nature–nurture questions.
- Define genetic determinism and identify how it relates to epigenetics.
- Review the developmental origins of health and disease and the impacts on long-term health outcomes.
- Establish how the exposome can influence gene expression.
- Determine the relationship between the social determinants of health and genetics and identify policy implications.
- Explore how adverse early childhood experiences or toxic stress can lead to adverse health outcomes later in life.
- Establish the significance of epigenetics to practice.

## Outline

Topics covered in this chapter include:

- Nature vs nurture
- Epigenetics
- Developmental origins of health and disease
- The exposome
- Adverse early childhood experiences
- Epigenetics in practice

# Competencies Nurses will Develop in this Chapter

## ANA (2023):

### Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).

### Provision of education, care, and support:

- Uses health promotion and disease prevention practices that consider genomic influences as well as personal and environmental risk factors.

## NHS (2023):

### Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the importance of family history in assessing predisposition to a genetic condition;

### Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions; and
  relating it to the prevention and management of a genomic condition or response to treatment.

### Provide ongoing nursing care and support to patients, carers, families and communities with genomic healthcare needs:

- being responsive to changing needs through the life-stages and during periods of uncertainty.

# Key terminology

## Adverse Childhood Experiences (ACEs)

ACEs are potentially traumatic events that occur in childhood (0-17 years) and can include, but are not limited to experiencing violence, abuse, or neglect, witnessing violence in the home or community, having a family member attempt of die by suicide, growing up with substance use or mental health issues in the home, parental separation or divorce, or having family members in prison. ACEs can have a lasting effect on health and well-being well into adulthood (CDC, 2024).

## Adoption study

A behavior genetic research method that involves comparison of adopted children to their adoptive and biological parents (Tuckheimer, 2024).

## Behavioral genetics

The empirical science of how genes and environments combine to generate behavior (Tuckheimer, 2024).

## Critical Periods

Periods of development where an organism is susceptible to the influence of environmental exposures on organ development and gene expression (OTIS, 2023).

## Deletion

A deletion, as related to genomics, is a type of mutation that involves the loss of one or more nucleotides from a segment of DNA. A deletion can involve the loss of any number of nucleotides, from a single nucleotide to an entire piece of a chromosome.

## Developmental Programming

The process where environmental exposures and experiences during critical developmental periods influence gene expression and shape the structure, function, and long-term health outcomes including growth, metabolism, and neurodevelopment of an individual (Padmanabhan et al., 2016).

## Diagnostic Odyssey

The often long period of time it can take for a patient to receive a diagnosis for their condition (Genomics Education Programme, 2021).

## Environmental Factors

Environmental factors, as related to genetics, refers to exposures to substances (such as pesticides or industrial waste) where we live or work, behaviors (such as smoking or poor diet) that can increase an individual's risk of disease or stressful situations (such as racism). Genetic studies often take environmental factors into consideration, as these exposures can increase an individual's risk of genetic damage or disease.

## Epigenetics

Epigenetics (also sometimes called epigenomics) is a field of study focused on changes in DNA that do not involve alterations to the underlying sequence. The DNA letters and the proteins that interact with DNA can have chemical modifications that change the degrees to which genes are turned on and off. Certain epigenetic modifications may be passed on from parent cell to daughter cell during cell division or from one generation to the next. The collection of all epigenetic changes in a genome is called an epigenome.

## Exposome

The measure of all the exposures of an individual in a lifetime and how those exposures relate to health (CDC, 2022).

## Fraternal Twins

Fraternal twins (also called dizygotic twins) result from the fertilization of two separate eggs with two different sperm during the same pregnancy. Fraternal twins may not have the same sex or appearance. They share half their genomes, just like any other siblings. In contrast, identical twins (or monozygotic twins) result from the fertilization of a single egg by a single sperm, with the fertilized egg then splitting into two. As a result, identical twins share the same genomes and are always the same sex.

## Gene Expression

Gene expression is the process by which the information encoded in a gene is used to either make RNA molecules that code for proteins or to make non-coding RNA molecules that serve other functions. Gene expression acts as an “on/off switch” to control when and where RNA molecules and proteins are made and as a “volume control” to determine how much of those products are made. The process of gene expression is carefully regulated, changing substantially under different conditions. The RNA and protein products of many genes serve to regulate the expression of other genes.

## Gene Regulation

Gene regulation is the process used to control the timing, location and amount in which genes are expressed. The process can be complicated and is carried out by a variety of mechanisms, including through regulatory proteins and chemical modification of DNA. Gene regulation is key to the ability of an organism to respond to environmental changes.

## Gene–Environment Interaction

Gene–environment interaction refers to the interplay of genes (and, more broadly, genome function) and the physical and social environment. These interactions influence the expression of phenotypes. For example, most human traits and diseases are influenced by how one or more genes interact in complex ways with environmental factors, such as chemicals in the air or water, nutrition, ultraviolet radiation from the sun and social context.

## Genetic Determination

Is the belief that one’s biological/genetic nature if fixed and is the sole determinant of phenotype (Harden, 2023).

## Genetic Imprinting

Genomic imprinting is the process by which only one copy of a gene in an individual (either from their mother or their father) is expressed, while the other copy is suppressed. Unlike genomic mutations that can affect the ability of inherited genes to be expressed, genomic imprinting does not affect the DNA sequence itself. Instead, gene expression is silenced by the epigenetic addition of chemical tags to the DNA during egg or sperm formation. Epigenetic tags on imprinted genes usually stay in place for the life of the individual.

## Heritability Coefficient

An easily misinterpreted statistical construct that purports to measure the role of genetics in the explanation of differences among individuals (Tuckheimer, 2024).

## Identical Twins

Identical twins (also called monozygotic twins) result from the fertilization of a single egg by a single sperm, with the fertilized egg then splitting into two. Identical twins share the same genomes and are nearly always the same sex. In contrast, fraternal (dizygotic) twins result from the fertilization of two separate eggs with two different sperm during the same pregnancy. Like most other siblings, fraternal twins share half of their genomes. The sex of one fraternal twin has no relation to the sex of the other and they may not have similar appearances.

## Neuronal (or synaptic) Pruning

Synaptic pruning is a process that occurs in the brain between early childhood and adulthood where the brain eliminates extra synapses that are not being used (Gill, 2018).

## Quantitative Genetics

Scientific and mathematical methods for inferring genetic and environmental processes based on the degree of genetic and environmental similarity among organisms (Tuckheimer, 2024).

## Rare Disease

A disease that affects less than 1 in 2,000 of the general population (EU definition). In the UK, approximately 3.5 million people will be affected by a rare disease at some point in their life (Rare Disease UK) (Genomics Education Programme, 2022).

## Twin Studies

A behavior genetic research method that involves comparison of the similarity of identical (monozygotic; MZ) and fraternal (dizygotic; DZ) twins (Tuckheimer, 2024).

### Uniparental Disomy

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent. UPD can occur as a random event during the formation of egg or sperm cells, or it may happen during early fetal development (NIH: National Library of Medicine, n.d.).

## Attribution & References



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- Definitions for Rare Disease & Diagnostic Odessey from *Genomics Glossary* by Genomics Education Programme, CC BY-NC

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# 3.2 NATURE VS. NURTURE

People have a deep intuition about what has been called the "nature-nurture question." Some aspects of our behaviour feel like they originate in our genetic makeup, while others feel like the result of our upbringing or our hard work. The scientific field of behaviour genetics attempts to study these differences empirically by examining similarities among family members with different degrees of genetic relatedness or, more recently, by studying differences in the DNA of people with different behavioural traits. The scientific methods that have been developed are ingenious but often inconclusive. Many of the difficulties encountered in the empirical science of behaviour genetics turn out to be conceptual, and our intuitions about nature and nurture get more complicated the harder we think about them. Ultimately, it is an oversimplification to ask how "genetic" some particular behaviour is. Genes and environments always combine to produce behaviour.

## Introduction

It may seem obvious that we are born with certain characteristics while others are acquired. Yet, of the questions about humans' relationship with the natural world, only nature–nurture gets referred to as a "debate." We are concerned with nature–nurture because our very sense of moral character seems to depend on it. While we may admire the athletic skills of a great basketball player, we think of his height as simply a gift, a payoff in the "genetic lottery." For the same reason, no one blames a short person for his height or someone's congenital disability on poor decisions. But we praise the concert violinist (and perhaps her parents and teachers) for her dedication, just as we condemn cheaters, slackers, and bullies for their bad behaviour.

The problem is most human characteristics aren't usually as clear-cut as height or instrument mastery, affirming our nature-nurture expectations strongly one way or the other. Even the great violinist might have some inborn qualities—perfect pitch or long, nimble fingers—that support and reward their hard work. And the basketball player might have eaten a diet while growing up that promoted their genetic tendency to be tall. When we think about our qualities, they seem under our control in some respects yet beyond our control in others. Often, the traits that don't seem to have an apparent cause are the ones that concern us the most and are far more personally significant.

Researchers have learned a great deal about the nature-nurture dynamic by working with animals. But many of the techniques used to study animals cannot be applied to people. Separating these two influences in human subjects is a more significant research challenge. **Source:** Photo by Sebastián Dario, CC BY-NC 2.0

One major problem with answering nature-nurture questions about people is how do you set up an experiment. In nonhuman animals, there are relatively straightforward experiments for tackling nature-nurture questions. Say, for example, you are interested in aggressiveness in dogs. You want to test for the more important determinant of aggression: being born to aggressive dogs or being raised by them. You could mate two aggressive dogs—angry Chihuahuas—together and two nonaggressive dogs—happy beagles—together, then switch half the puppies from each litter between the different sets of parents to raise. You would then have puppies born to aggressive parents (the Chihuahuas) but being raised by nonaggressive parents (the Beagles), and vice versa, in litters that mirror each other in puppy distribution. The big questions are: Would the Chihuahua parents raise aggressive beagle puppies? Would the beagle parents raise nonaggressive Chihuahua puppies? Would the puppies' nature win out, regardless of who raised them? Or... would the result be a combination of nature and nurture? Much of the most significant nature-nurture research has been done this way (Scott & Fuller, 1998), and animal breeders have been doing it successfully for thousands of years. It is fairly easy to breed animals for behavioural traits.

With people, however, we can't assign babies to parents at random, or select parents with certain behavioural characteristics to mate, merely in the interest of science (though history does include horrific examples of such practices in misguided attempts at "eugenics," the shaping of human characteristics through intentional breeding – we will explore this more in a subsequent unit). Despite our restrictions on setting up human-based experiments, we do see real-world examples of nature-nurture at work in the human sphere—though they only provide partial answers to our many questions.

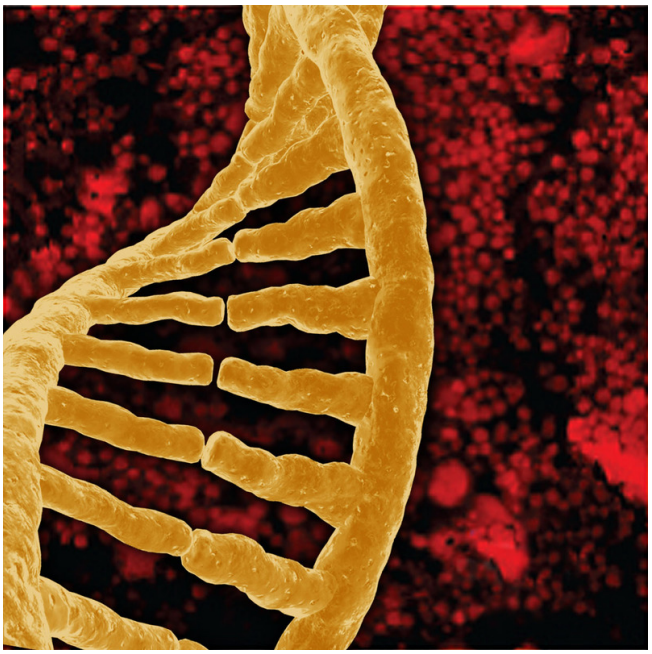
The science of how genes and environments work together to influence behaviour is called behavioural **genetics**. The easiest opportunity we have to observe this is the **adoption study**. When children are adopted, their biological parents do not raise them. If the biological child of tall parents were adopted into a family of short people, do you suppose the child's growth would be affected? What about the biological child of a Spanish-speaking family adopted at birth into an English-speaking family? What language would you expect the child to speak? And what might these outcomes tell you about the difference between height and language in terms of nature-nurture?

Studies focused on twins have led to important insights about the biological origins of many personality characteristics. **Source:** Photo by Pixabay/Pexels, CC0

Another option for observing nature-nurture in humans involves **twin studies**. Two types of twins are **monozygotic (MZ)** and **dizygotic (DZ)**. Monozygotic twins, also called "identical" twins, result from a single zygote (fertilized egg) and have the same DNA. They are essentially clones. Dizygotic twins, also known as "fraternal" twins, develop from two zygotes and share 50% of their DNA. Fraternal twins can be thought of as siblings who happen to have been born at the same time. To analyze nature–nurture using twins, we compare the similarity of MZ and DZ pairs. Sticking with the features of height and spoken language, let's take a look at how nature and nurture apply: Identical twins, unsurprisingly, are almost perfectly similar in height. The heights of fraternal twins, however, are like any other sibling pairs: more similar to each other than to people from other families, but hardly identical. This contrast between twin types gives us a clue about the role genetics plays in determining height. Now consider spoken language. If one identical twin speaks Spanish at home, the co-twin with whom she is raised almost certainly does. But the same would be valid for a pair of fraternal twins raised together. Concerning spoken language, fraternal twins are just as similar as identical twins, so it appears that the genetic match of identical twins doesn't make much difference.

Twin and adoption studies are two instances of a much broader class of methods for observing nature-nurture called **quantitative genetics,** the scientific discipline in which similarities among individuals are analyzed based on how biologically related they are. We can do these studies with siblings and half-siblings, cousins, and twins who have been separated at birth and raised separately (Bouchard, Lykken, McGue, & Segal, 1990; such twins are very rare and play a more minor role than is commonly believed in the science of nature-nurture), or with entire extended families (see Plomin, DeFries, Knopik, & Neiderhiser, 2012, for a complete introduction to research methods relevant to nature-nurture).

For better or for worse, contentions about nature-nurture have intensified because quantitative genetics produces a number called a **heritability coefficient**, varying from 0 to 1, that is meant to provide a single measure of genetics' influence on a trait. Generally, a heritability coefficient measures how strongly differences among individuals are related to differences in their genes. But beware: Heritability coefficients, although simple to compute, are deceptively challenging to interpret. Nevertheless, numbers that provide simple answers to complicated questions tend to strongly influence the human imagination, and a great deal of time has been spent discussing whether the heritability of intelligence or, personality or depression is equal to one number or another.



**Source:** Viral DNA by EMSL, CC BY-NC-SA 2.0

## What Have We Learned About Nature–Nurture?

It would be satisfying to be able to say that nature-nurture studies have given us conclusive and complete evidence about where traits come from, with some traits clearly resulting from genetics and others almost entirely from environmental factors, such as childrearing practices and personal will, but that is not the case. Instead, *everything* has turned out to have some footing in genetics. The more genetically-related people are, the more similar they are—for *everything*: height, weight, intelligence, personality, mental illness, etc. Sure, it seems like common sense that some traits have a genetic bias. For example, adopted children resemble their biological parents even if they have never met them, and identical twins are more similar to each other than are fraternal twins. And while certain psychological traits, such as personality or mental illness (e.g., schizophrenia), seem reasonably influenced by genetics, it turns out that the same is true for political attitudes, how much television people watch (Plomin, Corley, DeFries, & Fulker, 1990), and whether or not they get divorced (McGue & Lykken, 1992).

Over the last half century, research has revealed how central genetics are to behavior. The more genetically related people are, the more similar they are not just physically but also in terms of personality and behavior. **Source:** Photo by Paul Altobelli, CC BY 2.0

It may seem surprising, but the genetic influence on behaviour is a relatively recent discovery. In the middle of the 20th century, psychology was dominated by the doctrine of behaviourism, which held that behaviour could only be explained in terms of environmental factors. Psychiatry concentrated on psychoanalysis, which probed for the roots of behaviour in individuals' early life histories. The truth is, neither behaviourism nor psychoanalysis is incompatible with genetic influences on behaviour, and neither Freud nor Skinner was naive about the importance of organic processes in behaviour. Nevertheless, in their day, it was widely thought that children's personalities were shaped entirely by imitating their parents' behaviour and that schizophrenia was caused by certain kinds of "pathological mothering." Whatever the outcome of our broader discussion of nature-nurture, the basic fact that the best predictors of an adopted child's personality or mental health are found in the biological parents they have never met, rather than in the adoptive parents who raised them, presents a significant challenge to purely environmental explanations of personality or psychopathology. The message is clear: You can't leave genes out of the equation. But remember, no behavioral traits are entirely inherited, so you can't leave the environment out altogether, either.

Trying to untangle the various ways nature-nurture influences human behavior can be messy, and often, common-sense notions can get in the way of good science. One very significant contribution of behavioural genetics that has changed psychology for good can be very helpful to keep in mind: When your subjects are biologically related, no matter how clearly a situation may seem to point to environmental influence, it is never safe to interpret behaviour as wholly the result of nurture without further evidence. For example, when presented with data showing that children whose mothers read to them often are likely to have better reading scores in third grade, it is tempting to conclude that reading to your kids out loud is important to success in school; this may well be true, but the study as described is inconclusive, because there are genetic *as well as* environmental pathways between the parenting practices of mothers and the abilities of their children. This is a case where "correlation does not imply causation," as they say. To establish that reading aloud causes success, a scientist can either study the problem in adoptive families (in which the genetic pathway is absent) or by finding a way to assign children to oral reading conditions randomly.

The outcomes of nature-nurture studies have fallen short of our expectations (of establishing clear-cut

bases for traits) in many ways. The most disappointing outcome has been the inability to organize traits from *more*– to *less*-genetic. As noted earlier, everything has turned out to be at least *somewhat* heritable (passed down), yet nothing has turned out to be *absolutely* heritable, and there hasn't been much consistency as to which traits are *more* heritable and which are *less* heritable once other considerations (such as how accurately the trait can be measured) are taken into account (Turkheimer, 2000). The problem is conceptual: The heritability coefficient, and, in fact, the whole quantitative structure that underlies it, does not match up with our nature-nurture intuitions. We want to know how "important" the roles of genes and environment are to the development of a trait, but in focusing on "important" maybe we're emphasizing the wrong thing. First of all, genes and environment are both crucial to *every* trait; without genes, the environment would have nothing to work on, and genes cannot develop in a vacuum. Even more important, because nature-nurture questions look at the differences among people, the cause of a given trait depends not only on the trait itself but also on the differences in that trait between members of the group being studied.

The classic example of the heritability coefficient defying intuition is the trait of having two arms. No one would argue against the development of arms being a biological, genetic process. But fraternal twins are just as similar to "two-armedness," as identical twins, resulting in a heritability coefficient of zero for the trait of having two arms. Usually, according to the heritability model, this result (coefficient of zero) would suggest all nurture, no nature, but we know that's not the case. This result is not a tip-off that arm development is less genetic than we imagine because people *do not vary* in the genes related to arm development—which essentially upends the heritability formula. In this instance, the opposite is likely true: the extent that people differ in arm number is likely the result of accidents and, therefore, environmental. For reasons like these, we always have to be very careful when asking nature-nurture questions, especially when we try to express the answer in terms of a single number. The heritability of a trait is not simply a property of that trait, but a property of the trait in a particular context of relevant genes and environmental factors.

Another issue with the heritability coefficient is that it divides traits' determinants into two portions—genes and environment—which are then calculated together for the total variability. This is a little like asking how much of the experience of a symphony comes from the horns and how much from the strings; the ways instruments or genes integrate is more complex than that. It turns out to be the case that, for many traits, genetic differences affect behaviour under some environmental circumstances but not others—a phenomenon called gene-environment interaction, or G x E. In one well-known example, Caspi et al. (2002) showed that among maltreated children, those who carried a particular allele of the MAOA gene showed a predisposition to violence and antisocial behaviour, while those with other alleles did not. Whereas in children who had not been maltreated, the gene had no effect. Making matters even more complicated are very recent studies of what is known as epigenetics, which we will discuss in the next chapter of this unit.

Some common questions about nature–nurture are: how susceptible is a trait to change, how malleable is it, and do we "have a choice" about it? These questions are much more complex than they may seem at first glance. For example, phenylketonuria is an inborn error of metabolism caused by a single gene; it prevents the body from metabolizing phenylalanine. Untreated, it causes intellectual disability and death. However, it can be treated effectively by a straightforward environmental intervention: avoiding foods containing phenylalanine. Height seems like a trait firmly rooted in our nature and unchangeable. Still, the average height of many populations in Asia and Europe has increased significantly in the past 100 years due to changes in diet and the alleviation of poverty. Even the most modern genetics has not answered nature–nurture questions definitively. When it was first becoming possible to measure the DNA sequences of individual people, it was widely thought that we would quickly progress to finding the specific genes that account for behavioural characteristics, but that hasn't happened. A few rare genes have been found to have significant (almost always adverse) effects, such as the single gene that causes Huntington's disease, or the Apolipoprotein gene that causes early onset dementia in a small percentage of Alzheimer's cases. Aside from these rare genes of significant effect, the genetic impact on behavior is broken up over many genes, each with minimal effects. For most behavioural traits, the effects are so minor and distributed across so many genes that we have not been able to catalogue them in a meaningful way. The same is true of environmental effects. We know that extreme environmental hardship causes catastrophic effects for many behavioral outcomes, but fortunately, extreme environmental hardship is very rare. Within the usual range of environmental events, those responsible for differences (e.g., why some children in a suburban third-grade classroom perform better than others) are much more challenging to grasp.

The answer to the nature–nurture question has not turned out to be as straightforward as we would like. The many questions we can ask about the relationships among genes, environments, and human traits may have many different answers, and the answer to one tells us little about the answers to the others. **Source:** Photo by Sundaram Ramaswamy, CC BY 2.0

The difficulties with finding clear-cut solutions to nature-nurture problems bring us back to the other great questions about our relationship with the natural world: the mind-body problem and free will. Investigations into what we mean, when we say we are aware of something, reveal that consciousness is not simply the product of a particular area of the brain, nor does choice turn out to be an orderly activity that we can apply to some behaviours but not others. So it is with nature and nurture: What at first may seem a

straightforward matter, able to be indexed with a single number, becomes more and more complicated the closer we look. The many questions we can ask about the intersection among genes, environments, and human traits—how sensitive are traits to environmental change, and how common are those influential environments; are parents or culture more relevant; how sensitive are traits to differences in genes, and how much do the relevant genes vary in a particular population; does the trait involve a single gene or a great many genes; is the trait more easily described in genetic or more-complex behavioural terms?—may have different answers, and the answer to one tells us little about the answers to the others. It is tempting to predict that the more we understand the wide-ranging effects of genetic differences on all human characteristics—especially behavioural ones—our cultural, ethical, legal, and personal ways of thinking about ourselves will have to undergo profound changes in response. One of the most important things modern genetics has taught us is that almost all human behaviour is too complex to be nailed down. The science of nature and nurture has demonstrated that genetic differences among people are vital to human moral equality, freedom, and self-determination, not opposed to them. We should indulge our fascination with nature-nurture while resisting the temptation to oversimplify it.

### Questions for Reflection

1. Is your personality more like one of your parents than the other? If you have a sibling, is their personality like yours? In your family, how did these similarities and differences develop? What do you think caused them?
2. Can you think of a human characteristic for which genetic differences would play almost no role?
3. Do you think the time will come when we can predict almost everything about someone by examining their DNA on the day they are born?
4. Identical twins are more similar than fraternal twins for the trait of aggressiveness, and for criminal behavior. Do these facts have implications for the courtroom? If it can be shown that a violent criminal had violent parents, should it make a difference in culpability or sentencing?

## Outside Resources

- Web: Institute for Behavioral Genetics (http://www.colorado.edu/ibg/)

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# 3.3 EPIGENETICS

## Genetic Determinism

The belief that our biological nature, or genotype, is entirely responsible for an individual's phenotype is also known as "**genetic determinism**." There is no longer a debate over whether nature or nurture exerts the most significant influence on phenotype. We now know it is a combination of the two because our experiences and exposures can influence the expression of genes. The article by Harden (2023) in the optional reading list of 3.8 explores the differences between genetic determinism, essentialism, and reductionism.

## Key points from Harden (2023)

Genetic determinism, essentialism, and reductionism influence how people discuss human genetics, but they are often misunderstood or misused and can lead to everyday discrimination.

- **Genetic determinism** is the belief that a person's traits are entirely determined by their genes, regardless of the environment. In other words, this belief implies that knowing someone's genes would allow you to predict their traits with certainty. Genetic determinism is not the same as heritability. Genetic determinism suggests a causal relationship between genotype and phenotype. Heritability is a statistical measure of the variance due to genetic differences in a population.
    - Example: Having five fingers is often considered genetically determined. However, most traits, like how much education someone completes, are influenced by many factors.
    - Implications of misunderstanding and misuse: This can lead to the false idea that social inequalities are unchangeable.
- **Genetic essentialism** is the idea that DNA gives things an unchanging "essence" that defines what they are. Essentialism views group membership as based on biology, as opposed to social constructs, with distinct boundaries, stability, and exclusivity.
    - Example: It assumes that people with certain traits, like skin colour, also have a more profound genetic similarity.
    - Implications of misunderstanding and misuse can lead to prejudice and stereotypes.
- **Genetic reductionism** is the belief that understanding genes alone can fully explain complex traits or behaviours.
    - Example: It suggests that studying genes is enough to explain conditions like depression. Most scientists support looking at multiple factors, including social and environmental influences.

- Implications of misunderstanding and misuse: It can overemphasize genetic research while ignoring other important factors.

## Epigenetics

**Epigenetics** (sometimes called epigenomics) focuses on changes in DNA that do not involve alterations to the underlying sequence. The term "epigenetics" means above (epi) the gene. The DNA letters and the proteins that interact with DNA can have chemical modifications that change the degrees to which genes are expressed (referred to as **gene expression**) causing alterations to the normal production of proteins from these genes. Certain epigenetic modifications may be passed on from parent to daughter cell during cell division or from generation to generation. Others are acquired throughout life. The collection of all epigenetic changes in a genome is called an epigenome.

### Read

Fessele, K. L., & Wright, F. (2018). Primer in genetics and genomics, article 6: Basics of epigenetic control. *Biological Research for Nursing*, *20*(1), 103–110. https://doi.org/10.1177/1099800417742967 (https://doi.org/10.1177/1099800417742967) .

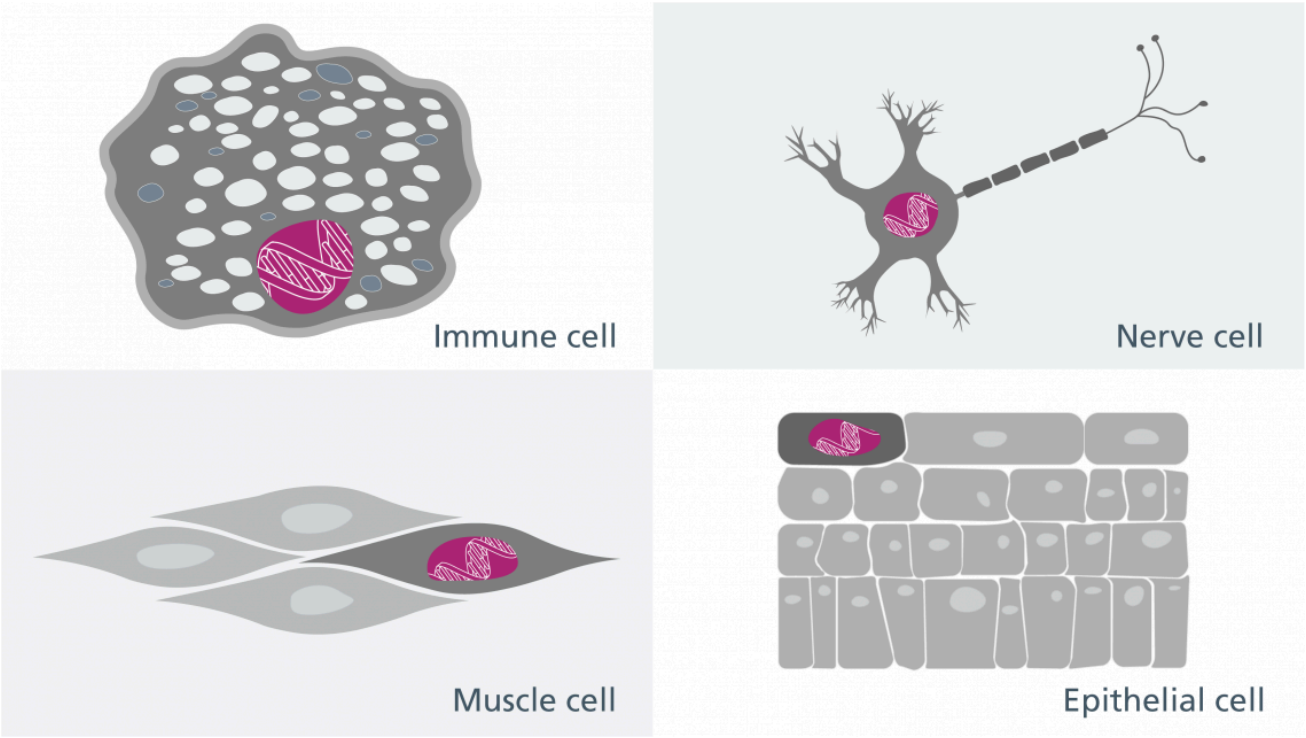


## Same Genome, Different Cell

To understand epigenetics, we must first consider our genome – our DNA. Nearly all the cells in our body contain an identical copy of our genome, which includes the instructions to build and repair us. Yet, despite having the same set of instructions, cells from different tissues and organs can be very diverse. They may look completely different and have very different functions.

Look at the images below to see how four different types of cells can be different despite having an identical genome.

So, if the genome is the same in all these cells, why are they different? The answer is in how the genes are regulated (how they are used in other cells). This process differs between cells and is partly controlled by something called epigenetics.




Differences in cell types despite the same genome. **Source:** Genomics Education Programme, CC BY-NC 4.0

## Types of epigenetic modifications

Many different forms of epigenetic modification take place in, or 'tag,' an organism's genome. – see the gallery below.

The most researched epigenetic modification is DNA methylation, which acts like a dimmer switch, altering gene expression. A chemical called a methyl group attaches to a region near the start of a gene and prevents it from being expressed or reduces expression. For example, methylation of one of the two X chromosomes in every female cell is inactivated during embryonic development. X-chromosome inactivation stops female cells from having twice as many X chromosome gene products as male cells. Hypermethylation often occurs, inhibiting gene expression, but hypomethylation can also occur, resulting in the opposite effect.

Another modification known as chromatin remodelling can alter how tightly the DNA is packaged in the chromosomes, relaxing the tightly packed chromosomes to allow the transcription factors which control gene expression access to the genes within.

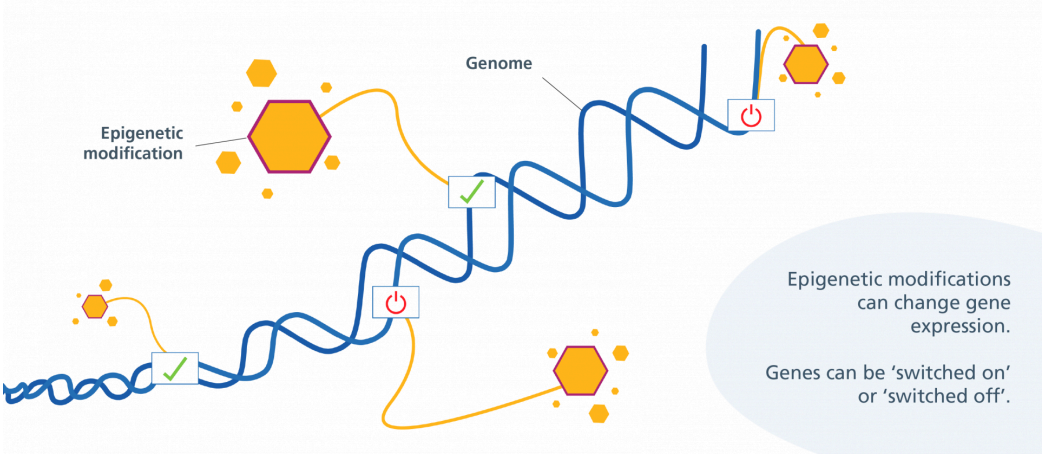
Another type of epigenetic modification degrades (breaks down) the messenger RNA (mRNA) created when DNA is copied by the cell – a process called transcription. Here, non-coding RNA (a type of RNA that does not code for proteins) attaches to the mRNA and marks it for degradation.

Most epigenetic modifications are transient and reversible, allowing our cells to respond and adapt to

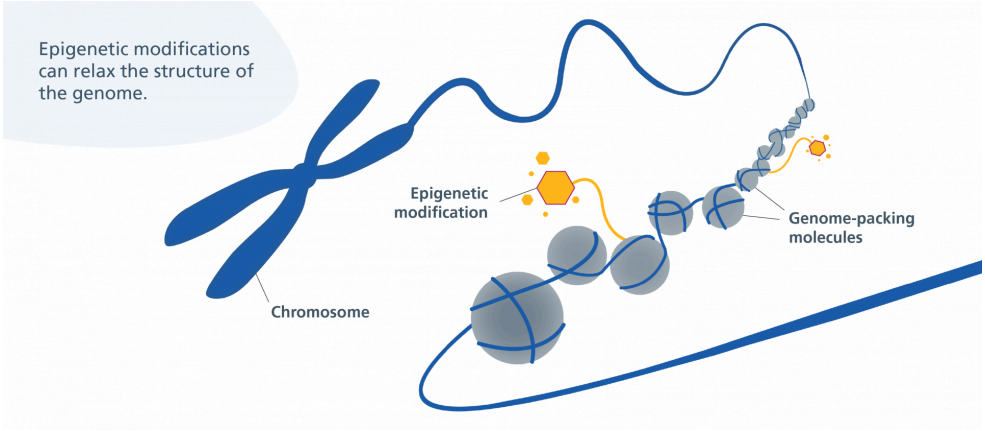
changes in environment and behaviour. Although they happen on a molecular level, they can have a considerable impact on us and can also be influenced by external factors, such as diet and lifestyle.

Without epigenetics, you wouldn't have developed from a fertilized egg to the multicellular organism you are today – and epigenetics will continue to impact on you, regulating specific genes in specific cells, in specific places and at specific times during your growth and development.

**Image slider – text version**




The image displays methyl groups being added to the genome resulting in changes to gene expresson. Epigenetic modifications can change gene expression. Genes can be 'switched on' or 'switched off'. **Source:** Genomics Education Programme, CC BY-NC 4.0




Epigenetic modifications can also relax the structure of the genome making it more accessible. **Source: Genomics Education Programme, CC BY-NC 4.0**

## Concept in Action

**Watch Epigenetics (3 mins) on YouTube (https://youtu.be/ga4n-rGfdVY)** for a short video that

gives a succinct overview of Epigenetics and some of the factors that influence epigenetic modifications.

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# 3.4 DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

## The Developmental Origins of Health and Disease

Epigenetic changes begin before you are born. All your cells have the same genes but look and act differently. As you grow and develop, epigenetics helps determine which function a cell will have. For example, it may become a heart cell, nerve cell, muscle cell, or skin cell.

EXAMPLE: Nerve cell and muscle cell. Your nerve cells and muscle cells have the same DNA, but they work differently. A nerve cell transports information to other cells in your body. A muscle cell has a structure that aids in your body's ability to move. Epigenetics allows the muscle cell to turn on genes to make proteins important for its job and turn off genes important for a nerve cell's job.

The developmental origins of health and disease (DOHaD) paradigm, rooted in the 1980s work of Barker, underscores the critical role of the intrauterine environment in shaping fetal development and influencing health outcomes across generations. The concept of "programming" was initially proposed by Dörner in 1974, who explored how early life exposures, including hormones and neurotransmitters, affect neurodevelopment and adult disease (Koletzko, 2005). Although Dörner suggested **gene-environment interactions** early on, empirical support emerged only with advances in epigenetics. In 1991, Lucas coined the term "developmental programming" (Lucas, 1991).

### Read

Padmanabhan, V., Cardoso, R. C., Puttabyatappa, M. (2016). Developmental programming, a pathway to disease. *Endocrinology*, *157*(4), 1328–1340. https://doi.org/10.1210/en.2016-1003

OPEN ACCESS ONLINE

### Concept in Action

**Watch Developmental origins of health and diseases (DOHaD) (3 mins) on YouTube (https://youtu.be/MDjBNlPyqvs).**

## What are critical periods of development?

In pregnancy, each part of the fetus' body forms during a specific time. This specific time is called the "critical period of development" for that body part. During this critical time of development, the body can be very sensitive to exposures. Examples of exposures may include medications, alcohol, infections, health conditions, or other substances.

### Critical Periods of Development – Fact Sheet

*An interactive H5P element has been excluded from this version of the text. You can view it online here: https://ecampusontario.pressbooks.pub/personalizedhealthnursing/?p=1330#h5p-32*

Access an HTML version of this fact sheet on the NIH Bookself (https://pubmed.ncbi.nlm.nih.gov/35951922).

**Source:** Critical Periods of Development – Mother to Baby Fact Sheet by Organization of Teratology Information Specialists (OTIS), CC BY-NC-ND 3.0.

## Does the chance for different types of birth defects change during pregnancy?

Every pregnancy starts out with a 3-5% chance of having a birth defect. This is called the background risk. If an exposure can increase the chance for birth defects, the chance depends on what body part is developing at the time of exposure. Once a body part has formed, it is no longer at risk to develop major birth defects. Some exposures could still affect a body part's growth and/or function even after that body part has formed.

The chart in the Critical Periods of Development – Fact Sheet (https://www.ncbi.nlm.nih.gov/books/NBK582659/) (above) shows the critical periods of development for different parts of the body. The chart starts from the time of conception when the egg and sperm join. The weeks listed on the chart are the "embryonic age" or "fetal age" of a pregnancy. This is different from a common way of dating a pregnancy called "gestational age." Gestational age begins with the first day of a person's last menstrual period. This day is usually about two weeks before a pregnancy is conceived. For example, 12 gestational weeks (since the first day of your last period) is the same as 10 fetal weeks (since the first day of conception).

Birth defects are physical or structural differences that may change how a body part looks and/or works. Birth defects are typically classified as "major" if they cause significant medical problems and may need surgery or other treatment. Heart defects, spina bifida, and clubfeet are examples of major birth defects. The solid bars on the chart show when each body part is most sensitive to harmful exposures and at risk for major birth defects.

"Minor" birth defects by themselves do not cause significant medical problems and usually do not require treatment or surgery. Minor birth defects can also be variations of typical development. Wide-set eyes and large ears are examples of minor birth defects. The striped bars show periods when the body parts are still at risk of developing minor birth defects and functional defects. "Functional defects" change how a part of the body works without changing how it looks. Intellectual disability and hearing loss are both examples of functional defects.

The chart also shows the location of the most common birth defects that can occur during each week. In general, major birth defects of the body and internal organs are more likely to happen between 3 to 12 embryonic/fetal weeks. This is the same as 5 to 14 gestational weeks (weeks since the first day of your last period). This is also referred to as the first trimester. Minor defects and functional defects, including those affecting how the brain works, can also occur later in pregnancy.

There are certain exposures that are known to contribute to fetal abnormalities, called teratogens, which include certain medications, illegal and legal substances, chemicals, and certain maternal infections. It is also known that environmental exposures can cause epigenetic changes and there is a greater likelihood of an impact on the epigenome during critical periods.

## The First 1000 days

Researchers have learned that the first 1000 days of a child's life are critical to a child's optimal growth and development. How did they come up with the number 1000?

### Concept in Action – the First 1000 Days

**The First 1000 Days (text version)**

- **Watch First 1,000 days Introduction (1 min) on YouTube (https://youtu.be/cLVZUDo41MA)**

**Activity source:** created by Andrea Gretchev, CC BY-NC 4.0 except where otherwise noted.

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- Critical Periods of Development – Mother to Baby Fact Sheet by Organization of Teratology Information Specialists (OTIS), CC BY-NC-ND 3.0.

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Organization of Teratology Information Specialists (OTIS). (2023, February). Critical periods of development, mother to baby | Fact sheets. https://www.ncbi.nlm.nih.gov/books/NBK582659/ CC BY-NC-ND 3.0.

# 3.5 THE EXPOSOME

## Epigenetics and the Influence of the Environment on Gene Expression – The Exposome

### Ontogeny

Ontogeny refers to an organism's development across its entire lifecycle, from fertilization to adulthood. During this process, the genetic blueprint of the organism is expressed under the influence of external factors. In cases of nutrient deficiency, essential organs like the brain receive the majority of the scarce nutrients, prioritizing them over less critical organs, such as the pancreas or kidneys. Research has indicated that if such nutrient allocation happens during a critical developmental period, changes in cellular structure and function may become permanent.

### Epigenetics and age

Your epigenetics change throughout your life. Your epigenetics at birth are not the same as your epigenetics during childhood or adulthood.

EXAMPLE: A newborn, 26-year-old, and 103-year-old. Scientists measured DNA methylation at millions of sites in a newborn, 26-year-old, and 103-year-old. The level of DNA methylation decreased with age. The newborn had the highest level of DNA methylation, the 103-year-old had the lowest level of DNA methylation, and the 26-year-old had a DNA methylation level that was between that of the newborn and the 103-year-old (Heyn et al., 2012).

### The Exposome

Success in mapping the human genome has fostered the complementary concept of the "exposome". The exposome can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health. An individual's exposure begins before birth and includes insults from **environmental factors** and occupational sources. Understanding how exposures from our environment, diet, lifestyle, etc. interact with our own unique characteristics such as genetics, physiology, and epigenetics impact our health is how the exposome will be articulated.

## Epigenetics and exposures

Your epigenetics can change in response to your behaviors and environment.

# Factors that influence the epigenome

Most epigenetic modifications are transient and reversible, allowing our cells to respond and adapt to changes in environment and behaviour. Although they happen on a molecular level, they can have a considerable impact on us. External factors, such as diet and lifestyle can also influence them.


Internal and external factors that influence the epigenome include medications, pollution, family history, toxins, diet/nutrition, alcohol, smoking, infection and exercise. **Source:** Genomics Education Programme (GEP), CC BY-NC 4.0

## Nutrition during pregnancy

A pregnant person's environment and behavior during pregnancy, such as whether they eat healthy food, can change the baby's epigenetics. Some of these changes can remain for decades and might make the child more likely to get certain diseases.

EXAMPLE: Dutch Hunger Winter famine (1944–1945). People whose mothers were pregnant with them during the famine were more likely to develop certain diseases, such as heart disease, schizophrenia, and type 2 diabetes (Roseboom, 2019). Around 60 years after the famine, researchers looked at DNA methylation levels in people whose mothers were pregnant with them during the famine. These people had increased DNA

methylation at some genes and decreased DNA methylation at other genes, compared with their siblings who were not exposed to famine before birth (Tobi et al., 2018). These differences in DNA methylation could help explain why these people had an increased likelihood for certain diseases later in life (Roseboom, 2019; Tobi et al., 2018; Dayeh et al., 2016).

### Concept in Action – Maternal Nutrition

Watch this short video to see how animals models contributed to this theory of maternal nutrition. How can two genetically identical mice look completely different?

**Watch Why do Two Genetically Identical Mice Look Vastly Different? (3 mins) on YouTube (https://youtu.be/IYJ_nd9glvw)**

## Smoking

Exposures such as smoking can cause epigenetic changes. However, these epigenetic changes can be reversible in some cases.

EXAMPLE: Smokers, nonsmokers, and former smokers. Smoking can result in epigenetic changes. For example, at certain parts of the *AHRR* gene, smokers tend to have less DNA methylation than nonsmokers. The difference is greater for heavy smokers and long-term smokers. After quitting smoking, former smokers can begin to have increased DNA methylation at this gene. Eventually, they can reach levels similar to those of nonsmokers. In some cases, this can happen in less than a year, but the length of time depends on how long and how much someone smoked before quitting (McCartney et al., 2018).

### Concept in Action – Foundational Studies

This video provides a good overview of some of the foundational studies that form the basis of what we know about epigenetics today. It also illustrates the many ways in which the exposome can impact the epigenome.

**Watch Epigenetics with Dr. Moshe Szyf (Part 1) (18 mins) on YouTube (https://youtu.be/OEAJmDPJz_I)**

**Food for thought:** Consider the legacy of generational trauma resulting from colonialism. What connections can you make between intergenerational trauma and some of the epidemiological

patterns you may be familiar with regarding non-communicable diseases in some of the populations affected by colonialization? What role does epigenetics play in these health outcomes?

## Exposomics

Exposomics is the study of the exposome and relies on the application of internal and external exposure assessment methods. Internal exposure relies on fields of study such as genomics, metabonomics, lipidomics, transcriptomics and proteomics. Commonalities of these fields include 1) use of biomarkers to determine exposure, effect of exposure, disease progression, and susceptibility factors, 2) use of technologies that result in large amounts of data and 3) use of data mining techniques to find statistical associations between exposures, effect of exposures, and other factors such as genetics with disease. External exposure assessment relies on measuring environmental stressors. Common approaches include using direct reading instruments, laboratory-based analysis, and survey instruments. The extent to which internal and external exposure assessment will contribute to our understanding of the exposome is being debated as each approach has certain merits.

A key factor in describing the exposome is the ability to accurately measure exposures and effect of exposures. Many of the "omics" technologies have the potential to further our understanding of disease causation and progression. Metabonomics and adductomics (DNA and protein adduct measurement) have been used in the past to establish exposure-disease relationships. Research is needed to determine the utility of the "omics" technologies in defining the exposome.

### Why should we study the exposome?

One of the promises of the human genome project was that it could revolutionize our understanding of the underlying causes of disease and aid in the development of preventions and cures for more diseases. However, genetics has been found to account for only about 10% of diseases, and the remaining causes appear to be from environmental causes. So to understand the causes and eventually the prevention of disease, environmental causes need to be studied.

### What are the challenges of advancing exposomics?

Some challenges that may limit the progress in this field of study are evident. An individual's exposome is highly variable and dynamic throughout their lifetime. The impact of exposures can also vary with the individual's stage of life. For examples, exposure to the drugs thalidomide or valproic acid during specific developmental periods in utero causes malformation of limbs; exposure to lead in infants and early childhood

can lead to cognitive deficiencies. Exposures during early years may also predispose an individual to certain chronic diseases later in life.

The impact of environmental or occupational exposures can be different for each individual because of differences in genetic and other personal factors. Some people will develop a disease while another person with the same or greater exposure will not. The exposome may help to determine the underlying causes for this difference. Mapping an entire exposome for an individual will be difficult, if not impossible because of the complexity of a life-time of exposure. Specific exposures can be difficult to measure due to lack of sensitive methods or not knowing that an exposure has even occurred. Even when the exposure is known, measuring that exposure can be difficult since the indicators of exposure may be transient, such as for most chemicals, which are rapidly excreted and only a short time frame exists to directly measure them. In other cases, past exposure can be defined using legacy biomarkers. A common example of a legacy biomarker is antibodies produced by exposures to environmental or occupational insults.

The experience in studying genetic involvement in diseases serves as a model for studying the relationship between exposures and disease. In the past, hypotheses of the role of specific genes in disease were tested. Currently, genome-wide association studies are performed with the aid of new technologies which produce cheaper and faster analyses to generate hypotheses about the relationship between genes and disease. These studies identify gene pathways associated with disease, and, when an association has been identified specific hypotheses about the role of specific genes in disease can be generated and tested. An approach to the exposome is to use internal biological media and measure multiple endpoints. The data would be analyzed to identify associations between health outcomes and biomarkers of exposures, biomarkers of response, or patterns of biomarkers (exposure-wide association studies).

One important aspect of the exposome will be adherence to strict ethical principles as the exposome is deciphered. This will be paramount to ensure that the rights of individuals are not compromised when determining exposures and the relationship to their health.

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# 3.6 ADVERSE EARLY CHILDHOOD EXPERIENCES

## Overview

As you review this material, reflect on how you think the social determinants of health align with the DOHaD paradigm and the influence of the exposome on phenotype development?

- Life history, sociology, and biology combine to create lifelong prospects for health and social success at the earliest stages of life.
- The branch of social epigenetics examines the impacts of health disparities on genetics or how inequities literally "get under our skin."
- Focusing on improving environments can change our biology and disease trajectory for future generations.

### Trigger Warning

This chapter contains material that may be upsetting or distressing. Contents may include discussion of traumatic experiences such as abuse, violence, suicide, mental illness, and racism.

## Adverse Childhood Experiences

Adverse childhood experiences (ACEs) are common and can have lasting, negative effects on health and well-being. They can also negatively impact education and job opportunities.

Children and families thrive when they have access to safe, stable, nurturing relationships and environments. These relationships and environments are essential to creating positive childhood experiences and preventing adverse childhood experiences. The harmful effects of ACEs can affect everyone in our communities, and everyone can help prevent and reduce their impact.

## What are adverse childhood experiences?

Adverse childhood experiences, or ACEs, are potentially traumatic events that occur in childhood (0-17 years). Examples include (Merrick et al., 2019):

- Experiencing violence, abuse, or neglect.

- Witnessing violence in the home or community.
- Having a family member attempt or die by suicide.

Also included are aspects of the child's environment that can undermine their sense of safety, stability, and bonding. Examples can include growing up in a household with (Merrick et al., 2019):

- Substance use problems.
- Mental health problems.
- Instability due to parental separation.
- Instability due to household members being in jail or prison.

The examples above are not a complete list of adverse experiences. Many other traumatic experiences could impact health and well-being. This can include not having enough food to eat, experiencing homelessness or unstable housing, or experiencing discrimination (Cain et al, 2022; *Experiencing discrimination*, 2021; Font et al, 2016; Smith-Grant et al., 2022).

## Quick facts and stats

ACEs are common. About 64% of adults in the United States reported they had experienced at least one type of ACE before age 18. Nearly one in six (17.3%) adults reported they had experienced four or more types of ACEs (Swedo et al., 2023).

Three in four high school students reported experiencing one or more ACEs, and one in five experienced four or more ACEs. ACEs that were most common among high school students were emotional abuse, physical abuse, and living in a household affected by poor mental health or substance abuse (Swedo, et al. 2024).

Preventing ACEs could potentially reduce many health conditions. Estimates show up to 1.9 million heart disease cases and 21 million depression cases potentially could have been avoided by preventing ACEs.1 Preventing ACEs could reduce suicide attempts among high school students by as much as 89%, prescription pain medication misuse by as much as 84%, and persistent feelings of sadness or hopelessness by as much as 66% (Swedo, et al. 2024).

Some people are at greater risk of experiencing one or more ACEs than others. While all children are at risk of ACEs, numerous studies show inequities in such experiences. These inequalities are linked to the historical, social, and economic environments in which some families live (Sedlak et al., 2010; Font et al., 2016). ACEs were highest among females, non-Hispanic American Indian or Alaska Native adults, and adults who are unemployed or unable to work (Swedo et al., 2023).

ACEs are costly. ACEs-related health consequences cost an estimated economic burden of $748 billion annually in Bermuda, Canada, and the United States (Bellis et al., 2019).

# Outcomes

ACEs can have lasting effects on health and well-being in childhood and life opportunities well into adulthood. Life opportunities include things like education and job potential. These experiences can increase the risks of injury, sexually transmitted infections, and involvement in sex trafficking. They can also increase risks for maternal and child health problems including teen pregnancy, pregnancy complications, and fetal death. Also included are a range of chronic diseases and leading causes of death, such as cancer, diabetes, heart disease, and suicide (Ciciolla et al, 2021; Diamond-Welch et al., 2020; Merrick et al., 2020; Mersky et al., 2019; Miller et al., 2021; Read et al., 2019; Sulaiman et al., 2021).

ACEs and associated social determinants of health, such as living in under-resourced or racially segregated neighborhoods, can cause toxic stress (Jones et al., 2020). Toxic stress, or extended or prolonged stress, from ACEs can negatively affect children's brain development, immune system, and stress-response systems (Clements et al., 2024; Ross et al., 2021; Yu et al., 2022).

Children growing up with toxic stress may have difficulty forming healthy and stable relationships. They may also have unstable work histories as adults and struggle with finances, job stability, and depression throughout life (Clements et al., 2024). These effects can also be passed on to their own children (Narayan et al., 2017; Schofield et al., 2018). Some children may face further exposure to toxic stress from historical and ongoing traumas, including experiences of racial discrimination.

### Concept in Action

**Watch Dr. Nadine Burke Harris discuss how childhood trauma can affect health across a lifetime (16 mins) on Ted.com (https://www.ted.com/talks/nadine_burke_harris_how_childhood_trauma_affects_health_across_a_lifetime?language=en)**

# Prevention

Adverse childhood experiences can be prevented. Certain factors may increase or decrease the risk of experiencing adverse childhood experiences. Preventing adverse childhood experiences requires understanding and addressing the factors that put people at risk for or protect them from violence. Creating safe, stable, nurturing relationships and environments for all children prevent ACEs and help all children reach their full potential. These relationships and environments are essential to creating positive childhood experiences.

# Risk factors

### Individual and family risk factors

- Families experiencing caregiving challenges related to children with special needs (for example, disabilities, mental health issues, chronic physical illnesses) (Crouch et al., 2019a).
- Children and youth who don't feel close to their parents/caregivers and feel like they can't talk to them about their feelings (Priyam, P., & Nath, 2021).
- Children and youth with few or no friends or with friends who engage in aggressive or delinquent behavior (Biglan et al., 2017).
- Families with caregivers who were abused or neglected as children (Schickedanz et al., 2018).
- Families with young caregivers or single parents (Crouch et al., 2019b).
- Families with low income (Giovanelli & Reynolds, 2021).
- Families with adults with low levels of education (Hughes et al., 2017).
- Families experiencing high levels of parenting stress or economic stress (Crouch et al., 2019b)
- Families with caregivers who use spanking and other forms of corporal punishment for discipline (Afifi et al., 2017).
- Families that are isolated from and not connected to other people (extended family, friends, neighbors) (Calvano et al., 2021).
- Families with high conflict and negative communication styles (Lackova Rebicova et al., 2020).

### Community risk factors

- Communities with high rates of violence and crime (Lopez-Tomayo et al., 2022).
- Communities with high unemployment rates (Manyema et al., 2019).
- Communities where neighbors don't know or look out for each other and there is low community involvement among residents (Khanijahani & Sualp., 2022).
- Communities with few community activities for young people (Bledsoe et al., 2021).
- Communities with unstable housing and where residents move frequently (Barnes et al., 2021).
- Communities where families frequently experience low socioeconomic status and food insecurity (Manyema et al., 2019).
- Communities with high levels of social and environmental disorder (Gentner & Leppert, 2019).

# Protective factors

### Individual and family protective factors

- Families who create safe, stable, and nurturing relationships, meaning children have a consistent family life where they are safe, taken care of, and supported (Asmundson, 2019; Luther, 2019)
- Children who have positive friendships and peer networks (Guo et al., 2021; Luther, 2019; Narayan et al., 2018)
- Children who do well in school (Bethell et al., 2022; Goetschius et al., 2021; Liu et al., 2020; Narayan et al., 2018)
- Children who have caring adults outside the family who serve as mentors or role models (Bellis et al., 2022; Narayan et al., 2018).
- Families where caregivers can meet basic needs of food, shelter, and health services for children (Narayan et al., 2018; Liu et al., 2020).
- Families where caregivers have college degrees or higher (Merrick et al., 2018; Nabors et al., 2021)
- Families where caregivers have steady employment (Liu et al., 2020; Merrick et al., 2018).
- Families with strong social support networks and positive relationships with the people around them (Bethell et al., 2019; Bethell et al., 2022; Guo et al., 2021; Letourneau et al., 2020; Luther, 2019; Narayan et al., 2018).
- Families where caregivers engage in parental monitoring, supervision, and consistent enforcement of rules (Bethell et al., 2022; Bethell et al., 2019; Guo et al., 2021; Liu et al., 2020).
- Families where caregivers/adults work through conflicts peacefully (Bethell et al., 2022; Bethell et al., 2019; Nabors et al., 2021).
- Families where caregivers help children work through problems (Bethell et al., 2022; Bethell et al., 2019; Nabors et al., 2021).
- Families that engage in fun, positive activities together (Bethell et al., 2019; Nabors et al., 2021).
- Families that encourage the importance of school for children (Liu et al., 2020).

**Community protective factors**

- Communities where families have access to economic and financial help (Dietz, 2017; Sege et al., 2017).
- Communities where families have access to medical care and mental health services (Dietz, 2017; Sege et al., 2017)
- Communities with access to safe, stable housing (Sege et al., 2017)
- Communities where families have access to nurturing and safe childcare (Sege et al., 2017).
- Communities where families have access to safe, engaging after school programs and activities (Dietz, 2017)
- Communities where adults have work opportunities with family-friendly policies (Dietz, 2017).
- Communities with strong partnerships between the community and business, health care, government, and other sectors (Dietz, 2017).
- Communities where residents feel connected to each other and are involved in the community (Narayan

et al., 2018; Dietz, 2017).

### Concept in Action

**Watch Moving Forward (3 mins) on YouTube**

## Why prevention is important (CDC, 2024)

Every child possesses incredible potential for health, well-being, and making a positive impact. When we prevent ACEs, we also prevent potential later involvement in violence, substance use, depression, and suicidal behavior. We also reduce the risk of other health challenges like cancer, diabetes, and heart disease.

All children deserve the best chance at lifelong health and well-being. Preventing, identifying, and responding to ACEs is the most powerful way to achieve this. Working together, we can help create neighborhoods, communities, and a world in which every child can thrive.

## Neurodevelopment

Neurodevelopment is the process by which the brain and nervous system grow and mature, particularly during early life. The growing brain is extremely susceptible to inputs from the environment, particularly during critical periods. During these times, factors such as attachment and environmental influences play a crucial role in shaping brain architecture and function. Secure attachment and a nurturing environment promote optimal cognitive, emotional, and social development, while adverse conditions, such as neglect or stress, can disrupt neurodevelopmental pathways, leading to long-term implications for behavior and mental health.

### Neurodevelopment and the importance of strong parental attachments

Review the four videos by using the interactive slide show, or click to watch on YouTube in the text version.

**Neurodevelopment and the importance of strong parental attachments (text version)**

1. Watch Experiences Build Brain Architecture (2 mins) on YouTube (https://youtu.be/VNNsN9IJkws)
2. Watch Serve & Return Interaction Shapes Brain Circuitry (2 mins) on YouTube (https://youtu.be/m_5u8-QSh6A)
3. Watch Toxic Stress Derails Healthy Development (2 mins) on YouTube (https://youtu.be/rVwFkcOZHJw)
4. Watch InBrief: The Science of Neglect (6 mins) on YouTube (https://youtu.be/bF3j5UVCSCA)



The first 1000 days is not the only critical period. Adolescence is also a period of vulnerability. Learn how early experiences and genetic predispositions can impact the develop of psychiatric disorders later in life.

**Watch Dr. Dan Siegel – Brainstorm: Adolescence, opportunity, vulnerability, and pruning (2 mins) on YouTube**

# Resilience

## What does resilience have to do with genetics? Resilience is a protective factor.

**Watch InBrief: The Science of Resilience (2 mins) on YouTube**

# Attribution & References

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Adaptation & use notes: Updated references have been added to original source material to enhance student learning. Use of CDC material does not imply endorsement by CDC. Material is otherwise available on the CDC website free of charge.

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# 3.7 EPIGENETICS IN PRACTICE

## The Impact on Health and Clinical Practice

Certain diseases can change your epigenetics. In addition, some epigenetic changes can make you more likely to develop certain diseases, such as cancer.

### Infections (CDC, n.d.)

Germs can change your epigenetics to weaken your immune system. This helps the germ survive.

EXAMPLE: *Mycobacterium tuberculosis* causes tuberculosis. Infections with these germs can cause epigenetic changes in some of your immune cells that result in turning off the *IL-12B* gene. Turning off the *IL-12B* gene weakens your immune system and improves the survival of *Mycobacterium tuberculosis* (Chandran et al., 2015).

### Cancer (CDC, n.d.)

Certain gene variants make you more likely to develop cancer. Likewise, some epigenetic changes increase your cancer risk. Most cancers display different epigenetic patterns than those of healthy cells, and these patterns can be important for the development of the disease. For example, some genes produce proteins that stop cell growth and division. If expression is suppressed in these genes when it shouldn't be, this could cause cells to divide uncontrollably, leading to cancer development. Additionally, having a mutation in the *BRCA1* gene that prevents it from working properly makes you more likely to get breast and other cancers. Similarly, increased DNA methylation that results in decreased *BRCA1* gene expression raises your risk for breast and other cancers (Tang et al., 2016). While cancer cells have increased DNA methylation at certain genes, overall DNA methylation levels are lower in cancer cells compared with normal cells. These differences can help us to understand, manage and treat cancers more effectively. However, epigenetics alone cannot diagnose cancer. Cancers would need to be confirmed with further screening tests. An example of the use of epigenetics in cancer diagnostics is the methylation profile of tumours can help to grade the current stage of a cancer or to track the disease as it progresses over time. Further, many drugs have been discovered that target specific epigenetic modifications, either by removing them or preventing their removal – depending on the desired effect. These drugs are mostly used to treat different types of cancer, but there is ongoing work to establish their effectiveness for other conditions.

EXAMPLE: Colorectal cancers have abnormal DNA methylation near certain genes, which affects

expression of these genes. Some commercial colorectal cancer screening tests (for example, Cologuard®) use stool samples to look for this abnormal DNA methylation. It is important to know that if the result of one of these tests is positive or abnormal, further screening is required with a colonoscopy (Chan & Liang, 2022).

## Epigenomic studies spotlight new level of cancer evolution (NHS, 2023 (https://www.genomicseducation.hee.nhs.uk/blog/epigenomic-studies-spotlight-new-level-of-cancer-evolution/))

Two studies cast a light on the role of epigenomics in oncology. A multi-omic level of cancer evolution has been characterized by researchers from the Institute of Cancer Research. In a pair of *Nature* publications, they highlighted the importance of epigenomic changes to a cancer's resilience, and how genome-only testing methods may be missing important cancer markers. Every cancer is different, yet even within one mass, its cells are not identical: the cells can differ by which genes they express and their susceptibility to treatment. Both studies examined the evolution of colorectal cancers and tried to understand why cells within a cancer differ in terms of what drives cancer growth and cancer cell survival.

### Epigenomic changes are common

In the first of the two studies (https://www.nature.com/articles/s41586-022-05202-1), researchers looked at 30 patients with bowel cancer. They examined each cancer's genome and its epigenome. Using this multi-omic approach, they found that changes to the epigenome were common around a cancer's driver genes. Cancer driver genes are genes that are normally involved in a cell's division and growth but gene variants alter their normal functioning. Additionally, the epigenomic changes were found to be passed on to the next generation of cells; they were present in cancer cells that had survival advantages over other cells.

### Tumours persist due to variation across its cells

Cells within a cancer mass can often be different from each other. The second study took a deep dive into the differences found within tumours (https://www.nature.com/articles/s41586-022-05311-x). The researchers did this by sampling many different sections of individual tumours to understand how and why the cells of a single cancer can be so diverse. They found that, while there is variation in the expression of genes within tumours, in most cases this doesn't alter the ability of cells to survive or grow. However, if the cancer's environment changes (such as during anti-cancer treatment), then this variation becomes important for its future survival as it may mean that some of its cells survive while others do not. Ultimately, it's the cancer's surviving cells that pass on their resistance to treatment to their daughter cells, meaning the cancer, in some form, persists.

"For years our understanding of cancer has focused on gene variants which permanently change the DNA code," said Institute of Cancer Research director and lead author Professor Trevor Graham, "But our research

has shown that the way the DNA folds up can change which genes are read without altering the DNA code, and this can be very important in determining how cancers behave."

## How is this being used in practice?

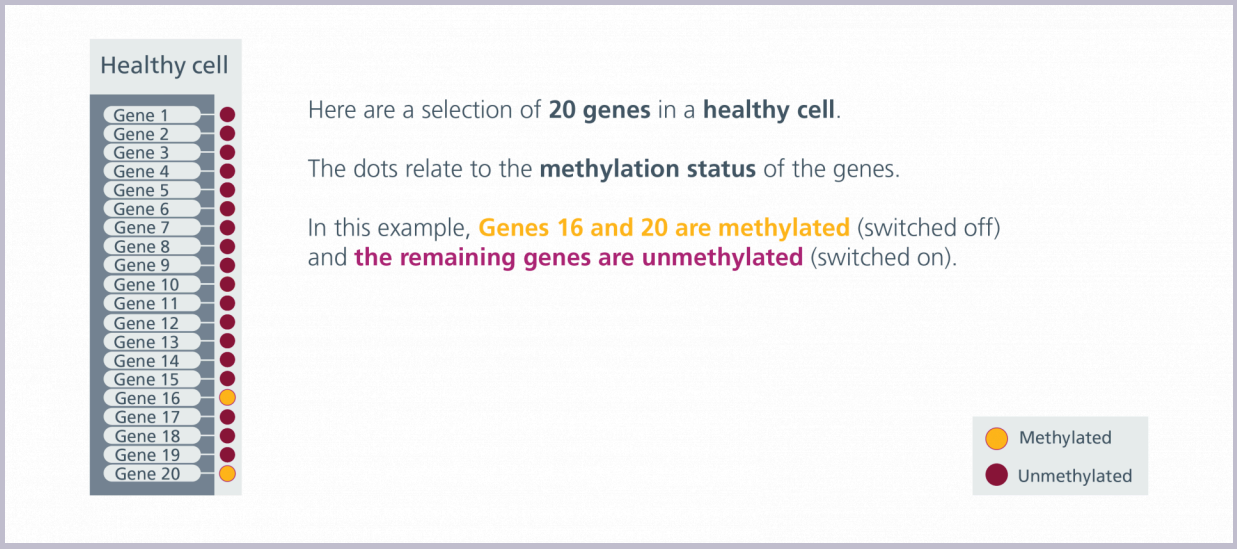
Knowledge around cancer epigenomics and how it fuels cancer growth is already being used in cancer detection. For example, the Galleri multi-cancer test (https://www.genomicseducation.hee.nhs.uk/blog/nhs-to-trial-new-multi-cancer-blood-test/), uses epigenomic markers to detect non-symptomatic cancers. Yet the epigenome is not widely being used in precision cancer treatment. If it was, Professor Graham noted that, "we could, potentially, much more accurately predict which treatments will work best for a particular person's cancer." Tools are available that could make personalized cancer treatment a reality, such as long-read sequencing approaches, like nanopore, which allow real-time 'reading' of DNA to understand the genome, and parts of the epigenome too.

To learn more about the latest advances in epigenetics and its real-world impact on healthcare, visit the dedicated epigenomics topic on the NHS Genomics Education Programme's blog (https://www.genomicseducation.hee.nhs.uk/blog/tag/epigenomics/).

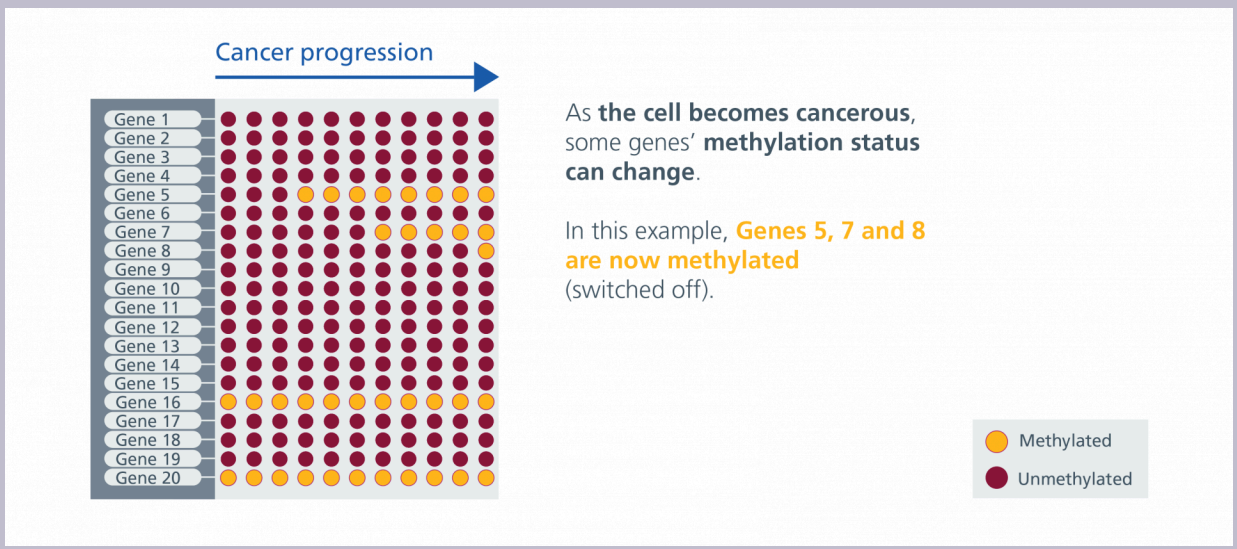
Check out the gallery below to see how epigenetic patterns can change between healthy cells and cancer cells.

Epigenetic Patterns in Health and Cancerous Cells – Gallery

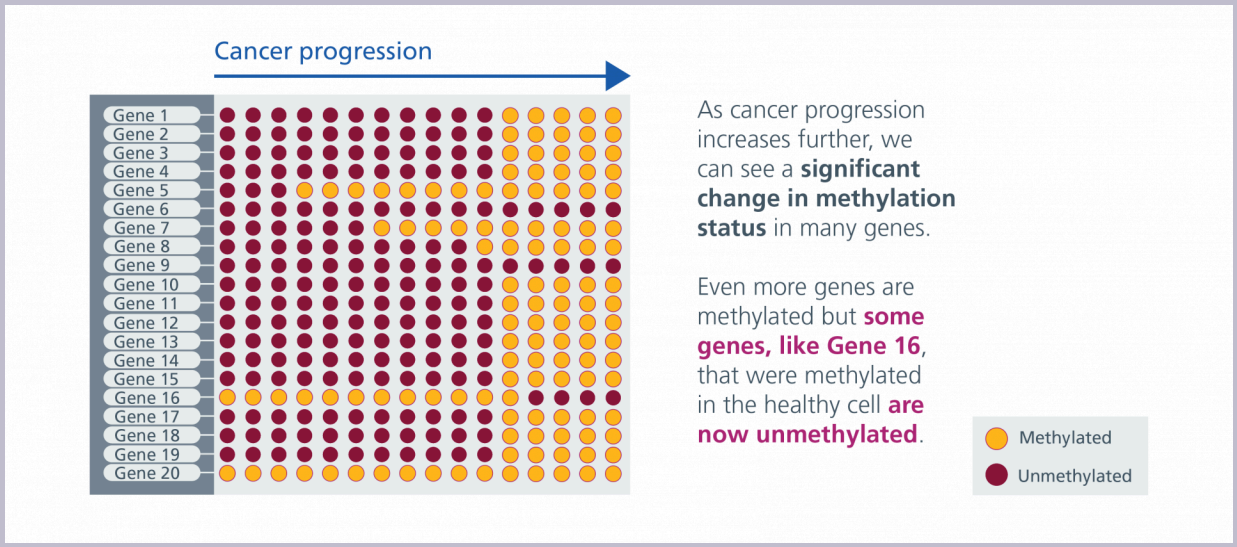
**Epigenetic Patterns in Health and Cancerous Cells – Gallery (text version)**



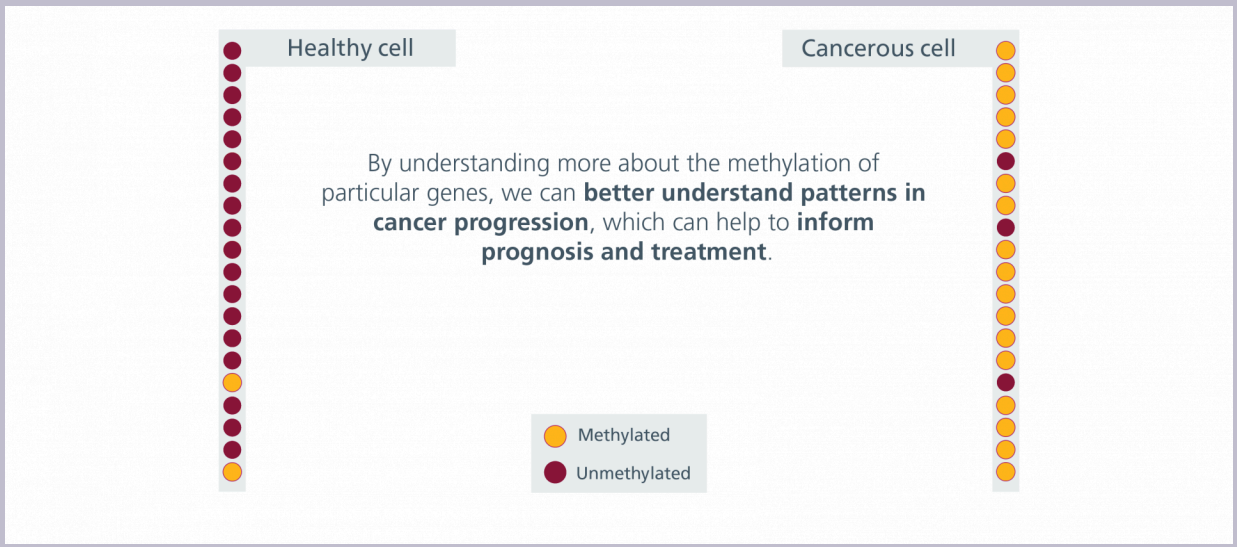

**Healthy Cell Methylation Status:** A healthy cell is shown with 20 genes. Dots represent methylation status of genes. Genes 16 and 20 are methylated (switched off) and the remaining genes are unmethylated (switched on). **Source:** Genomics Education Programme, CC BY-NC 4.0.




Cancer Progression: As the cell becomes cancerous some genes' methylation status changes. Now genes 5, 7, and 8 appear methylated (switched off). **Source:** Genomics Education Programme, CC BY-NC 4.0.




**Further cancer progression:** As cancer progresses further there is a significant change in methylation status in many genes. Even more genes are methylated but some genes, like Gene 16 that were methylated in the healthy cell are now unmethylated. **Source:** Genomics Education Programme, CC BY-NC 4.0.




**Cancer and Healthy Cell Comparison:** The image shows methylation in a healthy cell vs cancerous cell. Understanding methylation of genes helps us understand patterns in cancer progression, which can help to inform prognosis and treatment. **Source:** Genomics Education Programme, CC BY-NC 4.0.

**Source:** Genomics Education Programme, CC BY-NC 4.0

# Imprinting disorders

Individually a **rare disease** is rare, but collectively they are common. Many people with rare diseases often go through a **diagnostic odyssey** with many tests that do not necessarily lead to an explanation or treatment for their disease. It is thought that the majority of rare diseases have a genetic cause. Finding this cause can lead to a diagnosis and possibly treatment options. Increasingly, more people with undiagnosed rare diseases are undergoing genomic testing which is providing a diagnosis for some. Not everyone who has a genomic test will receive a diagnosis initially, but those without a diagnosis may receive one as more is discovered about the function of the genome.

A variety of factors can cause rare diseases. Many occur because of alterations to the DNA sequence itself, but some can be caused by epigenetic modifications: in other words, changes in gene expression. **Genomic imprinting** is one such modification that affects the regulation of certain genes, but how can it cause disease?

As we have learned, epigenetic changes happen because our gene expression is altered by various mechanisms. This suppression or amplification of gene expression is very common, and indeed is an important part of normal, healthy gene regulation. However, if this regulation is disrupted, it can lead to certain genes being over or under expressed, or silenced completely.

Although many of our genes are affected by epigenetic modifications, only a very small percentage are known to undergo genomic imprinting. These genes are mostly found in two clusters – one on the short arm of chromosome 11 and the other on the long arm of chromosome 15.

# How genomic imprinting works

Genomic imprinting refers to the process by which certain genes are 'branded' with the parent of origin. When gametes (sperm and eggs) are made, epigenetic markers that were inherited from our parents or accumulated in life are removed, but in genes that undergo genomic imprinting, new markers are added that identify the gene as coming from either the mother or the father.

These new markers change gene expression, resulting in the imprinted copy of the gene being turned off and the other copy being turned on. For example, if the allele inherited from the father is imprinted, it is silenced and only the allele from the mother is expressed; if the allele from the mother is imprinted, then only the allele from the father is expressed.

# Uniparental disomy

Genomic imprinting can cause disease when there are errors in gamete production, or during early embryonic development. One common complication is **uniparental disomy (UPD)**, which is when a person inherits two copies of a chromosome from one parent, and none from the other.

When the chromosome in question does not contain imprinted regions, UPD may have no deleterious effects, but when chromosomes 11 or 15 are involved, the situation can be more complex. Because some genes in these regions are inactivated by maternal or paternal imprinting, an individual who inherits two copies from one parent can lack an active copy of some essential genes – even though they are present in the genome.

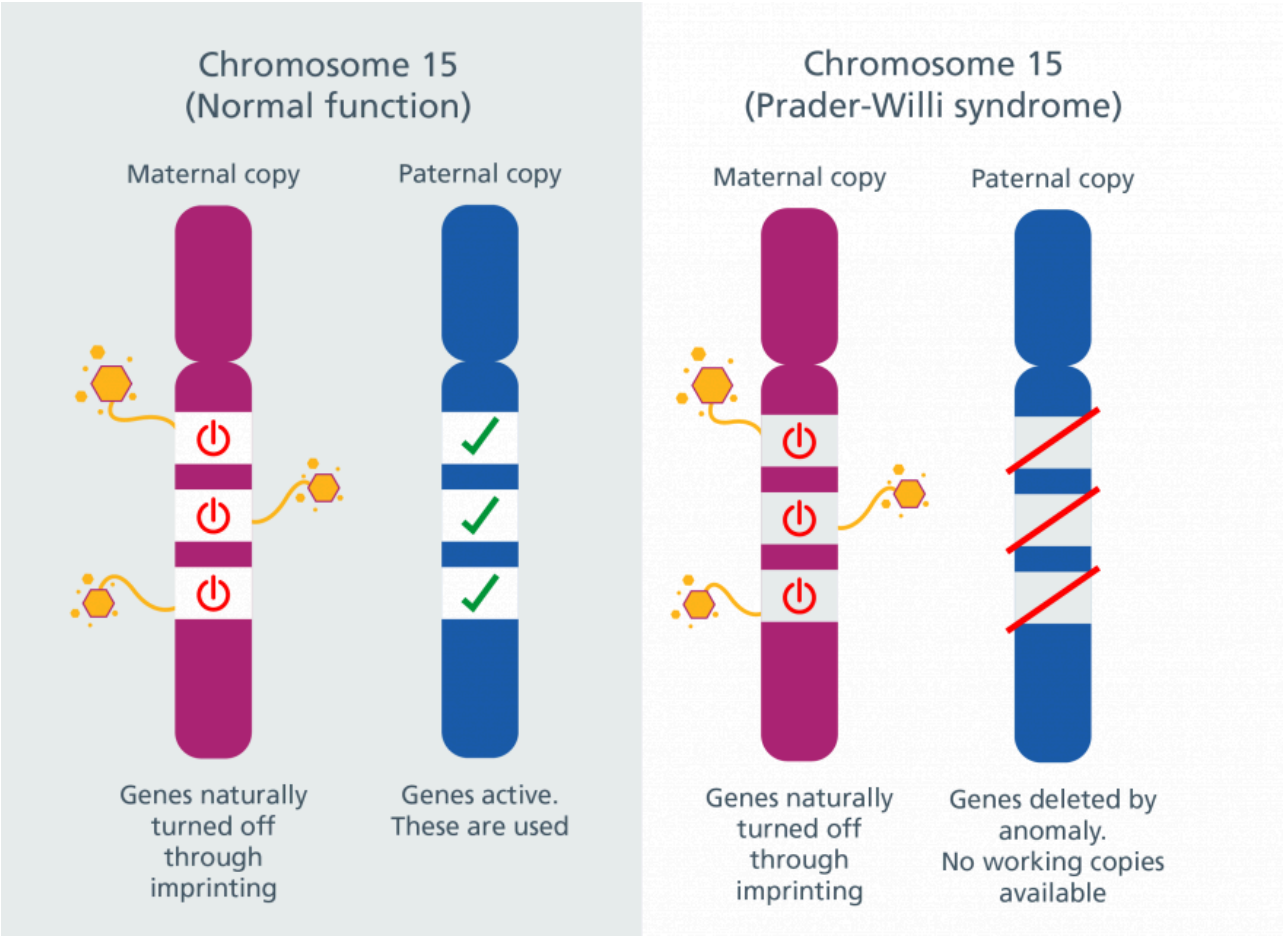
## Which conditions can it cause?

The first conditions that were identified as being caused by imprinting were Angelman Syndrome and Prader-Willi Syndrome. Both conditions are caused by missing genetic information on chromosome 15 – one of the chromosomes where genomic imprinting is common.

Angelman syndrome (https://www.nhs.uk/conditions/angelman-syndrome/) occurs when the *UBE3A* gene is not working properly or is missing entirely. The paternal copy of the gene is imprinted, or silenced, meaning that only the copy inherited from the person's mother is active. Problems with or **deletion** of the maternal copy of the gene, or the section of chromosome 15 where it resides, can lead to Angelman syndrome.

In Prader-Willi syndrome (PWS) (https://www.nhs.uk/conditions/prader-willi-syndrome/), the same region of chromosome 15 is involved. In this case, though, the condition is linked to problems with the paternal copy of the chromosome rather than the maternal copy. Certain genes in the region, such as *SNRPN*, are imprinted, with the maternal copy being silenced and the paternal copy being active. Problems with the paternal copies of these genes can lead to PWS.

Watch the video on Prader-Willi syndrome (https://www.nhs.uk/conditions/prader-willi-syndrome/) (bottom of the page) from the NHS to learn about the features of PWS.




**Comparison between two chromosomes:** Chromosome 15 (normal function) has genes turned off through normal imprinting on the maternal copy. The same genes are active in the paternal copy and are being used. In a Chromosome 15 with Prader-Willi Syndrome, genes are naturally turned off through imprinting on the maternal copy, but genes are deleted by anomaly (no working copies available) in the paternal copy. **Source:** *Genomics Education Programme*, CC BY-NC

Most cases of Angelman syndrome and PWS are caused by deletions, although a significant minority are due to UPD.

Another condition linked to genomic imprinting is Beckwith-Wiedemann syndrome (BWS) (https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/beckwith-wiedemann-syndrome-bws/). It is caused by changes to imprinted genes in the chromosome 11 cluster, with a number of genes being implicated thus far, including *H19* and *IGF2*. It is associated with abnormal growth and an increased chance of childhood cancers, especially in the liver and kidneys.

Scientists hope that continued research into the genetic pathways involved in BWS will help to improve treatment methods and outcomes for those with the condition.

## Implications for Policy: Social and Environmental

# Epigenetics

DNA methylation serves as a biological record of early social or environmental conditions, offering valuable insights for policy and interventions aimed at improving the social and structural determinants of health. Policy implications include (Schmidt, 2019):

- **Guiding Policy Directions:** Epigenetic research highlights the long-term health impact of early-life environments, similar to how evidence of second-hand smoke risks led to public smoking bans. Raising awareness about these biological effects could support child-focused interventions and policies that regulate environmental (e.g. air pollution) and social exposures (e.g. food security). For example, stricter regulations on industrial emissions or agricultural chemicals may be justified by findings demonstrating their long-term health impacts through epigenetic mechanisms.
- **Biomarkers for Early Screening:** Epigenetics may offer biomarkers for identifying children at risk of health conditions, like fetal alcohol spectrum disorder (FASD), allowing for screening and early interventions that maximize health outcomes as well as targeted health campaigns.
- **Evaluating Intervention Effectiveness:** Epigenetic markers may contribute to the assessment of the biological impact of interventions long before physical health outcomes manifest, enabling quicker and more cost-effective policy evaluations.
- **Shaping Global Environmental and Health Strategies:** As epigenetic research works toward finding evidence of how environmental factors affect health across generations, it has the potential to shape global agreements and policies. Collaborative efforts could focus on reducing environmental health disparities, addressing climate change, and prioritizing sustainable practices that protect vulnerable populations.

## Quiz – Units 1-3

See the Blackboard course shell for the syllabus which provides details about the quiz content and due dates.

# Attribution & References

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# 3.8 UNIT SUMMARY AND REVIEW

## Key Takeaways

This chapter highlighted the shift away from the nature versus nurture debate and explored the pitfalls of genetic determinism. It emphasized the importance of the developmental origins of health and disease, developmental programming, and ontogeny, particularly during critical periods of growth and development. Epigenetics can regulate gene expression without altering the DNA sequence by altering gene expression. Most of these changes are reversible, allowing for adaptability to environmental stimuli. The exposome—encompassing social and environmental exposures—significantly influences health outcomes through its impact on the epigenome, and is closely tied to the social determinants of health. This chapter also examined the link between epigenetic changes and diseases such as cancer and imprinting disorders and illustrated the use of epigenetics in tumour profiling and personalized treatment approaches. As epigenetic research progresses, it holds the potential for considerable policy implications.

## Brain story certification

Interested in learning more about this topic? The University of Oxford, in partnership with the Alberta Family Wellness Initiative, is working to share knowledge about the science of brain development for families and professionals. This is important information for everybody to understand how our earliest experiences can affect our long-term mental and physical health.

They offer a free, in-depth course (https://www.albertafamilywellness.org/training/) for anyone who wants to learn more about the science of brain development.

## Additional Optional Readings:


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# Attribution

# UNIT 4 - GENETIC DISORDERS

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 4 Contents


- 4.1 Unit Overview
- 4.2 Gene Variants
- 4.3 Genetic Disorders
- 4.4 Single Gene Disorders
- 4.5 Polygenic Disorders
- 4.6 Chromosomal Disorders
- 4.7 Mitochondrial Disorders
- 4.8 Unit Summary and Review


## Attribution

# 4.1 UNIT OVERVIEW

## Learning Objectives

- Describe a genomic variant and the potential impacts of variants on health and development.
- Distinguish between different forms of variants.
- Explain the difference between inherited (germline) and non-inherited (somatic) variants
- Compare monogenetic and polygenic disorders.
- Examine modifiable and non-modifiable risk factors and their impacts on the genome.
- Explore factors affecting phenotype variability, including penetrance, expressivity, and anticipation.
- Describe how errors in chromosome structure occur and explore some chromosomal disorders.
- Review the impacts of mitochondrial disorders.

## Outline

Topics covered in this chapter include:

- Gene variants
- Genetic disorders
- Single gene disorders
- Polygenic conditions
- Genotype-phenotype associations
- Modifiable and non-modifiable risk factors
- Disorders in chromosome number
- Mitochondrial disorders

# Competencies Nurses will Develop in this Chapter

## ANA (2023):

### Provision of education, care, and support:

- Uses health promotion and disease prevention practices that consider genomic influences as well as personal and environmental risk factors.

## NHS (2023):

### Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the key indicators of a potential genetic condition, or clinical situation where genomics-informed healthcare would be appropriate; and
- recognizing the importance of family history in assessing predisposition to a genetic condition.

### Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

### Provide ongoing nursing care and support to patients, carers, families and communities with genomic healthcare needs:

- promote healthy behaviours that may be beneficial to alleviate symptoms or, where applicable, implement management strategies or lifestyle changes to help reduce risk.

# Key terminology

## Aneuploid

An individual with an error in chromosome number.

## Barr body

Early in development, when female mammalian embryos consist of just a few thousand cells, one X chromosome in each cell inactivates by condensing into a structure called a Barr body.

## Codon

A codon is a DNA or RNA sequence of three nucleotides (a trinucleotide) that forms a unit of genomic information encoding a particular amino acid or signaling the termination of protein synthesis (stop signals). There are 64 different codons: 61 specify amino acids and 3 are used as stop signals.

## Conditional variants

Variants that rely on the concept of phenotype = genotype + environment + interaction. Organisms with this variant express a altered phenotype, but only under specific environmental conditions.

## Continuous variation

Many interesting and important traits exhibit continuous variation, meaning they exhibit a continuous range of phenotypes that are usually measured quantitatively, such as intelligence, body mass, blood pressure in animals (including humans), and yield, water use, or vitamin content in crops.

## Copy number variant (CNV)

Copy number variation (abbreviated CNV) refers to a circumstance in which the number of copies of a specific segment of DNA varies among different individuals' genomes. The individual variants may be short or include thousands of bases. These structural differences may have come about through duplications, deletions or other changes and can affect long stretches of DNA. Such regions may or may not contain a gene(s).

## De novo variants

Mosaicism (can be somatic or germline) refers to the presence of cells in a person that have a different genome from the body's other cells. This difference could be due to a specific genomic variant, for example, or the addition or loss of a chromosome. The condition can stem from a genetic error that occurs after fertilization of an egg, during very early embryo development, or it could occur later in development. Mosaicism can affect any type of cell and does not always cause disease.

## Deletion

A deletion, as related to genomics, is a type of mutation that involves the loss of one or more nucleotides from a segment of DNA. A deletion can involve the loss of any number of nucleotides, from a single nucleotide to an entire piece of a chromosome.

## Deletion-insertion

This variant occurs when a deletion and insertion happen at the same time in the same location in the gene. In a deletion-insertion variant, at least one nucleotide is removed and at least one nucleotide is inserted. However, the change must be complex enough to differ from a simple substitution. The resulting protein may not function properly. A deletion-insertion (delins) variant may also be known as an insertion-deletion (indel) variant.

## Discrete variation

Most of the phenotypic traits commonly used in introductory genetics are qualitative. This means the phenotype exists in only two (or possibly a few more) discrete, alternative forms, such as purple or white flowers, or red or white eyes.  These qualitative traits are therefore said to exhibit discrete variation.

## Down syndrome

Down syndrome (also called Trisomy 21) is a genetic condition caused by an error in the process that replicates and then divides up the pairs of chromosomes during cell division, resulting in the inheritance of an extra full or partial copy of chromosome 21 from a parent. This extra chromosomal DNA causes the intellectual disabilities and physical features characteristic of Down syndrome, which vary among individuals.

## Duplication

Duplication, as related to genomics, refers to a type of mutation in which one or more copies of a DNA segment (which can be as small as a few bases or as large as a major chromosomal region) is produced. Duplications occur in all organisms. For example, they are especially prominent in plants, although they can also cause genetic diseases in humans. Duplications have been an important mechanism in the evolution of the genomes of humans and other organisms.

## Essential genes

Variants in essential genes create recessive lethal alleles that arrest or derail the development of an individual at an immature (embryonic, larval, or pupal) stage. This type of variant may, therefore, go unnoticed in a typical variant screen because they are absent from the progeny being screened.

## Expressivity

The variability in mutant phenotypes observed in individuals with a particular phenotype.

## Euploid

An individual with the appropriate number of chromosomes for their species (22 pairs autosomes and one pair of sex chromosomes in humans).

## Frameshift

A frameshift mutation in a gene refers to the insertion or deletion of nucleotide bases in numbers that are not multiples of three. This is important because a cell reads a gene's code in groups of three bases when making a protein. Each of these "triplet codons" corresponds to one of 20 different amino acids used to build a protein. If a mutation disrupts this normal reading frame, then the entire gene sequence following the mutation will be incorrectly read. This can result in the addition of the wrong amino acids to the protein and/or the creation of a codon that stops the protein from growing longer.

## Gain-of-function variants

Some variants can have a positive effects, such as producing new proteins that help an individual better adapt to changes is the environment.

## Genetic disorder

Genetic disorders are caused by variants that alter or eliminate a gene's function leading to morphological or physiological changes.

## Genetic redundancy

The lack of phenotypic change from a loss-of-function variant by be attributed to genetic redundancy.

That is, the mutant gene's lost function is compensated by another gene, at another locus, encoding a similarly functioning product. Thus, the loss of one gene is compensated by the presence of another. The concept of genetic redundancy is an important consideration in genetic screens. A gene whose function can be compensated for my another gene, cannot be easily identified in a genetic screen for loss-of-function variants.

## Germline variants (inherited)

Are passed from parent to child and are present throughout a person's life in virtually every cell in the body. These variants are also called germline variants because they are present in the parent's egg or sperm cells, which are also called germ cells. When an egg and a sperm cell unite, the resulting fertilized egg cell contains DNA from both parents. Any variants that are present in that DNA will be present in the cells of the child that grows from the fertilized egg.

## Insertion

An insertion, as related to genomics, is a type of mutation that involves the addition of one or more nucleotides into a segment of DNA. An insertion can involve the addition of any number of nucleotides, from a single nucleotide to an entire piece of a chromosome.

## Karyotype

A karyotype is an individual's complete set of chromosomes. The term also refers to a laboratory-produced image of a person's chromosomes isolated from an individual cell and arranged in numerical order. A karyotype may be used to look for abnormalities in chromosome number or structure.

## Klinefelter syndrome

The XXY chromosome complement, corresponding to one type of Klinefelter syndrome, corresponds to male individuals with small testes, enlarged breasts, and reduced body hair.

## Intergenic regions

Intergenic regions are the stretches of DNA located between genes. In humans, intergenic regions are non-protein-coding and comprise a large majority of the genome. Some intergenic DNA is known to regulate the expression of nearby genes.

## Introns

An intron is a region that resides within a gene but does not remain in the final mature mRNA molecule following transcription of that gene and does not code for amino acids that make up the protein encoded by that gene. Most protein-coding genes in the human genome consist of exons and introns.

## Inversion

An inversion in a chromosome occurs when a segment breaks off and reattaches within the same chromosome, but in reverse orientation. DNA may or may not be lost in the process.

## Lethal variants

Variants that cause the premature death of an organism.

## Loss-of-function variant

Variants that cause the loss-of-function of a gene, yet do not cause a change in phenotype, even when the mutant allele is homozygous.

## Missense

A missense mutation is a DNA change that results in different amino acids being encoded at a particular position in the resulting protein. Some missense mutations alter the function of the resulting protein

## Mitochondrial DNA

Mitochondrial DNA is the circular chromosome found inside the cellular organelles called mitochondria. Located in the cytoplasm, mitochondria are the site of the cell's energy production and other metabolic functions. Offspring inherit mitochondria — and as a result mitochondrial DNA — from their mother.

## Mitochondrial encephalomyopathies

Mitochondrial disorders that cause both muscular and neurological problems.

## Mitochondrial myopathies

Mitochondrial disorders that mostly cause muscular problems.

## Monogenic disorder

Multifactorial inheritance disorder or polygenic inheritance.

## Morphological variants

Variants that cause changes in the visible form of the organism as they give rise to altered forms of a trait.

## Mutation

A mutation is a change in the DNA sequence of an organism. Mutations can result from errors in DNA replication during cell division, exposure to mutagens or a viral infection. Germline mutations (that occur in eggs and sperm) can be passed on to offspring, while somatic mutations (that occur in body cells) are not passed on. The preferred term is “variant,” though mutation can be used to refer to a pathogenic variant.

## Nonsense

A nonsense mutation occurs in DNA when a sequence change gives rise to a stop codon rather than a codon specifying an amino acid. The presence of the new stop codon results in the production of a shortened protein that is likely non-functional.

## Penetrance

The proportion of individuals with a particular genotype that display a corresponding phenotype.

## Permissive conditions

Under permissive conditions, conditional variants show a wild type phenotype.

## Pleiotropic

Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits. Such a gene that exhibits multiple phenotypic expression is called a pleiotropic gene.

## Polymorphisms

One of two or more variants of a particular DNA sequence.

## Polyploid

An individual with more than the correct number of chromosome sets (two for diploid species).

## Reciprocal translocation

Result from the exchange of chromosome segments between two nonhomologous chromosomes such that there is no gain or loss of genetic information.

## Repeat expansion

Some regions of DNA contain short sequences of nucleotides that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of sequences of three nucleotides, and a tetranucleotide repeat is made up of sequences of four nucleotides. A repeat expansion is a variant that increases the number of times that the short DNA sequence is repeated. This type of variant can cause the resulting protein to function improperly.

## Restrictive conditions

Under restrictive conditions, conditional variants express the altered phenotype.

## Silent variants

When the variant does not have an obvious effect on the phenotype. This could be because the change occurs in the DNA sequence in a non-coding region such as intergenic regions or introns. Alternatively, a change in a single nucleotide may result in a codon that produces the same amino acid.

## Single nucleotide polymorphisms (SNP – pronounced “snip)

A single nucleotide polymorphism (abbreviated SNP, pronounced snip) is a genomic variant at a single base position in the DNA. Scientists study if and how SNPs in a genome influence health, disease, drug response and other traits.

## Somatic variants (non-inherited)

Occur at some time during a person’s life and are present only in certain cells, not in every cell in the body. Because non-inherited variants typically occur in somatic cells (cells other than sperm and egg cells), they are often referred to as **somatic variants**. These variants cannot be passed to the next generation. Non-inherited variants can be caused by environmental factors such as ultraviolet radiation from the sun or can occur if an error is made as DNA copies itself during cell division.

## Substitution

Substitution, as related to genomics, is a type of mutation in which one nucleotide is replaced by a different nucleotide. The term can also refer to the replacement of one amino acid in a protein with a different amino acid.

## Translocation

A translocation, as related to genetics, occurs when a chromosome breaks and the (typically two) fragmented pieces re-attach to different chromosomes. The detection of chromosomal translocations can be important for the diagnosis of certain genetic diseases and disorders.

## Turner syndrome

Characterized by the presence of only one X chromosome in women instead of two.

## Variant

A difference in the DNA sequence. See mutation.

# Attribution & References



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# 4.2 GENE VARIANTS

## What is a Gene Variant and how do Variants Occur?

### Variant vs. Mutation

In Unit 2, we discussed gene variants and inheritance patterns. In our discussion of genetic conditions, we will revisit these concepts in this Unit. Recall that prior practice was to use the term "**mutation**." However, due to the negative connotations associated with this word, the preferred term is "**variant**." Not all variants cause a change in phenotype. The term mutation refers to a pathogenic variant which causes a change in the end product. The preferred term is "pathogenic variant."

## What is a genomic variant?

All humans have near-identical DNA sequences across the estimated six billion-letter code for their genome. Slight differences exist between individuals, making each of us unique. These differences, called genomic variants, occur at specific locations within the DNA. DNA is read like a code. Recall this code is made up of four types of chemical building blocks – adenine, thymine, cytosine and guanine, abbreviated with the letters A, T, C and G. A genomic variant occurs in a location within the DNA where that code differs among people. For example, in Person One below, the location shows a "C" base. But in the exact location in Person Two, it is a "T."

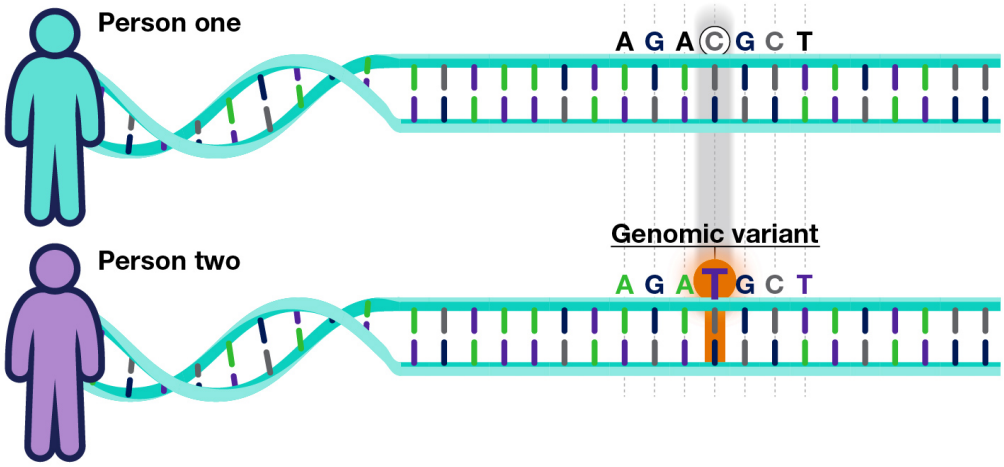


**Figure 4.1 courtesy**: National Human Genome Research Institute, PDM with attribution

An individual's genome has roughly 4 to 5 million such genomic variants. These variants may be unique to that individual or occur in others. Some variants increase the risk of developing diseases, while others may reduce such risk; others do not affect disease risk. In other words,

The question is: How do these genomic variants influence the risk for specific diseases?

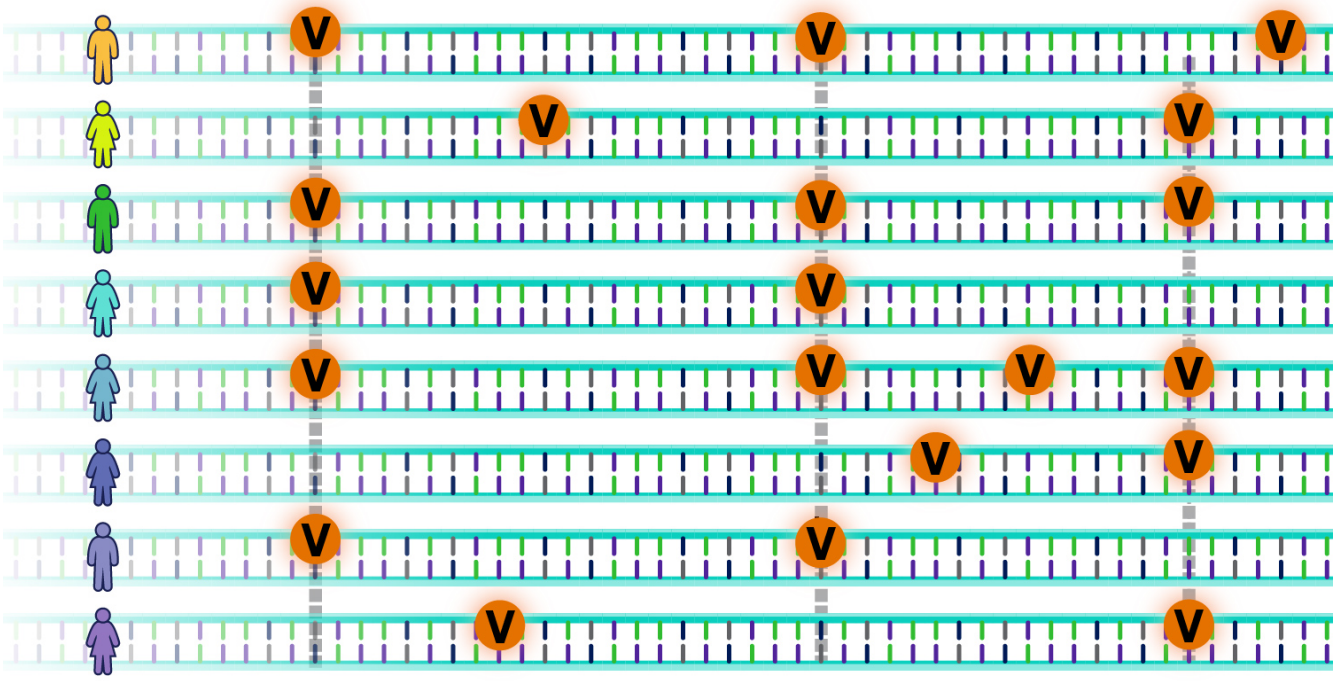


**Figure 4.2** Image shows genomic variants represented by the letter "V." Some are shared among individuals, while others are specific to one person. **Courtesy:** National Human Genome Research Institute, PDM with attribution

## Morphological Variants

**Morphological variants** cause changes in the visible form of the organism as they give rise to altered forms of a trait, e.g., change in size, shape (normal wing vs. curly wing in fruit flies), colour, number, etc.

**Figure 4.3** Examples of Morphological Variants in Dogs. Six different dogs, each of different species, display a wide range of physical attributes that point to morphological mutations, such as differences in fur colour and texture, tail length, height of limbs, facial features, ear presentation, etc. **Source:** Dog morphological variation by Mary Bloom, American Kennel Club, CC0.

## Lethal Variants

A **lethal variant** causes the premature death of an organism. For example, in Drosophila (fruit flies), lethal variants can result in death during the embryonic, larval, or pupal stages. Lethal variants are usually recessive, so both gene copies must be lost for premature death (homozygous lethal alleles will not be viable). Heterozygotes, which have one lethal allele and one wild-type allele, are typically viable. In the example shown in the figure below regarding yellow coat colour in mice, the lethal allele is recessive because it causes death only in homozygotes. Unlike its effect on survival, the effect of the allele on colour is dominant. A single copy of the allele in heterozygotes produces a yellow colour in mice. These examples illustrate the point that the type of dominance depends on the aspect of the phenotype examined.

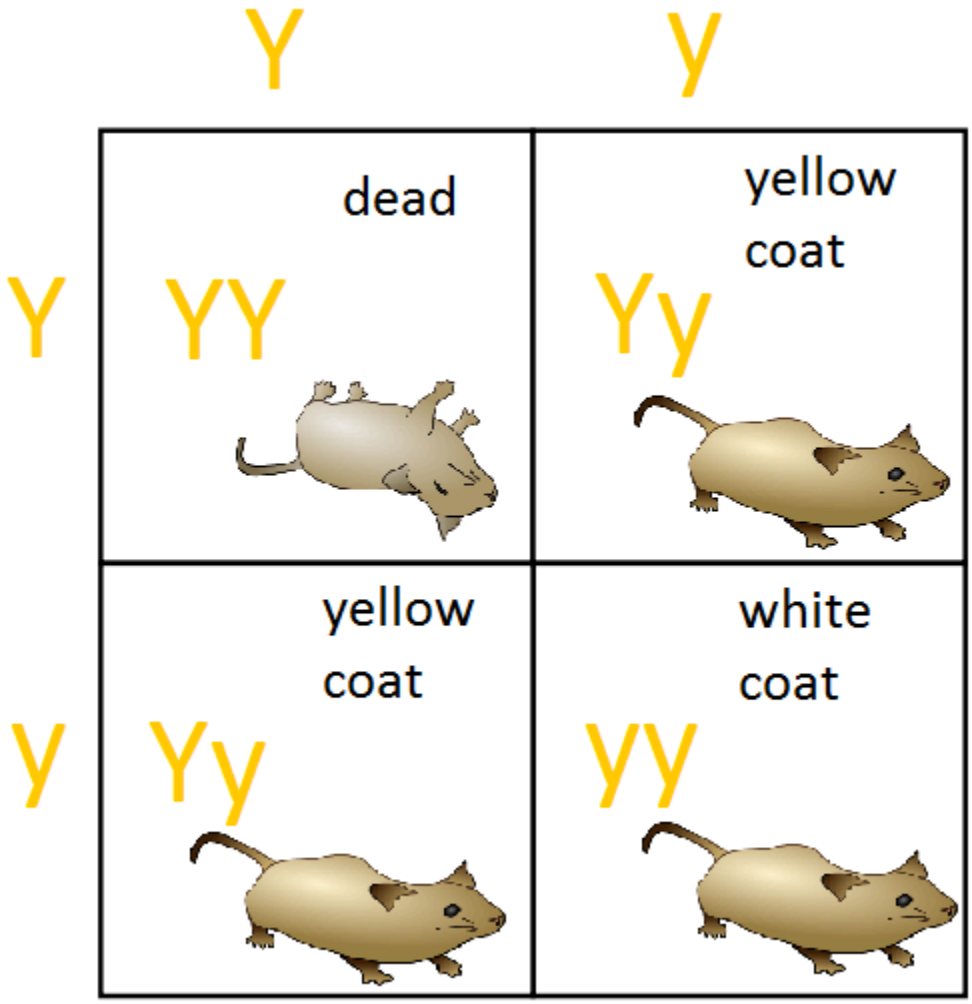


**Figure 4.4** A Punnett square shows the production of offspring from two parents, both of which carry the allele dominant for coat colour but recessive for lethality. Both parents are genotype Yy; both display a yellow coat colour. In the offspring, there is a 3:1 ratio of living to dead progeny, with the accumulation of the YY alleles in one-out-of-four offspring results in death. Yy in the offspring (50%) display yellow coat colour and are alive, and yy offspring (25%) display white coat colour, which is recessive to yellow, and are alive. **Source:** Lethal alleles punnett square by Dead_mouse.svg and Mouse.svg: Madprime derivative work: Adabow, CC BY-SA 3.0.

## Conditional Variants

**Conditional variations** rely on phenotype = genotype + environment + interaction. Organisms with this variant express an altered phenotype, but only under specific environmental conditions. Under **restrictive conditions**, they express the altered phenotype; under permissive conditions, they show a wild-type phenotype. One example of a conditional variant is the temperature-sensitive pigmentation of Siamese cats. Siamese cats have a temperature-sensitive fur colour; their fur appears unpigmented (light-coloured) when grown in a warm environment. The hair appears pigmented (dark) when grown at a cooler temperature. This is seen at the peripheral regions of the feet, snout, and ears. This is because, in warm temperatures, the enzyme needed for melanin pigment synthesis becomes nonfunctional. However, in cooler temperatures, the enzyme required for melanin synthesis is functional, and the deposition of melanin makes the fur look dark.

**Figure 4.5** Two Siamese cats display temperature sensitive colour, which is an example of conditional mutations, whereby the environment dictates the phenotype expressed. Their fur appears unpigmented (light coloured) when grown in a warm temperature environment. The fur appears pigmented (dark) when grown at a cooler temperature. This is seen at the peripheral regions of the feet, snout, and ears. **Source:** Two Siamese Cats by Steve Gilham, CC BY-NC-SA 2.0

## Do all gene variants affect health and development?

Only a small percentage of variants cause genetic disorders—most have no impact on health or development. For example, some variants alter a gene's DNA sequence but do not change the function of the protein made from the gene. Often, gene variants that could cause a genetic disorder are repaired by certain enzymes before the gene is expressed and an altered protein is produced. Each cell has a number of pathways through which enzymes recognize and repair errors in DNA. Because DNA can be changed or damaged in many ways, DNA repair is an important process by which the body protects itself from disease.

A very small percentage of all variants actually have a positive effect (**gain-of-function variant**). These variants lead to new versions of proteins that help an individual better adapt to environmental changes. For example, a beneficial variant could result in a protein that protects an individual and future generations from a new strain of bacteria.

Gene variants can be inherited from a parent or occur during a person's lifetime:

- **Inherited (or hereditary) variants** are passed from parent to child and are present throughout a person's life in virtually every cell in the body. These variants are also called **germline variants** because they are present in the parent's egg or sperm cells, which are also called germ cells. When an egg and a sperm cell unite, the resulting fertilized egg cell contains DNA from both parents. Any variants in that DNA will be present in the child's cells that grow from the fertilized egg.
- **Non-inherited variants** occur at some time during a person's life and are present only in certain cells, not in every cell in the body. Because non-inherited variants typically occur in somatic cells (cells other than sperm and egg cells), they are often called **somatic variants**. These variants cannot be passed to the next generation. Non-inherited variants can be caused by environmental factors such as sun ultraviolet radiation or an error when DNA copies itself during cell division.

Some genetic changes are described as new **(de novo) variants**; these variants are recognized in a child but not in either parent. The variant sometimes occurs in a parent's egg or sperm cell but is absent in other cells. In other cases, the variant occurs in the fertilized egg shortly after the egg and sperm cells unite. (It is often impossible to tell exactly when a de novo variant happened.) As the fertilized egg divides, each resulting cell in the growing embryo will have the variant. De novo variants are one explanation for genetic disorders in which an affected child has a variant in every cell in the body. Still, the parents do not, and there is no family history of the disorder.

Variants acquired during development can lead to **mosaicism**, in which a set of cells in the body has a different genetic makeup than others. In mosaicism, the genetic change is not present in a parent's egg or sperm cells or the fertilized egg but happens later, anytime from embryonic development through adulthood. As cells grow and divide, cells that arise from the cell with the altered gene will have the variant, while other cells will not. It is called somatic mosaicism when a proportion of somatic cells have a gene variant and others do not. Depending on the variant and how many cells are affected, somatic mosaicism may or may not cause health problems. When a proportion of egg or sperm cells have a variant and others do not, it is called **germline mosaicism**. In this situation, an unaffected parent can pass a genetic condition to their child.

Most variants do not lead to disease development, and those that do are uncommon in the general population. Some variants occur often enough in the population to be considered common genetic variation. Several variants are responsible for differences between people, such as eye colour, hair colour, and blood type. Although many of these common variations in the DNA have no adverse effects on a person's health, some may influence the risk of developing certain disorders.

## Silent Changes

After mutagen treatment, most base pair changes (especially substitutions) have no noticeable effect on the phenotype. Often, this is because the change occurs in the DNA sequence of a non-coding region of the DNA, such as in **the intergenic areas** (between genes) or within an **intron** where the sequence does not

code for protein and is not essential for proper mRNA splicing. Also, even if the change affects the coding region, it may not alter the amino acid sequence (recall that the genetic code is degenerate; for example, GCT, GCC, GCA, and GCG all encode alanine) so a change in a single nucleotide may result in a **codon** that produces the same amino acid. This is referred to as a **silent variant**. The base substitution may also change an amino acid, but this does not quantitatively or qualitatively alter the product's function so that no phenotypic change would occur.

## Environment and Genetic Redundancy

In some situations, a variant can cause a complete **loss of function** of a gene yet not produce a change in the phenotype, even when the mutant allele is homozygous. The lack of a visible phenotypic change can be due to environmental effects: losing that gene product may not be apparent in that specific environment but might be in another.

Alternatively, the lack of a phenotype might be attributed to **genetic redundancy**. That is, the mutant gene's lost function is compensated by another gene at another locus, encoding a similarly functioning product. Thus, the loss of one gene is compensated by the presence of another. The concept of genetic redundancy is an essential consideration in genetic screens. A gene whose function can be compensated for by another gene cannot be easily identified in a genetic screen for loss-of-function variants.

## How can gene variants affect health and development?

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. A variant can cause a protein normally expressed by a gene to malfunction or to not be produced at all. When a variant alters a protein that plays a critical role in the body, it can disrupt normal development or cause a health condition. A condition caused by variants in one or more genes is called a **genetic disorder.**

It is important to emphasize that ***genes do not cause disease—genetic disorders are caused by variants that alter or eliminate a gene's function***. For example, when people say someone has "the cystic fibrosis gene," they usually refer to a version of the *CFTR* (https://medlineplus.gov/genetics/gene/cftr/) gene that contains a variant that causes the disease. All people, including those without cystic fibrosis, have a version of the *CFTR* gene.

## Essential Genes and Lethal Alleles

In some cases, gene variants are so severe that they prevent an embryo from surviving until birth (lethal variants). Sometimes, it is required to reach a particular developmental stage before the phenotype resulting from a variant can be seen or scored. For example, flower colour can only be scored in plants that are mature

enough to make flowers, and eye colour can only be scored in flies that have developed to the adult stage. However, some organisms with variants may not develop sufficiently to reach a stage that can be scored for a particular phenotype. Variants in **essential genes** create recessive lethal alleles that arrest or derail the development of an individual at an immature (embryonic, larval, or pupal) stage. Therefore, this variant type may go unnoticed in a typical variant screen because they are absent from the screened progeny. Furthermore, the progeny of a monohybrid cross involving an embryonic lethal recessive allele may all be of a single phenotypic class, giving a phenotypic ratio of 1:0 (which is the same as 3:0). In this case, the variant may not be detected. Nevertheless, studying recessive lethal variants (those in essential genes) has elucidated many important biochemical pathways.

## What kinds of gene variants are possible?

The human genome's most common polymorphisms (or genetic differences) are single base-pair differences. Scientists call these differences SNPs for **single-nucleotide polymorphisms.** When two different haploid genomes are compared, SNPs occur, on average, about every 1,000 bases, other types of polymorphisms—for example, differences in copy number, insertions, deletions, duplications, and rearrangements—also occur, but much less frequently (NIH & BSCS, 2007).

Note: The images in the following section still use the term "mutation."

The DNA sequence of a gene can be altered in a number of ways. Gene variants can have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. Variant types include the following:

### Substitution

This variant type replaces one DNA building block (nucleotide) with another. Substitution variants can be further classified by their effect on protein production from the altered gene.

- **Missense**:A missense variant is a type of substitution in which the nucleotide change replaces one protein building block (amino acid) with another in the protein made from the gene. The amino acid change may alter the function of the protein.

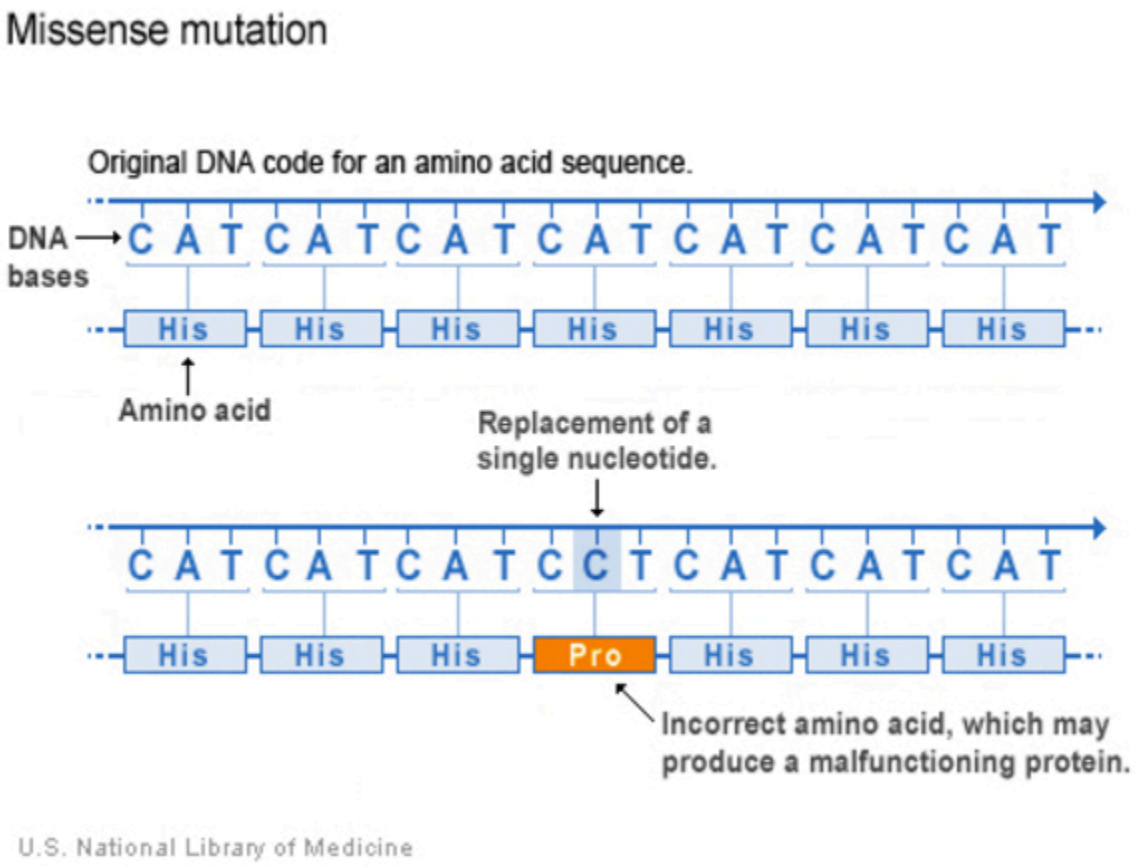


**Figure 4.6** Missense mutation courtesy of U.S. National Library of Medicine, PDM with attribution

- **Nonsense**: A nonsense variant is another type of substitution. However, instead of causing a change in one amino acid, the altered DNA sequence results in a stop signal that prematurely signals the cell to stop building a protein. This type of variant results in a shortened protein that may malfunction, be nonfunctional or get broken down.

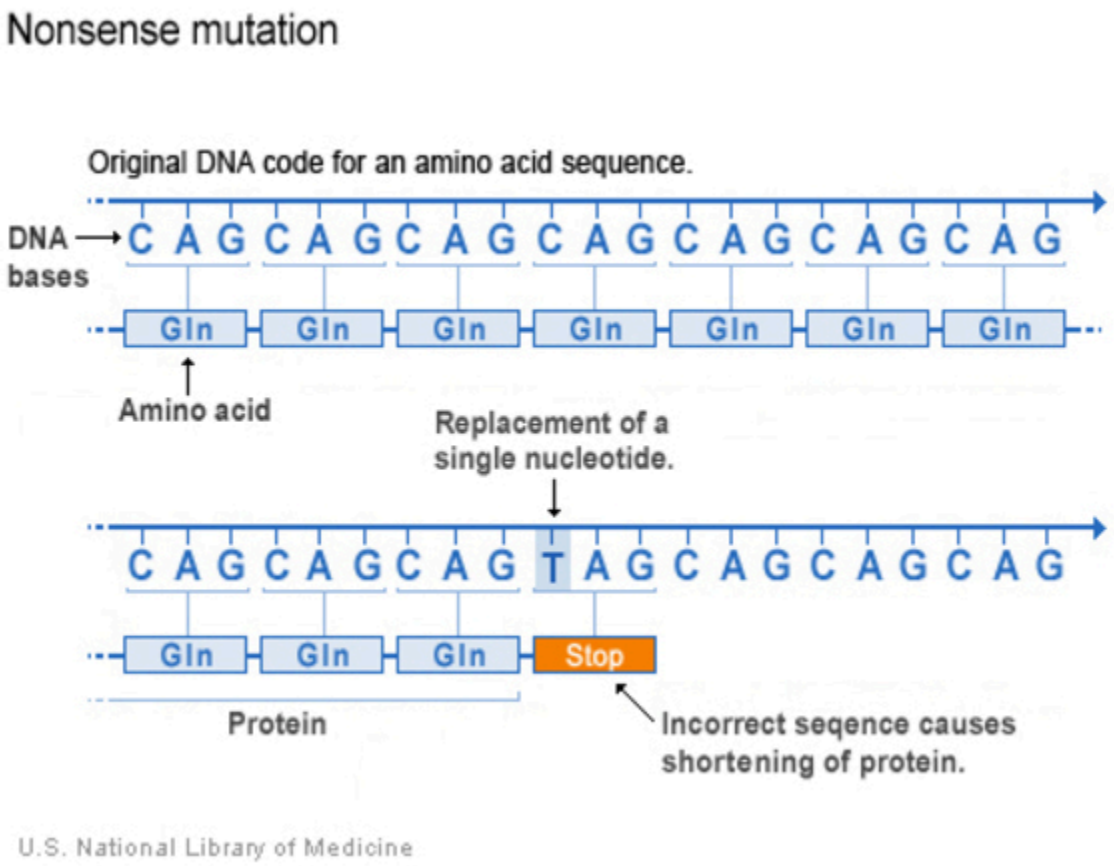


**Figure 4.7** Nonsense mutation courtesy of U.S. National Library of Medicine, PDM with attribution

## Insertion

An insertion changes the DNA sequence by adding one or more nucleotides to the gene. As a result, the protein made from the gene may not function properly.

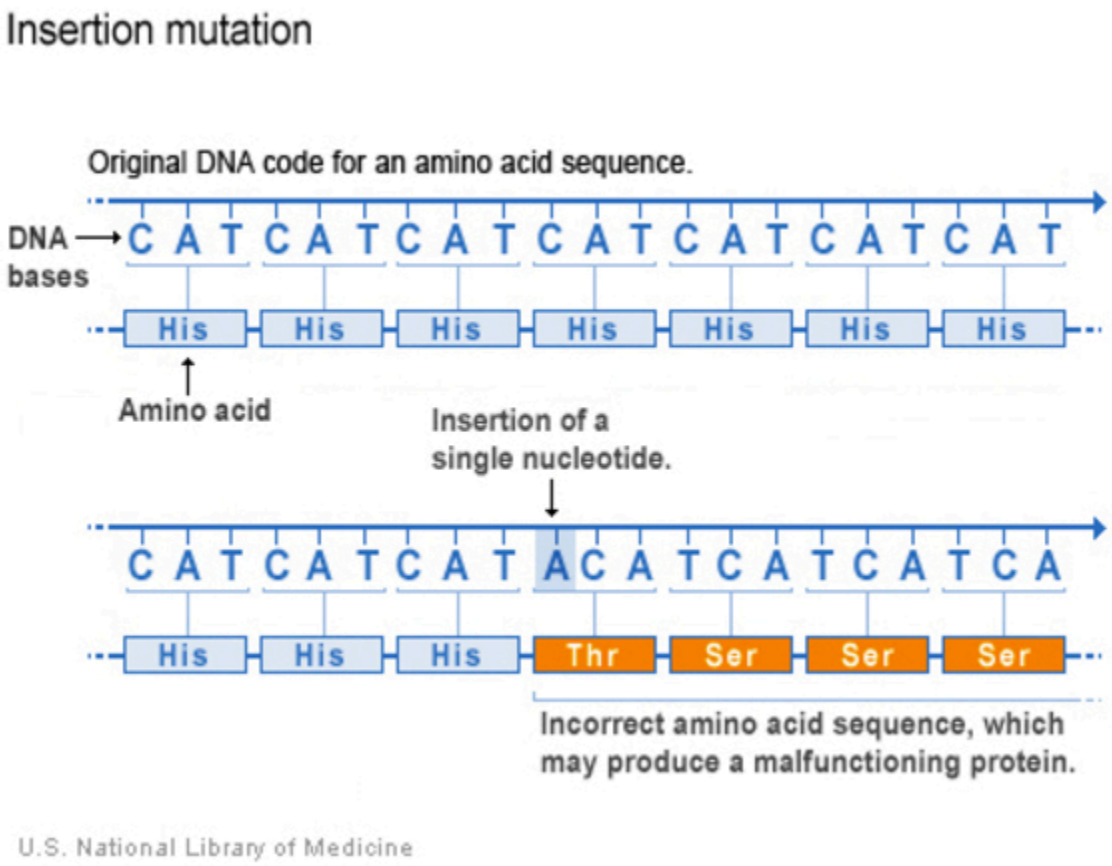


**Figure 4.8** Insertion mutation courtesy of U.S. National Library of Medicine, PDM with attribution

## Deletion

A deletion changes the DNA sequence by removing at least one nucleotide in a gene. Small deletions remove one or a few nucleotides within a gene, while larger deletions can remove an entire gene or several neighbouring genes. The deleted DNA may alter the function of the affected protein or proteins.

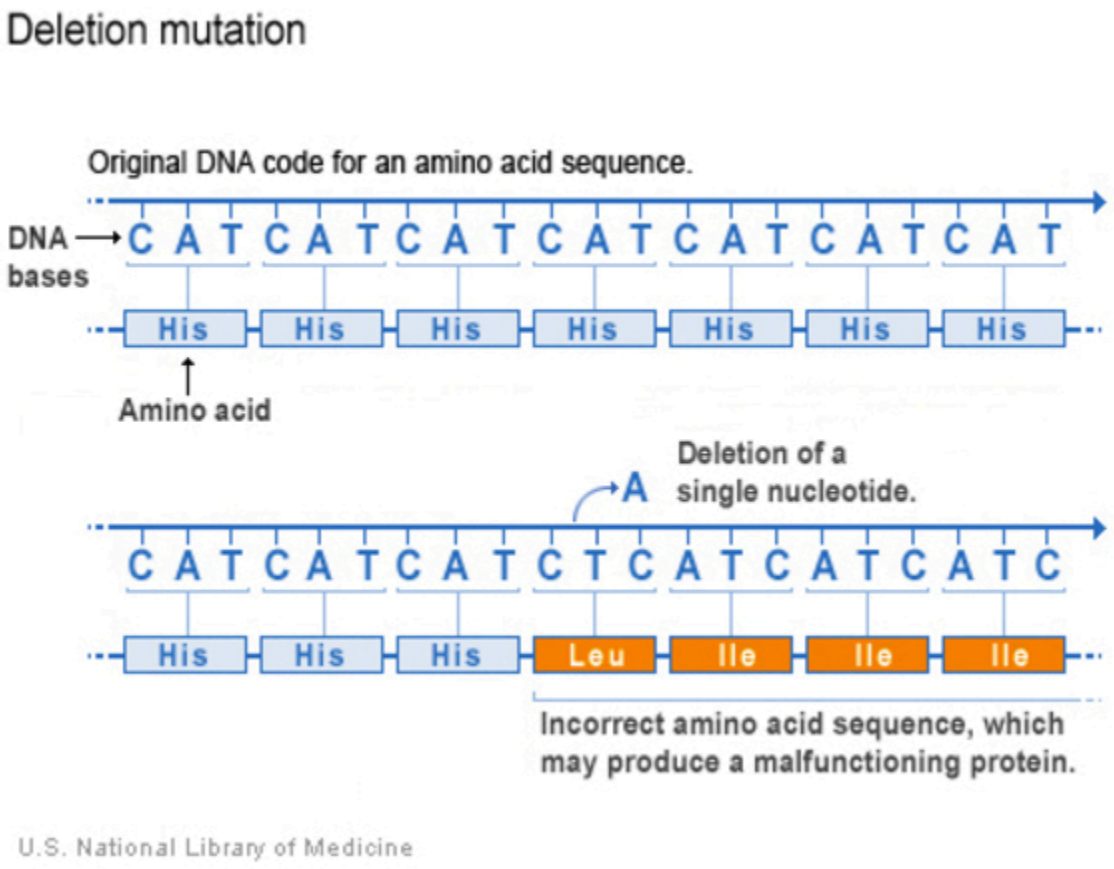


**Figure 4.9** Deletion mutation courtesy of U.S. National Library of Medicine, PDM with attribution

## Deletion-Insertion

This variant occurs when a deletion and insertion happen at the same time in the same location in the gene. In a deletion-insertion variant, at least one nucleotide is removed and at least one nucleotide is inserted. However, the change must be complex enough to differ from a simple substitution. The resulting protein may not function properly. A deletion-insertion (delins) variant may also be called an insertion-deletion (indel) variant.

## Duplication

A duplication occurs when a stretch of one or more nucleotides in a gene is copied and repeated next to the original DNA sequence. This type of variant may alter the function of the protein made from the gene.

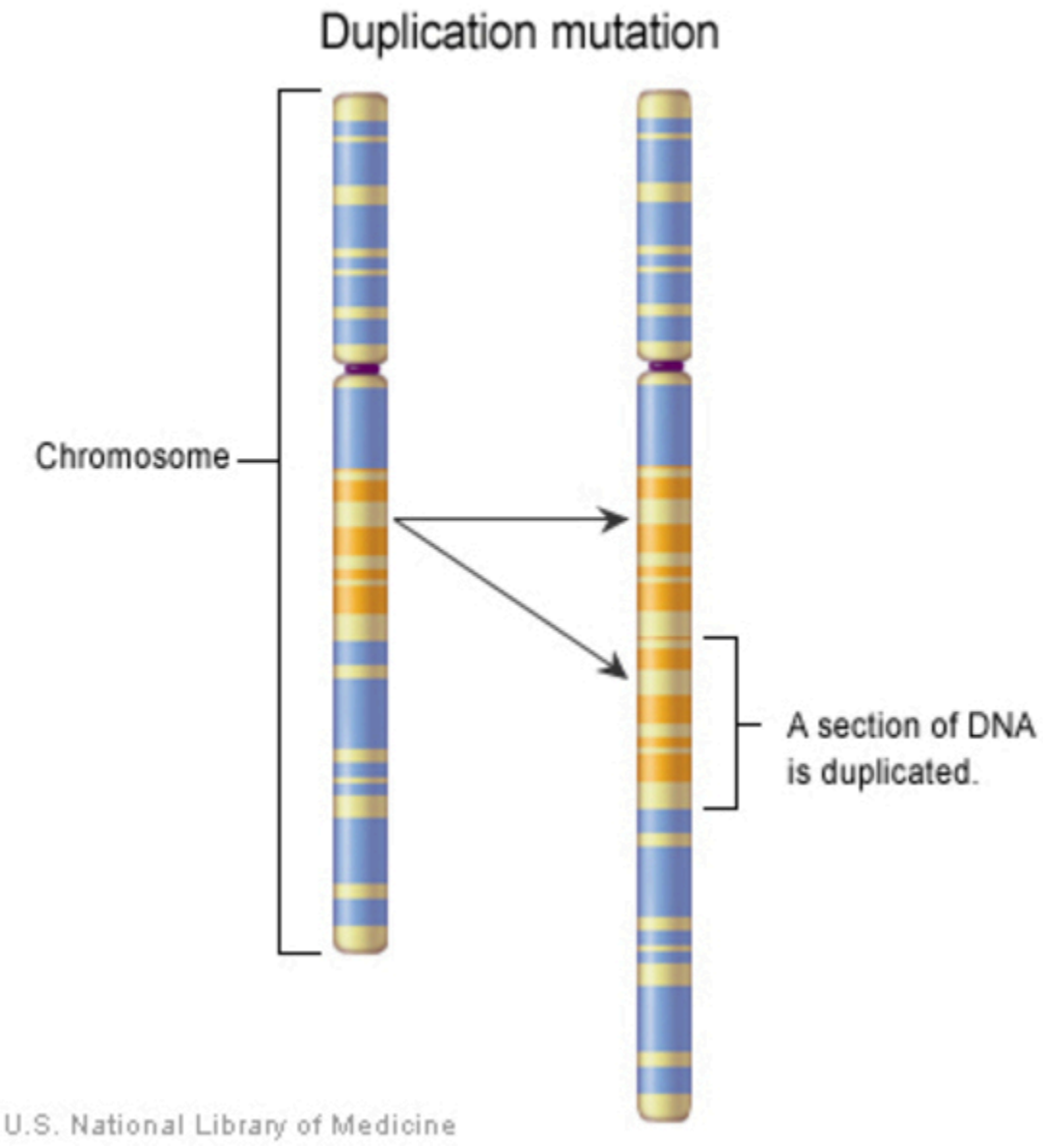


**Figure 4.10** Duplication mutation courtesy of U.S. National Library of Medicine, PDM with attribution

## Inversion

An inversion changes more than one nucleotide in a gene by replacing the original sequence with the same sequence in reverse order. We will discuss this further in the subsequent chapter on chromosomal disorders.

## Frameshift

A reading frame consists of groups of three nucleotides that each code for one amino acid.

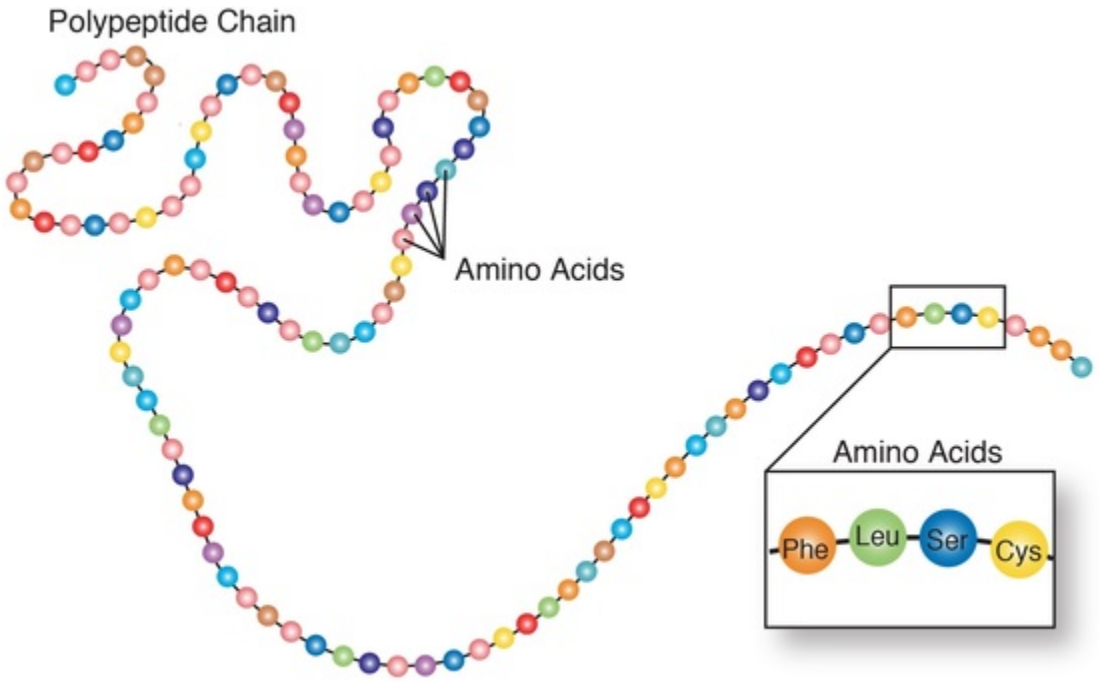


**Figure 4.11** Amino acids are a set of 20 different molecules used to build proteins. Proteins consist of one or more chains of amino acids called polypeptides. The sequence of the amino acid chain causes the polypeptide to fold into a shape that is biologically active. The amino acid sequences of proteins are encoded in the genes. **Source:** Darryl Leja, NHGRI

A frameshift variant occurs when there is an addition or loss of nucleotides that shifts the grouping and changes the code for all downstream amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift variants.

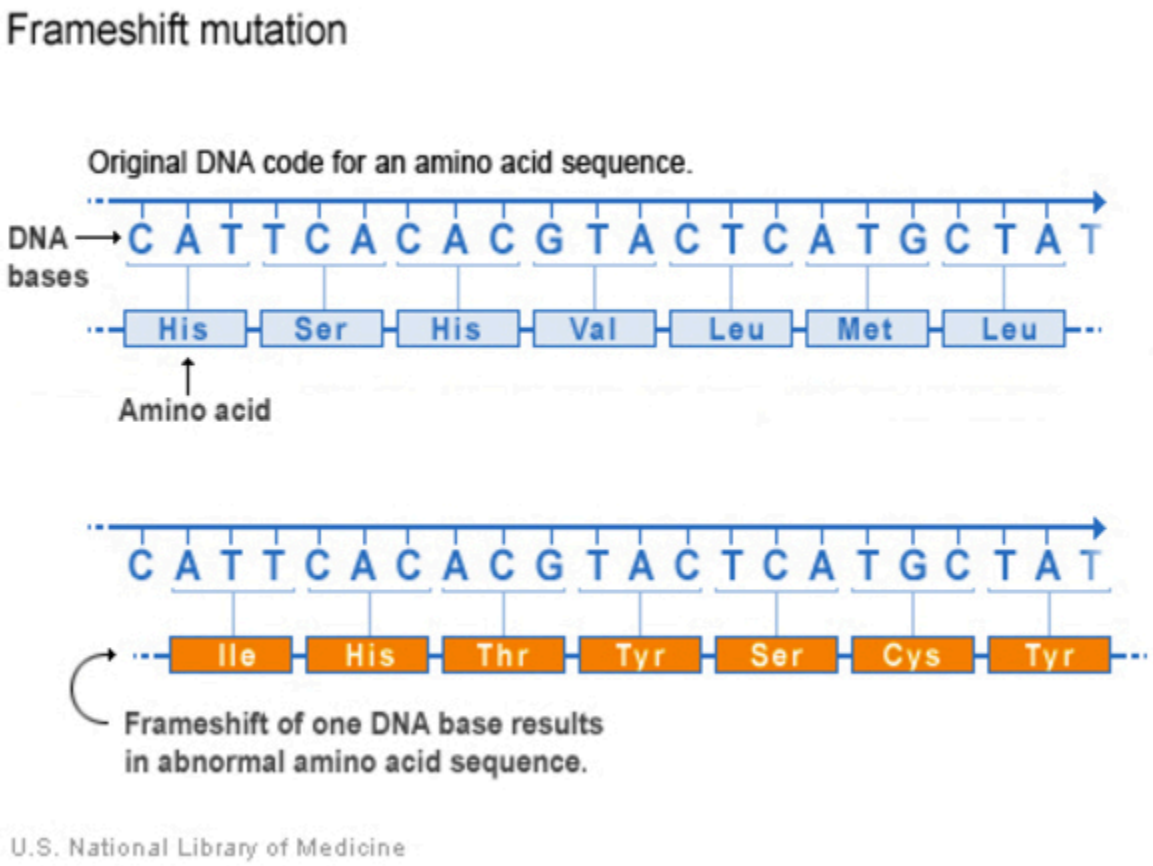


**Figure 4.12** Frameshift mutation courtesy of U.S. National Library of Medicine, PDM with attribution

## Repeat expansion

Some regions of DNA contain short sequences of nucleotides that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of sequences of three nucleotides, and a tetranucleotide repeat is made up of sequences of four nucleotides. A repeat expansion is a variant that increases the number of times that the short DNA sequence is repeated. This type of variant can cause the resulting protein to malfunction.

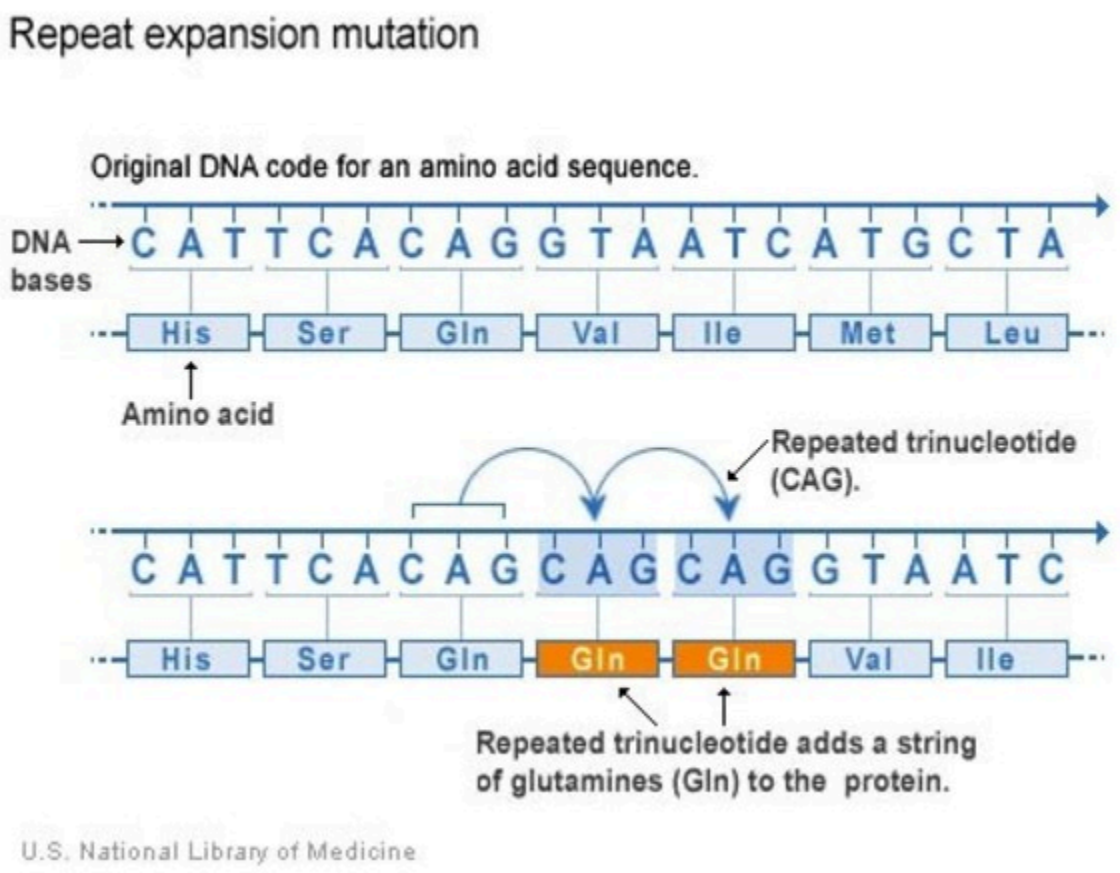


**Figure 4.13** Repeat Expansion mutation courtesy of U.S. National Library of Medicine, PDM with attribution

## Can a change in the number of genes affect health and development?

People have two copies of most genes, one copy inherited from each parent. In some cases, however, the number of copies varies—meaning that a person can have one, three, or more copies of particular genes. Less commonly, both copies of a gene may be missing. These genetic differences are known as **copy number variations (CNV)**.

Copy number variation results from insertions, deletions, and duplications of large segments of DNA that are at least one thousand nucleotides (also called one kilobase or 1kb) in length. These segments are often big enough to include whole genes. Variations in gene copy number can influence the activity of genes and the functioning of proteins made from them, which may affect body processes.

Copy number variation accounts for a significant amount of genetic difference between people. More than 10 percent of the human genome appears to contain differences in gene copy number. While much of this variation does not affect health or development, some differences influence a person's risk of disease, particularly some types of cancer, or response to certain drugs.

# Attribution & References

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National Institutes of Health (US) (NIH), & Biological Sciences Curriculum Study (BSCS). (2007). Understanding human genetic variation. *NIH Curriculum Supplement Series.* National Institutes of Health (US).https://www.ncbi.nlm.nih.gov/books/NBK20363/

# 4.3 GENETIC DISORDERS

## What is a genetic condition?

A genetic disorder is a disease caused in whole or in part by a change in the DNA sequence away from the normal sequence. Genetic disorders can be caused by a mutation in one gene (**monogenic disorder**), by mutations in multiple genes (**multifactorial inheritance disorder**), by a combination of gene mutations and environmental factors, or by damage to chromosomes (changes in the number or structure of entire chromosomes, the structures that carry genes).

As we unlock the secrets of the human genome (the complete set of human genes), we are learning that nearly all diseases have a genetic component. Some diseases are caused by mutations that are inherited from the parents and are present in an individual at birth, like sickle cell disease. Other diseases are caused by acquired mutations in a gene or group of genes that occur during a person's life. Such mutations are not inherited from a parent, but occur either randomly or due to some environmental exposure (such as cigarette smoke). These include many cancers, as well as some forms of neurofibromatosis.

## Genetic conditions can be grouped into four main categories:

### 1. Single gene conditions: caused by changes to one gene, often with simple and predictable inheritance patterns.

As discussed in unit 2, different patterns of inheritance exist:

- Dominant conditions occur when a person has one unaffected copy and one mutated copy of the gene. For example, Huntington's disease.
- Recessive conditions only occur when an individual has two mutated copies of the gene. If a person has only one copy of the mutated gene, they are a carrier of the condition and may pass it to their children. For example, cystic fibrosis.
- X-linked conditions are caused by genes altered on the X chromosome – people with XY chromosomes are missing lots of genes encoded by the X, so will develop the condition if they have an altered gene on the X. For example, muscular dystrophy.

### 2. Chromosome conditions result from changes in the number or structure of the chromosomes.

- For example, Downs syndrome results from an extra chromosome 21. It's also called trisomy 21, referring to three copies of chromosome 21

### 3. Multifactorial conditions (or complex diseases) are caused by changes in multiple genes, often in a complex interaction with environmental factors.

- Many types of cancer are caused in this way. For example, certain genetic mutations can put a person at higher risk of bowel cancer. This, combined with external factors like cigarette smoke or certain foods can make a person more likely to develop the disease.

### 4. Mitochondrial Disorders are caused by defects in the mitochondria (NINDS, 2024).

- They can affect one part of the body or many parts, including the brain, muscles, kidneys, heart, eyes, and ears. In most cases, mitochondrial disorders affect more than one type of cell, tissue, or organ.

We will explore these four types of conditions in the following chapters.

## How are genetic conditions and genes named?

### Naming genetic conditions

Genetic conditions are not named in one standard way (unlike genes, which are given an official name and symbol by a formal committee). Doctors who treat families with a new, previously unknown disorder are often the first to propose a name for the condition. Later, healthcare professionals, researchers, people affected by the condition, and other interested individuals may come together to revise the name to improve its usefulness. Naming is important because it allows accurate and effective communication about particular conditions, which will ultimately improve care and help researchers find new approaches to treatment.

Condition names are often derived from one or a combination of sources:

- The basic genetic or biochemical defect that causes the condition (for example, alpha-1 antitrypsin deficiency (https://medlineplus.gov/genetics/condition/alpha-1-antitrypsin-deficiency/));

- The gene in which the variant (or mutation) that causes the condition occurs (for example, *TUBB4A*-related leukodystrophy (https://medlineplus.gov/genetics/condition/tubb4a-related-leukodystrophy/));
- One or more major signs or symptoms of the disorder (for example, hypermanganesemia with dystonia (https://medlineplus.gov/genetics/condition/hypermanganesemia-with-dystonia/), polycythemia vera (https://medlineplus.gov/genetics/condition/polycythemia-vera/), and cryptogenic cirrhosis (https://medlineplus.gov/genetics/condition/cryptogenic-cirrhosis/));
- The parts of the body affected by the condition (for example, brain-lung-thyroid syndrome (https://medlineplus.gov/genetics/condition/brain-lung-thyroid-syndrome/));
- The name of a physician or researcher, often the first person to describe the disorder (for example, Marfan syndrome (https://medlineplus.gov/genetics/condition/marfan-syndrome/), which was named after Dr. Antoine Bernard-Jean Marfan);
- A geographic area (for example, familial Mediterranean fever (https://medlineplus.gov/genetics/condition/familial-mediterranean-fever/), which occurs mainly in populations bordering the Mediterranean Sea); or
- The name of a patient or family with the condition (for example, amyotrophic lateral sclerosis (https://medlineplus.gov/genetics/condition/amyotrophic-lateral-sclerosis/) is often called Lou Gehrig disease after the famous baseball player who was diagnosed with the condition).

Conditions named after a specific person are called eponyms. They can be in the possessive form (e.g., Alzheimer's disease (https://medlineplus.gov/genetics/condition/alzheimers-disease/)) or in the nonpossessive form (e.g., Down syndrome (https://medlineplus.gov/genetics/condition/down-syndrome/)).

## Naming genes

The HUGO Gene Nomenclature Committee (https://www.genenames.org/) (HGNC) designates an official name and symbol (an abbreviation of the name) for each known human gene. The HGNC is a nonprofit organization funded by the U.S. National Human Genome Research Institute and the UK's Wellcome Trust. The Committee has named more than 19,000 of the estimated 20,000 to 25,000 protein-coding genes in the human genome.

During the research process, genes often acquire several alternate names and symbols from researchers investigating the same gene. To resolve this confusion, the HGNC assigns a unique name and symbol to each human gene, which allows effective organization of genes in large databanks, aiding the advancement of research. For specific information about how genes are named, refer to the HGNC's Guidelines for Human Gene Nomenclature (https://www.genenames.org/about/guidelines).

## A note on genetic nomenclature in relation to variants

Many genes are first identified in variant screens and, so, they tend to be named after their variant phenotypes — not the normal function or phenotype. This can cause some confusion for students of genetics. For example, there is an X-linked gene named *white* in fruit flies. Null variants of the *white* gene have white eyes, but the normal *white+* allele has red eyes. This tells us that the wild type (normal) function of this gene is required to make red eyes. We now know its product is a protein that imports a colourless pigment precursor into developing cells of the eye. Why don't we call it the "red" gene, since that is what its product does? Because there are more than one-dozen genes that, when mutant, alter the eye colour: *violet, cinnabar, brown, scarlet*, etc. For all of these genes, their function is also needed to make the eye wild-type red, and not the mutant colour. If we used the name "red" for all these genes, it would be confusing. So we use the distinctive mutant phenotype as the gene name. However, this can be problematic, as with the "lethal" variants described above. This problem is usually handled by giving numbers or locations to the gene name, or making up names that describe how they die (e.g., *even-skipped, hunchback, hairy, runt*, etc.).

## What does it mean to have a genetic predisposition to a disease?

A genetic predisposition (sometimes also called genetic susceptibility) is an increased likelihood of developing a particular disease based on a person's genetic makeup. A genetic predisposition results from specific genetic variations that are often inherited from a parent. These genetic changes contribute to the development of a disease but do not directly cause it. Some people with a predisposing genetic variation will never get the disease while others will, even within the same family.

Genetic variations can have large or small effects on the likelihood of developing a particular disease. For example, certain variants (also called mutations) in the *BRCA1* (https://medlineplus.gov/genetics/gene/brca1/) or *BRCA2* (https://medlineplus.gov/genetics/gene/brca2/) genes greatly increase a person's risk of developing breast cancer (https://medlineplus.gov/genetics/condition/breast-cancer/) and ovarian cancer (https://medlineplus.gov/genetics/condition/ovarian-cancer/). Particular variations in other genes, such as *BARD1* and *BRIP1,* appear to have a much smaller impact on a person's breast cancer risk.

Current research is focused on identifying genetic changes that have a small effect on disease risk but are common in the general population. Although each of these variations only slightly increases a person's risk, having changes in several different genes may combine to increase disease risk significantly. Changes in many genes, each with a small effect, may underlie susceptibility to many common diseases, including cancer, obesity, diabetes, heart disease, and mental illness. Researchers are working to calculate an individual's estimated risk for developing a common disease based on the combination of variants in many genes across their genome. This measure, known as the polygenic risk score, is expected to help guide healthcare decisions in the future.

In people with a genetic predisposition, the risk of disease can depend on multiple factors in addition to an identified genetic change. These include other genetic factors (sometimes called modifiers) as well as lifestyle and environmental factors. Diseases that are caused by a combination of factors are described as multifactorial (https://medlineplus.gov/genetics/understanding/mutationsanddisorders/complexdisorders/). Although a person's genetic makeup cannot be altered, some lifestyle and environmental modifications (such as having more frequent disease screenings and maintaining a healthy weight) may be able to reduce disease risk in people with a genetic predisposition.

## Modifiable and non-modifiable risk factors

Traditional risk factors for health outcomes, such as age, sex, and genetic inheritance (non-modifiable) and diet, physical activity, and smoking (modifiable), are paralleled by social and environmental factors that impact the epigenome, such as experiencing racism or living near industrial pollution. This illustrates how gene expression and, consequently, disease risk can be altered throughout an individual's life.

## Family health history is a non-modifiable risk factor—or is it?

*"I met three different women who had been tested [genetic testing for mutations in the BReast CAncer susceptibility (BRCA) genes] early on, in 1996, when the* BRCA *test first came out. They told me their family history story of mothers, aunts, uncles, and a dad who suffered from breast or ovarian or related cancers, and it was heartbreaking. But then the story changed with them. They were diagnosed with cancer, they got testing, and they shared this information with their family members. So they had stories of children and grandchildren—one woman even had great grandchildren—who were old enough to decide whether or not they wanted to be counseled and some decided to get testing. Many did not carry any of the mutations in the family, and others did. And those who found out that they were a mutation carrier, they had actual things to do. And none of them—none of those family members as we cascade down—have died of cancer." Summer Lee Cox, Oregon Public Health Division* (as cited in Green, 2014).

### Read

CDC. (2024, September 25). *Family health history and adults*. Family Health History. https://www.cdc.gov/family-health-history/family-health-history-and-you/family-health-history-and-adults.html

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Alzheimer Society. (2021). *Risk factors* [Report]. https://alzheimer.ca/sites/default/files/documents/research_risk-factors.pdf

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# 4.4 SINGLE GENE DISORDERS

## Single-Gene Disorders

Single gene disorders are among the most well-understood genetic disorders, given their straightforward inheritance patterns (recessive or dominant) and relatively simple genetic etiology. Although the majority of these diseases are rare, in total, they affect millions of Americans. Some of the more common single-gene disorders include cystic fibrosis (https://www.genomicseducation.hee.nhs.uk/documents/cystic-fibrosis/), hemochromatosis (https://www.genome.gov/Genetic-Disorders/Hereditary-Hemochromatosis), Tay-Sachs (https://www.genome.gov/Genetic-Disorders/Tay-Sachs-Disease), and sickle cell disease (https://www.genomicseducation.hee.nhs.uk/documents/sickle-cell-disease/).

Even though a single gene primarily causes these diseases, several different mutations can result in the same disease but with varying degrees of severity and phenotype. However, even the same mutation can result in slightly different phenotypes. This may be caused by differences in the patient's environment and other genetic variations that may influence the disease phenotype or outcome. For example, other genes have been shown to modify the cystic fibrosis phenotype in children who carry the same CFTR mutation. In addition, mutations in different genes can result in similar phenotypes for some disorders, such as galactosemia.

Genetic testing is available for many single-gene disorders. However, the clinical examination is extremely important in the differential diagnosis, particularly in patients with no family history. For some genetic conditions, patients can often be treated for their symptoms or modify their diets to prevent the onset of symptoms if diagnosed at an early age (newborn screening). However, despite advancements in the understanding of genetic etiology and improved diagnostic capabilities, no treatments are available to prevent disease onset or slow disease progression for a number of these disorders.

Some useful resources to bookmark include GeneTests (http://www.genetests.org) and OMIM (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM). GeneTests is an online genetic testing laboratory database providing information about conditions and laboratory testing services. The Online Mendelian Inheritance in Man database is a comprehensive resource that includes information about the genetic etiology, clinical symptoms, and a bibliography. Of over 5,000 known genetic conditions, the molecular basis is known in almost 2,000.

**Table 1: Conditions, Genes & Inheritance Patterns**

| Condition | Gene (Chr. Location) | Inheritance Pattern |
|---|---|---|
| Congenital Deafness (nonsyndromic) | Connexin 26 (13q11) | Recessive |
| Tay-Sachs | hexosaminidase A (15q23) | Recessive |
| Familial hypercholesterolemia | LDL receptor (19p13) | Dominant |
| Sickle cell anemia | Beta-globin (11p15) | Recessive |
| Duchenne muscular dystrophy | Dystrophin (Xq21) | X-linked Recessive |
| Cystic Fibrosis | CFTR (7q31) | Recessive |
| Hemochromatosis | HFE (6p21) | Recessive |
| Huntington disease | Huntington (4p16) | Dominant |

## Cystic Fibrosis (CF) — Autosomal Recessive

Cystic fibrosis (CF) is one of many diseases that geneticists have shown to be primarily caused by mutation in a single, well-characterized gene. Cystic fibrosis is the most common ($\frac{1}{2,500}$) life-limiting autosomal recessive disease among people of European heritage, with ~ 1 in 25 people being carriers. The frequency varies in different populations. Most of the deaths caused by CF are the result of lung disease, but many CF patients also suffer from other disorders, including infertility and gastrointestinal disease. The disease is due to a mutation in the *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) gene, first identified by Lap-chee Tsui's group at the University of Toronto (Tsui, 1995). Lap-Chee Tsui was inducted into the Canadian Medical Hall of Fame in March 2012 and is still a leader in CF research (Canadian Medical Association, n.d.).

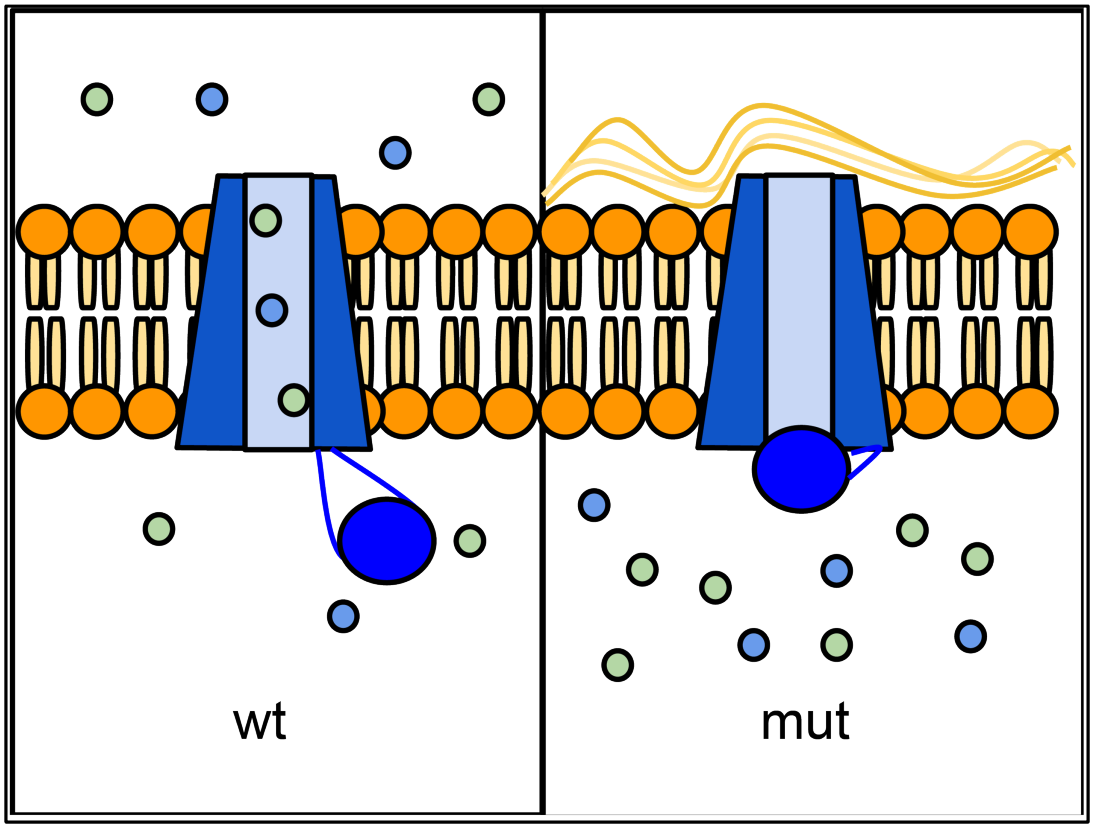


**Figure 4.14** Wild-Type and Mutant Forms of CFTR in the Cell Membrane. In wild-type, the CFTR ion channel is gated. When activated by ATP, the channel opens and allows ions to move across the membrane. In some CFTR mutants, the channel does not open. This prevents ions and water movement, allowing mucus to build up on the lung epithelium. **Source:** CFTR Protein by Lbudd14, CC BY-SA 3.0.

Epithelial tissues in some organs rely on the CFTR protein to transport ions (especially Cl-) across their cell membranes. The passage of ions through a six-sided channel is gated by another part of the CFTR protein, which binds to ATP. If there is insufficient activity of CFTR, an imbalance in ion concentration results, which disrupts the properties of the liquid layer that normally forms on the epithelial surface. In the lungs, this causes mucus to accumulate and can lead to infection. Defects in CFTR also affect the pancreas, liver, intestines, and sweat glands — all of which need this ion transport. CFTR is also expressed at high levels in the salivary gland and bladder. Still, defects in CFTR function do not cause problems in these organs, probably because other ion transporters can compensate.

## Concept in Action

**Watch The video Cystic Fibrosis | Molecular Mechanism & Genetics (4 mins) by Hussain**

**Biology (2018) on YouTube (https://youtu.be/QfjIGXNey3g) which discusses the genetic basis and mechanism by which cystic fibrosis occurs.**

Over one thousand different mutant alleles of *CFTR* have been described. Any mutation that prevents CFTR from sufficiently transporting ions can lead to cystic fibrosis (CF). Worldwide, the most common *CFTR* allele among CF patients is called *ΔF508* (delta-F508; or PHE508DEL), which is a deletion of three nucleotides that eliminates phenylalanine from position 508 of the 1480 aa wild-type protein. Mutation *ΔF508* causes CFTR to be folded improperly in the endoplasmic reticulum (ER), preventing CFTR from reaching the cell membrane. *ΔF508* accounts for approximately 70% of CF cases in North America, with ~1/25 people of European descent being carriers. The high frequency of the *ΔF508* allele has led to speculation that it may confer some selective advantage to heterozygotes, perhaps by reducing dehydration during cholera epidemics or by reducing susceptibility to certain pathogens that bind to epithelial membranes.

CFTR is also notable because it is one of the well-characterized genetic diseases for which a drug has been developed that compensates for the effects of a specific mutation. The drug, **Kalydeco (Ivacaftor)** (https://www.cysticfibrosis.ca/our-programs/advocacy/access-to-medicines/kalydeco), was approved by the FDA and Health Canada in 2012, decades after the *CFTR* gene was first mapped to DNA markers (in 1985) and cloned (in 1989). Kalydeco is effective on only some *CFTR* mutations, most notably *G551D* (i.e., where glycine is substituted by aspartic acid at position 551 of the protein *GLY551ASP*). This mutation is found in less than 5% of CF patients. The *G551D* mutation affects the ability of ATP to bind to CFTR and open the channel for transport. Kalydeco compensates for this mutation by binding to CFTR and holding it in an open conformation. Kalydeco is expected to cost approximately $250,000 per patient per year.

## Exercises

Explore the National Human Genome Research Institute website or the Genomics Education Programme (https://www.genomicseducation.hee.nhs.uk/doc-type/genetic-conditions/page/3/) website for the following genetic disorders:

- Beta-thalassemia
- Down syndrome
- Duchenne muscular dystrophy

- Familial adenomatous polyposis
- Familial hypercholesterolemia
- Fragile X syndrome
- Hemophilia
- Huntington's disease
- Klinefelter syndrome
- Lynch syndrome
- Marfan syndrome
- Parkinson's disease
- Phenylketonuria
- Sickle cell disease

Consider the following:

1. Are these disorders caused by a single gene? If so, what is the pattern of inheritance?
2. Is it a chromosomal or mitochondrial condition?
3. Is it a multifactorial condition?
4. What is the gene and chromosome that is affected?
5. How do penetrance and expressivity affect the phenotype in these disorders?
6. What is anticipation, and which disorders does it apply to?

Assignment tip: the Scholarly Poster Presentation assignment asks you to select an actionable gene variant. Reviewing these disorders may lead you to choose a variant that can cause a disorder you would be interested in doing the project on.

## Attribution & References

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- Understanding Genetics: A District of Columbia Guide for Patients and Health Professionals by Genetic Alliance; District of Columbia Department of Health, CC BY 4.0
- 7.6 Cystic Fibrosis in Humans In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University, CC BY-NC-SA 4.0

## References

Canadian Medical Association. (n.d.). 2012 Inductee: Lap-Chee Tsui, PhD. *Canadian Medical Hall of Fam*e. https://cdnmedhall.ca/laureates/lapcheetsui

Cystic Fibrosis Canada. (n.d.). *What is Kalydeco*? https://www.cysticfibrosis.ca/our-programs/advocacy/access-to-medicines/kalydeco

Hussain Biology. (2018, January 17). *Cystic fibrosis | Molecular mechanism & genetics* (video file). YouTube. https://www.youtube.com/watch?v=QfjIGXNey3g

Tsui L. C. (1995). The cystic fibrosis transmembrane conductance regulator gene. *American Journal of Respiratory and Critical Care Medicine*, *151*(3 Pt 2), S47–S53. https://doi.org/10.1164/ajrccm/151.3_Pt_2.S47

# 4.5 POLYGENIC DISORDERS

## Phenotype Variability

The phenotypes described thus far correlate nearly perfectly with their associated genotypes. In other words, an individual with a particular genotype always has the expected phenotype. However, most phenotypes are not determined entirely by genotype alone. Instead, they are determined by an interaction between genotype and environmental factors and can be conceptualized in the following relationship:

**Genotype + Environment**

**$\Rightarrow$ Phenotype (G + E $\Rightarrow$ P)**

Or:

**Genotype + Environment + InteractionGE**

**$\Rightarrow$ Phenotype (G + E + IGE $\Rightarrow$ P)**

***GE = Genetics and Environment**

This interaction is especially relevant in studying economically important phenotypes, such as human diseases or agricultural productivity. For example, a particular genotype may predispose an individual to cancer, but cancer may only develop if the individual is exposed to certain DNA-damaging chemicals or carcinogens. Therefore, not all individuals with a particular genotype will develop the cancer phenotype; only those who experience a particular environment will. The terms penetrance and expressivity are also helpful to describe the relationship between certain genotypes and their phenotypes.

## Penetrance

**Penetrance** is the proportion of individuals with a particular genotype that display a corresponding phenotype (see figure below). It is usually expressed as a percentage of the population. Because all pea plants are homozygous for the allele for white flowers, this genotype is entirely (100%) penetrant. In contrast, many human genetic diseases are incompletely penetrant since not all individuals with the disease genotype develop symptoms associated with the disease (less than 100%).

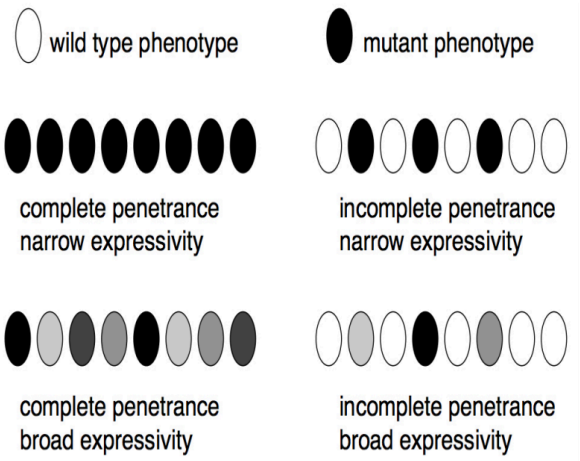


**Figure 4.15** Relationship Between Penetrance and Expressivity in Eight Individuals With a Mutant Genotype. Penetrance can be complete (all eight have the mutant phenotype) or incomplete (only some have the mutant phenotype). Among those individuals with the mutant phenotype, the expressivity can be narrow (minimal variation) to broad (lots of variation). **Source:** Original by Locke (2017), CC BY-NC 3.0, Open Genetics Lectures.

## Expressivity

**Expressivity** describes the variability in mutant phenotypes observed in individuals with a particular phenotype (see figure below). Many human genetic diseases provide examples of broad expressivity since individuals with identical genotypes may vary significantly in the severity of their symptoms. Incomplete penetrance and broad expressivity are due to random chance, non-genetic (environmental), and genetic factors (mutations in other genes).

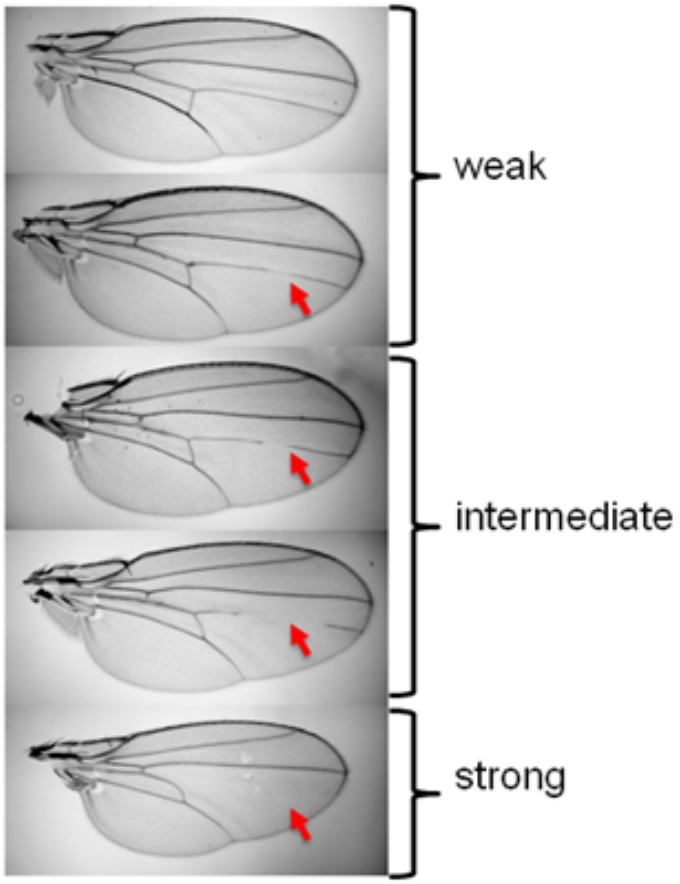


**Figure 4.16** Five different mutations demonstrated in the wings of Drosophila show weak to strong expressivity, which describes the variability in mutant phenotypes observed in individuals with a particular phenotype, which can be due to random chance, environment and/or other genetic factors. **Source:** Original by Locke (2017), CC BY-NC 3.0, Open Genetics Lectures

## Concept in Action

**Watch the video Penetrance vs. Expressivity (3 mins) by The Excel Cycle (2020) on YouTube (https://youtu.be/nurrFUIDBHc) which discusses the difference between expressivity and penetrance.**

## Read

Wright, F., & Fessele, K. (2017). Primer in genetics and genomics, article 5 further defines the concepts of genotype and phenotype and explores genotype-phenotype associations. *Biological Research for Nursing*, *19*(5), 576–585. https://doi.org/10.1177/1099800417725190

OPEN ACCESS ONLINE

# Genotype as a predictor for the development of disease

This unit taught us that our genotype can predispose us to disease development, but multiple factors influence it, including polygenic contributions and epigenetic mechanisms. While some individuals may inherit genetic variants that increase susceptibility, the expression of these genes can be significantly modified by epigenetic changes, which are often influenced by environmental and lifestyle factors.

Usually, no one-to-one correspondence between a gene and a physical characteristic exists. Often, a gene is responsible for several phenotypic traits and is said to be **pleiotropic**. Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits. Such a gene that exhibits multiple phenotypic expression is called a pleiotropic gene. For example, mutations in Drosophila's vestigial gene (vg) result in an easily visible short-wing phenotype. However, mutations in this gene also affect the number of egg strings, the position of the bristles on the scutellum, and the lifespan of Drosophila. Therefore, the *vg* gene is said to be pleiotropic in that it affects many different phenotypic characteristics. During his study of inheritance in pea plants, Mendel made several interesting observations regarding the colour of various plant components. Specifically, Mendel noticed that plants with coloured seed coats always had coloured flowers and coloured leaf axils — axils are the parts of the plant that attach leaves to stems. Mendel also observed that pea plants with colourless seed coats always had white flowers and no pigmentation on their axils. In other words, in Mendel's pea plants, seed coat colour was always associated with specific flower and axil colours. We know that Mendel's observations resulted from pleiotropy, or the phenomenon in which a single gene contributes to multiple phenotypic traits. In this case, the seed coat colour gene, denoted *a*, was responsible for seed coat colour and flower and axil pigmentation.

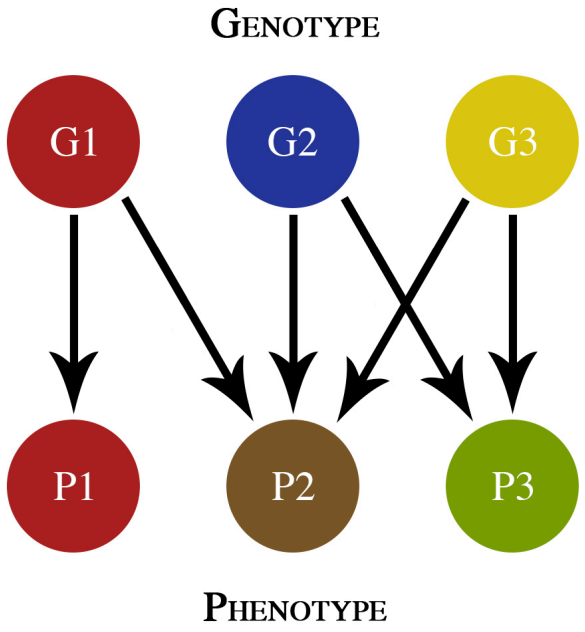


**Figure 4.17** Image result for pleiotropy. Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits. This relationship between genes and phenotypes is demonstrated by mapping one genotype; e.g., G1 to multiple phenotypes; e.g.; P1 and P2. **Source:** Simple Genotype Phenotype Map by Alphillips6, CC BY-SA 4.0

On the other hand, single characteristics can be affected by mutations in multiple, different genes. This implies that many genes are needed to make each characteristic. For example, if we return to the Drosophila wing, there are dozens of genes that, when mutant, alter the normal shape of the wing, not just the *vg* locus. Thus, many genes are needed to make a normal wing; the mutation of any one causes an abnormal, mutant phenotype. This type of arrangement is called **polygenic inheritance**.

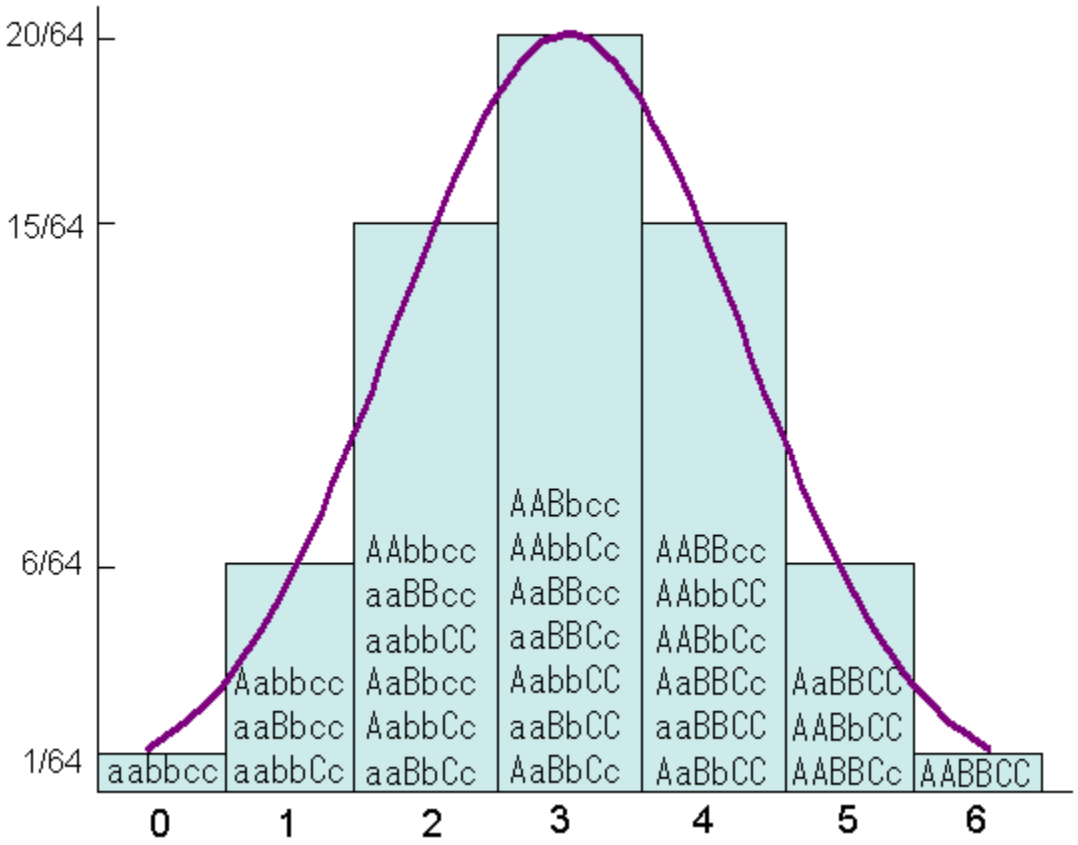


**Figure 4.18** Typical Distribution of Phenotypes in Polygenic Inheritance. Traits that display a continuous distribution, such as height or skin colour, are polygenic. A bell curve showing the typical distribution of phenotypes in Polygenic Inheritance. On the extreme left and the extreme right of the curve, a small frequency of outlier genotypes are represented. As the curve approaches the middle, the frequency of more common genotypes increases. At the very centre of the curve, a maxima is achieved, producing the typical bell shaped graph. **Source:** Polygene00 by Maulits, CC BY-SA 4.0

## What are complex or multifactorial disorders?

Researchers are learning that nearly all conditions and diseases have a genetic component. Some disorders, such as sickle cell disease (https://medlineplus.gov/genetics/condition/sickle-cell-disease/) and cystic fibrosis (https://medlineplus.gov/genetics/condition/cystic-fibrosis/), are caused by variants (also known as mutations) in single genes. The causes of many other disorders, however, are much more complex. Common health problems such as heart disease, type 2 diabetes (https://medlineplus.gov/genetics/condition/type-2-diabetes/), and obesity do not have a single genetic cause—they are influenced by multiple genes (polygenic) in combination with lifestyle and environmental factors, such as exercise, diet, or pollutant exposures. Conditions caused by many contributing factors are called complex or multifactorial disorders.

Although complex disorders often cluster in families, they do not have a clear-cut inheritance pattern. Identifying the role of genetics in these disorders may be challenging, mainly because families often share

environments and have similar lifestyles. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. Researchers continue to look for major contributing genes for many common, complex disorders.

## Continuous Variation

Most of the phenotypic traits commonly used in introductory genetics are qualitative. This means the phenotype exists in only two (or possibly a few more) discrete, alternative forms, such as purple or white flowers, or red or white eyes. These qualitative traits are, therefore, said to exhibit **discrete variation**. On the other hand, many interesting and important traits exhibit **continuous variation**, meaning they exhibit a continuous range of phenotypes that are usually measured quantitatively, such as intelligence, body mass, blood pressure in animals (including humans), and yield, water use, or vitamin content in crops. Traits with continuous variation are often complex, and do not show the simple Mendelian segregation ratios (e.g., 3:1) observed with some qualitative traits. The environment heavily influences many complex traits; nevertheless, complex traits can often have a heritable component, which must involve one or more genes.

How can genes, which are inherited (in the case of a diploid) as, at most, two variants each, explain the wide range of continuous variation observed for many traits? The lack of an immediately obvious explanation to this question was one of the early objections to Mendel's explanation of the mechanisms of heredity. However, upon further consideration, it becomes clear that the more loci that contribute to the trait, the more phenotypic classes may be observed for that trait (see figure below).

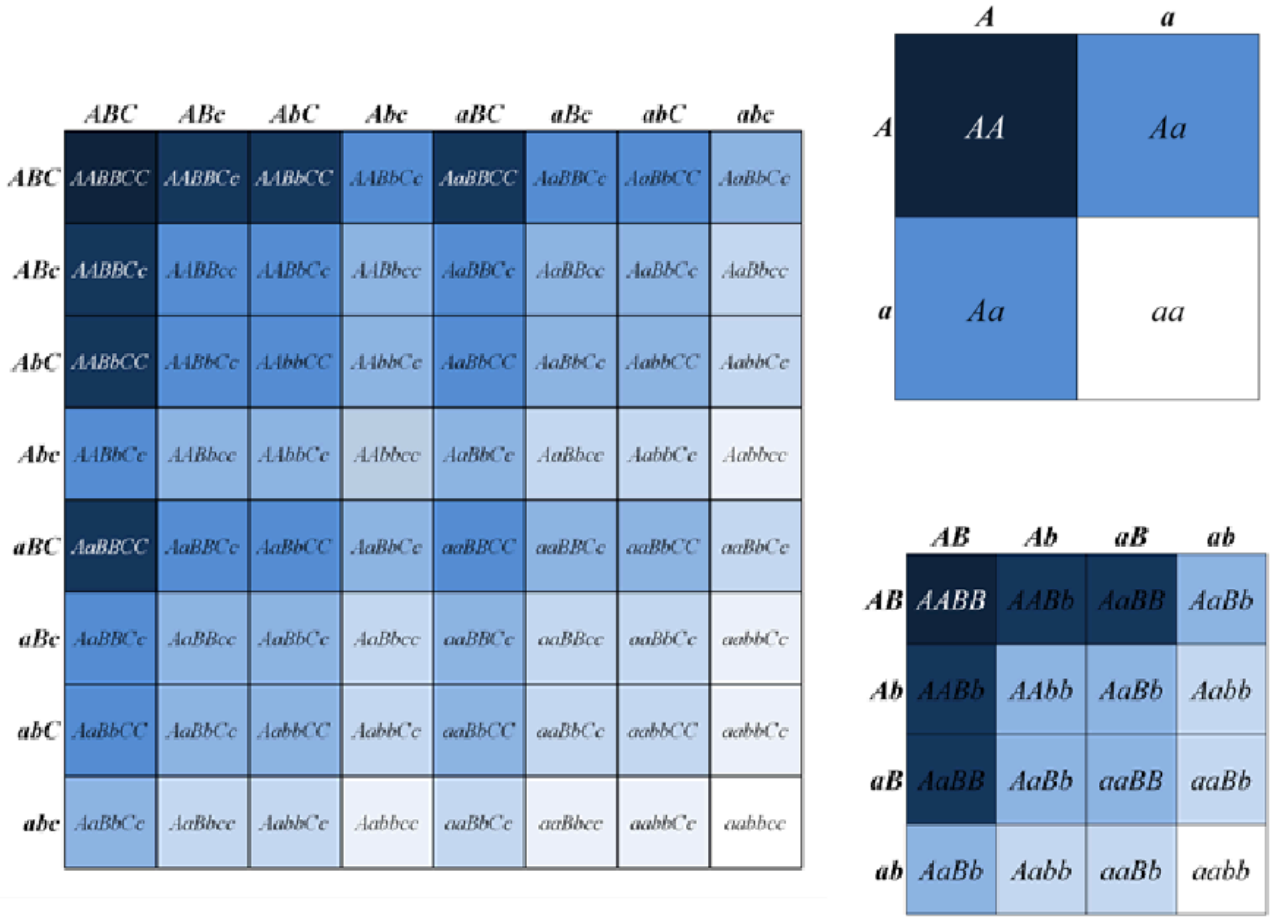


**Figure 4.19** Punnett Squares for One, Two, or Three Loci. This is a simplified example of up to three semi-dominant genes, and in each case, the effect on the phenotype is additive, meaning the more "upper case" alleles present, the stronger the phenotype. A comparison of the Punnett squares and the associated phenotypes shows that the larger the number of genes that affect a trait, the more intermediate phenotypic classes will be expected under these conditions. **Source:** Original by Deyholos (2017), CC BY-NC 3.0, Open Genetics Lectures

If the number of phenotypic classes is sufficiently large (as with three or more loci), individual classes may become indistinguishable (particularly when environmental effects are included), and the phenotype appears as a continuous variation (see figure below). Thus, quantitative traits are sometimes called **polygenic traits**, because it is assumed that the combined activity of many genes controls their phenotypes. Note that this does not imply that each of the individual genes has an equal influence on a polygenic trait — some may have a major effect, while others are only minor. Furthermore, any single gene may influence more than one trait, whether these traits are quantitative or qualitative traits.

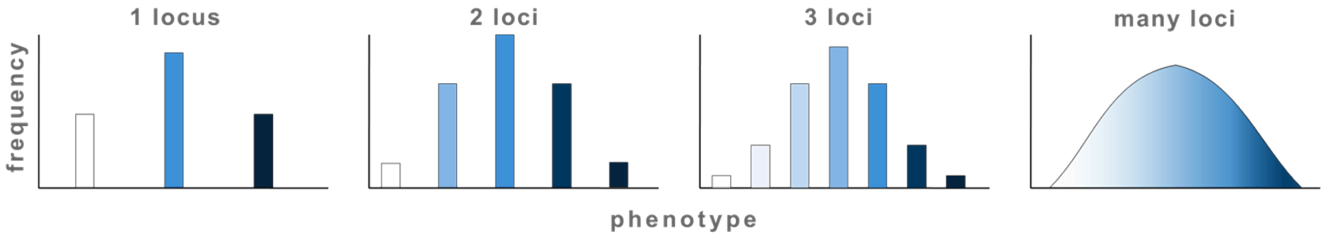


**Figure 4.20** The More Loci that Affect a Trait, the Larger the Number of Phenotypic Classes Can Be Expected. The number of contributing loci is so large that the phenotypic classes blend in apparently continuous variation for some traits. Bar charts and bell curves demonstrate that the more loci that are affecting a trait, the larger the number of phenotypic classes can be expected. For some traits, the number of contributing loci is so large that the phenotypic classes blend together in apparently continuous variation. **Source:** Original by Deyholos (2017), CC BY-NC 3.0, Open Genetics Lectures

### Concept in Action

**Watch the video, *Polygenic Inheritance* (13 mins) by AK Lectures (2015) on YouTube (https://youtu.be/tKnOvPtwZL4), which discusses the genetic basis of Polygenic Inheritance.**

## Attribution & References

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- 8.4 Polygenic Inheritance In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University, CC BY-NC-SA 4.0
- What are complex or multifactorial disorders? In *Help Me Understand Genetics* by MedlinePlus, National Library of Medicine, Public Domain with attribution

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Locke, J. (2017). Figures: 18. Relationship between penetrance and expressivity; and 19. Mutations in wings of Drosophila melanogaster... [digital images]. In Locke, J., Harrington, M., Canham, L. and Min Ku Kang (Eds.), *Open Genetics Lectures, Fall 2017* (Chapter 26, p. 11). Dataverse/ BCcampus. http://solr.bccampus.ca:8001/bcc/file/7a7b00f9-fb56-4c49-81a9-cfa3ad80e6d8/1/OpenGeneticsLectures_Fall2017.pdf

# 4.6 CHROMOSOMAL DISORDERS

Inherited disorders can arise when chromosomes behave abnormally during meiosis. Chromosome disorders can be divided into two categories: chromosome number abnormalities and structural rearrangements. Because even small segments of chromosomes can span many genes, chromosomal disorders are characteristically dramatic and often fatal.

## Disorders in Chromosome Number

The isolation and microscopic observation of chromosomes form the basis of cytogenetics and is the primary method by which clinicians detect chromosomal abnormalities in humans. A **karyotype** is the number and appearance of chromosomes, including their length, banding pattern, and centromere position. To obtain a view of an individual's karyotype, cytologists photograph the chromosomes and then cut and paste each chromosome into a chart or karyogram (see figure below).

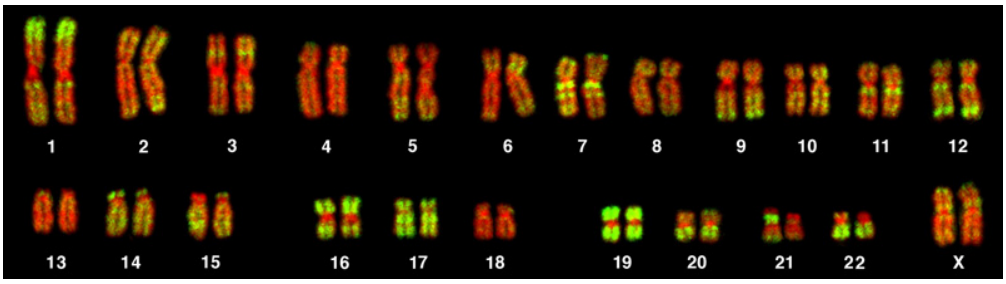


**Figure 4.21** This karyogram shows the chromosomes of a female human immune cell during mitosis. **Source**: Image by Andreas Bolzer, et al, CC BY 2.5

## Geneticists Use Karyograms to Identify Chromosomal Aberrations

The karyotype is a method by which traits characterized by chromosomal abnormalities can be identified from a single cell. A person's cells (like white blood cells) are first collected from a blood sample or other tissue to observe an individual's karyotype. In the laboratory, the isolated cells are stimulated to begin actively dividing. A chemical is then applied to the cells to arrest mitosis during metaphase. The cells are then fixed to a slide.

The geneticist then stains chromosomes with one of several dyes to better visualize each pair's distinct and reproducible banding patterns. Following staining, chromosomes are viewed using bright-field microscopy.

An experienced cytogeneticist can identify each band. In addition to the banding patterns, chromosomes are further determined based on size and centromere location. The geneticist obtains a digital image, identifies each chromosome, and manually arranges the chromosomes into this pattern to get the classic depiction of the karyotype in which homologous pairs of chromosomes are aligned in numerical order from longest to shortest.

At its most basic, the karyogram may reveal genetic abnormalities in which an individual has too many or too few chromosomes per cell. Examples of this are **Down syndrome**, identified by a third copy of chromosome 21, and Turner syndrome, characterized by the presence of only one X chromosome in women instead of two. Geneticists can also identify large deletions or insertions of DNA. For instance, Jacobsen syndrome, which involves distinctive facial features as well as heart and bleeding defects, is determined by a deletion on chromosome 11. Finally, the karyotype can pinpoint translocations, which occur when a segment of genetic material breaks from one chromosome and reattaches to another or a different part of the same chromosome. Translocations are implicated in certain cancers, including chronic myelogenous leukemia.

By observing a karyogram, geneticists can visualize an individual's chromosomal composition to confirm or predict genetic abnormalities in offspring even before birth.

## Nondisjunctions, Duplications, and Deletions

Of all the chromosomal disorders, abnormalities in chromosome number are the most easily identifiable from a karyogram. Disorders of chromosome number include the duplication or loss of entire chromosomes and changes in the number of complete sets of chromosomes. They are caused by **nondisjunction**, which occurs when pairs of homologous chromosomes or sister chromatids fail to separate during meiosis. The risk of nondisjunction increases with the age of the parents.

Nondisjunction can occur during either meiosis I or II, with different results (see figure below). If homologous chromosomes fail to separate during meiosis I, the result is two gametes that lack that chromosome and two gametes with two copies of the chromosome. If sister chromatids fail to separate during meiosis II, the result is one gamete that lacks that chromosome, two normal gametes with one copy of the chromosome, and one gamete with two copies.

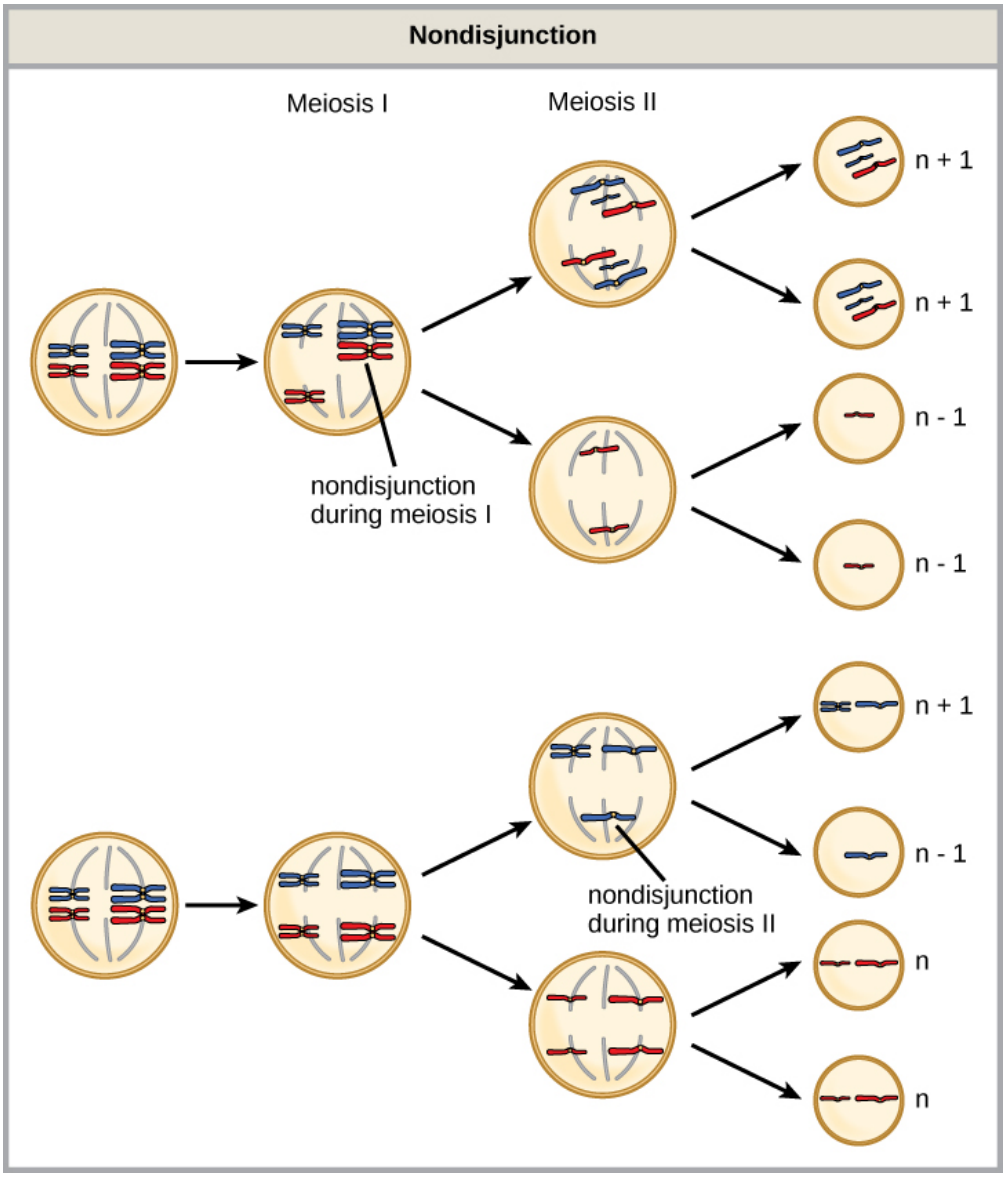


**Figure 4.22** Figure 7.8 Following meiosis, each gamete has one copy of each chromosome. Nondisjunction occurs when homologous chromosomes (meiosis I) or sister chromatids (meiosis II) fail to separate during meiosis. **Source:** *Concepts of Biology (OpenStax)*, CC BY 4.0

An individual with the appropriate number of chromosomes for their species is called **euploid**; in humans, euploidy corresponds to 22 pairs of autosomes and one pair of sex chromosomes. An individual with an error in chromosome number is described as **aneuploid**, a term that includes **monosomy** (loss of one chromosome) or **trisomy** (gain of an extraneous chromosome). Monosomic human zygotes missing any one copy of an autosome invariably fail to develop to birth because they have only one copy of essential genes. Most autosomal trisomies also fail to develop to birth; however, duplications of some smaller chromosomes

(13, 15, 18, 21, or 22) can result in offspring that survive for several weeks to many years. Trisomic individuals suffer from a different genetic imbalance: an excess gene dose. Cell functions are calibrated to the amount of gene product produced by two copies (doses) of each gene; adding a third copy (dose) disrupts this balance. The most common trisomy is that of chromosome 21, which leads to **Down syndrome**. Individuals with this inherited disorder have characteristic physical features and developmental delays in growth and cognition. The incidence of Down syndrome is correlated with maternal age, such that childbearing people over the age of 35 experience an increased probability of giving birth to children with Down syndrome (see figure below). It should be noted that the majority of children with Down syndrome are born to mothers under 35, likely because pre-natal screening for those over 35 is common. The probability related to age and the actual incidence are separate and distinct.

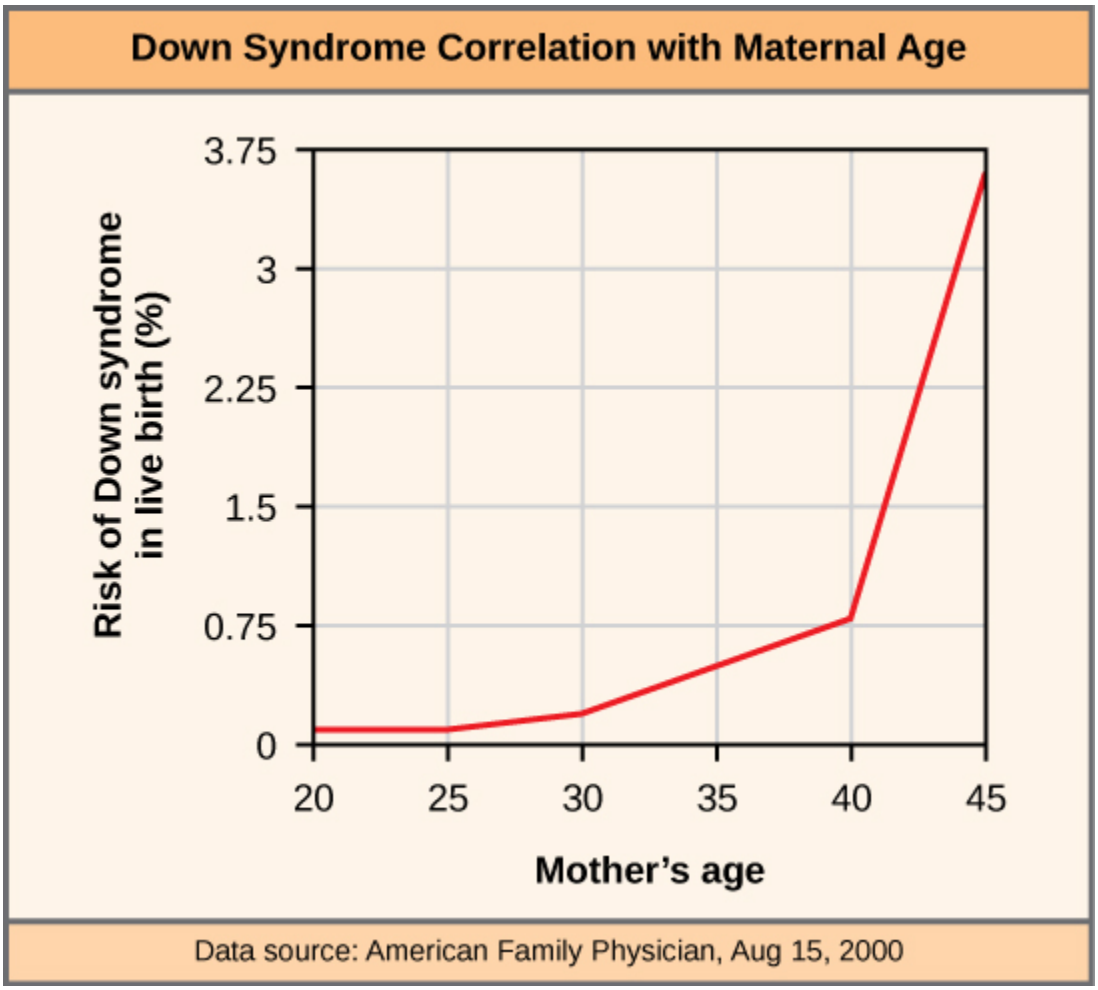


**Figure 4.23** The incidence of having a fetus with trisomy 21 increases dramatically with maternal age. **Source:** *Concepts of Biology (OpenStax)*, CC BY 4.0

## Concept in Action

Visualize the various outcomes of nondisjunction in this animation.

**Watch Chromosome Nondisjunction Animation (5 mins) on YouTube (https://youtu.be/4bzY9e-YQqI)**

Humans display dramatic deleterious effects with autosomal trisomies and monosomies. Therefore, it may seem counterintuitive that human females and males can function normally despite carrying different numbers of the X chromosome. In part, this occurs because of a process called X inactivation. Early in development, when female mammalian embryos consist of just a few thousand cells, one X chromosome in each cell inactivates by condensing into a Barr body structure. The genes on the inactive X chromosome are not expressed. The particular X chromosome (maternally or paternally derived) that is inactivated in each cell is random, but once the inactivation occurs, all cells descended from that cell will have the same inactive X chromosome. By this process, females compensate for their double genetic dose of X chromosome.

In so-called "tortoiseshell" cats, X inactivation is observed as coat-colour variegation (see figure below). Females heterozygous for an X-linked coat colour gene will express one of two different coat colours over other regions of their body, corresponding to whichever X chromosome is inactivated in the embryonic cell progenitor of that region. When you see a tortoiseshell cat, you will know it must be a female.

Embryonic inactivation of one of two different X chromosomes encoding different coat colours gives rise to the tortoiseshell phenotype in cats. (credit: ) Photo of a tortoiseshell cat. **Source:** Michael Bodega – Concepts of Biology (OpenStax), CC BY 4.0

In an individual carrying an abnormal number of X chromosomes, cellular mechanisms will inactivate all but one X in each cell. As a result, X-chromosomal abnormalities are typically associated with mild mental and physical defects and sterility. If the X chromosome is absent altogether, the individual will not develop.

Several errors in sex chromosome numbers have been characterized. Individuals with three X chromosomes, called triple-X, appear female but express developmental delays and reduced fertility. The XXY chromosome complement, corresponding to one type of **Klinefelter syndrome**, corresponds to male individuals with small testes, enlarged breasts, and reduced body hair. The extra X chromosome undergoes inactivation to compensate for the excess genetic dosage. Turner syndrome, characterized as an X0 chromosome complement (i.e., only a single sex chromosome), corresponds to a female individual with short stature, webbed skin in the neck region, hearing and cardiac impairments, and sterility.

An individual with more than the correct number of chromosome sets (two for diploid species) is called **polyploid**. For instance, fertilizing an abnormal diploid egg with a normal haploid sperm would yield a triploid zygote. Polyploid animals are scarce, with only a few examples among the flatworms, crustaceans, amphibians, fish, and lizards. Triploid animals are sterile because meiosis cannot proceed normally with an odd number of chromosome sets. In contrast, polyploidy is very common in the plant kingdom, and polyploid plants tend to be larger and more robust than euploids of their species.

## Chromosome Structural Rearrangements

Cytologists have characterized numerous structural rearrangements in chromosomes, including partial duplications, deletions, inversions, and translocations. Duplications and deletions often produce offspring that survive but exhibit physical and mental abnormalities. **Cri-du-chat** (from the French for “cry of the cat”) is a syndrome associated with nervous system abnormalities and identifiable physical features that result from a deletion of most of the small arm of chromosome 5 (see figure below). Infants with this genotype emit a characteristic high-pitched cry upon which the disorder’s name is based.

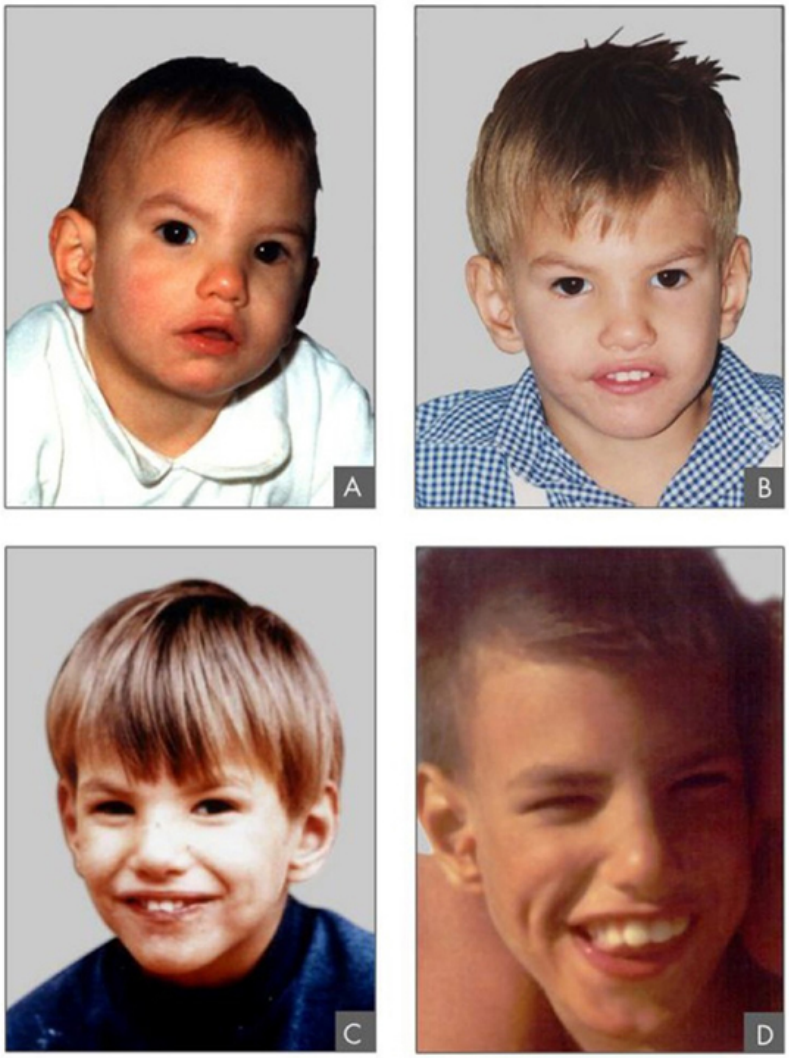


**Figure 4.24** This individual with cri-du-chat syndrome is shown at various ages: (A) age two, (B) age four, (C) age nine, and (D) age 12. **Source:** Paola Cerruti Mainardi – *Concepts of Biology (OpenStax)*, CC BY 4.0.

Chromosome inversions and translocations can be identified by observing cells during meiosis because homologous chromosomes with a rearrangement in one of the pairs must contort to maintain appropriate gene alignment and pair effectively during prophase I.

A chromosome inversion is the detachment, 180° rotation, and reinsertion of part of a chromosome. Unless they disrupt a gene sequence, inversions only change the orientation of genes and are likely to have milder effects than aneuploid errors.

A **translocation** occurs when a chromosome segment dissociates and reattaches to a different, nonhomologous chromosome. Translocations can be benign or have devastating effects, depending on how the positions of genes are altered concerning regulatory sequences. Notably, specific translocations have been

associated with several cancers and with schizophrenia. **Reciprocal translocations** result from the exchange of chromosome segments between two nonhomologous chromosomes such that there is no gain or loss of genetic information (see figure below).

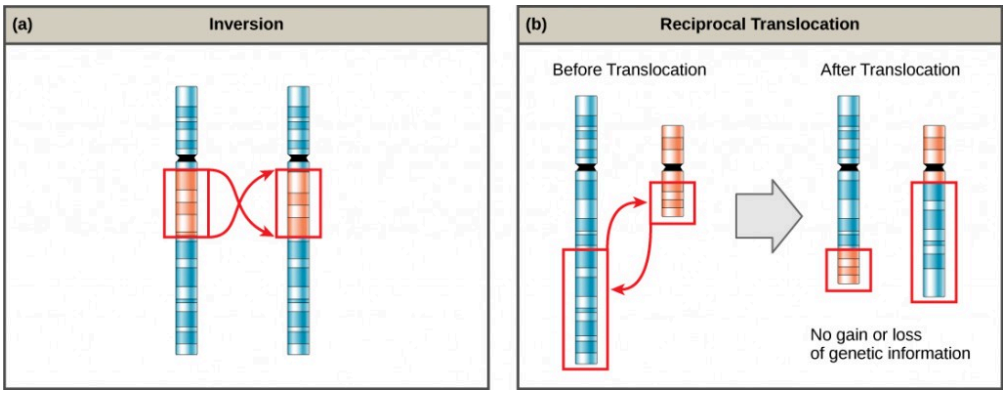


**Figure 4.25** An (a) inversion occurs when a chromosome segment breaks from the chromosome, reverses its orientation, and then reattaches to the original position. A (b) reciprocal translocation occurs between two nonhomologous chromosomes and does not cause any genetic information to be lost or duplicated. **Source:** modification of work by National Human Genome Research Institute (USA) – *Concepts of Biology (OpenStax)*, CC BY 4.0

When an individual's cells differ in their chromosomal makeup, it is known as chromosomal mosaicism.

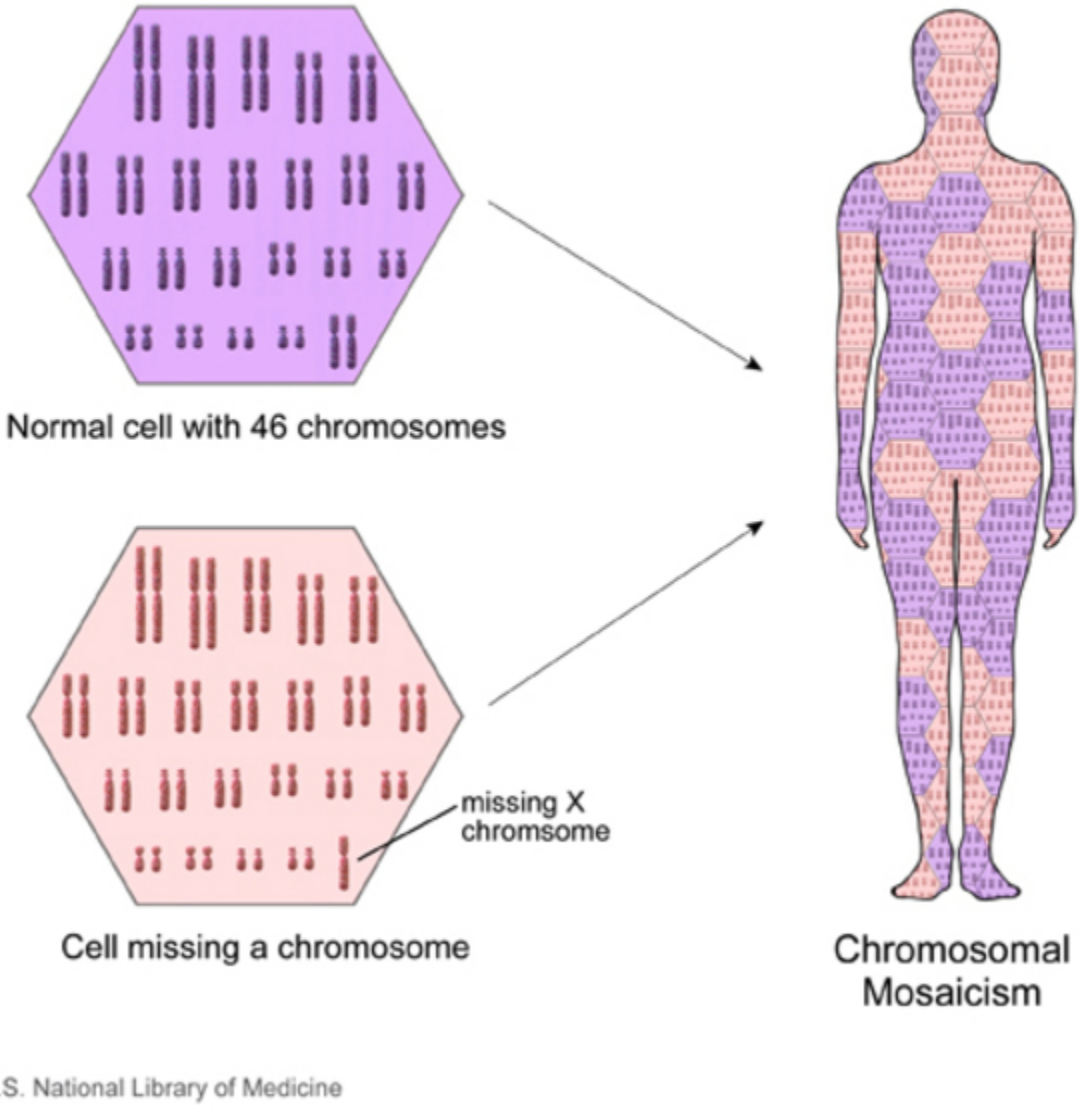


**Figure 4.26** U.S. National Library of Medicine, PDM with attribution

Chromosomal mosaicism occurs from an error in cell division in cells other than eggs and sperm. Most commonly, some cells end up with one extra or missing chromosome (for a total of 45 or 47 chromosomes per cell), while other cells have 46 chromosomes. Mosaic Turner syndrome is one example of chromosomal mosaicism. In females with this condition, some cells have 45 chromosomes because they are missing one copy of the X chromosome, while other cells have the usual number of chromosomes.

Many cancer cells also have changes in their number of chromosomes. These changes are not inherited; they occur in somatic cells (cells other than eggs or sperm) during the formation or progression of a cancerous tumour.

# Attribution & References

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# 4.7 MITOCHONDRIAL DISORDERS

## Can changes in mitochondrial DNA affect health and development?

Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, *mitochondria also have a small amount of their own DNA* (known as **mitochondrial DNA** or mtDNA). In some cases, inherited changes in mitochondrial DNA can cause problems with growth, development, and function of the body's systems. These variants disrupt the mitochondria's ability to generate energy efficiently for cells.

Conditions caused by variants in mitochondrial DNA often involve multiple organ systems. The effects of these conditions are most pronounced in organs and tissues that require a lot of energy (such as the heart, brain, and muscles). Although the health consequences of inherited mitochondrial DNA alterations vary widely, frequently observed features include muscle weakness and wasting, problems with movement, diabetes, kidney failure, heart disease, loss of intellectual functions (dementia), hearing loss, and problems involving the eyes and vision.

Genetic changes that are not inherited (somatic variants) may also occur in mitochondrial DNA. Recall that somatic variants occur in the DNA of certain cells (not sperm or egg cells) during a person's lifetime and are not passed to future generations. Because mitochondrial DNA cannot repair errors, these variants tend to build up over time. A buildup of somatic variants in mitochondrial DNA has been associated with some forms of cancer and an increased risk of certain age-related disorders such as heart disease, Alzheimer's disease (https://medlineplus.gov/genetics/condition/alzheimer-disease/), and Parkinson's disease (https://medlineplus.gov/genetics/condition/parkinson-disease/). Additionally, research suggests that the progressive accumulation of these variants over a person's lifetime may play a role in the normal aging process.

Symptoms of mitochondrial disorders vary because a person can have a unique mixture of healthy and defective mitochondria, with a unique distribution of each within the body.

Mitochondrial disorders that mainly cause muscular problems are called **mitochondrial myopathies** ("myo" means muscle and "pathos "means disease), while mitochondrial disorders that cause both muscular and neurological problems are called **mitochondrial encephalomyopathies** (encephalo refers to the brain).

## Mitochondrial myopathy

The main symptoms of mitochondrial myopathy are:

- Muscle fatigue
- Weakness
- Exercise intolerance

The severity of any of these symptoms varies greatly from one person to the next, even within the same family.

In some individuals, the weakness is most prominent in the muscles that control eye and eyelid movements. This can lead to these muscles eventually becoming paralyzed, called progressive external ophthalmoplegia (PEO). People with PEO may also experience a drooping of the upper eyelids, called ptosis. They also have difficulty moving their eyes up and down and side to side. Often, people automatically compensate for PEO by moving using their necks to look in different directions and might not notice any visual problems. Ptosis can impair vision and cause a listless expression. Surgery can help correct this.

Mitochondrial myopathies can cause weakness and wasting in other muscles of the face and neck, which can lead to difficulty with swallowing and, more rarely, slurred speech. People with mitochondrial myopathies also may experience muscle weakness in their arms and legs.

Exercise intolerance, also called exertional fatigue, refers to unusual feelings of exhaustion brought on by physical exertion. The degree of exercise intolerance varies significantly among individuals. Some people might need help with athletic activities like jogging, while others might experience problems with everyday activities such as walking to the mailbox or lifting a milk carton. In rare instances, this exercise intolerance can lead to muscle breakdown after exercise. This breakdown causes a protein called myoglobin to leak from a person's muscles into their urine. The leakage, sometimes accompanied by muscle cramps, usually occurs when a person with exercise intolerance "overdoes it" and can happen during physical activity or several hours afterward.

While people with mitochondrial myopathy should avoid overdoing it, moderate exercise can help them maintain strength.

## Mitochondrial encephalomyopathy

Mitochondrial encephalomyopathy often includes some symptoms of myopathy plus one or more neurological symptoms.

In addition to affecting the muscles around the eye, mitochondrial encephalomyopathy can affect the eye and parts of the brain involved in vision. For instance, vision loss is a common symptom of mitochondrial encephalomyopathy. This can be caused by shrinkage of the optic nerve or a breakdown of the cells that line the back of the eye.

Other common symptoms of mitochondrial encephalomyopathy include migraine headaches and seizures. There are many effective medications for treating and helping to prevent migraines and seizures, including anticonvulsants and other drugs developed to treat epilepsy.

Hearing loss is another common symptom of mitochondrial disorders. It is caused by damage to the inner

ear or the auditory nerve, which connects the inner ear to the brain. This kind of hearing loss is permanent, but it can be managed. Alternative forms of communication (like sign language), hearing aids, or cochlear implants can help.

Mitochondrial disorders can cause ataxia, which is trouble with balance and coordination. People with ataxia are prone to falls and may need to use supportive aids such as railings, a walker, or a wheelchair. Physical and occupational therapy also may help.

In some cases, mitochondrial disorders can lead to issues with breathing, heart health, kidney issues, diabetes, or digestive problems. People with mitochondrial disorders should get regular health check-ups to identify and monitor these potential problems.

## Mitochondrial disorders in children

Although PEO and ptosis typically cause only mild visual impairment in adults, they can be much more harmful in children. During childhood, these conditions can cause permanent damage to the brain's visual system. Children with signs of PEO or ptosis need to have their vision checked by a specialist.

Children with mitochondrial disorders may have difficulty developing specific skills due to either muscle weakness, neurological problems, or both. For example, they might take longer than usual to learn to sit, crawl, or walk. As they get older, they may be unable to get around as easily as other children their age or may have problems with speech or learning. Children affected by these problems may benefit from early intervention and services such as physical and speech therapy or an individualized education program at school.

To read about different types of mitochondrial disorders, visit this NIH web resource (https://www.ninds.nih.gov/health-information/disorders/mitochondrial-disorders#toc-types-of-mitochondrial-disorders)or this mitochondrial myopathies fact sheet (https://www.mda.org/disease/mitochondrial-myopathies) from the Muscular Dystrophy Association.

# How are mitochondrial disorders diagnosed and treated?

## Diagnosing mitochondrial disorders

A diagnosis generally includes:

- An evaluation of medical and family history.
- Physical and neurological exams. The physical exam typically includes tests of strength and endurance, such as an exercise test (which can involve repeatedly making a fist). The neurological exam can consist of tests of reflexes, vision, speech, and basic cognitive (thinking) skills.
- Laboratory tests to look for diabetes, liver and kidney problems, and elevated lactic acid in the blood and

urine. Lactic acid in the cerebral spinal fluid may be measured using a spinal tap or estimated via less invasive MRI imaging.

- EKG (electrocardiogram) to check the heart for signs of arrhythmia and cardiomyopathy.
- Diagnostic imaging, such as CT (computed tomography) or MRI, to inspect the brain for developmental abnormalities or signs of damage. In an individual with seizures, the doctor might order an EEG (electroencephalogram), which involves placing electrodes on the scalp to record brain activity.
- Genetic testing can determine whether someone has a genetic mutation. Although a positive test result can confirm the diagnosis of a mitochondrial disorder, a negative test result can be more complex to interpret and does not definitively rule out the presence of a genetic mutation. It could mean a person has a mutation that the test could not detect.
- Muscle biopsy involves removing and examining a small sample of muscle tissue. When treated with a dye that stains mitochondria red, muscles affected by mitochondrial disorders often show ragged red fibres—muscle cells (fibres) with excessive mitochondria. Other stains can detect the absence of essential mitochondrial enzymes in the muscle. It also is possible to extract mitochondrial proteins from the muscle and measure their activity. Genetic testing for mutations in mitochondrial DNA is more sensitive than testing for mutations in blood in certain mitochondrial disorders. Noninvasive techniques like MR spectroscopy can examine muscle without taking a tissue sample.

## Treating mitochondrial disorders

There are currently no cures or specific treatments for mitochondrial disorders. Generally, treatment is focused on managing symptoms and may include physical and occupational therapy, moderate, physician-led exercise programs, anti-seizure medications, heart medications, vitamins and supplements, or special diets. People with eye and vision symptoms may benefit from assistive devices and surgery, as can individuals with hearing loss. People with any unique issues mentioned below should be monitored by their healthcare provider to track their symptoms and identify appropriate treatments.

People with mild respiratory problems might require occasional respiratory support, such as pressurized air. Someone with more severe problems might require permanent support from a ventilator.

Some mitochondrial disorders may cause cardiomyopathy (heart muscle weakness) or arrhythmia (irregular heartbeat). Although dangerous, cardiac arrhythmia is treatable with a pacemaker, which stimulates a normal heartbeat.

People with mitochondrial disease may experience gastrointestinal problems, diabetes, and kidney problems. These associated conditions and disorders should be managed with appropriate treatments for each. While some of these problems are directly related to mitochondrial disorders, others may be indirectly affected by the disorder. For example, having myoglobin in a person's urine causes the kidneys to work harder to filter it out, which can lead to kidney damage.

# Attribution & References

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- Can changes in mitochondrial DNA affect health and development? In *Help Me Understand Genetics* by MedlinePlus, National Library of Medicine, Public Domain with attribution
- Mitochondrial Disorders by National Institute of Neurological Disorders and Stroke (NINDS) & National Institutes of Health, Public Domain with attribution . / Content has been streamlined and a few sections removed to improve student understanding

# 4.8 UNIT SUMMARY AND REVIEW

## Key Takeaways

Gene variants are slight differences in DNA sequences that occur at specific locations in the genome, contributing to individual uniqueness. While many variants do not impact health, some may increase or reduce disease risk. Variants can be inherited (germline) or occur during a person's lifetime (somatic). Variants can be classified by their effects, such as morphological, lethal, or conditional, depending on their influence on traits, development, or survival. Some variants are "silent," meaning they do not alter protein function or phenotype.

Genetic disorders are categorized into four main types: single gene disorders, chromosomal conditions, multifactorial conditions, and mitochondrial disorders. Naming genetic conditions varies based on factors such as the genetic mutation involved or affected body parts, while a formal committee standardizes gene nomenclature. Genetic predisposition is an increased likelihood of developing certain diseases based on inherited genetic variations, although lifestyle and environmental factors can also play a significant role.

Mutations in a single gene cause single-gene disorders and can follow dominant, recessive, or X-linked inheritance patterns. Despite their rarity, these diseases affect millions globally, including conditions like cystic fibrosis (CF), sickle cell anemia, and Tay-Sachs disease. Advances in genetic testing have improved diagnostics, but treatments for many single-gene disorders remain limited.

The concepts of penetrance and expressivity explain the extent to which a genotype results in the expected phenotype and the variability of phenotypes among individuals with the same genotype. Pleiotropy, where one gene affects multiple traits, and polygenic inheritance, where multiple genes influence a single trait, further illustrate the complexity of genotype-phenotype relationships. Complex traits and diseases often result from multifactorial influences, combining genetic, environmental, and epigenetic components, leading to continuous phenotypic variation.

Inherited disorders can result from abnormal chromosomal behaviour during meiosis, leading to numerical or structural chromosome abnormalities. Chromosomal disorders, such as Down

syndrome (trisomy 21) and Turner syndrome (monosomy X), can be identified using karyograms, revealing chromosome number or structure abnormalities. Nondisjunction, a failure in chromosome separation during meiosis, can cause aneuploidy, leading to trisomy or monosomy. Structural rearrangements, including inversions and translocations, may cause genetic disorders or contribute to cancer. X inactivation helps mitigate the effects of extra X chromosomes, as seen in conditions like Klinefelter syndrome. Chromosomal mosaicism occurs when some cells have differing chromosomal compositions, as observed in conditions like mosaic Turner syndrome.

Mitochondrial disorders result from mutations in mitochondrial DNA, which impair energy production in cells and can affect multiple organ systems, particularly those with high energy demands, such as the heart, brain, and muscles. Symptoms range from muscle weakness, exercise intolerance, and vision problems to neurological issues like seizures, hearing loss, and ataxia. In children, developmental delays may occur. Diagnosis typically involves medical history, physical exams, genetic testing, and muscle biopsies. While no cure exists, treatment focuses on managing symptoms through therapies, medications, and supportive care.

## Additional Optional Readings

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## Attribution & References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

## References

ChatGPT: OpenAI. (2024). *ChatGPT (Version 4.0)* [Large language model]. https://openai.com

# UNIT 5 - GENOMICS NURSING RESEARCH

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 5 Contents


- 5.1 Unit Overview
- 5.2 Genomic Research in Nursing
- 5.3 Human Genetic Research in Canada and Internationally
- 5.4 Research Priorities and Funding
- 5.5 Knowledge Translation and Mobilization
- 5.6 Scholarly Posters
- 5.7 Unit Summary and Review


## Attribution

# 5.1 UNIT OVERVIEW

## Learning Objectives

- Identify key genomic approaches utilized in nursing research and their relevance to patient care.
- Explore barriers to achieving diversity in genomics research and strategies for equitable and inclusive participation.
- Outline the ethical, legal, and social challenges associated with genomic research, with a focus on informed consent, privacy, and inclusion of diverse populations.
- Explain how strategic plans like CIHR's *Sequencing our Future* shape research priorities and funding decisions.
- Describe practical examples of knowledge translation (KT) and knowledge mobilization (KM) outputs.

## Outline

Topics covered in this chapter include:

- Genomic research in nursing
- Human genetic research in Canada and Internationally
- Research priorities and funding
- Knowledge translation and mobilization
- Scholarly Posters

# Competencies Nurses will Develop in this Chapter

## ANA (2023):

### Identification:

- Identifies ethical, ethnic or ancestral, cultural, religious, legal, fiscal, and societal issues related to genomic information and technologies.
- Recognizes issues that undermine the rights of all clients for autonomous, informed genomic-related decision-making and voluntary action.

### Provision of education, care, and support:

- Advocates for autonomous, informed genomic-related decision-making.
- Evaluates the impact and effectiveness of genomic interventions on clients' outcomes.

## NHS (2023):

### Advocate for the rights of all individuals to make informed decisions and act voluntarily:

- ensuring that the consent process is person centred; and
- promoting and supporting equitable access to genomic services.

### Apply knowledge, understanding and context of genomic testing and information to underpin care and support for individuals and families prior to, during and following decision-making:

- incorporating awareness of the ethical, legal and social issues related to testing, recording, sharing and storage of genomic information and data.

### Examine your own competency of practice on a regular basis:

- recognizing areas where professional development related to genomics would be beneficial; and
- maintaining awareness of clinical developments in genomics that are likely to be of most relevance to your area of practice, seeking further information on a case-by-case basis.

### Obtain and communicate reliable, current information about genomics, for self, patients, families and colleagues:

- using information technologies and other information sources effectively to do so; and
- applying critical appraisal skills to assess the quality of information accessed.

# Key terminology

## Candidate gene analysis

The term candidate gene refers to a gene that is believed to be related to a particular trait, such as a disease or a physical attribute. Because of its genomic location or its known function, the gene is suspected to play a role in that trait, thus making it a candidate for additional study. Candidate Gene. The more you know about a trait the better job you can do selecting a candidate gene for further study. For instance, if you're studying the genetics of body size, genes that control bone growth, lipid processing, and insulin growth factors are all excellent candidate genes.

## Genome-wide association study (GWAS)

A genome-wide association study is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. Once new genetic associations are identified, researchers can use the information to develop better strategies to detect, treat and prevent the disease. Such studies are particularly useful in finding genetic variations that contribute to common, complex diseases, such as asthma, cancer, diabetes, heart disease and mental illnesses (NGHRI, 2020, para. 1).

## Next-Generation DNA Sequencing (NGS)

DNA sequencing establishes the order of the bases that make up DNA. Next-generation DNA sequencing (abbreviated NGS) refers to the use of technologies for sequencing DNA that became available shortly after the completion of the Human Genome Project (which relied on the first-generation method of Sanger sequencing). Faster and cheaper than their predecessors, NGS technologies can sequence an entire human genome in a single day and for less than 1,000.

## Symptom science

A field of research focused on understanding the biological and behavioral mechanisms underlying symptoms experienced by patients, such as pain, fatigue, and cognitive impairment.

### Translational research

Often described as "bench to bedside," because it involves taking discoveries from basic science (the bench) and applying them to clinical practice (the bedside).

### Omics

The branches of science known informally as omics are various disciplines in biology whose names end in the suffix *-omics*, such as genomics (https://en.wikipedia.org/wiki/Genomics), proteomics (https://en.wikipedia.org/wiki/Proteomics), metabolomics (https://en.wikipedia.org/wiki/Metabolomics), metagenomics (https://en.wikipedia.org/wiki/Metagenomics), phenomics (https://en.wikipedia.org/wiki/Phenomics) and transcriptomics (https://en.wikipedia.org/wiki/Transcriptomics). Omics aims at the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism or organisms. The related suffix **-ome** is used to address the objects of study of such fields, such as the genome (https://en.wikipedia.org/wiki/Genome), proteome (https://en.wikipedia.org/wiki/Proteome) or metabolome respectively ("Omics", 2024, para. 1).

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- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.
- Symptom science and translational research definitions written by Andrea Gretchev

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# 5.2 GENOMIC RESEARCH IN NURSING

One of the best aspects of a nursing career is the diverse range of roles nurses can pursue, from direct patient care to leadership positions and specialized areas such as research. This variety allows nurses to continually grow and adapt in their careers, contributing to advancements in healthcare and improving patient outcomes in numerous ways. Advanced practice nurses such as clinical nurse specialists, nurse educators, and nurse practitioners typically have a research component to their role.

## Role of Nurses

Nurses play a key role in genomic research by bridging the gap between complex scientific data and patient care. There are many roles for nurses in research. They can contribute by participating in research studies, collecting and managing genetic data, and ensuring ethical standards are upheld. There are many opportunities for nurses to be part of research or simply to refer patients who may be eligible for particular research projects.

**Nurses – Research Roles**

| Type of Research | Role | Description |
|---|---|---|
| **Bench Scientist** | Laboratory Researcher | Conducts lab-based research on biological and physiological processes. |
| **Symptom Science** | Symptom Scientist | Studies patient symptoms to improve management and quality of life. |
| **Qualitative Research** | Qualitative Researcher | Explores patient experiences and behaviors using interviews, focus groups, and ethnography. |
| **Quantitative Research** | Quantitative Researcher | Uses statistical methods to test hypotheses and measure outcomes in clinical trials and surveys. |
| **Mixed Methods Research** | Mixed Methods Researcher | Combines qualitative and quantitative approaches for a comprehensive understanding of research questions. |
| **Clinical Research** | Clinical Research Nurse | Manages and coordinates clinical trials, ensuring ethical conduct and patient recruitment. |
| **Health Services Research** | Health Services Researcher | Studies the organization, delivery, and financing of healthcare services to improve systems and policies. |
| **Implementation Science** | Implementation Scientist | Focuses on translating research findings into clinical practice. |
| **Bioinformatics** | Bioinformatics Nurse | Analyzes biological data using computational tools to understand complex biological systems. |
| **Genomics** | Genomics Nurse | Applies genomic information in clinical care, including genetic testing and counseling. |

There is some excellent work being done in genomics research by nurse scholars that has impacts on clinical practice, policy, the nursing workforce, healthcare system transformation, leadership, and education. The following article provides an introductory overview of genomic approaches in nursing research. It reviews essential concepts in genetics and genomics, provides an overview of the research process, and highlights nursing studies that have used genomic technologies. The authors emphasize the potential of genomics to advance nursing research and encourage nurses to incorporate genomics into their research practice. Nurse researchers can utilize diverse methodologies and measurements, consider biological plausibility studies, case studies, patient surveys, qualitative and quantitative research. Table 1 of the article also highlights commonly utilized approaches to genomic analysis such as the more traditional **candidate gene analysis**, which can be effective for investigating specific hypotheses, and a **genome-wide association study (GWAS),** which has become increasingly favored due to advancements like **Next-Generation Sequencing (NGS)** technologies. NGS allows for high-throughput sequencing of the entire genome, transcriptome, and epigenome, offering a more detailed understanding of the intricate interplay between genetic factors and disease.

In order for nurses at the point-of-care to base their practices in current evidence, they must be research consumers. Nurses learn how to critically appraise research and ensure they are accessing quality, peer

reviewed, and current literature. It is critical to stay abreast of new evidence in this rapidly evolving area in order to build and maintain genomic literacy.

### Read

Bueser, T., Skinner, A., Bolton Saghdaoui, L., & Moorley, C. (2022). Genomic research: The landscape for nursing. *Journal of Advanced Nursing*, *78*(9), e99–e100. https://doi.org/10.1111/jan.15396


### Question for reflection

1. What steps can you take as a future nurse to stay informed about the latest developments in genomics and their implications for nursing?
2. What is the difference between a GWAS and an EWAS (hint: you may need to consult an external source to answer this)?

## The Current State of the Science

Thomas et al. (2023) recently conducted a scoping review examining the progress made over the last decade in nursing and midwifery genomics, demonstrating significant growth in the number of publications on the subject. In order for the advances that have been made in genomic technology to truly benefit patients, nurses need to focus on conducting research that generates clinically relevant evidence. The authors emphasize the need for future research to move away from descriptive studies to interventional studies and implementation research.

### Symptom Science

**Symptom science** is a field of research focused on understanding the biological and behavioral mechanisms

underlying symptoms experienced by patients, such as pain, fatigue, and cognitive impairment. This research aims to identify the causes of these symptoms, develop effective interventions, and improve patient outcomes. Symptom science is closely related to **translational research**, often described as "bench to bedside," because it involves taking discoveries from basic science (the bench) and applying them to clinical practice (the bedside). By translating findings from laboratory studies into practical treatments and interventions, symptom science helps bridge the gap between research and patient care, ensuring that new knowledge directly benefits patients. By engaging in symptom science, nurses can develop and implement evidence-based interventions that improve patient outcomes and quality of life. This field also empowers nurses to advocate for patients, ensuring that symptom management strategies are personalized and effective, ultimately enhancing the overall healthcare experience. To read more about advancing symptom science in a precision health context, see Hickey et al. (2019) in the optional readings list at the end of this unit.

## Omics

This article explores the use of "**omics**" measures in nursing science research to better understand the biological determinants of health. The authors provide excellent examples of nursing genomics research into health outcomes such as chronic lower back pain and variation in pain outcomes, irritable bowel syndrome, the use of the microbiome in maternal health research, and how metabolomics, the study of chemicals involved in biological function, is used to analyze the impact of dietary interventions on multiple sclerosis. As in the other articles, the authors note the gap between "omics" and clinical practice and recommend integrating "omics" content into core PhD and healthcare provider training. They emphasize the need to educate a larger group of nursing scientists who are skilled in designing experiments, capturing data, and analyzing data in combination with endophenotypic and phenotypic data.

Examples of research nurse scholars and scientists are involved in:

### Read

Ferranti, E. P., Grossmann, R., Starkweather, A., & Heitkemper, M. (2017). Biological determinants of health: Genes, microbes, and metabolism exemplars of nursing science. *Nursing outlook*, *65*(5), 506–514. https://doi.org/10.1016/j.outlook.2017.03.013

### Question for reflection:

1. How do you envision incorporating knowledge of genomics, the microbiome, and metabolomics into your future nursing practice?

## Attribution & References



## References

Thomas, J., Keels, J., Calzone, K. A., Badzek, L., Dewell, S., Patch, C., Tonkin, E. T., & Dwyer, A. A. (2023, October 27). Current state of genomics in nursing: A scoping review of healthcare provider oriented (clinical and educational) outcomes (2012-2022). *Genes*, *14*(11), 2013. https://doi.org/10.3390/genes14112013

# 5.3 HUMAN GENETIC RESEARCH IN CANADA AND INTERNATIONALLY

## Ethical Practice for Human Genetic Research in Canada

While we will delve into the ethical, legal, and social aspects of genomics in a later unit, it is crucial to address the ethical considerations that arise when discussing genomic research. These include special considerations related to privacy and confidentiality of genomic data, complexities related to informed consent and the unspecified future use of specimens (broad consent), underrepresentation in genomic data, equity and access to genomic services, genetic discrimination, return of findings including incidental findings, cultural considerations, ethical oversight, emerging treatments that pose ethical concerns, and genetic testing in children. It is beyond the scope of this course to delve into all of these ethical issues. A brief review of select issues will be provided as well as information on where to seek guidance to resolve ethical concerns. These concerns are not specific to research in Canada. Globally, genomics research experiences the same ethical issues. However, this chapter will focus on policy that guides human genetics research in Canada.

The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2 – 2022) is the policy that governs research involving humans conducted by Canadian researchers under the three federal funding agencies: the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council of Canada (SSHRC). As a condition of funding, researchers must adhere to this policy. It is based upon the Belmont Report (https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html) and the Nuremberg Code (https://research.unc.edu/human-research-ethics/resources/ccm3_019064/). It should also be noted that TCPS2 (2022) uses the term "genetics." For the purposes of this chapter, this should be considered synonymous with "genomics."

There are learning modules (https://tcps2core.ca/welcome) that all Canadian researchers complete in order to conduct research in Canada and a certificate of completion can be downloaded.

Many of the chapters in the TCPS2 (2022) are specifically applicable to ethical issues arising from genomics research, such as consent, privacy and confidentiality, and storage and use of human biological materials. Additionally, chapter 13 is dedicated to human genetic research considerations.

### Read

Briefly Review: Chapter 13: Human Genetic Research in the TCPS2 (https://ethics.gc.ca/eng/tcps2-eptc2_2022_chapter13-chapitre13.html#a).

This chapter focuses on the ethical conduct of human genetic research. It addresses the application of core principles, management of information revealed through genetic research, genetic counselling, and considerations for research involving families, communities, and groups. The chapter emphasizes the importance of privacy, consent, and the potential social impacts of genetic research.

### Questions for reflection:

1. How can nurses ensure that patients fully understand the implications of consenting to genetic research, especially regarding privacy and potential future use of their genetic information?
2. What strategies can nurses employ to address the ethical challenges that arise when genetic research findings have implications for a patient's family members or community?
3. As nurses enter a healthcare landscape increasingly reliant on data, how can they advocate for responsible and ethical use of data, especially concerning patient privacy and confidentiality in the context of precision health?

## Diversity in Genomic Research (NHGRI, 2023)

The code embedded within the human genome is complex, and genomics research has only scratched the surface of determining everything there is to know about what makes us all different at the DNA level. Historically, the people who have provided their DNA for genomics research have been overwhelmingly of European ancestry, which creates gaps in knowledge about the genomes from people in the rest of the world. Scientists are now expanding their data collection to better understand how genomics can be used to improve the health and wellbeing of all people.

Based on work completed before and after the Human Genome Project, researchers found that the genome

sequences of human populations have changed significantly over 250,000 years of our species' expansion and migration across the Earth. Even with the high degree of similarity between any two human genomes, enough differences exist that it is not appropriate to use a single, or even a few, genomes to represent the world's populations. This highlights that the original human genome reference sequence, produced by the Human Genome Project and based on just a handful of research participants, was just the starting point for human genomics.

To address this limitation, efforts are underway to create human reference genome sequences that better represent diverse populations. NHGRI funds the Human Pangenome Reference Program (https://www.genome.gov/Funded-Programs-Projects/Human-Genome-Reference-Program), which is generating a collection of reference genome sequences that better represent human diversity.

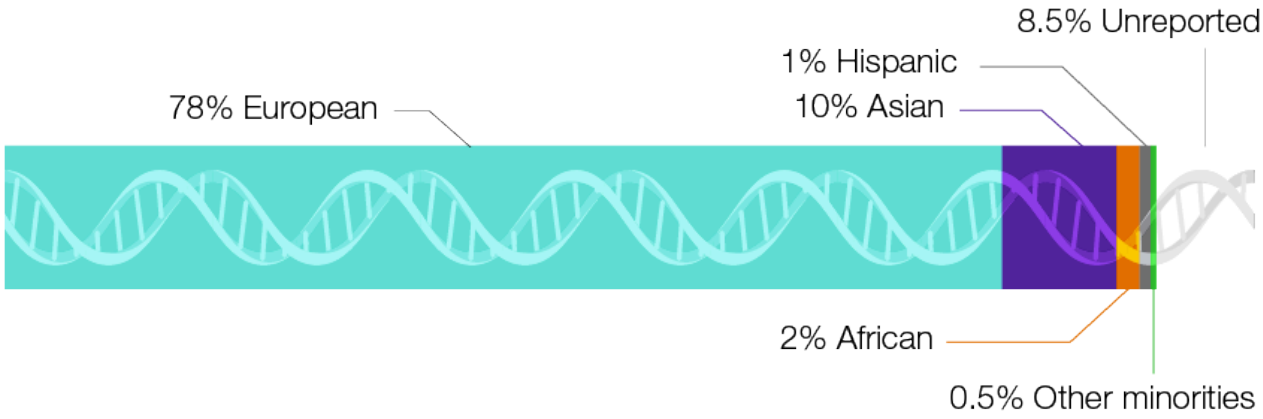


**Figure 5.1** The percentage of ancestry populations included in large-scale genomic studies is overwhelmingly European(78%). 10% Asian, 1% Hispanic, 8.5% unreported, 2% African and 0.5% other minorities. **Source:** courtesy: National Human Genome Research Institute, Public Domain with Attribution

## How does studying diverse human genomes improve health outcomes?

Every human has some baseline genetic risk of developing a given disease. Extensive research has been performed to both understand and learn how to respond to these risks. In some cases, the same variant consistently causes a disease (e.g., Huntington's disease and cystic fibrosis), but this might not be the case for more complex diseases (e.g., coronary artery disease, obesity, cancer and Alzheimer's disease).

By including populations that reflect the full diversity of human populations in genomic studies, researchers can identify genomic variants associated with various health outcomes at the individual and population levels. This way, researchers can better define a person's risk of developing a specific disease (https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores) and design a clinical management strategy that is tailored to the individual. In addition, they can pursue genomic medicine strategies that benefit specific populations.

## Why has enhancing diversity in genomics research been a difficult task?

Increasing the representation of diverse participants in genomics research requires an investment of both resources and time to intentionally establish trusting and respectful long-term relationships between communities and researchers. To ensure that genomics research is both equitable and inclusive, it is crucial for the genomics research workforce to reflect a similar diversity as the communities that the research is intended to serve.

In the past, both inaccessible and insufficient communication left some research participants unclear about the benefits of their participation and how their data would be used after the studies concluded. To overcome this, researchers must seek to understand people's reasons for not participating in genomic studies and to communicate with participants in a more accessible manner. This can take additional time, effort and resources, which may discourage some researchers from including these important, diverse populations in their studies. However, such exclusion can lead to notable gaps in scientific understanding and potentially reenforce existing disparities in genomics research.

## Tracking Resource

The GWAS Diversity Monitor (https://gwasdiversitymonitor.com/) (Mills, 2020) is an interactive dashboard that tracks the diversity of participants in all published Genome Wide Association Studies (GWAS).

## What are some genomics research projects that are enhancing the diversity?

Genomics researchers have initiated dozens of research projects to enhance the representation of research participants in genomics research. These studies are addressing a variety of research topics, including the effects of genomic diversity on disease risk, how to tailor genomic medicine for underrepresented populations, the impact of genomics research on diverse and the history of the human population.

NIH's *All of Us (https://allofus.nih.gov/)* Research Program is working to build a diverse health resource by collecting genome-related data and other information from about 1 million people. The Global Alliance for Genomics and Health (https://www.ga4gh.org/about-us/) (GA4GH) is developing a framework for storing, analyzing and sharing genomic data among international researchers. The Human Cell Atlas (https://www.humancellatlas.org/) aims to be a resource that includes in-depth information about all cell types found in people across the world.

## How is NHGRI helping to improve diversity in genomics research?

NHGRI is dedicated to increasing diversity of the genomics workforce (https://www.genome.gov/about-nhgri/leadership-initiatives/diversity-in-genomics-workforce). In addition, NHGRI supports projects that work to increase the diversity of people participating in genomics research, including:

- The 1,000 Genomes Project (https://www.internationalgenome.org/) (2002 – 2015)
  The most extensive public catalog of human variation and genomic data, with over 2,000 genomic samples from 26 populations across the North and South America, Africa, Asia and Europe.
- Human Heredity and Health in Africa (H3Africa) (https://h3africa.org/) (2012 – 2022)
  The largest pan-African genomic research consortium that investigates the genomics of disease in Africa. The project also aims to build a sustainable African genomics research enterprise. This project is a collaborative effort that also involves the NIH Common Fund, the Wellcome Trust and the African Academy of Sciences.
- Polygenic Risk Score (PRS) Diversity Consortium (https://www.genome.gov/Funded-Programs-Projects/Polygenic-Risk-Score-Diversity-Consortium) (2021 – 2027)
  The consortium uses insights from genomic diversity to predict health and disease risk across diverse populations using a PRS approach.
- Implementing Genomics in Practice (IGNITE) Network (https://www.genome.gov/Funded-Programs-Projects/Implementing-Genomics-in-Practice-IGNITE) (2018 – 2022)
  This network assesses approaches for real-world applications of genomic medicine in diverse clinical settings.
- Electronic Medical Records and Genomics (eMERGE) Network (https://www.genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE) (2020 – 2025)
  This network establishes protocols and methodologies for improved genomic risk assessments for diverse populations and to integrate their use in clinical care.

# Unethical Research Conduct Consequences

Historical abuses of research ethics have led to a lack of trust in scientific research and medical systems. This has led to the development of stricter policies guiding research ethics to protect participants and researchers. Ethical guidelines draw particular attention to the protection of vulnerable subjects because history has taught us that these populations are most easily exploited and have the most to lose. We will explore scientific racism more in the unit on ethical, legal and social implications of genomics. However, it seems fitting to include mention of this research history here.

## HeLa Cells: A Lasting Contribution to Biomedical Research

**Figure 5.2 Source:** National Institutes of Health Office of Science Policy, PDM

In 1951, Henrietta Lacks, a 31-year-old African-American woman, went to Baltimore's Johns Hopkins Hospital to be treated for cervical cancer. Some of her cancer cells began being used in research due to their unique ability to continuously grow and divide in the laboratory. These so-called "immortal" cells were later named "HeLa" after the first two letters of **He**nrietta **La**cks first and last name.

Since Ms. Lacks' untimely death in 1952, HeLa cells have been a vital tool in biomedical research, leading to an increased understanding of the fundamentals of human health and disease. Some of the research involving HeLa cells also served as the underpinning of several Nobel Prize winning discoveries.

While Henrietta Lacks' story has been known in the research community for some time, it raised further awareness after the publication of the best-selling book *The Immortal Life of Henrietta Lacks* (https://search.worldcat.org/title/The-immortal-life-of-Henrietta-Lacks/oclc/326529053) (Skloot, 2010).

To honor Ms. Lacks' and her family's continued support of biomedical research, NIH analyzed and evaluated the scientific literature involving HeLa cells and found over 110,000 publications that cited the use of HeLa cells between 1953 to 2018. This analysis further highlights the persistent impact of HeLa cells in science and medicine, proving that they have been a consistent, essential tool that has allowed researchers to expand the knowledge base in fields such as cancer biology, infectious disease, and many others.

This website aims to act as a transparent, accessible resource to the general public, scientific researchers, and the Lacks' family that is in keeping with the spirit of the historic 2013 NIH-Lacks Family Agreement. NIH remains grateful to Henrietta Lacks and her family for the contributions of HeLa cells to science and medicine, and for her family's continued support of biomedical research.

**Source:** HeLa Cells: A Lasting Contribution to Biomedical Research courtesy of the NIH Office of Science Policy.

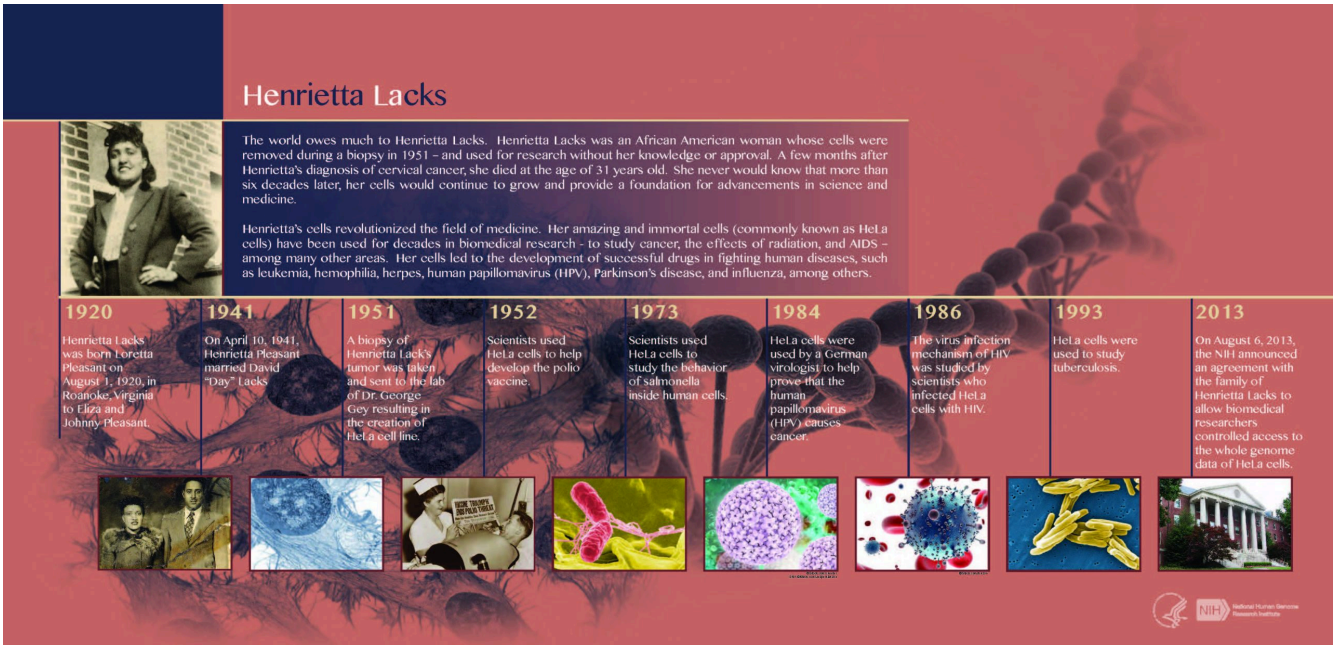


**Figure 5.3** HeLa timeline. Courtesy: National Human Genome Research Institute. Figure 5.3 image description. **Source:** Image by Darryl Leja, NHGRI. PDM

## Concept in Action: Henrietta Lacks

Use the bars on the bottom of the interactive slide show to navigate and watch the following videos, or use the text links below to access the videos on YouTube.

**Concept in Action: Henrietta Lacks (text version)**

- Watch Henrietta Lacks: The 'immortal' cells that changed the world – BBC REEL (8 mins) on YouTube (https://youtu.be/pgB1lqGp8BE)
- Watch Henrietta Lacks' family settles with biotech company over cancer cells (2 min) on YouTube (https://youtu.be/AENPGhVWBvE)



Here in Canada, the Nuu-chah-nulth case brought attention to the ethical concerns surrounding the use of stored biological samples, especially those collected from indigenous communities. The Nuu-chah-nulth tribe donated blood samples for research into the genetic causes of rheumatoid arthritis but later learned their samples were used for unrelated research without their consent, which they considered an example of exploitation. The tribe's blood samples were collected by geneticist Ryk Ward at the University of British Columbia, who took the samples with him when he left the university, continuing his research at the

University of Utah and later at the University of Oxford. Ward shared data from the samples with collaborators and published half a dozen articles based on his research. In response to the case, the University of British Columbia and the University of Utah implemented new policies requiring researchers to obtain consent for any new research conducted on stored samples.

## Special Considerations for Genomics Research with Indigenous Populations

The article below focuses on consultations with First Nations communities in northern British Columbia regarding the establishment of a First Nations biobank for use in genomic health research. Some key ethical considerations that emerged in the consultations were: the need to rebuild trust in research among First Nations communities, the need to incorporate cultural safety and traditional knowledge into all stages of the biobank's development and implementation, the importance of ensuring First Nations ownership and control of the biobank and all research undertaken using its materials, and the need for comprehensive and culturally sensitive consent processes.

### Read

Caron, N. R., Adam, W., Anderson, K., Boswell, B. T., Chongo, M., Deineko, V., Dick, A., Hall, S. E., Hatcher, J. T., Howard, P., Hunt, M., Linn, K., & O'Neill, A. (2023). Partnering with First Nations in Northern British Columbia Canada to reduce inequity in access to genomic research. *International Journal of Environmental Research and Public Health, 20*(10), 5783-. https://doi.org/10.3390/ijerph20105783

OPEN ACCESS ONLINE

Other important work being done to protect the rights and interests of Indigenous Peoples include the Silent Genomes Project (https://www.bcchr.ca/silent-genomes-project)is a collaborative effort involving various partners, including the First Nations, Inuit, and Métis communities, and is led by experts in the field of genomics and Indigenous health. It is aimed at reducing health care disparities, and improving diagnostic success and health outcomes for Indigenous children in Canada with genetic diseases. Some key aspects of the project include addressing health inequities, Indigenous governance, creating an Indigenous biobank and variant library, and providing culturally safe genomic testing.

### Concept in Action: First Nations Principles of OCAP™

Research with Indigenous Peoples should follow the principles of OCAP® which "asserts that First Nations alone have control over data collection processes in their communities, and that they own and control how this information can be stored, interpreted, used, or shared" (First Nations Information Governance Centre, 2024, para. 2).

**Watch Understanding the First Nations Principles of OCAP™ : Our Road Map to Information Governance (6 min) on YouTube (https://youtu.be/y32aUFVfCM0) to learn about these principles.**

# Image Description

## 5.3 HeLa Timeline: Henrietta Lacks

The world owes much to Henrietta Lacks. Henrietta Lacks was an African American woman whose cells were removed during a biopsy in 1951 – and used for research without her knowledge or approval. A few months after Henrietta's diagnosis of cervical cancer, she died at the age of 31 years old. She would never know that more than six decades later, her cells would continue to grow and provide a foundation for advancements in science and medicine.

Henrietta's cells revolutionized the field of medicine. Her amazing and immortal cells (commonly known as HeLa cells) have been used for decades in biomedical research – to study cancer, the effects of radiation, and AIDS – among many other areas. Her cells led to the development of successful drugs in fighting human diseases, such as leukemia, hemophilia, herpes, human papillomavirus (HPV), Parkinson's disease, and influenza, among others.

### HeLa Timeline

- 1920: Henrietta Lacks was born Loretta Pleasant on August 1, 1920 in Roanoke, Virginia to Eliza and Johnny Pleasant.
- 1941: On April 10, 1941, Henrietta Pleasant married David "Day" Lacks.
- 1951: A biopsy of Henrietta Lacks' tumour was taken and sent to the lab of Dr. George Gey resulting in the creation of the HeLa cell line.
- 1952: Scientists used HeLa cells to help develop the polio vaccine.
- 1973: Scientists used HeLa cells to study the behavior of samonella inside human cells.

- 1984: HeLa cells were used by a German virologist to help prove that the human papillomavirus (HPV) causes cancer.
- 1986: The virus infection mechanism of HIV w2as studied by scientists who infected HeLa cells with HIV.
- 1993: HeLa cells were used to study tuberculosis.
- 2013: On August 6, 2013, the NIH announced an agreement with the family of Henrietta Lacks to allow biomedical researchers controlled access to the whole genome data of HeLa cells. [Back to Fig. 5.3]

## Attribution & References



- Diversity in Genomic Research section is adapted from Diversity in Genomic Research, Courtesy: National Human Genome Research Institute, Public Domain with Attribution
- HeLa Cells: A Lasting Contribution to Biomedical Research is reused from the NIH Office of Science Policy, Public Domain, with additional content added in (videos)

## References

First Nations Information Governance Centre. (2024). *The First Nations principles of OCAP®*. https://fnigc.ca/ocap-training/

Mills, M.C & Rahal, C. (2020). The GWAS Diversity Monitor Tracks diversity by disease in real time. *Nature Genetics, 52,* 242-243. https://doi.org/10.1038/s41588-020-0580-y

National Human Genome Research Institute (NHGRI). (n.d.). *Diversity in genomic research*. Genome.gov. https://www.genome.gov/about-genomics/fact-sheets/Diversity-in-Genomic-Research

Skloot, R. (2010). The immortal life of Henrietta Lacks. Crown Publishers. https://search.worldcat.org/title/The-immortal-life-of-Henrietta-Lacks/oclc/326529053

# 5.4 RESEARCH PRIORITIES AND FUNDING

## Research Funding in Canada

The Canadian Institutes of Health Research (CIHR) is Canada's primary federal agency responsible for funding health research. Within it, there are 13 virtual institutes, each focusing on specific areas of health research, such as cancer, genetics, and indigenous health (CIHR, 2021; CIHR, 2022). These institutes bring together researchers, health professionals, and policymakers to collaborate on improving the health of Canadians through innovative research and knowledge translation (CIHR, 2022).

Another important source of research funding for genomics come from Genome Canada [PDF] (https://genomecanada.ca/wp-content/uploads/2023/02/Genome-Canada-Corporate-Plan-2023-24-EN-Accessible-Version.pdf). The organization supports genomics research impact areas of health, climate and environment, and food and agriculture.

## Setting Research Priorities

Although there are many excellent research questions, funding research is competitive. How can a researcher know what topics have the best chance of being funded? Competitions for research grants are established through the various funding agencies and organizations, each with specific mandates and priorities. Major funding bodies like the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC) regularly announce calls for proposals. These calls outline the eligibility criteria, application guidelines, and evaluation processes for different types of research projects.

The CIHR has an Institute of Genetics (CIHR-IG) (https://cihr-irsc.gc.ca/e/13147.html) which facilitates research on human and model genomes, encompassing all areas of genetics related to health and disease. This includes translating research findings into health policies and practices, as well as addressing the societal impacts of genetic discoveries. The Institute's strategic plan titled *Sequencing our Future (2022-2027) [PDF]* (https://cihr-irsc.gc.ca/e/documents/ig-strat-plan-2022-2027-en.pdf). This document describes the Institute's strategic priorities for genomic research. Funding for research is often prioritized based on these types of documents which outline key research priorities and goals to guide funding decisions to areas that promise the most significant impacts.

Priorities for nursing genomics research are determined through a combination of national health priorities, emerging scientific evidence, and the needs identified by healthcare professionals and patients.

Additionally, professional organizations and academic institutions play a significant role in setting research agendas and securing funding to advance the field of nursing genomics.

## Attribution & References



## References

Canadian Institutes of Health Research (CIHR). (2021). *CIHR Strategic Plan 2021-2031*. https://cihr-irsc.gc.ca/e/52331.html

Canadian Institutes of Health Research (CIHR). (2022). *Annual Report 2021-22*. https://cihr-irsc.gc.ca/e/53108.html

# 5.5 KNOWLEDGE TRANSLATION AND MOBILIZATION

## Knowledge Translation and Mobilization

"**Knowledge translation (KT)** is defined as a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products, and strengthen the health care system" (CHIR, 2010, para. 4).

Download the Government of Canada *Knowledge Translation Planner (https://www.canada.ca/en/health-canada/corporate/about-health-canada/reports-publications/grants-contributions/knowledge-transfer-planner.html#section2.4).*

"**Knowledge mobilization (KM)** is an umbrella term encompassing a wide range of activities relating to the production and use of research results, including knowledge synthesis, dissemination, transfer, exchange, and co-creation or co-production by researchers and knowledge users" (SSHRC, 2023, para 4.).

Examples of KM outputs include, but are not limited to:

- Toolkits
- Websites
- Policy briefs
- Journal articles
- Videos

While both concepts aim to bridge the gap between research and practice, knowledge translation is more focused on the application of research in specific fields like healthcare, whereas knowledge mobilization emphasizes a collaborative and inclusive approach across various disciplines.
Research Impact Canada (RIC) has created an excellent online learning resource, KMb101: Introduction to Knowledge Mobilization (https://rise.articulate.com/share/qV54-kftJACqH_QXUcaMODQ3W9qDw3-Y#/). This is a free short course containing 8 modules and numerous useful resources. Have a brief look and file this away for when you next need to plan for knowledge mobilization. RIC also has an excellent learning module on Infographic Design for Knowledge Mobilization (https://rise.articulate.com/share/sUG_m7CTkldQ6phbVlUqV45evvihETL4#/).

# Examples of Knowledge Translation and Mobilization in Nursing and Genomics

Examples of knowledge mobilization in genomics for nurses include these excellent resources which will enhance your practice. Bookmark or save these for future reference. It is not required to read these in detail now though readers may wish to explore them in brief.

## Online Resources

1. The Genetics and Genomics Toolkit for Canadian Nurses: (https://genomicstoolkit.my.canva.site/) A resource developed to enhance the genomic literacy of Canadian nurses, providing essential knowledge and tools for integrating genomics into nursing practice.
2. Canadian Nurses and Genomics: (https://www.nursingandgenomics.com/) An initiative aimed at supporting Canadian nurses in developing genomic literacy and integrating genomics into their practice to improve patient care and health outcomes.
3. Linkage: (https://linkage.trubox.ca/) an online knowledge engagement hub which includes educational content about foundational genomic concepts in the context of nursing practice. There are opportunities for nurses to learn about how health, genes, and nursing care are connected.
4. Oncology Nursing Society Genetics and Genomics: (https://www.ons.org/taxonomy/term/876) A professional organization dedicated to advancing excellence in oncology nursing through education, research, and advocacy, supporting over 35,000 members in providing high-quality cancer care.
5. Many of the NGHRI resources for nurses in genomics are the result of knowledge mobilization from nurse scientists. The Talking Glossary (https://www.genome.gov/genetics-glossary) that definitions are drawn from at the start of each unit in this book is one example. The Method for Introducing a New Competency (MINC) (https://www.genome.gov/minc) is a toolkit for healthcare professional that is the output of an implementation study.

## Policies Examples

These have already been introduced but the competency documents for nurses working with genomics are examples of evidence-based policies developed by nurses.

- NHS. (2023). Genomic competency framework for UK nurses [PDF] (https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2023/12/2023-Genomic-Competency-Framework-for-UK-Nurses.pdf).
- ANA. (2023). Essentials of genomic nursing: Competencies and outcome indicators (https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/) (3rd ed.).

## Journal Articles Featuring Nursing Genomics Knowledge Mobilization

This paper discusses how the new regulatory model for nurse practitioners in Canada can be optimized to better integrate genomics into healthcare, highlighting the potential benefits and challenges of this integration:

> Acorn, M., Chiu, P., Limoges, J., & **Gretchev, A**. (2024). Optimizing the new model of nurse practitioner regulation in Canada to support the integration of genomics. *Canadian Journal of Nursing Leadership, 37*(2), 49-56. https://doi.org/10.12927/cjnl.2024.27468

This case study explores the collaborative efforts across Canada to advance nursing practices through genomics, emphasizing the importance of nationwide cooperation and shared learning to enhance healthcare outcomes:

> Chiu, P., **Gretchev, A.**, Limoges, J., Puddester, R., Carlsson, L., Pike, A., Leslie, K., Dordunoo, D. (2024). Fostering pan-Canadian collaboration to advance new nursing practice: A case study from the genomics experience. *Canadian Journal of Nursing Leadership, 37*(2), 41.48. https://doi.org/10.12927/cjnl.2024.27470

# Genomics Medicine Professional Organizations

There are several organizations that foster collaboration, networking, research, policy development, and professional development for nurses working in genomics. Many of these organizations are interdisciplinary. Many of these organizations offer discounts or free membership for students. These are another excellent avenue for knowledge translation and mobilization.

**Nursing Specific**

- ISONG (https://www.isong.org/memberbenefits) – International Society of Nurses in Genetics
- G2NA (https://g2na.org/index.php?option=com_content&view=article&layout=edit&id=47) – Global Genomics Nursing Alliance
- CANO (https://www.cano-acio.ca/page/member_benefits) – Canadian Association of Nurses in Oncology – has a special interest group for genomics oncology nursing

**Interdisciplinary**

- DOHAD – (https://dohadsoc.org/join-us/) International and local chapters
- ACMG (https://www.acmg.net/ACMG/Membership/ACMG_Membership.aspx?hkey=1827209f-0d45-4c96-8771-267c281ac3a1&WebsiteKey=6e814a8c-3077-4552-ba39-f7fcacff42d6) – American College of Medical Genetics
- ASHG (https://www.ashg.org/membership/member-benefits/) – American Society of Human

Genetics

## Attribution & References

Except where otherwise noted, this section is written by Andrea Gretchev, CC BY-NC 4.0

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Canadian Institutes of Health Research (CHIR). (2010). *About us: Knowledge translation*. https://www.cihr-irsc.gc.ca/e/29418.html

Social Sciences and Humanities Research Council (SSHRC). (2023, November 24). *Guidelines for effective knowledge mobilization*. https://www.sshrc-crsh.gc.ca/funding-financement/policies-politiques/knowledge_mobilisation-mobilisation_des_connaissances-eng.aspx#a1

# 5.6 SCHOLARLY POSTERS

## Scholarly Posters

Scholarly posters are an effective form of knowledge translation, serving as a visual and concise medium to communicate research findings to a broad audience. They distill complex information into accessible formats, using visuals like charts, graphs, and images to enhance understanding and retention. At academic conferences, posters facilitate direct interaction between researchers and attendees, fostering discussions that can clarify and expand on the presented data. This interactive element not only aids in the dissemination of new knowledge but also encourages feedback and collaboration, further advancing the research field. By making research more approachable and engaging, scholarly posters play a crucial role in bridging the gap between scientific discovery and practical application.

### Assignment – Scholarly Poster

See the Blackboard course shell for resources to develop a scholarly poster.

Scholarly poster assignment guidelines and due dates can be located in Blackboard under Assessments.

## Attribution

# 5.7 UNIT SUMMARY AND REVIEW

## Key Takeaways

Nurses are integral to advancing genomic research, leveraging their expertise to bridge the gap between complex scientific discoveries and patient care. Through roles in direct research, data management, and ethical oversight, nurses contribute significantly to the genomics field. Studies using genomic approaches, such as genome-wide association studies (GWAS), have highlighted the potential of genomics to improve clinical practice, policy, education, and healthcare systems. However, the integration of genomic findings into clinical settings remains an ongoing challenge.

Diversity and ethical considerations are critical considerations in genomics research. Historically, studies have overrepresented populations of European ancestry, creating knowledge gaps about diverse genomic variants and their impact on health outcomes. Efforts such as the Human Pangenome Reference Program and initiatives like the NIH's *All of Us* Research Program aim to address these disparities by including underrepresented populations. Additionally, ethical frameworks, such as Canada's Tri-Council Policy Statement (TCPS), guide the conduct of human genetic research, emphasizing informed consent, privacy, and inclusivity. Addressing diversity challenges requires building trust with communities and ensuring equitable participation, which enhances the global applicability and fairness of genomic medicine.

Research funding in Canada is primarily supported by organizations such as the Canadian Institutes of Health Research (CIHR) and Genome Canada. CIHR operates through 13 virtual institutes focused on areas such as genetics, cancer, and Indigenous health, promoting collaboration among researchers, health professionals, and policymakers. Genome Canada funds genomics research in areas like health, climate, and food systems. Setting research priorities involves understanding the mandates and strategic plans of funding agencies. Nursing genomics research priorities are informed by national health needs, emerging evidence, and input from professional and academic organizations.

Knowledge translation (KT) and knowledge mobilization (KM) are integral to bridging research and

practice. KT emphasizes the application of research findings to specific fields, while KM promotes collaborative and inclusive approaches across disciplines. Examples include resources like the *Genetics and Genomics Toolkit for Canadian Nurses* and initiatives supporting genomic literacy among nurses. Policymakers, educators, and researchers play a critical role in developing tools, policies, and competencies to advance nursing genomics. Collaborative efforts among organizations and professionals are vital for integrating genomics into healthcare and nursing practice.

# Resources

See **Appendix A** for a list of online resources for genomics.

# Additional Optional Readings:

## Guidelines for Genomic Data

World Health Organization. (2024, November 20). *Guidance for human genome data collection, access, use and sharing*. https://www.who.int/publications/i/item/9789240102149

## Diversity in Genomics Research

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2. Koch, L. Global genomic diversity for All of Us. (2024). *Nature Reviews Genetics,25*, 303. https://doi.org/10.1038/s41576-024-00727-9

## Developing Nursing Research Priorities

This is an older article which is in the process of being updated. However, this paper provides an excellent example of priority areas of nursing genomics research mapped to the National Institute of Nursing Research Strategic Plan.

1. Genomic Nursing State of the Science Advisory Panel, Calzone, K. A., Jenkins, J., Bakos, A. D., Cashion, A. K., Donaldson, N., Feero, W. G., Feetham, S., Grady, P. A., Hinshaw, A. S., Knebel, A. R.,

Robinson, N., Ropka, M. E., Seibert, D., Stevens, K. R., Tully, L. A., & Webb, J. A. (2013). A blueprint for genomic nursing science. *Journal of Nursing Scholarship*, *45*(1), 96–104. https://doi.org/10.1111/jnu.12007

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## Health Disparities

1. Caron, N. R., Adam, W., Anderson, K., Boswell, B. T., Chongo, M., Deineko, V., Dick, A., Hall, S. E., Hatcher, J. T., Howard, P., Hunt, M., Linn, K., & O'Neill, A. (2023). Partnering with First Nations in Northern British Columbia Canada to reduce inequity in access to genomic research. *International Journal of Environmental Research and Public Health, 20*(10), 5783-. https://doi.org/10.3390/ijerph20105783
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## Public Trust and Ethics Review

1. Samuel, G.N., & Farsides, B. (2018). Public trust and 'ethics review' as a commodity: the case of Genomics England Limited and the UK's 100,000 genomes project. *Medicine, Health Care and Philosophy,* 21, 159–168. https://doi.org/10.1007/s11019-017-9810-1
2. Milne, R., Morley, K. I., Almarri, M. A., Anwer, S., Atutornu, J., Baranova, E. E., Bevan, P., Cerezo, M., Cong, Y., Costa, A., Critchley, C., Fernow, J., Goodhand, P., Hasan, Q., Hibino, A., Houeland, G., Howard, H. C., Hussain, S. Z., Malmgren, C. I., ... Middleton, A. (2021). Demonstrating trustworthiness when collecting and sharing genomic data: public views across 22 countries. *Genome Medicine, 13*(1), 92–92. https://doi.org/10.1186/s13073-021-00903-0

## Symptom Science

1. Hickey, K. T., Bakken, S., Byrne, M. W., Bailey, D. E., Demiris, G., Docherty, S. L., Dorsey, S. G., Guthrie, B. J., Heitkemper, M. M., Jacelon, C. S., Kelechi, T. J., Moore, S. M., Redeker, N. S., Renn, C. L., Resnick, B., Starkweather, A., Thompson, H., Ward, T. M., McCloskey, D. J., Austin, J. K., & Grady, P. A. (2019). Precision health: Advancing symptom and self-management science. *Nursing Outlook, 67*(4), 462-475. https://doi.org/10.1016/j.outlook.2019.01.003.

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# Attribution & References

Key takeaways generated using ChatGPT. Prompt: “summarize this text in a few sentences, ignoring images, captions, citations and web references.” The output was then edited by Andrea Gretchev.

## References

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# UNIT 6 - ASSESSING GENETIC RISK

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 6 Contents


- 6.1 Unit Overview
- 6.2 Family History
- 6.3 Constructing a Pedigree Chart
- 6.4 Pedigree Analysis and Modes of Inheritance
- 6.5 Calculating Probabilities Using Pedigree Charts
- 6.6 Polygenic Risk Scores
- 6.7 Unit Summary and Review


## Attribution

# 6.1 UNIT OVERVIEW

## Learning Objectives

- Explain the importance and the process of taking a detailed three-generation family health history.
- Identify and use the symbols found in pedigree charts.
- Analyze pedigree charts to determine the genotypes and phenotypes of individuals in the chart and the probabilities of inheritance.
- Identify the patterns of inheritance of autosomal dominant and recessive, x-linked dominant and recessive, and y-linked traits in humans.
- Recognize the numerous interacting factors that contribute to polygenic risk.

## Outline

Topics covered in this chapter include:

- Family history
- Constructing a pedigree chart
- Pedigree analysis and modes of inheritance
- Calculating probabilities using pedigree charts
- Polygenic risk scores

# Competencies Nurses will Develop in this Chapter

## ANA (2023):

Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).
- Assesses clients' knowledge, perceptions, and responses to genomic information about themselves and their family members.

Identification:

- Evaluates assessment data to identify clients who may benefit from specific genomic information and services.
- Recognizes issues that undermine the rights of all clients for autonomous, informed genomic-related decision-making and voluntary action.

### Referral activities:

- Facilitates referrals for specialized genomic services for clients as needed.

### Provision of education, care, and support:

- Develops a plan of care in collaboration with the interdisciplinary team that incorporates genomic assessment information.
- Advocates for autonomous, informed genomic-related decision-making.
- Demonstrates in practice the importance of tailoring genomic information and services that are responsive to the unique attributes of every person.
- Uses health promotion and disease prevention practices that consider genomic influences as well as personal and environmental risk factors.
- Provides genomic health care in collaboration with interdisciplinary professionals and when possible clients and their families.

## NHS (2023):

### Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the key indicators of a potential genetic condition, or clinical situation where genomics-

informed healthcare would be appropriate; and
- recognizing the importance of family history in assessing predisposition to a genetic condition.

### Advocate for the rights of all individuals to make informed decisions and act voluntarily:

- promoting and supporting equitable access to genomic services.

### Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

### Obtain and communicate reliable, current information about genomics, for self, patients, families and colleagues:

- using information technologies and other information sources effectively to do so;
- applying critical appraisal skills to assess the quality of information accessed; and
- ensuring the information is appropriate for the intended audience.

### Provide ongoing nursing care and support to patients, carers, families and communities with genomic healthcare needs:

- being responsive to changing needs through the life-stages and during periods of uncertainty.

## Key terminology

### Absolute risk

The likelihood of a disease occurring which remains true without any comparison to any groups of people (NHGRI, 2020, para. 10).

### Affected

An individual that is known to have symptoms of the disease (Singh, 2023a, para. 4).

## Carrier

A carrier, as related to genetics, is an individual who "carries" and can pass on to its offspring a genomic variant (allele) associated with a disease (or trait) that is inherited in an autosomal recessive or sex-linked manner, and who does not show symptoms of that disease (or features of that trait). The carrier has inherited the variant allele from one parent and a normal allele from the other parent. Any offspring of carriers is at risk of inheriting a variant allele from their parents, which would result in that child having the disease (or trait).

## Consanguinity

Generally defined as a union between two individuals related as second cousins or closer (GECKO, n.d., para. 7).

## Consultand

A person receiving genetic counseling (Singh, 2023a).

## Pedigree chart

A pedigree, as related to genetics, is a chart that diagrams the inheritance of a trait or health condition through generations of a family. The pedigree particularly shows the relationships among family members and, when the information is available, indicates which individuals have a trait(s) of interest.

## Polygenic risk score

A polygenic risk score (abbreviated PRS) uses genomic information alone to assess a person's chances of having or developing a particular medical condition. A person's PRS is a statistical calculation based on the presence or absence of multiple genomic variants, without taking environmental or other factors into account.

## Proband

A proband is an individual who is affected by a genetic condition or who is concerned they are at risk. Usually, the proband is the first person in a family who brings the concern of a genetic disorder to the attention of healthcare professionals (Singh, 2023b).

### Relative risk

A polygenic risk score tells you how a person's risk compares to others with a different genetic constitution.

Risk, as related to genetics, refers to the probability that an individual will be affected by a particular heritable or genetic disorder. Both a person's genome and environmental exposures can influence risk. An individual's risk may be higher because they inherit a genetic variant (or allele) in one gene or a combination of many variants in different genes that increases susceptibility to or overtly causes a disorder. Other individuals may be at higher risk because they have been exposed to one or more environmental factors that promote the development of a certain disorder (NHGRI, 2020)

### Sporadic

A disease not caused by a mutation inherited from a parent (Singh, 2023a).

## Attribution & References



Except where otherwise noted, this page is adapted from:

- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.

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# 6.2 FAMILY HISTORY

## Family Health History

Family health history-based risk assessment is still the **gold standard** in the initial assessment for heritable conditions. It is the least expensive genetic test available. The best way to identify red flags is by taking a family history (in addition to a personal health history).

A family health history records the health conditions of an individual and their biological relatives (alive and deceased), helping to identify genetic and heritable risks for certain diseases. It is often depicted through a family tree or pedigree.

Discussing genetic risk can be upsetting for some individuals. Nurses must consider the psychosocial aspects of risk assessment and use their training in relational practice and counseling during these conversations. Genetic counselors specialize in providing guidance and support to individuals and families about genetic conditions and their potential health implications. When genetic counselors are available, nurses should collaborate with them, ensuring that each professional works within their respective scope of practice. This collaborative approach ensures comprehensive care and support for patients.

## Why take a family history?

1. All diseases have *some* genetic component, and the strength of the genetic component may be revealed by a family history.
   Family history, alone or in combination with other risk factors, increases the risk for common diseases, (i.e. heart disease, diabetes, and various cancers) much more than genetic variants, alone or in combination, can predict.
2. Even with advancing genomic technology, family history is still the gold standard to assess the likelihood of a genetic condition and to identify individuals who may benefit from referral to a specialist.
3. Pattern of inheritance can be demonstrated by a family history.
4. Family history can help to make or refine a diagnosis, particularly in conditions of variable expressivity (where not all individuals present with the same symptoms of a condition). For example, in hereditary hemochromatosis, a family history could reveal diabetes, liver failure, heart disease and/or early death in multiple family members.
5. Family history can affect testing, treatment, surveillance and management recommendations. For example, a woman's eligibility for the Ontario Breast Screening Program (OBSP) could be determined.
6. Taking the time to explore your patient's family history is an opportunity to build rapport, provide

patient education, and to correct misconceptions.

7. Drawing the family history in a pedigree format makes it easy to be read by other healthcare providers and easy to update.

### Read

Hickey, K.T., Katapodi, M.C., Coleman, B., Reuter-Rice, K. & Starkweather, A.R. (2017). Improving utilization of the family history in the electronic health record. *Journal of Nursing Scholarship, 49*, 80-86. https://doi.org/10.1111/jnu.12259



## When should I take a family history?

A good place to start is at your first visit with a new patient. Risk assessment is an ongoing process, so the family history should be regularly updated. Take note of the life stage of your patient as questions may vary as patients age. For example, questions relevant for a pediatric patient will be different than those for a woman of childbearing age or a man in his late sixties.

## How is a family history taken?

For each individual in the family:

- Ask about general health now and in earlier life
- Ask about development and intellectual functioning
- If deceased, ask about the age and cause

Start with your patient and ask about his/her children and his/her partner. Note:

- **Consanguinity** (*"Are you and your partner related by blood e.g. cousins?"*)
- Children from previous relationships
- Miscarriages and terminations of pregnancy (note if for medical reason and at what gestational age)

Ask about your patient's siblings and his/her children (nieces and nephews) and his/her partner's siblings and their children. Note full or half siblings *("Do your brothers and sisters have the same mother and*

*father?*"). Ask about your patient's parents and his/her partner's parents. If your patient does not have children, ask about grandparents on both sides of the family.

A three generation pedigree is generally accepted as the standard. Once this is complete, ask in general about other relatives, have your patient think of aunts, uncles and cousins, and ask:

- Are there any diseases that seem to run in the family?
- Is there a history of infertility, a couple that had more than three miscarriages, or a couple that had difficulty getting pregnant? If yes, do you know the reason?
- Are there any known genetic conditions in the family, for example cystic fibrosis or muscular dystrophy?
- Was anyone born with a physical difference, for example a hole in the heart or extra digits, or with congenital hearing loss?
- Did any children die at birth or at a young age?
- Is there a history of intellectual disability or developmental delay?
- Is there any cancer in the family? If so, what type and at what age?
- Is there any heart disease at an early age (under age 60)?

## Example – Family History Risk Assessment Questionnaire

This risk assessment focuses on your close relatives including parents, children, brothers and sisters who are either living or dead.

| Items | Yes | No |
|---|---|---|
| Have any of your close relatives had heart disease before the age of 60?<br>'Heart disease' includes cardiovascular disease, heart attack, angina and bypass surgery. | ☐ | ☐ |
| Have any of your close relatives had diabetes?<br>'Diabetes' is also known as type 2 diabetes or non-insulin dependent diabetes | ☐ | ☐ |
| Do you have any close relatives who have had melanoma? | ☐ | ☐ |
| Have any of your close relatives had bowel cancer before the age of 55? | ☐ | ☐ |
| Do you have more than one relative on the same side of the family who has had bowel cancer at any age?<br>Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren. | ☐ | ☐ |
| Have any of your close male relatives had prostate cancer before the age of 60? | ☐ | ☐ |
| Have any of your close female relatives had ovarian cancer? | ☐ | ☐ |
| Have any of your close relatives had breast cancer before the age of 50? | ☐ | ☐ |
| Do you have more than one relative on the same side of your family who has had breast cancer at any age?<br>Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren. | ☐ | ☐ |

**Figure 6.1 Source:** Emery et al. (2014) © 2024 Annals of Family Medicine. Figure 3 republished here under CC-BY-NC-ND 4.0 with permission from Dr. Emery. Figure 6.1 Image Description. Full text available from Annals of Family Medicine.

# Red Flags

## Identifying Red Flags

**Identifying Red Flags (text version)**

### GECKO: Genetics Education Canada: Knowledge Organization Point of Care Tool – Family History

Red flags that suggest that an individual (or his/her/their family) may be at increased risk for a genetic condition.

The best way to identify red flags is by taking a family history (in addition to a personal health history).

1. **Multiple affected family members (with the same or related disorder)**
    - breast and ovarian cancer (https://geneticseducation.ca/resources-for-clinicians/cancer-genomics/hereditary-breast-ovarian-cancer)
    - iron overload and diabetes (https://geneticseducation.ca/resources-for-clinicians/other-genomic-topics/hereditary-hemochromatosis/point-of-care-tool-13)
    - very high cholesterol (https://geneticseducation.ca/resources-for-clinicians/cardiogenomics/familial-hypercholesterolemia/point-of-care-tool-6)
2. **Earlier age of onset of disease (or symptom) than typically expected**
    - May demonstrate genetic predisposition in an individual who is more susceptible to environmental risk factors
        - e.g. pre-menopausal breast cancer (https://geneticseducation.ca/resources-for-clinicians/cancer-genomics/hereditary-breast-ovarian-cancer) (*BRCA1* or *BRCA2* mutation); premature ovarian failure before age 40 (fragile X syndrome carrier (https://www.cdc.gov/ncbddd/fxs/index.html))
3. **Disease occurring in an individual of the less commonly affected sex**
    - e.g. breast cancer in a person assigned male at birth

4. **Presence of disease in the absence of other precipitating factors**
    - e.g. sudden unexplained death (https://geneticseducation.ca/resources-for-clinicians/cardiogenomics/long-qt-syndrome) in an athletic 20-year-old; diabetes mellitus (hereditary hemochromatosis (https://geneticseducation.ca/resources-for-clinicians/other-genomic-topics/hereditary-hemochromatosis) or myotonic dystrophy)
5. **Ethnicity**
    - Some genetic disorders (https://geneticseducation.ca/resources-for-clinicians/prenatal-and-preconception-genomics/carrier-screening-in-canada/point-of-care-tool-14) are more common in certain ethnic groups
    - e.g. Tay-Sachs disease Ashkenazi Jewish (https://geneticseducation.ca/resources-for-clinicians/prenatal-and-preconception-genomics/carrier-screening-in-canada/point-of-care-tool-14) individuals, Gaucher disease, Familial dysautonomia, Canavan disease in Ashkenazi Jewish individuals; Hemoglobinopathies (thalassemia, sickle cell anemia) in individuals of Mediterranean, African, Middle Eastern and South East Asian (https://geneticseducation.ca/resources-for-clinicians/prenatal-and-preconception-genomics/carrier-screening-in-canada/point-of-care-tool-14) ancestry
6. **Consanguinity**
    - Generally defined as a union between two individuals related as second cousins or closer
    - Higher than average chance for both members of a couple to be carriers of the same autosomal recessive condition
7. **History of congenital anomalies (e.g. heart defect, imperforate anus), still birth, childhood death, infertility, more than three unexplained miscarriages**
    - May be suggestive of underlying genetic etiology

**Source:** GECKO: Genetics Education Canada: Knowledge Organization Point of Care Tool – Family History, used with permission.

## Disease specific tools:

After a general, three-generation family history is obtained, if there are red flags (e.g. multiple **affected** relatives, young age of diagnosis, see this point of care tool for more) you can use the tools below to complete

a more *targeted history* can help to identify those who may qualify for modified screening (e.g. starting earlier, more frequent, alternate modality), a genetic assessment and/or genetic testing.

- Cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#cancergen) (general)
  - Hereditary breast/ovarian cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#breastovary)
  - Hereditary Colorectal/Lynch syndrome (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#colon)
  - Prostate cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#prostate)
  - Skin cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#skin)
  - Renal cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#renal)
- Cardiovascular disease (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#cardio)
  - Sudden unexplained death (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#sud)
- Diabetes

# Image Descriptions

## Fig 6.1 Example – Family History Risk Assessment Questionnaire

This risk assessment focuses on your close relatives including parents, children, brothers and sisters who are either living or dead.

- Have any of your close relatives had heart disease before the age of 60? 'Heart disease' includes cardiovascular disease, heart attack, angina and bypass surgery.
- Have any of your close relatives had diabetes? 'Diabetes' is also known as type 2 diabetes or non-insulin dependent diabetes.
- Do you have any close relatives have had melanoma?
- Have any of your close relatives had bowel cancer before the age of 55?
- Do you have more than one relative on the same side of the family who has had bowel cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren.

- Have any of your close male relatives had prostate cancer before the age of 60?
- Have any of your close female relatives had ovarian cancer?
- Have any of your close relatives had breast cancer before the age of 50?
- Do you have more than one relative on the same side of your family who has had breast cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren. [Back to Fig 6.1]

## Attribution & References

Except where otherwise noted, this content is adapted from:

- Family history by Genetics Education Canada: Knowledge Organization (GECKO), Used with permission for educational purposes
- Identifying Red Flags reused from Family history red flags (general) by Genetics Education Canada: Knowledge Organization (GECKO), Used with permission for educational purposes
- Disease specific tools is reused from Family history tools for practice by Genetics Education Canada: Knowledge Organization (GECKO), Used with permission for educational purposes

## References

Emery, J. D., Reid, G., Prevost, A. T., Ravine, D., & Walter, F. M. (2014). Development and validation of a family history screening questionnaire in Australian primary care. *The Annals of Family Medicine*, *12*(3), 241–249. https://doi.org/10.1370/afm.1617

# 6.3 CONSTRUCTING A PEDIGREE CHART

## Taking and drawing a family history

Asking a patient about their family's medical history is a familiar scenario for most healthcare professionals. In nursing school, the formal process of recording this information is taught. The production of a family history diagram, sometimes referred to as a genogram, is an example of this.

Many traits which run in human families do not exhibit a simple pattern of Mendelian inheritance. This is usually because these traits are coded for by more than one gene. Conversely, traits that are governed by one gene are typically an abnormality that is life-threatening or debilitating (e.g., Huntington's Disease, caused by a dominant allele, and Cystic Fibrosis, caused by a recessive allele)]. From a methodical analysis of pedigree charts, we can determine if a particular trait is encoded for by different alleles of a particular (single) gene, as well as if the single-trait gene is recessive or dominant. We may also be able to determine if a trait is autosomal or sex-linked.

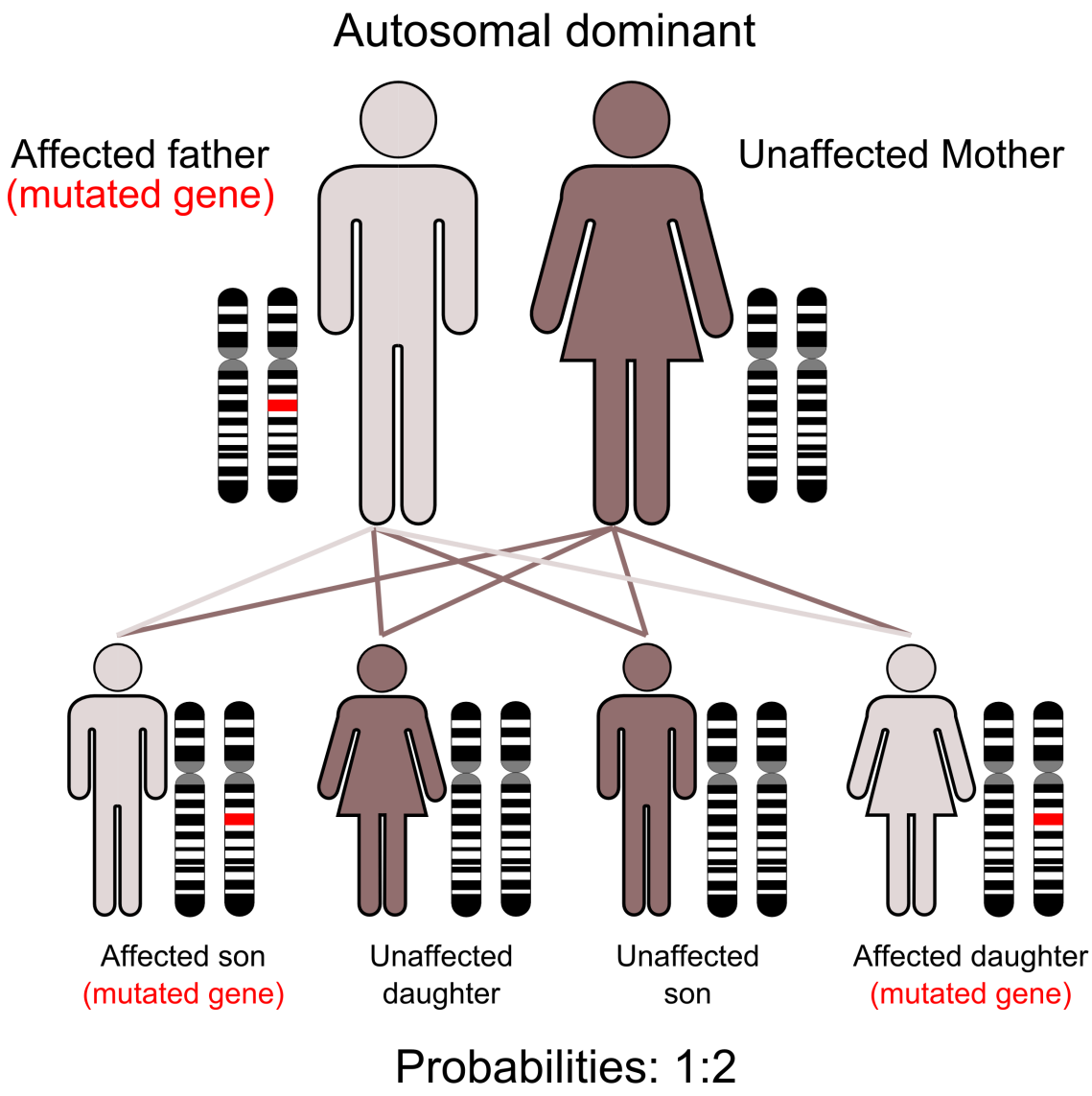



**Figure 6.3** Inheritance of an autosomal dominant trait. Two parents are shown: male possesses the mutated gene, and female is unaffected. Their offspring are outlined, whereby they produce one affected son with the mutated gene, one unaffected son, an unaffected daughter, and finally, an affected daughter with the mutated gene. Alongside each individual is an image of the pair of homologous chromosomes which contains the gene loci for the trait under consideration. Affected individuals are shown via a red shading of the mutated gene locus on an otherwise black and white image of the homologous chromosomes. **Source:** Autodominant en 01 by Armin Kübelbeck, CC BY-SA 3.0.

## What is a genetic pedigree?

A genetic **pedigree chart** is a family history diagram that differs from a genogram in that it does not include the psychosocial history that is collected when drawing a genogram and ecomap. A genetic pedigree captures details about the health of multiple generations. This information can be important in diagnosing

an inherited condition, revealing a pattern of inheritance, and informing clinical decisions regarding testing and management. Understanding the relationships between family members can also be useful when considering the communication of information and the clinical management of the whole family.

A genetic pedigree is a visual representation of several generations in a patient's family. It shows how family members are related to each other and notes any medical conditions they may have along with any other pertinent information. For example, a family's ethnic background may be relevant, as this could indicate whether certain tests should be considered based on the frequency of conditions in different populations.

The information needed to draw a pedigree is usually collected through a series of questions about each member of the family. Standardized symbols and lines are used to represent the family members and their relationships.

The example here shows a four-generation pedigree. The person giving the information is Julie Smith, as noted by the small arrow. Julie, her mother Mollie, her grandmother Alice, and her cousin Mary, have all been affected the same medical condition, indicated by the shaded circles.

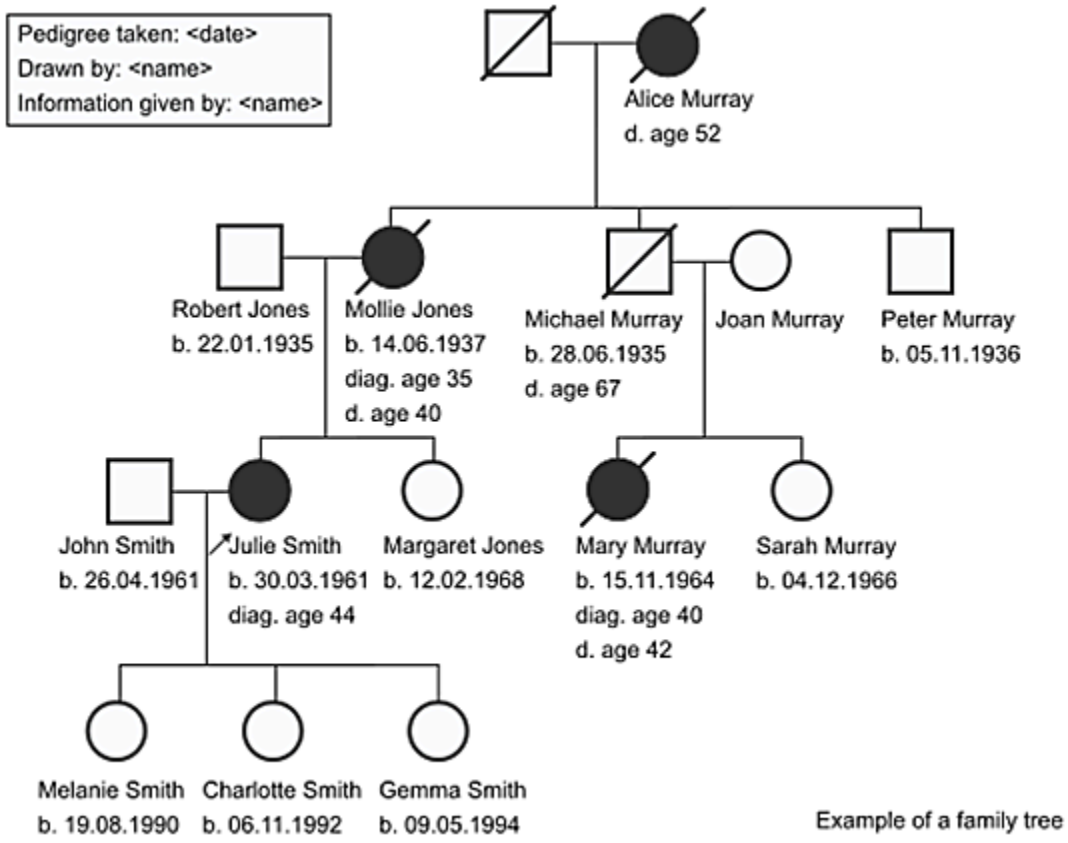
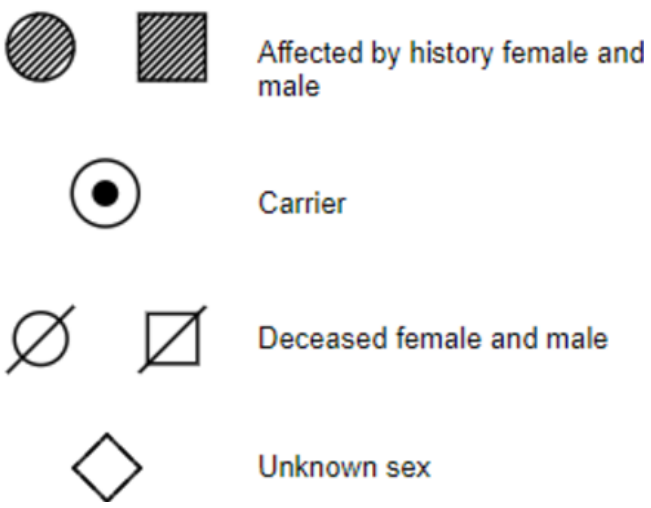



**Figure 6.4** Example of a family pedigree from the Genome Education Programme, NHS
**Source:** Genomics Education Programme, CC BY-NC 4.0

# The symbols and lines

So that any health professional can read and understand a genetic pedigree, they use a set of internationally recognized symbols and lines, based on the proposed system by the National Society of Genetic Counselors (https://www.ncbi.nlm.nih.gov/pubmed/18792771).




Symbols used in constructing a pedigree chart by John Locke (2019), CC BY-NC-SA 3.0. / Cropped.

These diagrams are used to determine the mode of inheritance of a particular disease or trait, and to predict the probability of its appearance among offspring. Each pedigree chart represents all the available information about the inheritance of a single trait (most often a disease) within a family. The pedigree chart is therefore drawn using phenotypic information, but there is always some possibility of errors in this information, especially when relying on family members' recollections or even clinical diagnoses. In real pedigrees, further complications can arise due to incomplete penetrance (including age of onset) and variable expressivity of disease alleles, but for the examples presented in this book, we will presume complete accuracy of the pedigrees — that is, the phenotype accurately reflects the genotype. A pedigree may be drawn when trying to determine the nature of a newly discovered disease, or when an individual with a family history of a disease wants to know the probability of passing the disease on to their children.

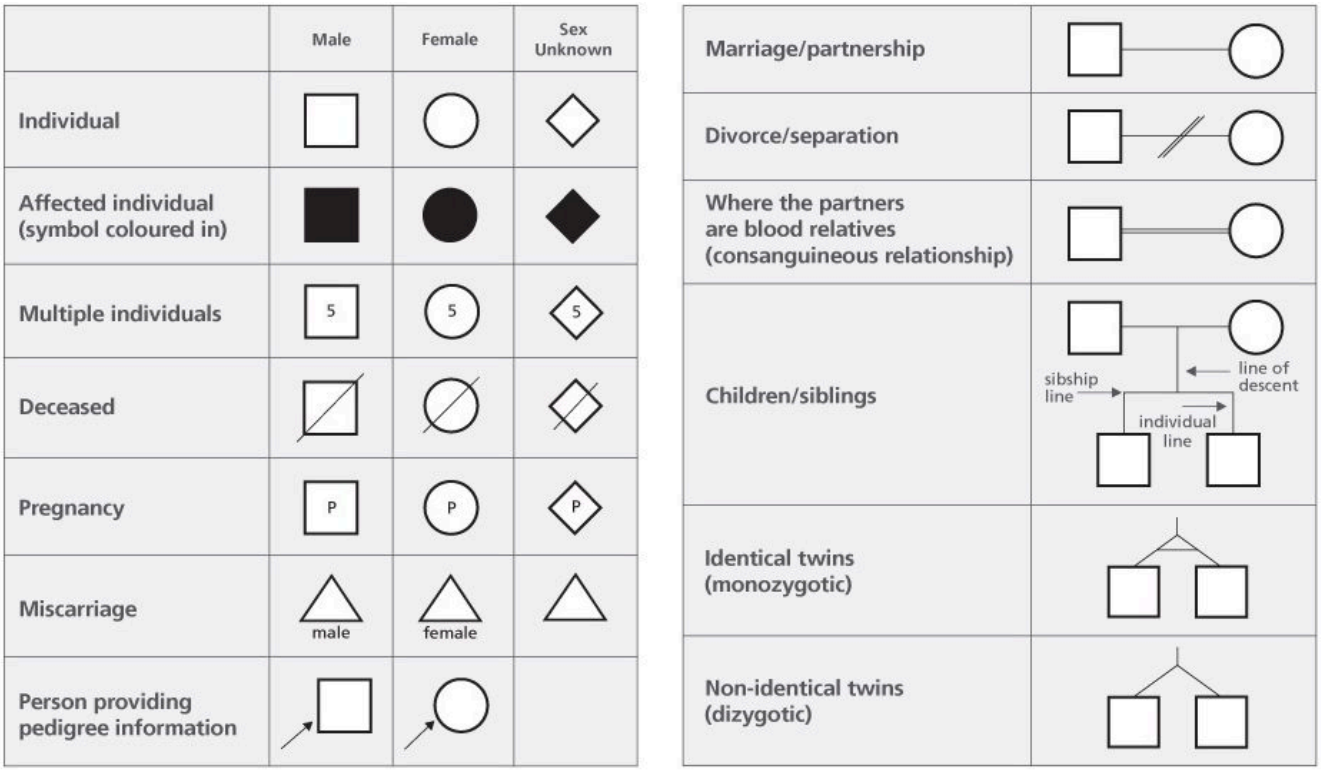



**Figure 6.5** Genetic Pedigree Symbols and Lines. **Source:** Genomics Education Programme, CC BY-NC 4.0

## Additional symbols

Symbols are used to construct pedigree charts. The major ones are as follows: male – square; female – circle; marriage – square and circle linked by a horizontal line. Males partners are usually to the left of the female partner; an individual affected by the trait has their symbol shaded; carrier – sex symbol with a dot inside; deceased – sex symbol with a diagonal line running through it; unknown sex – a diamond; Roman numerals symbolize generations, and Arabic numbers symbolize individuals within a given generation; birth order within each group of offspring is drawn left to right, from first-born to last-born.

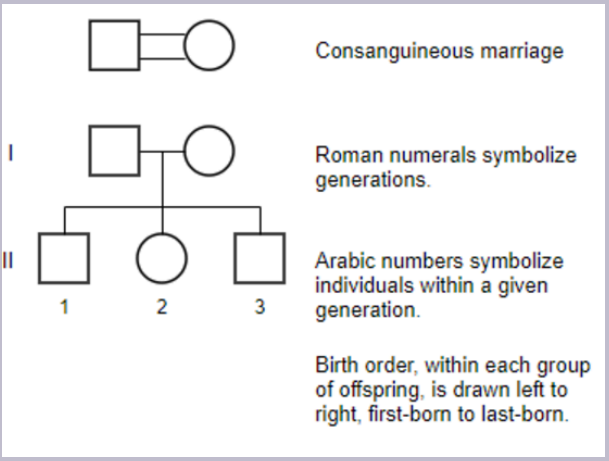



**Figure 6.6** Additional symbols. **Source:** Introduction to Genetics, CC BY-NC SA 4.0. / Image cropped to focus on consanguineous marriage, generations notation, and birth order.

## A note on how sex is depicted in pedigrees

Historically, circles have been used to represent females and squares males in pedigrees. As geneticists gain a better understanding of sex and gender, however, it becomes increasingly apparent that this is not always an accurate representation of either an individual's sex or gender. There are multiple ways to define "male" and "female". For example, an individual with chromosomes typically associated with males (XY) can have gonads and/or external anatomy that is typically associated with females. Likewise, an individual with chromosomes typically associated with females can have gonads and/or external anatomy that is typically associated with males. Depending on the purpose of the pedigree, different definitions of male and female may be more useful than others.

In this module, we will use pedigrees to determine mode of inheritance, including whether a gene is carried on the X- or Y- chromosome. Therefore, unless otherwise indicated, we will most often use the symbols to represent chromosomal sex, with circles to represent people with the most common female chromosomal genotype (XX) and squares to represent people with the most common male chromosomal genotype (XY). It should be understood that this is not a complete description of any individual's sex (sex assigned at birth, sex

determined by external genitalia, or gonadal sex may be different may be different from chromosomal sex) or gender (which may be cisgender or transgender).

Other symbols may offer a more complete or accurate representation of a person's sex or gender. While there is not currently a single standard for representation of transgender and gender diverse individuals or individuals with differences of sex development, there are a number of proposals from within the genetic counseling community (Sheehan et al., 2020; Tuite et al., 2020). One example, from Tuite et al (2020), is shown in Table 1.

The affected individual that brings the family to the attention of a geneticist is called the **proband** (or propositus). If the individual is unaffected, they are called the consultand. If an individual is known to have symptoms of the disease (affected), the symbol is filled in. Sometimes, a *half filled-in symbol* is used to indicate a known **carrier** of a disease; this is someone who does not have any symptoms of the disease, but who passed the disease on to subsequent generations because they are a heterozygote. Note, that when a pedigree is constructed, it is often unknown whether a particular individual is a carrier or not, so not all carriers are always explicitly indicated in a pedigree. For simplicity, in this chapter we will assume that the pedigrees presented are accurate, and represent fully penetrant traits.

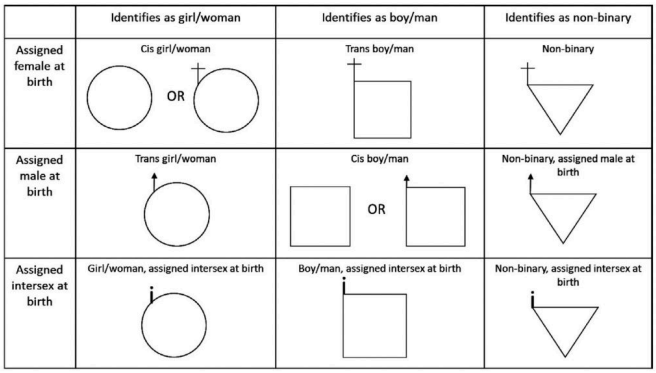



**Table 1** Gender inclusive pedigree symbols. **Source:** National Society of Genetic Counselors from *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-NC-SA 4.0.

Other conventions:

- Female carriers of X-linked traits are indicated by a circle with a dot in the centre.
- If possible, the male partner should be left of female partner on relationship line.
- Siblings should be listed from left to right in birth order, oldest to youngest.

Answers to frequently asked questions can be found here (https://www.genomicseducation.hee.nhs.uk/taking-and-drawing-a-family-history/#toggle-id-1). This page also contains a number of high quality video interview of a healthcare provider taking a family history and drawing a pedigree chart. These are excellent for further review or practice.

## Attribution & References

Except where otherwise noted, this content is adapted from:

- Taking and drawing a family history: Constructing a Pedigree Chart by Genomics Education Programme, CC BY-NC 4.0
- 4.1 Introduction In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University, CC BY-NC SA 4.0
- 4.2 Symbols used in Pedigree Charts In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University, CC BY-NC SA 4.0
- Pedigree analysis In *Chromosomes, Genes, and Traits: An Introduction to Genetics* by Amanda Simons, Framingham State University, CC BY-NC SA 4.0

## References

Mayo Clinic Staff. (n.d.). *Cystic Fibrosis*. MayoClinic.org. Retrieved January 18, 2022 from https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700

Mayo Clinic Staff. (n.d.). *Huntington's disease*. MayoClinic.org. Retrieved January 18, 2022 from https://www.mayoclinic.org/diseases-conditions/huntingtons-disease/symptoms-causes/syc-20356117

Sheehan, E., Bennett, R. L., Harris, M., & Chan-Smutko, G. (2020). Assessing transgender and gender non-conforming pedigree nomenclature in current genetic counselors' practice: The case for geometric inclusivity. *Journal of genetic counseling*, *29*(6), 1114–1125. https://doi.org/10.1002/jgc4.1256

Tuite, A., Dalla Piazza, M., Brandi, K., & Pletcher, B. A. (2020). Beyond circles and squares: A commentary on updating pedigree nomenclature to better represent patient diversity. *Journal of genetic counseling*, *29*(3), 435–439. https://doi.org/10.1002/jgc4.1234

# 6.4 PEDIGREE ANALYSIS AND MODES OF INHERITANCE

## Analyzing Pedigree Charts to Determine Genotype

Usually, we are presented with a pedigree of an uncharacterized disease or trait, and one of the first tasks is to determine which modes of inheritance are possible, and then, which mode of inheritance is most likely. This information is essential in calculating the probability that the trait will be inherited in any future offspring. We will mostly consider five major types of inheritance: autosomal dominant (AD), autosomal recessive (AR), X-linked dominant (XD), X-linked recessive (XR), and Y-linked (Y) inheritance.

We generally make two assumptions in analyzing Pedigree Charts. These are as follows:

1. Complete Penetrance — an individual in the pedigree will be affected (express the phenotype associated with a trait) when the individual carries at least one dominant allele of a dominant trait, or two recessive alleles of a recessive a trait.
2. Rare-in-Population — generally, the trait in question is rare in the general population.

The following are some hints and clues to help us interpret Pedigree Charts:

1. An unaffected individual cannot have any alleles of a dominant trait (because a single allele of a dominant trait causes an individual to be affected).
2. Individuals marrying into the family are assumed to have no disease alleles – they will never be affected and can never be carriers of a recessive trait (because the trait is rare in the population).
3. An unaffected individual can be a carrier (have one allele) of a recessive trait (because two alleles of a recessive trait are required for an individual to be affected).
4. When a trait is X-linked, a single recessive allele is sufficient for a male to be affected (because the male is hemizygous – he only has one allele of an X-linked trait).
5. A father transmits his allele of X-linked genes to his daughters, but not his sons. A mother transmits an allele of X-linked genes to both her daughters and her sons.

**Watch the video, *Pedigree Analysis*, by AK Lecture Series (2015) (15 mins) on YouTube**

**(https://youtu.be/Wgmgt_Ph6Ko), which discusses Pedigree Charts and how to analyze them.**

Let us now take a look at the various modes of inheritance and typical pedigree charts which are characteristic of each mode.

## Autosomal Dominant (AD)

When a disease is caused by a dominant allele of a gene, every person with that allele will show symptoms of the disease (assuming complete penetrance), and only one disease allele needs to be inherited for an individual to be affected. Thus, every affected individual must have an affected parent. A pedigree with affected individuals in every generation is typical of AD diseases. However, beware that other modes of inheritance can also show the disease in every generation, as described below. It is also possible for an affected individual with an AD disease to have a family without any affected children, if the affected parent is a heterozygote. This is particularly true in small families, where the probability of every child inheriting the normal, rather than disease allele is not extremely small. Note that AD diseases are usually rare in populations, therefore affected individuals with AD diseases tend to be heterozygotes (otherwise, both parents would have had to been affected with the same rare disease). Huntington Disease, Achondroplastic dwarfism, and Polydactyly are all examples of human conditions that may follow an AD mode of inheritance.

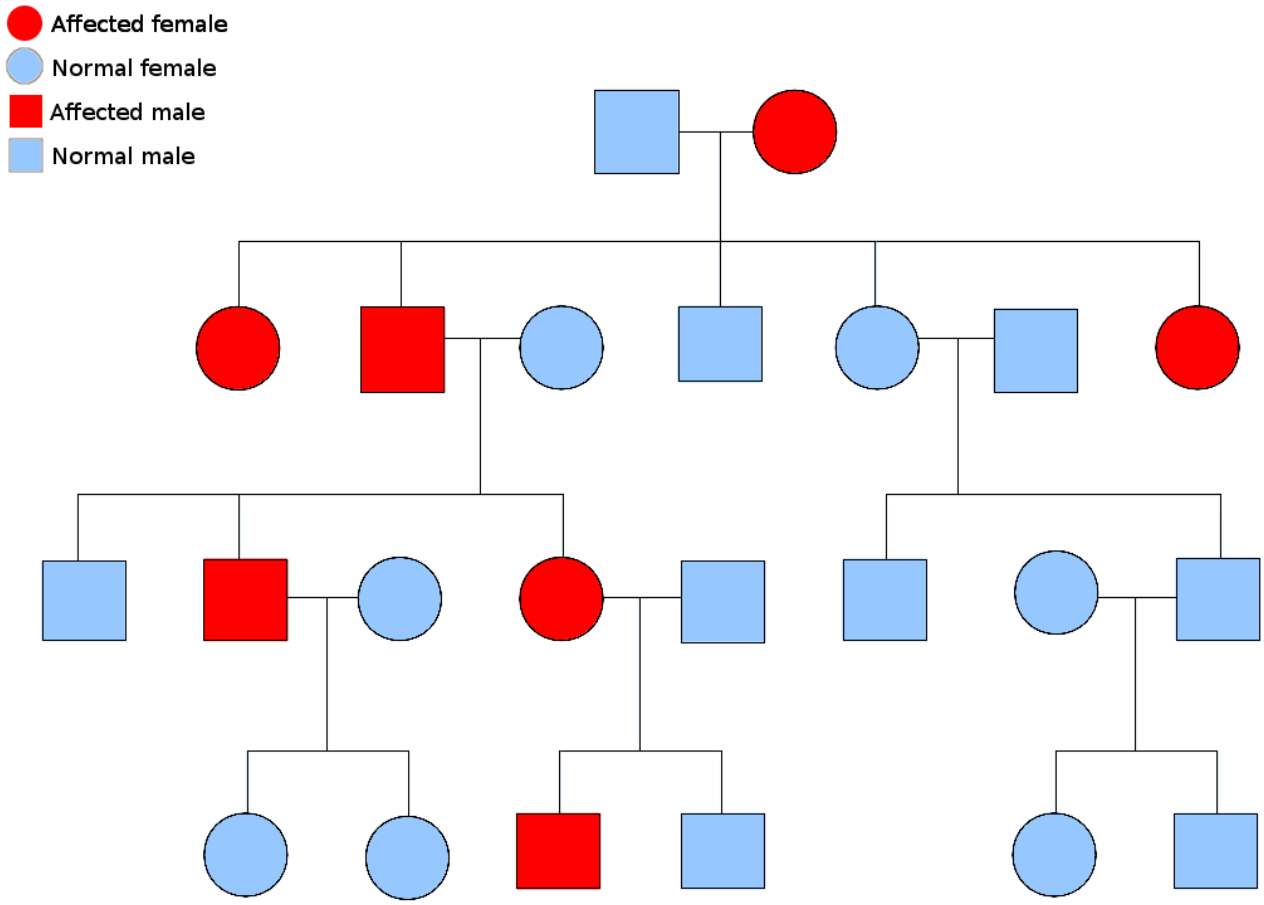



**Figure 6.7** A Pedigree Chart Showing Autosomal Dominant Inheritance. Pedigree chart showing inheritance of an autosomal dominant trait over four generations. Affected females are shown as red-coloured circles; normal females are blue-coloured circles; affected males are red-coloured squares; normal males are blue-coloured squares. Generation I begins with a normal male and an affected female, mating to produce five offspring. Their offspring are: two affected and three unaffected. Two of these Generation II individuals mate, and their progeny is shown, along with a final Generation IV, with the characteristic pattern for autosomal dominant traits depicted. **Source:** Autosomal dominant by Simon Caulton, CC BY-SA 3.0

Example: Achondroplasia is a common form of dwarfism. *FGFR3* gene at 4p16 (chromosome 4, p arm, region 1, band 6) encodes a receptor protein that negatively regulates bone development. A specific base pair substitution in the gene makes an over-active protein and this results in shortened bones. Achondroplasia is considered autosomal dominant because the defective proteins made in A / a embryos halt bone growth prematurely. A / A embryos do not make enough limb bones to survive. Most, but not all dominant mutations are also recessive lethal. In achondroplasia, the A allele shows dominant visible phenotype (shortness) and recessive lethal phenotype.

## X-Linked Dominant (XD)

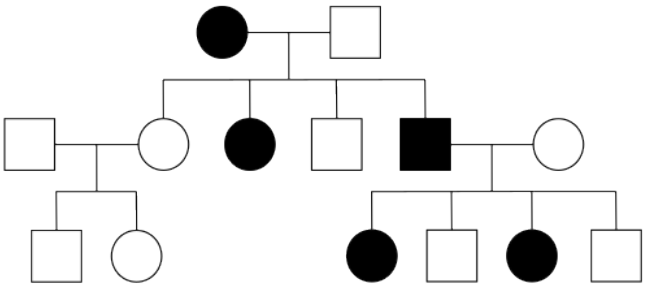


**Figure 6.8** Pedigree chart showing the inheritance of a X-linked dominant trait over three generations. An affected female mates with a normal male in Generation I, to produce four offspring – one normal male, one affected male, one normal female and one affected female. The normal female mates with a normal male, and they produce two unaffected children. The affected male of Generation II mates with a normal female, and they produce four children – two affected females and two unaffected males. This pattern is characteristic for X-linked dominant inheritance. **Source:** Wiki Drawing – X-Linked Dominant (1) by Madibc68, CC BY-SA 4.0

In X-linked dominant inheritance, the gene responsible for the disease is located on the X-chromosome, and the allele that causes the disease is dominant to the normal allele in females. Because females have twice as many X-chromosomes as males, females tend to be more frequently affected than males in the population. However, not all pedigrees provide sufficient information to distinguish XD and AD. One definitive indication that a trait is inherited as AD, and not XD, is that an affected father passes the disease to a son; this type of transmission is not possible with XD, since males inherit their X chromosome from their mothers.

Example: fragile x syndrome — The *FMR1* gene at Xq21 (X chromosome, q arm, region 2, band 1) encodes a protein needed for neuron development. There is a (CGG)n repeat array in the 5'UTR (untranslated region). If there is expansion of the repeat in the germline cell the child will inherit a non-functional allele. $X^A$ / Y males have fragile X mental retardation (IQ < 50) because none of their neurons can make FMR1 proteins. Fragile X syndrome is considered X-linked dominant because only some neurons in $X^A$ / $X^a$ females can make FMR1 proteins. The severity (IQ 50 – 70) in these females depends upon the number and location of these cells within in the brain.

## Autosomal Recessive (AR)

Diseases that are inherited in an autosomal recessive pattern require that both parents of an affected individual carry at least one copy of the disease allele. With AR traits, many individuals in a pedigree can be carriers, probably without knowing it. Compared to pedigrees of dominant traits, AR pedigrees tend to show fewer affected individuals and are more likely than AD or XD to "skip a generation". Thus, the major feature that distinguishes AR from AD or XD is that unaffected individuals can have affected offspring. Attached earlobes is a human condition that may follow an AR mode of inheritance.

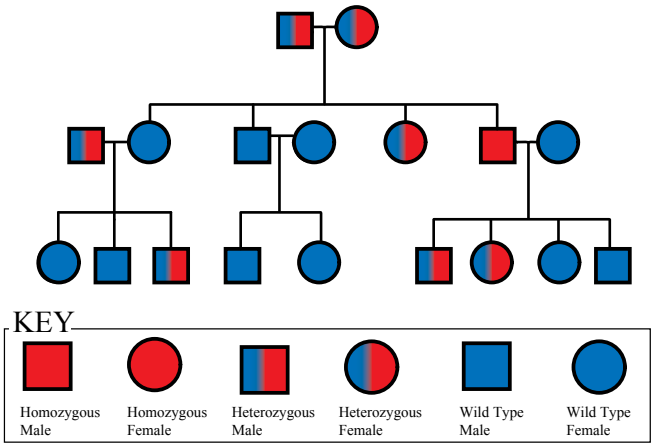



**Figure 6.9** Pedigree chart showing the inheritance of an autosomal recessive trait, over three generations. Red and blue colours depict differences in the male and female. Both colours mean heterozygous, solid red colour means homozygous recessive, and solid blue color means wild type or homozygous dominant. Generation I begins with two carrier parents, who are therefore heterozygous. They produce four children, two are normal, one is a carrier and one is affected. This pattern is consistent with the inheritance of autosomal recessive traits. **Source:** Autosomal Recessive Pedigree Chart by Jerome Walker, CC BY-SA 3.0.

AR example: phenylketonuria (PKU) – Individuals with phenylketonuria (PKU) have a mutation in the *PAH* gene at 12q24 (chromosome 12, q arm, region 2, band 4), which encodes an enzyme that breaks down phenylalanine into tyrosine called phenylalanine hydrolase (PAH). Without PAH, the accumulation of phenylalanine and other metabolites, such as phenylpyruvic acid, disrupts brain development, typically within a year after birth, and can lead to intellectual disability. Fortunately, this condition is both easy to diagnose and can be successfully treated with a low phenylalanine diet. There are over 450 different mutant alleles of the PAH gene, so most people with PKU are **compound heterozygotes**. Compound heterozygotes have two different mutant alleles (different base pair changes) at a given locus, in this case the *PAH* gene.

## X-Linked Recessive (XR)

Because males have only one X-chromosome, any male that inherits an X-linked recessive disease allele will be affected by it (assuming complete penetrance). Therefore, in XR modes of inheritance, males tend to be affected more frequently than females in a population. This contrasts with AR and AD, where both sexes tend to be affected equally, and XD, in which females are affected more frequently. Note, however, in the small sample sizes typical of human families, it is usually not possible to accurately determine whether one sex is affected more frequently than others. On the other hand, one feature of a pedigree that can be used to definitively establish that an inheritance pattern is not XR is the presence of an affected daughter from unaffected parents; because she would have had to inherit one X-chromosome from her father, he would also have been affected in XR.

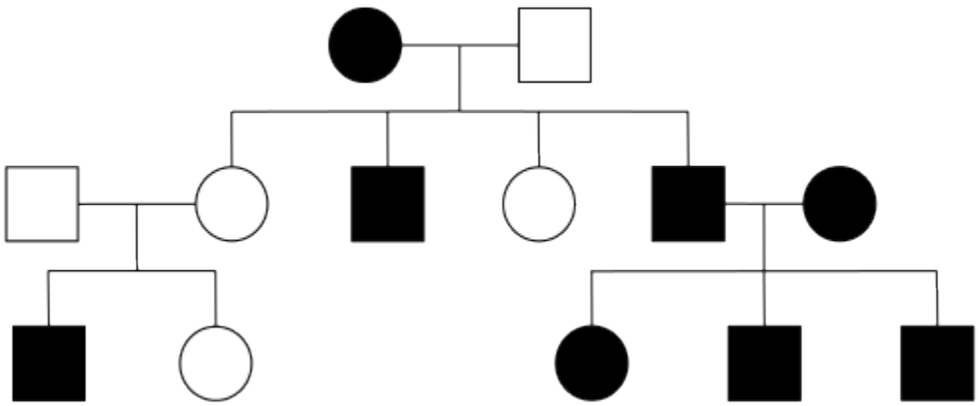


**Figure 6.10** Pedigree chart showing the inheritance of a X-linked recessive trait over three generations. Generation I outlines one affected female and one affected male, mating to produce four children, two unaffected females and two affected males. One of the unaffected females mates with a normal man, and they produce two children: one affected male and an unaffected female. This indicates the unaffected mother was a carrier. This pattern of inheritance is typical of an X-linked recessive trait. **Source:** Wiki Drawing – X-Linked Recessive (1) by Madibc68, CC BY-SA 4.0

XR example: hemophilia A- *F8* gene at Xq28 (X chromosome, q arm, region 2, band 8) encodes blood clotting factor VIIIc. Without Factor VIIIc, internal and external bleeding can't be stopped. Back in the 1900s, Xa / Y male's average life expectancy was 1.4 years, but in the 2000s it has increased to 65 years with the advent of Recombinant Human Factor VIIIc. Hemophilia A is recessive because XA / Xa females have normal blood coagulation, while Xa / Xa females have hemophilia.

## Y-Linked

Only males are affected in human Y-linked inheritance (and other species with the X/Y sex determining system). There is only father-to-son transmission. This is the easiest mode of inheritance to identify, but it is one of the rarest because there are so few genes located only on the Y-chromosome.

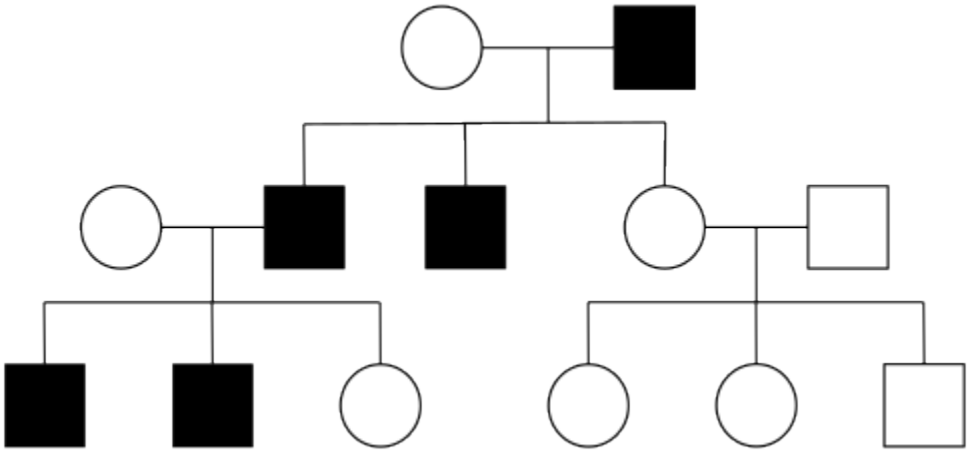


**Figure 6.11** Pedigree chart showing the inheritance of a Y-linked trait. Three generations are shown, starting with a normal female and an affected male, who produce three offspring. Offspring are: one normal female and two affected males. One affected male mates with a normal female, and their offspring comprises one normal female and two affected males. This pattern of inheritance is typical of Y-linked traits. **Source:** Wiki Drawing – Y-Linked (1) by Madibc68, CC BY-SA 4.0

A common, but incorrect, example of Y-linked inheritance is the hairy-ear-rim phenotype seen in some Indian families. A better example are the Y-chromosome DNA polymorphisms that have been used to follow the male lineage in large families or through ancient ancestral lineages. For example, the Y-chromosome of Mongolian ruler Genghis Khan (1162-1227 CE), and his male relatives, accounts for ~8% of the Y-chromosome lineage of men in Asia (0.5% world wide).

## Attribution & References

Except where otherwise noted, this section is adapted from 4.3 Modes of Inheritance In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University CC BY-NC-SA 4.0

# 6.5 CALCULATING PROBABILITIES USING PEDIGREE CHARTS

In practice, where available, model risk calculators are used. Examples include:

NCI (2024) **Breast Cancer Risk Assessment Tool: Online Calculator (The Gail Model)** (https://bcrisktool.cancer.gov/)

> "The Breast Cancer Risk Assessment Tool (BCRAT), also known as The Gail Model, allows health professionals to estimate a woman's risk of developing invasive breast cancer over the next five years and up to age 90 (lifetime risk)
>
> The tool uses a woman's personal medical and reproductive history and the history of breast cancer among her first-degree relatives (mother, sisters, daughters) to estimate absolute breast cancer risk-her chance or probability of developing invasive breast cancer in a defined age interval.
>
> This calculator takes about five minutes to complete" (para 1).

The University of Cambridge (2024) **CanRisk for Breast and Ovarian Cancer (https://www.canrisk.org/)**

> "CanRisk is an online tool that enables healthcare professionals to calculate an individual's future risks of developing *breast and ovarian cancer* using cancer family history, genetic and other risk factors. CanRisk also calculates mutation carrier probabilities in breast and ovarian cancer susceptibility genes" (para 1).

MagView (2024). **Tyrer-Cuzick Risk Assessment Calculator** (https://ibis-risk-calculator.magview.com/)

> "This risk calculator asks questions about your personal and family history to determine the possibility of developing breast cancer. The results will display your lifetime risk score. The purpose of this tool is simply to inform you" (para 1).

Pedigree analysis can also be used to calculate risk. If the mode of inheritance of a trait is known, we can use information about others in the family to calculate the likelihood that another individual will develop the trait. This is useful in situations like genetic counseling: if a couple comes to a genetic counselor due to a family history of a genetic disorder, what is the risk that their child will also suffer from the disorder?

If the mode of inheritance is known, it's often possible to assign probable genotypes to some individuals in the pedigree, based on their phenotypes and relationships to others in the pedigree. For example, all individuals affected by an autosomal recessive trait have genotype "aa", and any of their offspring who are unaffected by the trait must have genotype "Aa". With this information, it's then possible to calculate the probability of other individuals either having the allele (being unaffected carriers) or having kids with the

trait. This makes pedigrees an important tool in genetic counseling if, for example, parents with a family history of a genetic disease would like to know the likelihood of passing the disease to their child.

## Calculating risk from a pedigree chart

The rules of probability – and the laws of Mendelian inheritance – make these calculations possible. Remember from unit 2.5, we used two rules of probability: the product and sum rules. The product rule of probability states that the probability of two independent events occurring is the product of the probability of each event occurring independently. For example, in a cross between parents of genotypes Aa and Aa, the probability of having a child with phenotype A *and* a child with phenotype a is ¾ * ¼ = 3/8.

The sum rule of probability states that the probability of one event *or* another is the sum of their individual probabilities. In a cross between parents of genotypes Aa and Aa, the probability of having a child of genotype AA *or* Aa is ¼ + ½ = ¾.

In many of these complex family pedigrees, in order for a child to have a particular trait, the allele for the trait must be passed down from multiple individuals, often through several generations. But because all of these inheritance events must happen, we use the multiplication rule to calculate the combined probability.

When calculating the probabilities for a rare trait in the general population, unless there is evidence otherwise in the pedigree, we usually assume that unrelated individuals who are joining the family do not carry the same rare allele that "blood" relatives do, since this would be a pretty unlikely occurrence.

An example of this is shown using the pedigree shown in Figure 6.12. What is the probability that a child of III-1 and III-2 will be affected by the autosomal recessive trait?

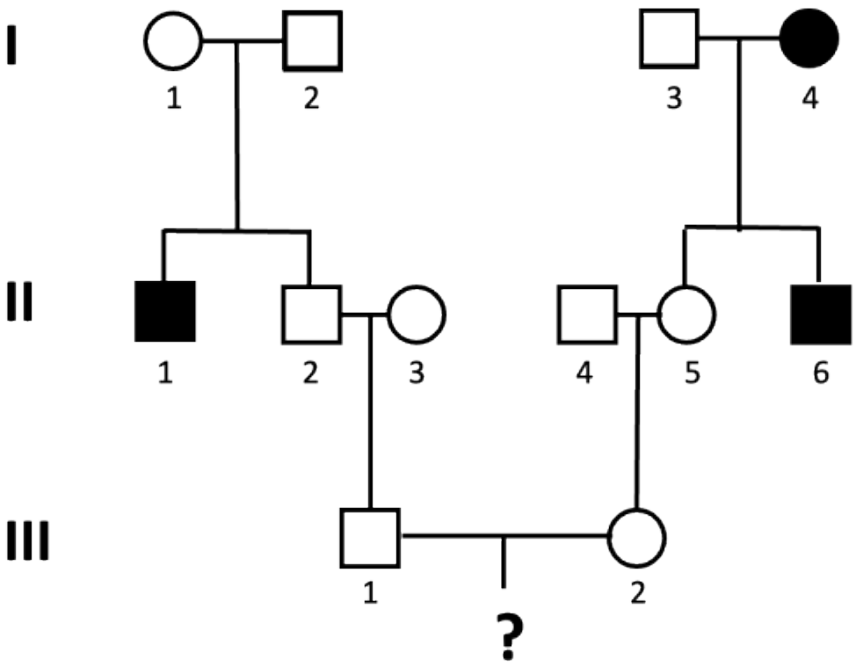



**Figure 6.12** Pedigree tracking an autosomal recessive trait. Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

We solve this type of problem by determining the genotypes of the direct ancestors to the individual for whom we will calculate the probability. The next figures walk through this process, step by step. Let's assume the allele associated with the recessive trait is "a".

## Steps to determining the genotypes of direct ancestors

1. We can assign genotypes to all of the individuals in generation I.
   Individuals I-1 and I-2 must both have genotype Aa, since they have an affected child (II-1) who is presumed to have genotype aa. This is also true for individual I-3, who has a child with the trait as well. I-4 has the genotype aa, since they have the trait.

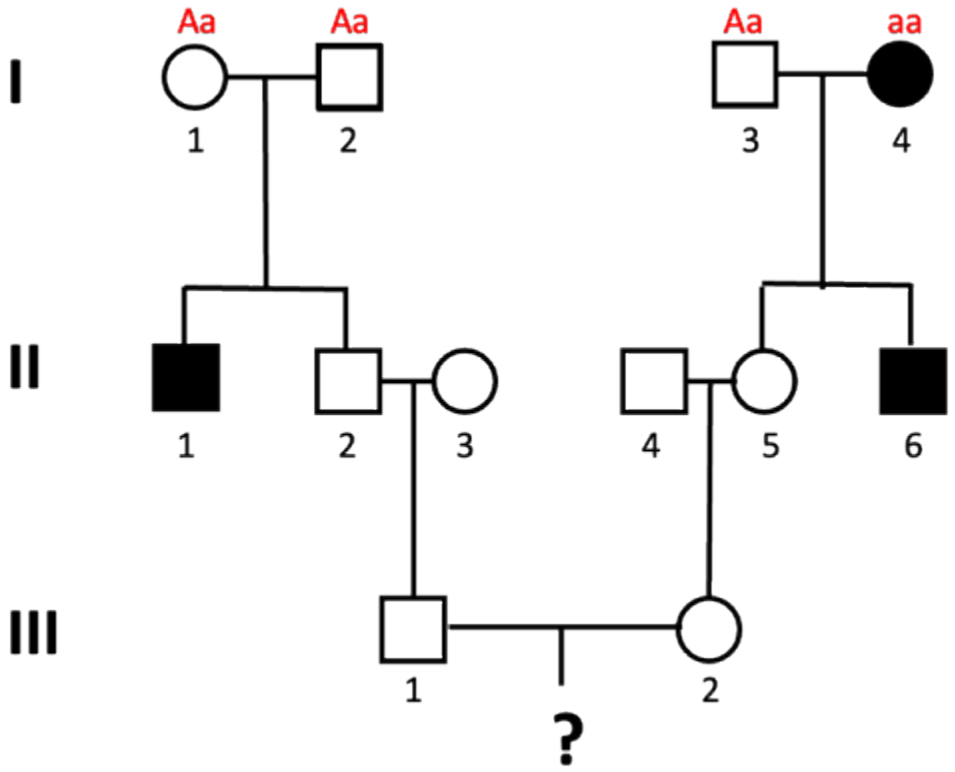



**Figure 6.13** Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated: Aa, Aa, Aa, and aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

2. Since this is a rare trait in the population, in Generation II we assume that individuals II-3 and II-4 do not carry the allele (they have genotype AA).

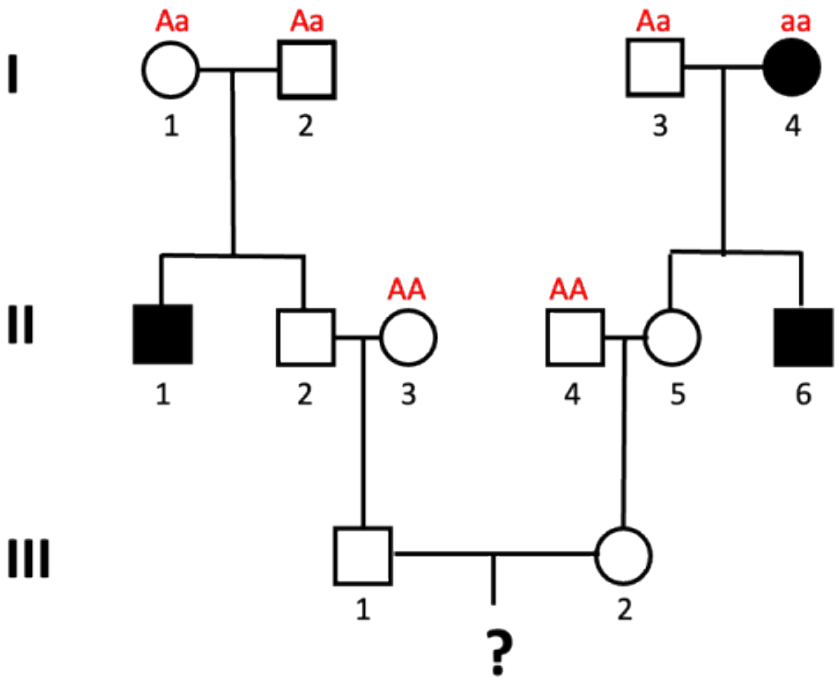



**Figure 6.14** Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated: Aa, Aa, Aa, and aa. In generation II, II-3 and II-4 are also labeled with genotypes AA. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

3. Individual II-5 must have genotype Aa, since she inherits a dominant (unaffected) allele from her dad, but must inherit the recessive allele from mom.

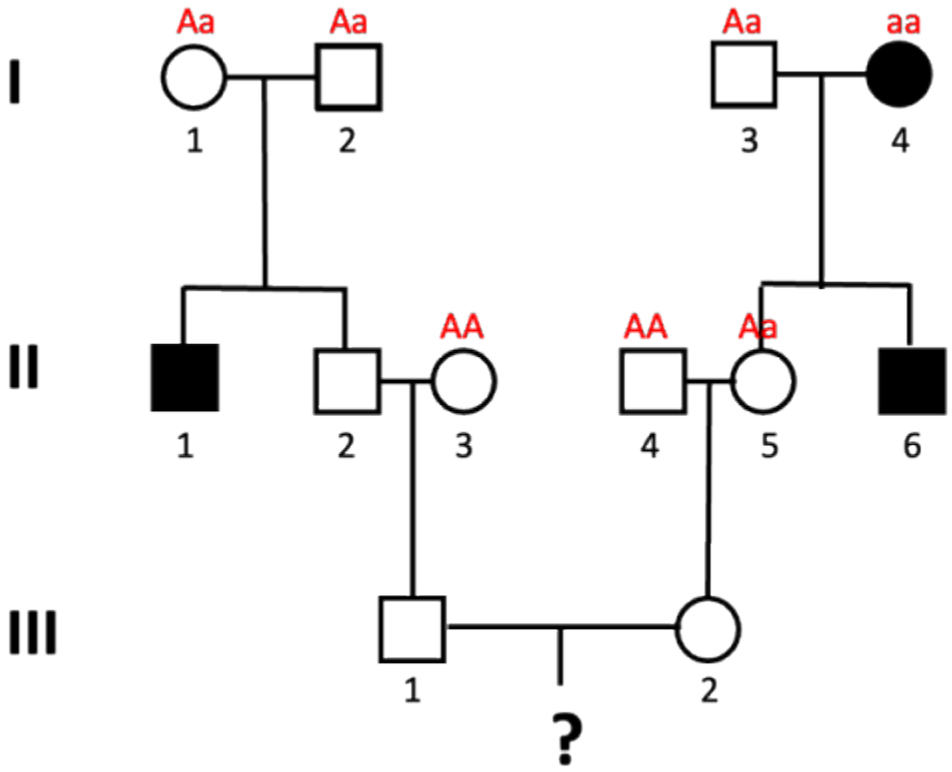



**Figure 6.15** Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated as well as II-3 and II-4. Individual II-5 is labeled Aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

4. What about individual II-2? In order for our final offspring to show the trait, individual II-2 must be a carrier of the "a" allele.
   What's the probability that they inherited the "a" allele? Well, let's look at the Punnett Square expected from Aa x Aa parents (which is what individual II-2 has). This requires a bit of tricky reasoning: it might be tempting to say that ½ are Aa, but that is incorrect. We know that II-2 does not have an aa genotype because II-2 does not show the trait. Of the remaining possibilities, 2/3 are Aa.

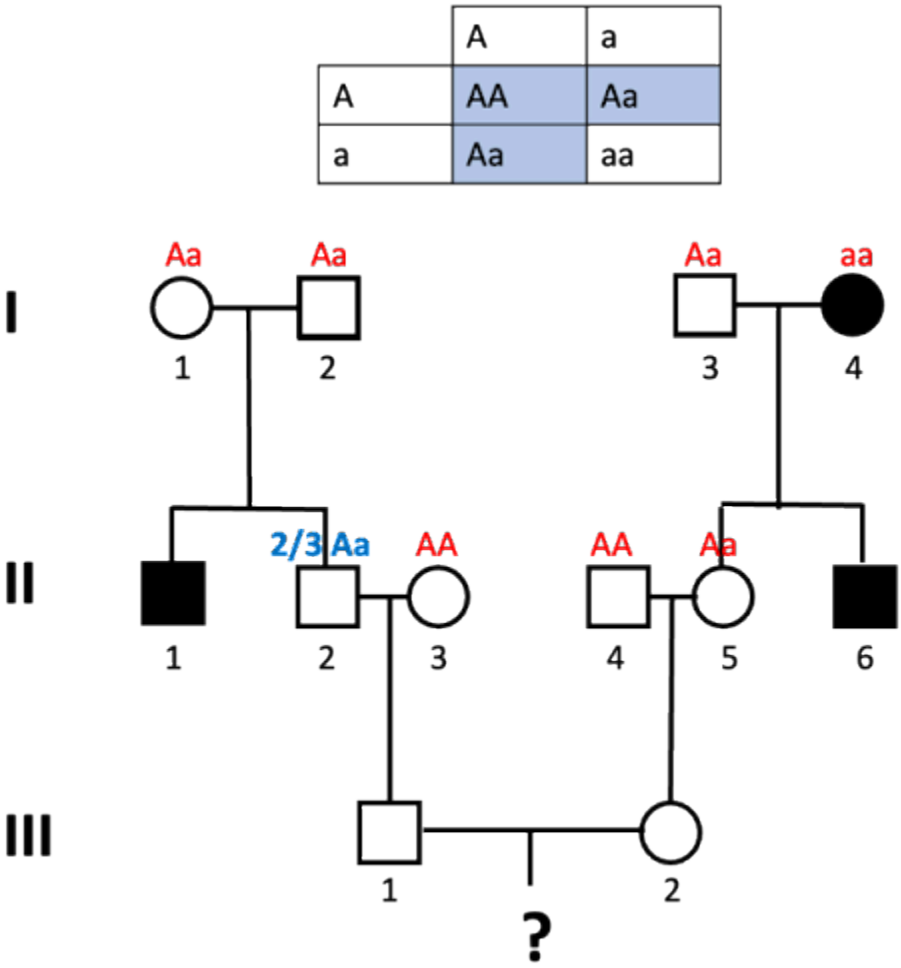



**Figure 6.16** Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated as well as II-3, II-4, and II-5. Individual II-2 is labeled as having a 2/3 chance of genotype Aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

5. In generation III, we likewise need to determine the probability of III-1 and III-2 carrying the allele. We do this as we did for II-2: we draw a Punnett square to illustrate the cross, and determine which fraction of offspring carry the allele. For both III-1 and III-2, there is a ½ probability that they will carry the allele (and have the Aa genotype).

| | A | A |
|---|---|---|
| A | AA | AA |
| a | Aa | Aa |

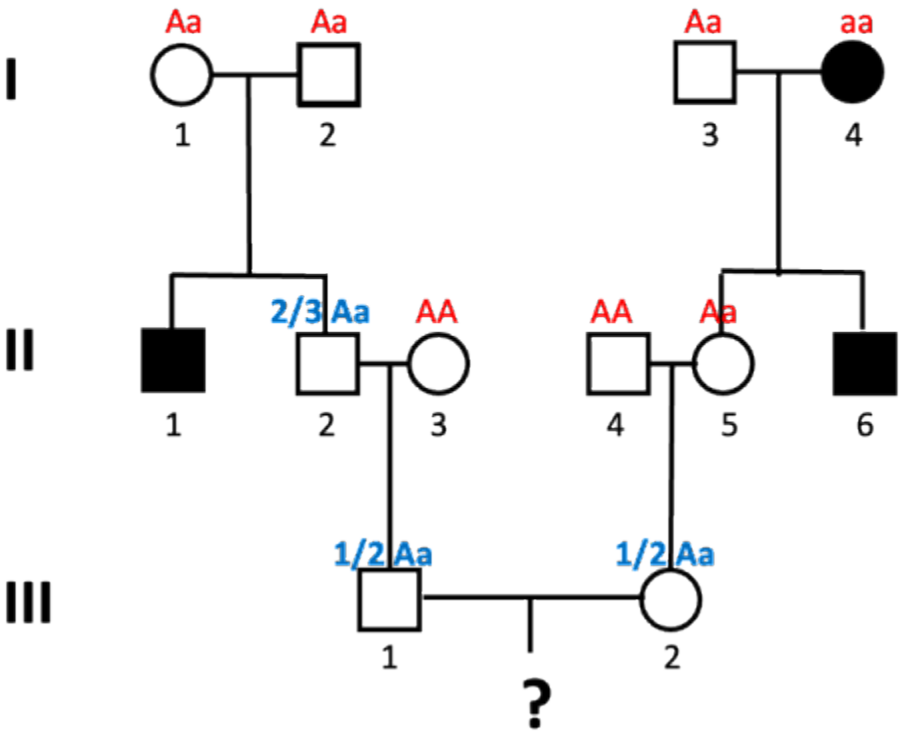



**Figure 6.17** Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated as well as II-2, II-3, II-4, and II-5. Individuals III-1 and III-2 are labeled with a 1/2 probability of having genotype Aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

6. Lastly, we can't forget the child! A Punnett square of Aa x Aa shows that there is a ¼ chance of aa offspring.

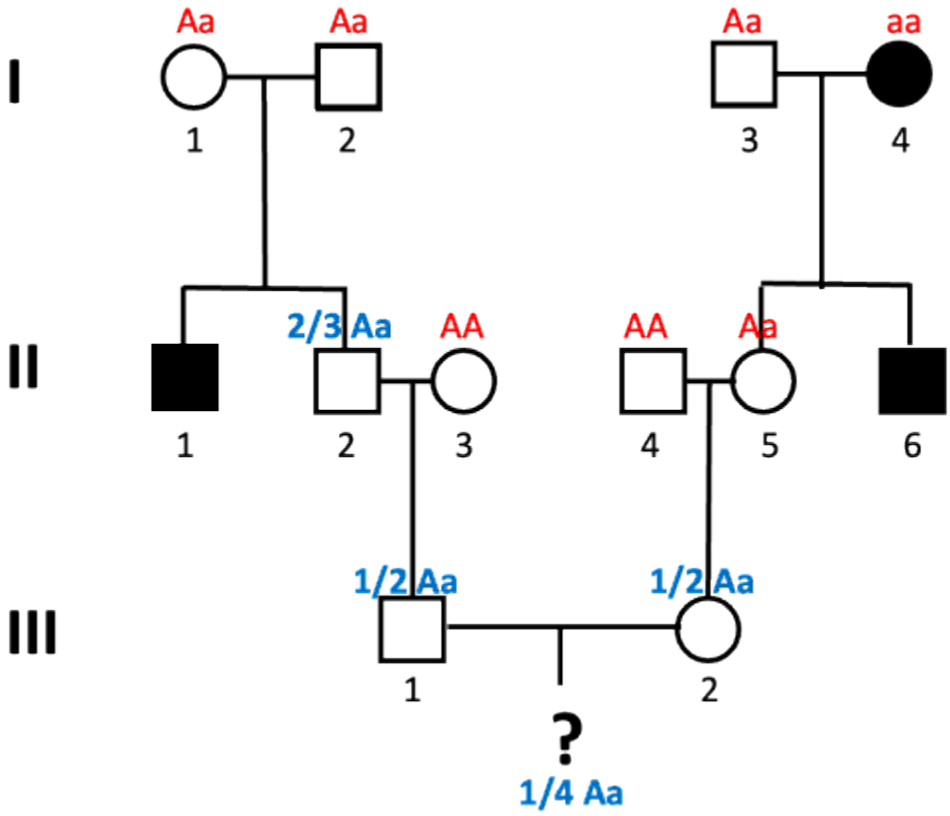



**Figure 6.18** Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I, II, and III are labeled. The probability that unborn child that would inherit two "a" alleles is indicated: 1/4 aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

In order for the child of III-1 and III-2 to show the trait, all these four things shown in blue in the images must be true: II-2 must be Aa, III-1 must be Aa, III-2 must be Aa, *and* the child must be aa. We use the multiplication rule to determine the overall probability:

2/3 * 1/2 *1/2 * 1/4 = 2/48

Some things to keep an eye out for, as you solve these problems: it's *very common to forget the last step: the probability of the final offspring showing the trait*! Don't forget to do this, even if there isn't a symbol representing the unborn child. And watch out for those Aa x Aa crosses, where you can rule out aa as a possible genotype. 2/3 of the possible unaffected offspring are Aa, not ½.

Practice exercises are provided in the next unit.

## Attribution & References

Except where otherwise noted, this section is adapted from Pedigree Analysis In *Chromosomes, Genes, and Traits: An Introduction to Genetics*, by Amanda Simons, Framingham State University, CC BY-NC-SA 4.0

## References

MagView. (2024). *Tyrer-Cuzick risk assessment calculator.* https://ibis-risk-calculator.magview.com/

National Cancer Institute (NCI). (2024). *Breast cancer risk assessment tool: Online calculator (The Gail Model).* NIH. https://bcrisktool.cancer.gov/

The University of Cambridge. (2024). *CanRisk for breast and ovarian cancer.* https://www.canrisk.org/

# 6.6 POLYGENIC RISK SCORES

## Beyond Family History: Sporadic and Non-Heritable Diseases

Not all the characterized human traits and diseases are attributed to mutant alleles at a single gene locus. Many diseases that have a heritable component, have more complex inheritance patterns due to (1) the involvement of multiple genes, and/or (2) environmental factors. On the other hand, some non-genetic diseases may appear to be heritable because they affect multiple members of the same family, but this is due to the family members being exposed to the same toxins or other environmental factors (e.g., in their homes).

Finally, diseases with similar symptoms may have different causes, some of which may be genetic while others are not. One example of this is Amyotrophic lateral sclerosis (ALS) (https://www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022); approximately 5–10% of cases are inherited in an AD pattern, while most of the remaining cases appear to be **sporadic**, in other words, not caused by a mutation inherited from a parent. We now know that different genes or proteins are affected in the inherited and sporadic forms of ALS. The physicist Stephen Hawking and baseball player Lou Gehrig both suffered from sporadic ALS.

**Watch the video *Neuroscience: Amyotrophic Lateral Sclerosis (ALS)*video (2 mins), by Neuroscientifically Challenged (2017) on YouTube (https://youtu.be/kOnk9Hh20eg), which describes how ALS arises in humans.**

## Polygenic Risk

### Concept in Action

**Watch this What Your Family History Can't Tell you (7 mins) on YouTube (https://youtu.be/tkJhdXt2G8k) to learn about how genes can interact to create a combined risk for developing disease.**

## Calculating polygenic risk scores

Researchers identify genomic variants associated with complex diseases by comparing the genomes of individuals with and without those diseases. The enormous amount of genomic data now available enables researchers to calculate which variants tend to be found more frequently in groups of people with a given disease. There can be hundreds or even thousands of variants per disease. Researchers put this information into a computer and use statistics to estimate how the collection of a person's variants affect their risk for a certain disease.

This yields **polygenic risk scores**. A polygenic risk score is one way by which people can learn about their risk of developing a disease, based on the total number of changes related to the disease. All of this can be done without knowing the specific genes involved in the complex disease. While we may someday know all the genes involved, researchers can estimate risk now without this link.

## Interpreting polygenic risk scores

A polygenic risk score can only explain the **relative risk** for a disease. Why relative? The data used for generating a polygenic risk score comes from large scale genomic studies. These studies find genomic variants by comparing groups with a certain disease to a group without the disease.

A polygenic risk score tells you how a person's risk compares to others with a different genetic constitution. However, polygenic scores do not provide a baseline or timeframe for the progression of a disease. For example, consider two people with high polygenic risk scores for having coronary heart disease. The first person is 22 years old, while the latter is 98. Although they have the same polygenic risk score, they will have different lifetime risks of the disease. Polygenic risk scores only show correlations, not causations.

**Absolute risk** is different. Absolute risk shows the likelihood of a disease occurring. Women who carry a *BRCA1* mutation have a 60-80% absolute risk of breast cancer. This would be true even without any comparison to any groups of people.

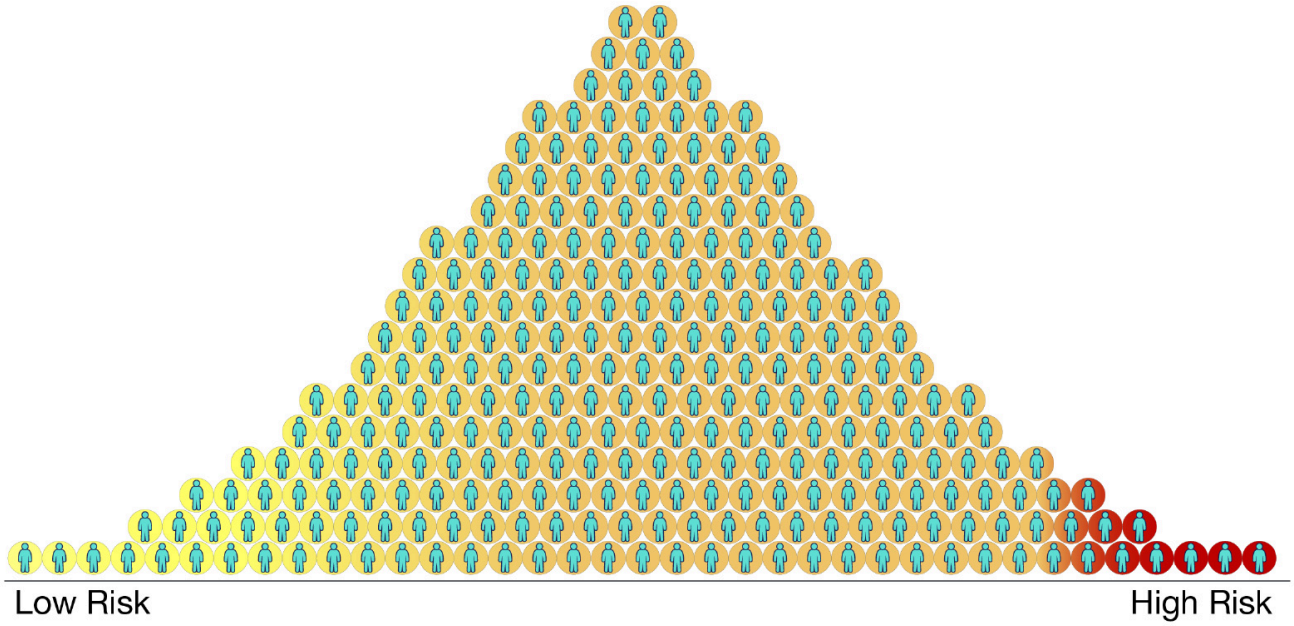



**Figure 6.19** Each polygenic risk score can be put on a bell curve distribution. Most people will find their scores to be in the middle, indicating average risk for developing a disease. Others may find themselves on the tail ends, putting them at either low or high risk. People with scores on the high-risk portion of the spectrum may benefit from discussions about this risk with their physicians and genetic counselors for further health assessments. **Source:** Courtesy National Human Genome Research Institute, PDM with attribution.

Who benefits from a polygenic risk score?

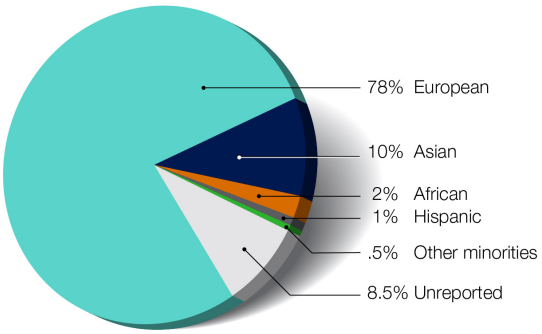



**Figure 6.20** The percentage of ancestry populations included in large-scale genomic studies is overwhelmingly European. **Source:** Courtesy National Human Genome Research Institute, PDM with attribution.

Because the majority of genomic studies to date have examined individuals of European ancestry, there may not be adequate data about genomic variants from other populations for calculating a polygenic risk score in those populations. This historic lack of diversity in genomic studies is also a concern for other genomics-related research areas and contributes to a widespread concern about increasing health disparities beyond polygenic risk scores. At this point in time, the accuracy of polygenic risk scores may only be valid and useful for European ancestry populations. More research is needed to derive the data for making polygenic risk scores useful for other populations.

## Looking into the future

***Polygenic risk scores are not yet routinely used by health professionals because there are no guidelines for practice and researchers are still improving how these scores are generated. However, private healthcare and direct-to-consumer companies (private commercial companies that individuals can pay for out-of-pocket) have already begun generating polygenic risk scores for their consumers and they may someday serve as an important new tool to guide healthcare decisions.***

Polygenic risk scores will always be probabilities, not certainties. Understanding how polygenic risk scores can impact peoples' lives and health is an active area of research being supported by the National Human Genome Research Institute.

# Attribution & References

Except where otherwise noted, this section is adapted from

- 4.4 Sporadic and Non-Heritable Diseases In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University, CC BY-NC-SA 4.0
- Polygenic risk scores courtesy: National Human Genome Research Institute (NHGRI), Public Domain with attribution

## References

Mayo Clinic Staff (n.d.). Amyotrophic lateral sclerosis (ALS). MayoClinic.org. https://www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022

# 6.7 UNIT SUMMARY AND REVIEW

## Key Takeaways

Taking a family health history is crucial for assessing genetic risks and identifying heritable conditions. It remains the gold standard for initial risk assessment, helping to reveal genetic components, inheritance patterns, and inform testing and treatment decisions.

Constructing a genetic pedigree involves creating a visual representation of a patient's family health history across multiple generations, which helps in diagnosing inherited conditions, understanding inheritance patterns, and informing clinical decisions. Standardized symbols and lines are used to depict family relationships and medical conditions, making the pedigree easy to read and update for healthcare professionals.

When analyzing pedigree charts to determine genotype, the goal is to identify the most likely mode of inheritance for a trait, which helps in predicting its inheritance in future offspring. This involves considering five major types of inheritance (autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and Y-linked) and making assumptions about complete penetrance and the rarity of the trait in the population. Different modes of inheritance can be identified through characteristic patterns in pedigree charts. These charts help determine how a disease or trait is passed down through generations, aiding in predicting the likelihood of inheritance in future offspring.

Not all diseases are caused by single gene mutations; many have complex inheritance patterns involving multiple genes and environmental factors. Some non-genetic diseases may appear heritable due to shared environmental exposures. Polygenic risk scores, which estimate disease risk based on multiple genetic variants, are emerging tools but currently have limitations, including a lack of diversity in genomic studies. These scores provide relative risk but not absolute certainty, and their use in healthcare is still evolving.

Once the mode of inheritance for a disease is identified, we can infer the genotypes of individuals in a pedigree based on their phenotypes and positions in the family tree. Using Mendelian inheritance

rules and probability calculations, we can determine the likelihood of specific genotypes being passed to future generations, which is valuable for genetic counseling and assessing the risk of offspring inheriting certain diseases.

# Additional Optional Readings


1. Andrusko, D. & Paradiso, C. (2022). Establishing a process to improve the collection of family health history. *The Nurse Practitioner, 47* (4), 32-40. https://doi.org/10.1097/01.NPR.0000822532.65525.5a.
2. Hays, L. (2023). The three-generation pedigree. Advances in Family Practice Nursing, 5(1), 77–91. https://doi.org/10.1016/j.yfpn.2022.11.006
3. Mahon, S.M. (2016). The three-generation pedigree: A critical tool in cancer genetics care. Genetics, Patient Education, Risk Assessment, 43(5), 655-660. https://doi.org/10.1188/16.ONF.655-660
4. Stanfill, A. G., & Starlard-Davenport, A. (2018). Primer in genetics and genomics, Article 7—Multifactorial concepts: Gene–gene interactions. *Biological Research For Nursing*, *20*(3), 359-364. https://doi.org/10.1177/1099800418761098
5. Wildin, R. S., Messersmith, D. J., & Houwink, E. J. F. (2021). Modernizing family health history: achievable strategies to reduce implementation gaps. *Journal of community genetics*, *12*(3), 493–496. https://doi.org/10.1007/s12687-021-00531-6
6. Xiang, R., Kelemen, M., Xu, Y., Harris, L. W., Parkinson, H., Inouye, M., & Lambert, S. A. (2024). Recent advances in polygenic scores: translation, equitability, methods and FAIR tools. *Genome Medicine, 16*, 33. https://doi.org/10.1186/s13073-024-01304-9


# Tools and Resources

## Pedigree Analysis

- For a visual walk-through of a pedigree analysis work through this short Khan Academy module on pedigrees (https://www.khanacademy.org/science/high-school-biology/hs-classical-genetics/hs-pedigrees/v/pedigrees) which includes practice exercises.

## Family History and Pedigree Chart Tools

- Students will use My Family Health Portrait (https://cbiit.github.io/FHH/html/index.html) to create a pedigree chart for their chosen case study.

- Another good clinical resource for creating an electronic pedigree is from Progeny Genetics (https://pedigree.progenygenetics.com/)
- For those who prefer a paper template, the Jackson Laboratory provides a template and printable symbol sheet (https://www.jax.org/education-and-learning/clinical-and-continuing-education/clinical-topics/cancer-resources/pedigree-tool).
- GECKO has also created this family history tool [PDF] (https://www.geneticseducation.ca/wp-content/uploads/2013/03/Family-history-tool-GECKO-April-20141.pdf).
- The NHS Genomics Education Programme has a family history worksheet [PDF] (https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2019/05/Family-history-worksheet-blank.pdf)
- Families Sharing Health Assessment and Risk Evaluation (SHARE) (https://www.genome.gov/research-at-nhgri/Projects/Families-SHARE) helps you and your family learn how your family health history affects your risk for diseases. Includes disease risk worksheets and workbooks in multiple languages.

## Variant Classification

- ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/)

Landrum, M. J., Chitipiralla, S., Kaur, K., Brown, G., Chen, C., Hart, J., Hoffman, D., Jang, W., Liu, C., Maddipatla, Z., Maiti, R., Mitchell, J., Rezaie, T., Riley, G., Song, G., Yang, J., Ziyabari, L., Russette, A., & Kattman, B. L. (2024). ClinVar: updates to support classifications of both germline and somatic variants, *Nucleic Acids Research*, gkae1090, https://doi.org/10.1093/nar/gkae1090

# Attribution and References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

## References

ChatGPT: OpenAI. (2024). *ChatGPT (Version 4.0)* [Large language model]. https://openai.com

# UNIT 7 - APPLICATION OF THEORY IN PRACTICE PART 1

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 7 Contents


- 7.1 Unit Overview
- 7.2 Application of Theory in Practice – Case Studies
- 7.3 Group Discussion


## Attribution

# 7.1 UNIT OVERVIEW

## Learning Objectives

- Apply course content to practice scenarios

Practice questions and case studies are provided for independent practice for students to apply what they have learned thus far in the course. Please see Blackboard for the group discussion assignment for this week which will also provide an opportunity to apply learning.

## Attribution

# 7.2 APPLICATION OF THEORY - READINGS & CASE STUDIES

## Optional Reading

This article uses a case study of a family with a history of breast and prostate cancer to highlight the importance of coordinated genetic care by genetics professionals. The article argues that fragmented genetic care can lead to errors such as inappropriate testing, miscommunication of results, and missed opportunities for cancer prevention and early detection, ultimately resulting in psychosocial distress and increased healthcare costs.

### Read

Mahon S. M. (2019). Coordination of genetic care: More important and complicated than it seems. *Journal of the National Comprehensive Cancer Network*, *17*(11), 1272–1276. https://doi.org/10.6004/jnccn.2019.7343

OPEN ACCESS ONLINE

## Case Study – Clinical Application

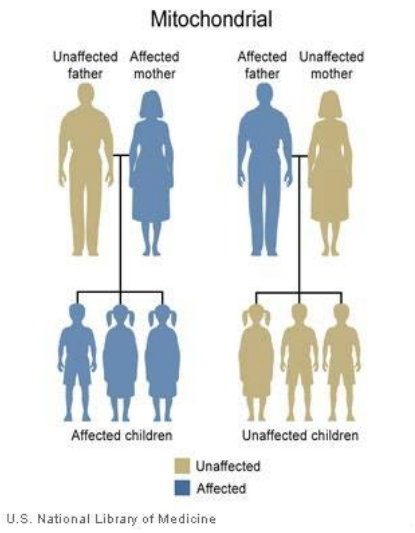
Mitochondrial DNA mutation A1555G and aminoglycoside-induced hearing loss and deafness Case study – a mitochondrial DNA variant causes susceptibility to hearing loss on administration of aminoglycosides.

**Key Takeaway:**
Carriers of the mutation who undergo even one course of aminoglycoside antibiotic therapy can suffer severe an irreversible loss of hearing.

**Clinical Scenario:**

A term newborn is noted to have an elevated temperature (39 C) and an elevated respiratory rate (45/minute). Sepsis is suspected, blood cultures and laboratory studies are obtained and the child is moved to the intermediate care unit for IV antibiotics (Clinical guidelines recommend Ampicillin and Gentamicin for rule out sepsis). When the mother is informed of the need to start antibiotics she tells the care team that she has hearing loss that she says occurred after receiving an antibiotic that she doesn't remember. "Some kind of mycin I was told," She is very concerned that this could happen to her child and asks that the baby be 'checked out'.

A quick PubMed search using the terms 'antibiotics' and 'hearing loss' identifies many articles that discuss the risk of hearing loss in individuals exposed to aminoglycoside antibiotics that have a specific mitochondrial pathogenic variant. Given this information the decision is made to start the baby empirically on Ampicillin and a cephalosporin and pursue investigation of the mitochondrial variant.




**Source:** National Human Genome Research Institute, PDM with attribution.

**Description of relevant genomic information and how this information would be used:**

Mitochondria undergo a special type of inheritance called maternal inheritance. Only the mother contributes mitochondria to her children. Thus, when a mitochondrial DNA mutation occurs in one of the maternal mitochondrial genes, she will pass it to all of her offspring. Males do not pass mitochondria to any of their offspring. Mitochondria are involved in the intermediate metabolism of many ingested substances and drugs. Mutations in two mitochondrial genes, MT-RNR1 and MT-TS1, confer susceptibility to non-syndromic mitochondrial hearing loss or deafness after treatment with aminoglycoside antibiotics (e.g. gentamicin, kanamycin, streptomycin). Specifically a change from alanine to glycine in position 1555 ("A1555G mutation") in the MT-RNR1 gene has been associated with aminoglycoside-induced (as well as late onset non-syndromic) sensorineural hearing loss. There are population differences in the prevalence of the A1555G mutation: 2.9% – 5.3% in Asian, 0.6% – 2.5 % of Caucasian and as high as 17% of the Spanish population with nonsyndromic hearing loss. Therefore, Asian and Spanish populations have the highest frequency of the A1555G mutation followed by other populations of European ancestry. A higher frequency of the mutation is found among the deaf population with a history of aminoglycoside exposure accounting for 15-30%. Both males and females are affected equally. The hearing loss is generally bilateral and in the moderate to profound range. Once exposed to aminoglycoside antibiotics,

most individuals with the variant go on to develop hearing loss or deafness (Usami & Nishio, 2018; Rehm et al., n.d.; Vivero et al., 2012; Xing et al., 2007).

Recommended clinical action: Genetic testing for the A1555G mutation should be performed in individuals with moderate to profound hearing loss in the presence of either a family history of hearing loss suggestive of maternal inheritance or onset of hearing loss following administration of an aminoglycoside antibiotic such as gentamicin. For women who carry the A1555G mutation, with or without hearing loss, carrier testing is recommended for other maternal family members with instructions for their children and all other maternal members to strictly avoid the administration of aminoglycoside antibiotics if they carry the mutation. Carriers of the mutation who undergo even one course of aminoglycoside antibiotic therapy can suffer severe and irreversible loss of hearing. As a cautionary note, lack of identification of the mutation does not rule out hearing loss attributable to other variants within mitochondrial genes (e.g. the MT-RNR1 gene) or due to other genes known to be involved in hearing loss (Guan et al., 2006).

Family Implications: Hearing loss caused by this pathogenic variant (A1555G) is consistent with a maternal pattern of inheritance.

Evidence to support the use of genomic information in this scenario: ACMG Practice Guideline: Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss

**Source:** Case study: Mitochondrial DNA mutation A1555G and aminoglycoside-induced hearing loss and deafness [PDF] from *Family Health History for Healthcare Professionals* Courtesy: National Human Genome Research Institute (NHGRI), Public Domain with attribution .

## Resources:

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# Attribution & References

- Case study: Mitochondrial DNA mutation A1555G and aminoglycoside-induced hearing loss and deafness [PDF] from *Family Health History for Healthcare Professionals* courtesy: National Human Genome Research Institute (NHGRI), Public Domain with attribution . / References changed to APA format.

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# 7.3 - APPLICATION: PRACTICING PEDIGREE ANALYSIS

**Practicing Pedigree Analysis (text version)**

1. **Gender Inclusive Pedigree Symbols**

   Symbols:

   1. a square with an up arrow on the upper left corner
   2. circle with up arrow on the upper left side
   3. triangle with an up arrow on the upper left corner
   4. circle with a cross on the upper left corner
   5. square with a cross on the upper left corner
   6. triangle with a cross on the upper left corner
   7. circle with the letter i on the upper corner
   8. square with the letter i on the upper corner
   9. triangle with the letter i on the upper left corner

**Identify the symbols by placing their number in the correct row/column on the chart.**

| Assigned Gender | Identifies as girl/ woman | Identifies as boy/man | Identifies as non-binary |
|---|---|---|---|
| Assigned female at birth | | | |
| Assigned male at birth | | | |
| Assigned intersex at birth | | | |

**Check your answer in footnote**[1]

1. **Gender Inclusive Pedigree Symbols – Activity Solution**

| Assigned Gender | Identifies as girl/woman | Identifies as boy/man | Identifies as non-binary |
|---|---|---|---|
| Assigned female at birth | 4 | 5 | 6 |
| Assigned male at birth | 2 | 1 | 3 |
| Assigned intersex at birth | 7 | 8 | 9 |

**Determining modes of inheritance**

2. **True or false?** In the pedigree shown (Fig. 7.4a), generation II shows a male with the trait with an affected son. An X-linked trait cannot be passed from father to son. Therefore x-linked dominance can be ruled out as a mode of inheritance. This pedigree shows an autosomal dominant mode of inheritance.

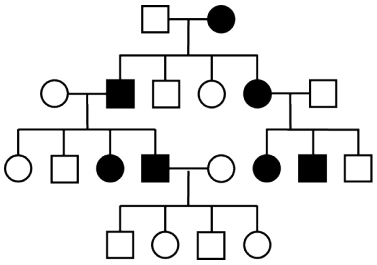

Fig. 7.4a

**Check your answer in footnote**[2]

3. The pedigree shown (Fig. 7.4b) tracks an X-linked recessive trait. As is typical of X-linked recessive traits, only males appear to be affected. Y-linked traits also only affect males. What feature(s) of this pedigree allow you to rule out Y-linked as a mode of inheritance in this pedigree?

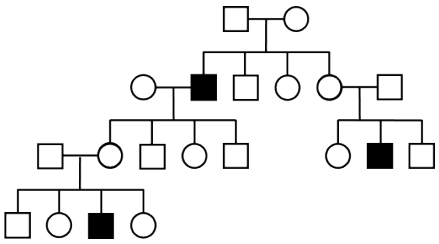

Fig. 7.4b

   a. Y-linked traits pass from father to son, and fathers and sons always share the same phenotype. In the X-linked pedigree shown in this figure, fathers who are affected by the trait have sons who are unaffected. This rules out Y-linkage.
   b. Y-linked traits pass from father to son, and fathers and sons always share the same phenotype. In the X-linked pedigree shown in this figure, fathers who are affected by the trait have sons who are unaffected. This rules out X-linkage.
   c. Y-linked traits pass from father to son, and fathers and sons always share the same phenotype. In the X-linked pedigree shown in this figure, fathers who are affected by the trait have daughters who are unaffected. This rules out Y-linkage.

**Check your answer in footnote**[3]

4. Match the correct words to the blanks for the pedigree chart in Fig 7.4c:

---

2. **True.** An X-linked trait is associated with genes located on the X chromosome. Males have one X chromosome and one Y chromosome (XY), while females have two X chromosomes (XX). When a father contributes genetic material to his child, he passes his Y chromosome to his son, which determines the male sex, and his X chromosome to his daughter. Since sons inherit the Y chromosome from their father, they do not inherit any genes located on the father's X chromosome. Therefore, any X-linked traits or conditions carried by the father cannot be transmitted to his sons. Instead, if the father carries an X-linked trait, it can only be passed to his daughters, as they inherit his X chromosome.

3. a.

**Words:** affected, unaffected

For a daughter to be [Blank a] by an X-linked recessive trait, she must inherit the X-linked allele from both her father and mother. Her hemizygous father must also be [Blank b] by the trait if he carries the allele. In this pedigree, we see an [Blank c] daughter of an [Blank d] father, which rules out an X-linked recessive mode of inheritance.

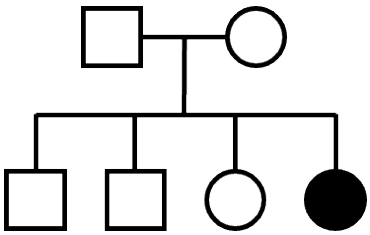

Fig. 7.4c

**Check your answer in footnote**[4]

5. Why are the offspring of consanguineous matings at higher risk for rare genetic disorders?
   a. Rare recessive disorders are uncommon because the causative alleles are uncommon among the larger population. However, everyone likely carries at least a few rare, disease-associated alleles.
   b. When choosing a partner randomly, it is unlikely (but not impossible) that the partner will share the same set of rare, disease associated alleles.
   c. Close relations may share the same disease-associated alleles, making it more likely for offspring of a consanguineous relationship to inherit two disease-associated alleles of the same gene

   **Check your answer in footnote**[5]
6. Match the words to the correct blanks, according to the pedigree chart in Fig. 7.4d.

   **Words:** II-1, aa, Aa

   Individuals I-1 and I-2 must both have genotype [Blank a]*Aa*, since they have an affected child (II-1) who is presumed to have genotype [Blank b]*aa*. This is also true for individual I-3, who has a child with the trait as well. I-4 has the genotype [Blank c]*aa*, since they have the trait.

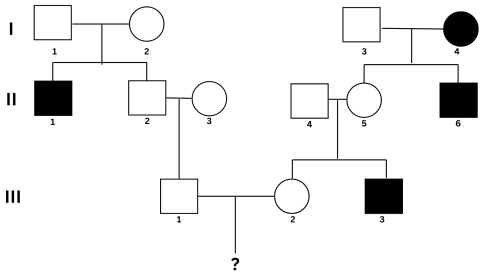


Fig. 7.4d

   **Check your answer in footnote**[6]
7. Since this is a rare trait in the population, in generation II, we assume that individual II-3 is not a carrier. If this is the case, what is the genotype of II-3? (See Fig. 7.4d)
   a. AA
   b. Aa
   c. aa

   **Check your answer in footnote**[7]

---

4. Blank a – affected, Blank b – affected, Blank c – affected, Blank d- unaffected

5. a, b & c.

6. Blank a: Aa, Blank b: aa, Blank c: aa

8. True or false? Individuals II-4 and II-5 in Fig. 7.4.d must have genotype AA since they are unaffected (click image to enlarge).
   **Check your answer in footnote**[8]
9. If the final offspring (see Fig. 7.4d) is affected and exhibits the trait, individual II-2 must be a carrier of the recessive allele "a" since individual II-3 was determined to be AA. What is the probability that they inherited the "a" allele?
   a. 1/4
   b. 3/4
   c. 2/3
   d. 1/3
   **Check your answer in footnote**[9]
10. Match the words to the correct blanks according to the pedigree chart in Fig. 7.4d.
    **Words:** 3/4, aa, 1/4
    Assume individuals III-1 and III-2 have parents with the same genotypes. In each of these parental pairs, one parent is homozygous AA and the other is heterozygous (**[Blank a]**). The probability that III-1 and III-2 will be unaffected carriers (genotype As) is **[Blank b]***.
    **Check your answer in footnote**[10]
11. What is the probability that the offspring of III-1 and III-2 is affected (see Fig. 7.4d). Hint: Both parents are heterozygous.
    2. 3/4
    3. 1/2
    4. 1/4
    **Check your answer in footnote**[11]



---

7. A. AA

8. False. AA is not the genotype for these two individuals. They are Aa since they have an affected child. II-5 inherits a dominant allele from her father and a recessive allele from her mother.

9. c. The probability of Aa is 2/3.

10. Blank a: Aa, Blank b: 1/2.

11. a. There is a 3/4 chance the offspring will be unaffected and a 1/4 chance of being affected.

# Attribution

# 7.4 APPLICATION: PRACTICING INHERITANCE PROBABILITIES

## Practicing Inheritance Probabilities: Earlobes, Duchenne Muscular Dystrophy, Dimples

*An interactive H5P element has been excluded from this version of the text. You can view it online here: https://ecampusontario.pressbooks.pub/personalizedhealthnursing/?p=4457#h5p-52*

**Practicing Inheritance Probabilities: Earlobes, Duchenne Muscular Dystrophy, Dimples (text version)**

1. The pedigree in **Fig. 7.5a** tracks the presence of attached earlobes through a family's generations. Having attached earlobes is an autosomal recessive trait. If individual III-6 married a man who was homozygous for unattached earlobes, what is most likely to be true regarding their children? **Check your answer in footnote**[1]
    a. The children would all have partially attached earlobes.
    b. All the female children will have unattached earlobes, and all the male children will have attached earlobes.
    c. All of their children would have unattached earlobes.
    d. All of their children would have attached earlobes.

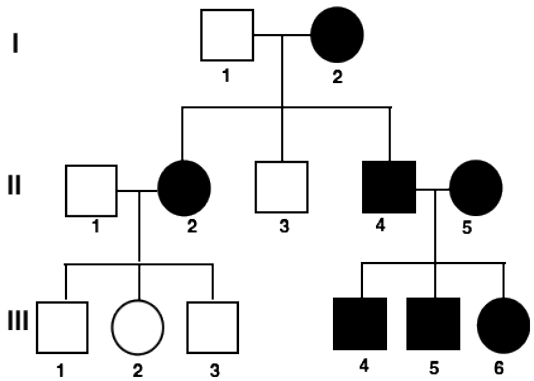


**Fig. 7.5a** Attached earlobes

2. The pedigree in **Fig. 7.5a** tracks the presence of attached earlobes through a family's generations. Having attached earlobes is an autosomal recessive trait. If individuals I-1 and I-2 had a fourth child, what is the chance that the child would have attached earlobes? **Check your answer in footnote**[2]
    a. 50%

1. c. All of their children would have unattached earlobes.

b. 75%
c. 0%
d. 100%

3. The pedigree in **Fig. 7.5a** above tracks the presence of attached earlobes through a family's generations. Having attached earlobes is an autosomal recessive trait. What is the genotype of individual I-1? **Check your answer in footnote**[3]
   a. ee
   b. $X^eY$
   c. EE
   d. Ee
4. The pedigree **Fig. 7.5a** above tracks the presence of attached earlobes through a family's generations. Having attached earlobes is an autosomal recessive trait. What is the genotype of individual II-3? **Check your answer in footnote**[4]
   a. ee
   b. $X^eY$
   c. EE
   d. Ee
5. The pedigree in Fig. 7.5b tracks Duchenne Muscular Dystrophy (DMD) through several generations. DMD is an X-linked recessive trait.

   If individuals I-1 and I-2 had another son, what is the chance that he would have DMD? **Check your answer in footnote**[5]
   a. 0%
   b. 25%
   c. 50%
   d. 100%

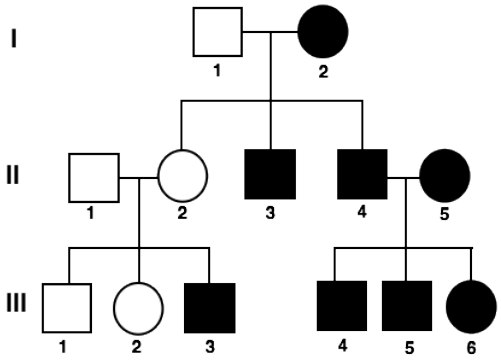


**Fig. 7.5b** Duchenne Muscular Dystrophy

6. The pedigree in **Fig. 7.5b** tracks Duchenne Muscular Dystrophy (DMD) through several generations.
   DMD is an X-linked recessive trait.Based on the pedigree, which of the following is true? **Check your**

---

2. a. A cross between I-1 and I-2 would produce two offspring with unattached earlobes (**Ee**) and two offspring boxes with attached earlobes (**ee**).

3. d. I-1 must have a heterozygous genotype because he is able to pass on a recessive allele to some of his offspring (II-2 and II-4).

4. d. II-3 must have a heterozygous genotype because he has a mother with attached earlobes, but shows the dominant condition.

5. d. Because individual I-2 is affected, she can only pass on a recessive DMD allele to her sons. This means that all of her sons will have DMD.

**answer in footnote**[6]

a. Individual II-3 has a genotype of $X^DY$.
b. If individuals II-4 and II-5 have a fourth child, there is a 50% chance that it will not have DMD.
c. Individual II-1 is a carrier for DMD.
d. If individual III-1 marries an unaffected, non-carrier female, none of their offspring will have DMD.

7. The pedigree in **Fig. 7.5b** tracks Duchenne Muscular Dystrophy (DMD) through several generations. DMD is an X-linked recessive trait.What is the genotype of individual II-2? **Check your answer in footnote**[7]
   a. $X^dY$
   b. $X^dX^d$
   c. $X^DD^d$
   d. $X^DX^D$
8. The pedigree in **Fig. 7.5b** tracks Duchenne Muscular Dystrophy (DMD) through several generations. DMD is an X-linked recessive trait.If individual II-3 has a child with a carrier woman, what is the percent chance that the child will be a *daughter* with DMD? **Check your answer in footnote**[8]
   a. 100%
   b. 50%
   c. 25%
   d. 0%

6. d. Individual III-1 is an unaffected male. If he mates with an unaffected, non-carrier female, there is no chance that the children will inherit the DMD allele.

7. d. Since DMD is X-linked, individual II-2 needs to be able to pass on a DMD allele to her son. A homozygous dominant genotype would not allow for that.

8. c. In order for a daughter to be affected, she must have a genotype $X^dX^d$. There is a 1 in 4 chance that they will produce a child with this genotype.

9. The pedigree in **Fig. 7.5c** tracks the presence of dimples through a family's generation. Having dimples is an autosomal dominant trait.

   If individuals II-1 and II-2 have a fourth child, what is the probability that the child will have dimples? **Check your answer in footnote**[9]

   a. 25%
   b. 50%
   c. 75%
   d. 100%

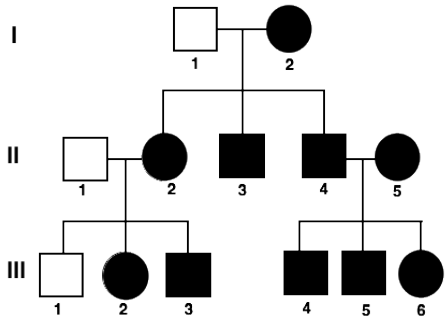


**Fig. 7.5c** Presence of dimples.

10. The pedigree in **Fig. 7.5c** tracks the presence of dimples through a family's generation. Having dimples is an autosomal dominant trait.What is the phenotype of individual III-4? **Check your answer in footnote**[10]

    a. Dimples
    b. No dimples
    c. dd
    d. DD

11. The pedigree in **Fig. 7.5c** tracks the presence of dimples through a family's generation. Having dimples is an autosomal dominant trait.Which of the following individuals is correctly matched with its genotype? **Check your answer in footnote**[11]

    a. I-1 → **Dd**
    b. II-3 → **dd**
    c. II-2 → **DD**
    d. III-2 → **Dd**

12. The pedigree in **Fig. 7.5c** tracks the presence of dimples through a family's generation. Having dimples is an autosomal dominant trait.If individual III-3 married a woman who was heterozygous for dimples, what is the percent chance their children will have dimples? **Check your answer in footnote**[12]

    1. 0%

---

9. b. A cross between II-1 and II-2 would produce two boxes with dimpled offspring (**Dd**) and two boxes with non-dimpled offspring (**dd**).

10. a. Because we are tracking dimples, shaded individuals represent those who have dimples.

11. d. Individual III-2 has dimples, meaning she must have 1 **D** allele. Her father does not have dimples, so he donates a **d** allele, giving her a genotype of **Dd**.

12. c. This cross has a 3/4 chance of producing individuals that have at least one **D** allele. Because dimples **D** is dominant, these individuals will have dimples.

2. 25%
3. 75%
4. 100%

## Step by step solutions

**Click to expand the step by step solutions for the above problems**

1. If individual III-6 married a man who was homozygous for unattached earlobes, what is most likely to be true regarding their children?
    1. Because the trait we are tracking (attached earlobes) is autosomal recessive, shaded individuals, like III-6, will have a homozygous recessive genotype (**ee**).
    2. If III-6 (**ee**) were to have a child with a man who was homozygous for unattached earlobes (**EE**), then all of the children would be heterozygous – getting one *E* from their father and one *e* from their mother.
       Attached earlobes is a recessive trait and will only occur in **ee** genotypes. Heterozygotes (**Ee**) will have unattached earlobes, as that is the dominant condition.
    3. The correct answer is
       All of their children would have unattached earlobes.
2. If individuals I-1 and I-2 had a fourth child, what is the chance that the child would have attached earlobes?
    1. Because the trait we are tracking (attached earlobes) is autosomal recessive, shaded individuals, like I-2, will have a homozygous recessive genotype (**ee**).
       I-1 must have a heterozygous genotype because he is able to pass on a recessive allele to some of his offspring (II-2 and II-4).
    2. If I-1 and I-2 had another child, the cross would be:

| – | **E** | **e** |
|---|---|---|
| e | Ee | ee |
| e | Ee | ee |

       Only offspring with **ee** genotypes will have attached earlobes (2/4 boxes).
       $2 \div 4 = 0.5 = 50\%$
    3. The correct answer is 50%
3. What is the genotype of individual I-1?
    1. Individual I-1 is represented by a non-shaded square, indicating that it is a male with unattached

earlobes.

2. Because the trait we are tracking, attached earlobes, is autosomal recessive, shaded individuals will have a homozygous recessive genotype (**ee**).
   Individuals that are non-shaded will have at least one **E** allele.
3. I-1 has children with attached earlobes (II-2 and II-4 are **ee**), meaning he must be able to pass on at least **e** allele. However, he shows the dominant condition, so he must also have one **E** allele.
   Therefore, his genotype is **Ee**.
4. The correct answer is **Ee**

4. What is the genotype of individual II-3?
   1. Individual II-3 is represented by a non-shaded square, indicating that it is a male with unattached earlobes.
   2. Because the trait we are tracking, attached earlobes, is autosomal recessive, shaded individuals will have a homozygous recessive genotype (**ee**).
      Individuals that are non-shaded will have at least one **E** allele.
   3. II-3 has a mother with attached earlobes (**ee**), meaning he must get one **e** allele from her. However, he shows the dominant condition, so he must also have one **E** allele.
      Therefore, his genotype is **Ee**.
   4. The correct answer is **Ee**
5. If individuals I-1 and I-2 had another son, what is the chance that he would have DMD?
   1. Individual I-2 is represented by a shaded circle, indicating that it is an affected female.
      Therefore, she must have a homozygous recessive genotype of $X^dX^d$
   2. Because males always get their X chromosome from their mother, all of the sons that individual 2 has will receive a recessive $X^d$ allele.
   3. Males will also receive their Y chromosome from their father, giving any son of individuals I-1 and I-2 a genotype of $X^dY$
   4. The correct answer is 100%.
6. Based on the pedigree, which of the following is true?
   1. Unaffected males, such as individual II-1 have a genotype of $X^DY$.
      On the other hand, affected males, such as individual II-3, have a genotype of $X^dY$.
      Since males only have one X chromosome, they cannot be carriers.
   2. Individuals II-4 and II-5 are both shaded in, indicating that they are affected.
      In order to be affected, they must have the recessive genotypes $X^dY$ and $X^dX^d$. This means that any child they have will have DMD because each parent can only pass on a recessive DMD allele.
   3. Individual III-1 is an unaffected male, meaning that he has a genotype of $X^DY$.
      If he mates with an unaffected, non-carrier female ($X^DX^D$), there is no chance that the children will inherit the DMD allele.
   4. The correct answer is

If individual III-1 marries an unaffected, non-carrier female, none of their offspring will have DMD.

7. What is the genotype of individual II-2?
    1. Individual II-2 is represented by a non-shaded circle, indicating that it is an unaffected female.
    2. In order for individual II-2 to have a normal phenotype, but also produce an affected son, she must be a carrier for DMD. This means that she has one of each allele, $X^DX^d$.
    3. The correct answer is $X^DX^d$
8. If individual II-3 has a child with a carrier woman, what is the percent chance that the child will be a daughter with DMD?
    1. Individual I-3 is represented by a shaded square, indicating that it is an affected male. Therefore, he must have a genotype of $X^dY$.
    If he has a child with a DMD carrier ($X^DX^d$), the cross would be:

| – | $\mathbf{X^D}$ | $\mathbf{X^d}$ |
|---|---|---|
| $X^d$ | $X^DX^d$ | $X^dX^d$ |
| Y | $X^DY$ | $X^dY$ |

    2. In order for a daughter to be affected, her genotype must be $X^dX^d$.
    Only one box has this genotype, so the chances of having an affected daughter is: ¼ =25%
    3. The correct answer is 25%
9. If individuals II-1 and II-2 have a fourth child, what is the probability that the child will have dimples?
    1. Because the trait we are tracking, dimples, is autosomal dominant, any *shaded* individuals will have at least one dominant allele (**D**).
    Any *unshaded* individuals will have the recessive genotype (**dd**).
    2. II-2 has dimples, meaning she must have at least one **D** allele. In addition, she has a recessive parent, and one of her children has no dimples (**dd**), so she must also have at least one **d** allele. This makes her genotype **Dd**.
    Individual II-1 has no dimples, meaning that he must have a homozygous recessive genotype (**dd**).
    3. Now that we know their genotypes, if we perform a cross between individuals II-1 and II-2 we find:

| – | **D** | **d** |
|---|---|---|
| d | Dd | dd |
| d | Dd | dd |

2÷4=50%

4. The correct answer is 50%.

10. What is the phenotype of individual III-4?
    1. Phenotype is the physical characteristic that we see (ex: dimples).
       A genotype is the allele combination (ex: DD)
    2. Because the trait we are tracking is having dimples, shaded individuals, like III-4, have dimples.
       Unshaded individuals, like III-1, do not have dimples.
    3. The correct answer is Dimples
11. Which of the following individuals is correctly matched with its genotype?
    1. The trait that we are tracking, dimples, appears to be dominant, as all offspring who have the trait have an affected parent.
       Having dimples also does not skip a generation, which suggests that it is likely dominant.
    2. Shaded individuals have dimples, meaning that they must have at least one **D** allele.
       Unshaded individuals, like I-1, do not have dimples, meaning that they must have the homozygous recessive genotype **dd**.
    3. An individual with dimples can be either **DD** or **Dd**.
       Individuals like II-2, II-3, and III-2 all have at least one recessive parent. Since the recessive parent can only donate a **d**, each of them must have a **d** in their genotype.
       Because they all have dimples, we know they must have one **D** allele as well, giving them all the genotype of **Dd**.
    4. The correct answer is III-2 → **Dd**
12. If individual III-3 married a woman who was heterozygous for dimples, what is the percent chance their children will have dimples?
    1. Because the trait we are tracking (dimples) is autosomal dominant, any *shaded* individuals have at least one dominant allele (**D**).
       Any *unshaded* individuals have the recessive genotype (**dd**).
    2. Individual III-3 must be heterozygous (**Dd**) because he has an unshaded father (**dd**).
       If he was to have a child with a woman who was heterozygous for dimples (**Dd**), then the cross would be:

| – | **D** | **d** |
|---|---|---|
| D | DD | Dd |
| d | Dd | dd |

    3. Dimples is a dominant trait and will occur whenever a dominant allele is present in the genotype.
       Homozygous recessive individuals (**dd**) will have no dimples, as that is the recessive condition.
       Looking at the Punnett square, we find that ¾ =75% offspring will have at least one **D** allele.
    4. The correct answer is 75%

**Activity source:** Classical Genetics (Khan Academy) By LibreTexts, a derivative of Pedigrees by Khan Academy, CC BY-NC-SA 4.0

## Attribution & References

# 7.5 GROUP DISCUSSION

## Assignment – Group Discussion

This week students will engage in group discussions on Blackboard. Students will be randomly assigned to groups. See the Blackboard course shell for assignment directions and rubric. Students may also want to use this unit and unit 11 to work on their case study assignment.

## Attribution

# UNIT 8 - GENETIC TESTING

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 8 Contents


- 8.1 Unit Overview
- 8.2 Genetic Testing Overview
- 8.3 Types of Genetic Tests
- 8.4 Interpreting Genetic Test Results
- 8.5 Unit Summary and Review


## Attribution

# 8.1 UNIT OVERVIEW

## Learning Objectives

- Describe different types and applications of genetic testing
- Discuss ethical and legal protections for genetic testing
- Examine the role of the nurse in working with patient's receiving genetic testing
- Review genomic variant classification

## Outline

Topics covered in this chapter include:

- Genetic testing overview
- Types of Genetic tests
- Genetic tests validity and reliability
- Interpreting genetic test results

## Competencies Nurses will Develop in this Chapter

### ANA (2023):

#### Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).

### Identification:

- Identifies credible, accurate, appropriate, and current genomic information, resources, services, and technologies specific to given clients.
- Recognizes issues that undermine the rights of all clients for autonomous, informed genomic-related decision-making and voluntary action.

### Provision of education, care, and support:

- Facilitates clients' access to credible, accurate, appropriate, and current genomic information, resources, services, and technologies.
- Advocates for autonomous, informed genomic-related decision-making.
- Demonstrates in practice the importance of tailoring genomic information and services that are responsive to the unique attributes of every person.

### Provision of education, care, and support:

- Performs interventions appropriate to clients' genomic health care needs.

## NHS (2023):

### Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the key indicators of a potential genetic condition, or clinical situation where genomics-informed healthcare would be appropriate;
- recognizing the importance of family history in assessing predisposition to a genetic condition; and
- taking appropriate and timely action to seek assistance from and refer individuals to genomics specialists, other specialists and peer support resources.

### Demonstrate effective communication in tailoring genomic information and services to the individual:

- recognizing factors (such as ethnicity, culture, religion, ethical values, developmental stage or language) that may influence the individual's ability to use information and services.

### Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

### Apply knowledge, understanding and context of genomic testing and information to underpin care and support for individuals and families prior to, during and following decision-making:

- including types, uses and limitations of genomic tests to prevent, predict or treat a health condition, and an awareness of the processes for testing and return of results;
- recognizing that decision-making and testing in some situations may be time-critical;
- incorporating awareness of the ethical, legal and social issues related to testing, recording, sharing and storage of genomic information and data; and
- incorporating awareness of the potential physical, emotional, psychological and social consequences of genomic information for individuals, family members and communities.

### Examine your own competency of practice on a regular basis:

- based on an understanding of the boundaries of your professional role in delivering genomic healthcare including the referral, provision or follow-up to genomic services.

### Obtain and communicate reliable, current information about genomics, for self, patients, families and colleagues:

- using information technologies and other information sources effectively to do so; and
- applying critical appraisal skills to assess the quality of information accessed.

### Provide ongoing nursing care and support to patients, carers, families and communities with genomic healthcare needs:

- demonstrating awareness about how a genomic test result can have implications for family members and might impact on family dynamics.

## Key terminology

### Analytical validity

How well a test predicts the presence or absence of a particular gene or genetic change (Medline, 2024).

### Carrier screening

Carrier screening involves testing to see if a person “carries” a genetic variation (allele) associated with a specific disease or trait. A carrier has inherited a normal and a variant allele for a disease- or trait-

associated gene, one from each parent. Most typically, carrier screening is performed to look for recessively inherited diseases when the suspected carrier has no symptoms of the disease, but that person's offspring could have the disease if the other parent is a carrier of a harmful variant in the same gene.

**Expanded carrier screening** refers to reproductive genetic carrier screening beyond one's ethnicity and family history (GECKO, 2024).

## Chromosomal tests:

These tests analyze whole chromosomes or long lengths of DNA to identify large-scale changes, such as an extra or missing copy of a chromosome (trisomy or monosomy, respectively) or abnormalities of large segments of chromosomes, that underlie certain genetic conditions (Medline, 2021a).

## Clinical validity

How well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease (Medline, 2024).

## Clinical utility

Whether the test can provide helpful information about diagnosis, treatment, management, or prevention of a disease (Medline, 2024).

## Direct-to-consumer testing

Genetic testing that can be ordered by any individual; it is not a clinical test therefore does not need to be ordered by a medical professional.

## Exome

An exome is the sequence of all the exons in a genome, reflecting the protein-coding portion of a genome. In humans, the exome is about 1.5% of the genome.

## Molecular gene tests:

These tests determine the order of DNA building blocks (nucleotides) in an individual's genetic code, a process called DNA sequencing. The purpose of these tests is to identify pathogenic genetic variants (Medline, 2021a).

## Multigene panels

Look for variants in many genes in the same test (Medline, 2021a).

## Newborn screening

Used to test babies one or two days after birth to find out if they have certain diseases known to cause problems with health and development (NHGRI, 2019).

## Next-generation DNA sequencing

DNA sequencing establishes the order of the bases that make up DNA. Next-generation DNA sequencing (abbreviated NGS) refers to the use of technologies for sequencing DNA that became available shortly after the completion of the Human Genome Project (which relied on the first-generation method of Sanger sequencing). Faster and cheaper than their predecessors, NGS technologies can sequence an entire human genome in a single day and for less than 1,000.

## Pharmacogenomic testing

Provides information about how certain medicines are processed by an individual's body (NHGRI, 2019).

## Predictive/pre-symptomatic genetic test

Used to find gene changes that increase a person's likelihood of developing diseases. The results of these tests provide information about the risk of developing a specific disease. Such information may be useful in decisions about lifestyle and healthcare (NHGRI, 2019).

## Prenatal screening

Is offered during pregnancy to help identify fetuses that have certain diseases (NHGRI, 2019).

## Reproductive genetic carrier screening

Facilitates informed decision-making by future parents through identifying those couples at increased risk of having an affected child with a serious genetic disorder (autosomal or X-linked recessive) (GECKO, 2024).

### Research genetic testing

Used to learn more about the contributions of genes to health and to disease (NHGRI, 2019).

### Sanger sequencing

A method of DNA sequencing that involves electrophoresis and is based on the random incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication. After first being developed by Frederick Sanger and colleagues in 1977, it became the most widely used sequencing method for approximately 40 years (Wikipedia, 2024).

### Screening (genetic)

Used in people who do not have signs or symptoms of a disorder. These tests estimate whether an individual's risk of having a certain condition is increased or decreased compared with the risk in other people in a similar population (Medline, 2021a).

### Single gene tests

Look for variants in only one gene (monogenic disorder) (Medline, 2021a).

### Whole exome sequencing

Looks at all the genes in the DNA (whole exome) or just the genes that are related to medical conditions (clinical exome) (Medline, 2021b).

### Whole genome sequencing

Looks at all of a person's DNA, not just the genes (Medline, 2021b).

## Attribution & References



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- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.

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# 8.2 GENETIC TESTING OVERVIEW

## What is genetic testing?

Genetic testing is a type of medical test that looks for changes in DNA. Genetic tests analyze cells or tissue to look for changes in genes, chromosomes, and proteins.

Genetic testing may be done for many different reasons:

**Predictive** and **pre-symptomatic** genetic tests are used to find gene changes that increase a person's likelihood of developing diseases. The results of these tests provide information about the risk of developing a specific disease. Such information may be useful in decisions about lifestyle and healthcare.

**Carrier testing** is used to find people who "carry" gene variants linked to disease. Carriers may show no signs of the disease. However, they can pass on the gene change to their children, who may develop the disease or become carriers themselves. Some diseases require a gene change to be inherited from both parents for the disease to occur. This type of testing is usually offered to people who have a family history of a specific inherited disease or who belong to certain ethnic groups that have a higher risk of specific inherited diseases.

**Prenatal testing** is offered during pregnancy to help identify fetuses that have certain diseases. This type of testing is offered during pregnancy if there is an increased risk that the baby will have a genetic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them make decisions about a pregnancy. However, it cannot identify all possible inherited disorders and congenital disabilities.

**Newborn screening** is used to test babies one or two days after birth to determine if they have certain diseases that cause health and development problems.

**Pharmacogenomic testing** gives information about how an individual's body processes certain medicines. This type of testing can help healthcare providers choose the drugs that work best with an individual's genetic makeup.

**Research genetic testing** is used to learn more about the contributions of genes to health and disease. Sometimes, the results may not be directly helpful to participants, but they may benefit others by helping researchers expand their understanding of the human body, health, and disease.

## What are the benefits of genetic testing?

Genetic testing may be beneficial whether the test identifies a mutation or not. Test results are a relief for some people, eliminating some uncertainty surrounding their health. These results may also help doctors make recommendations for treatment or monitoring and give people more information for making decisions

about their and their family's health, allowing them to take steps to lower their chance of developing a disease. For example, as a result of such a finding, someone could be screened earlier and more frequently for the disease and could change health habits like diet and exercise. Such a genetic test result can lower a person's feelings of uncertainty, and this information can also help people make informed choices about their future, such as whether to have a baby.

## What are the risks and limitations of genetic testing?

The physical risks associated with most genetic tests are minimal, particularly for those tests that require only a blood sample or buccal smear. The procedures used for prenatal diagnostic testing carry a small but real risk of miscarriage because they require a sample of amniotic fluid or tissue from around the fetus.

Many of the risks associated with genetic testing involve the results' emotional, social, or financial consequences. Genetic testing can cost anywhere from less than $100 to more than $2,000. Health insurance companies may cover part or all of the cost of testing.

People may feel angry, depressed, anxious, or guilty about their results. Because family members share DNA, some family members may have the same variants. For this reason, in some cases, genetic testing creates tension within a family.

Genetic testing can provide only limited information about an inherited condition. The test often can't determine if a person will show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. Another major limitation is the lack of treatment strategies for many genetic disorders once they are diagnosed.

The possibility of genetic discrimination in employment or insurance is also a concern. This will be explored in greater detail in chapter 10.2.

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# 8.3 TYPES OF GENETIC TESTS

## How are genetic screening tests different from genetic diagnostic tests?

Screening tests evaluate an individual's *risk* of developing a genetic condition, while diagnostic tests identify genetic conditions. All genetic tests have both benefits and limitations.

Genetic **screening tests** are generally used in people who do not have signs or symptoms of a disorder. These tests estimate whether an individual's risk of having a certain condition is increased or decreased compared with the risk in other people in a similar population. A positive result means that a person's risk of developing the condition is higher than average. A negative screening test means that a person's risk is lower than average. However, *having a positive screening result does not mean the individual has the condition.* Because screening tests are only estimates, the results, in some cases, indicate an increased risk for a genetic abnormality when the person is unaffected (false positive), or the results indicate a decreased risk for a genetic abnormality when the person is affected (false negative). While genetic screening tests do not provide a conclusive answer, they can help guide the following steps, such as whether additional diagnostic testing is needed.

Genetic **diagnostic tests** are often used in people who have signs and symptoms. These tests are used to *confirm or rule out suspected genetic conditions*. Diagnostic tests can also help inform a person's chance of developing a genetic condition or passing it to their children. Diagnostic testing can be performed before birth or at any time during a person's life, but it is not available for all genes or all genetic conditions. The results of a diagnostic test can be used to guide a person's choices about health care and the management of the disorder.

### Concept in Action

**Watch Genetic Testing's Impact on Patient Care – Page's Story (4 mins) on YouTube (https://youtu.be/-UHg0oEqdAg) to learn how genetic testing can impact a patient's diagnostic odyssey.**

## How are genetic tests performed?

Genetic tests are performed on a sample of blood, hair, skin, amniotic fluid (the fluid that surrounds a fetus during pregnancy), or other tissue. For example, a buccal (pronounced buh-kl (https://dictionary.cambridge.org/pronunciation/english/buccal#google_vignette)) smear uses a small brush or cotton swab to collect a sample of cells from the inside surface of the cheek. Depending on the suspected disorder, the sample is sent to a laboratory where technicians look for genetic variants in chromosomes, DNA, or proteins. If requested, the laboratory reports the test results in writing to a person's doctor, genetic counsellor, or patient. Before a person has a genetic test, it is important to obtain informed consent to be sure they understand the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results. The International Society of Nurses in Genetics (ISONG) has a position statement on informed decision-making related to genetic testing and the nurse's role [PDF] (https://www.isong.org/resources/Documents/Informed%20decision%20making%20position%20statement%20approved%20Dec%202018.pdf).

## Examples of genetic screening tests

**Reproductive genetic carrier screening** Carrier screening supports informed decision-making for prospective parents by identifying couples at higher risk of having a child affected by a severe genetic condition, whether autosomal or X-linked recessive (Henneman et al., 2016; Plantinga et al., 2016; Yao et al., 2016). The optimal time to discuss carrier screening is during the preconception period, when individuals are planning pregnancy, or at a woman's first prenatal visit, regardless of gestational age (Edwards et al., 2015; Wilson et al., 2016). Current Canadian and international guidelines recommend offering carrier screening based on an individual's ethnic background or the presence of specific personal or family history risk factors (Edwards et al., 2015; Henneman et al., 2016; Wilson et al., 2016). Canadian recommendations for Point of Care tools (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/expanded-carrier-screening/point-of-care-tool-9) on reproductive genetic screening are available. "**Expanded carrier screening** refers to reproductive genetic carrier screening beyond one's ethnicity and family history" (GECKO, n.d.-d).

**Noninvasive prenatal testing/screening** (NIPT/NIPS): This screening test is performed before birth to help determine the risk that a fetus will be born with certain genetic abnormalities, such as Down syndrome and other chromosomal disorders (MedlinePlus, n.d.-a).

For more information, see GECKO *on the run:* Non-invasive prenatal testing (NIPT) (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/non-invasive-prenatal-testing/gecko-on-the-run-10) – a 2-page, evidence-based summary for healthcare providers. Features include current Canadian recommendations, red flags to consider regarding the offer of NIPT, what the results mean, and the benefits and limitations of the test.

**Prenatal Screening** is available to all pregnant women in Canada. Different methods are used for prenatal screening, depending on the purpose and gestation. Here is a comprehensive guide to understanding prenatal screening [PDF], (https://www.geneticseducation.ca/uploads/patientresources/guide_to_prenatal_screening.pdf) an excellent patient resource (GECKO, n.d.-c).

With prenatal screening and detailed second-trimester ultrasound, the chance to have a baby with some specific genetic conditions or developmental differences can be more precisely determined. Prenatal screening is about risk assessment [PDF]. (https://www.geneticseducation.ca/uploads/patientresources/guide_to_prenatal_screening.pdf) (GECKO, n.d.-c).

**Newborn screening tests (NBS)** are done shortly after birth on a small blood sample (blood spot), taken by pricking the baby's heel. A nurse places a few drops of blood onto a special filter paper attached to a blood spot card (Perinatal Services BC, 2024). A NBS tests for treatable disorders that manifest their symptoms during childhood and are not otherwise easily identifiable at birth. This allows for early diagnosis and treatment. Unlike other types of genetic testing, a parent will usually only receive the result if it is positive. If the test result is positive, *additional testing is needed* to determine whether the baby has a genetic disorder. ISONG also has a position statement on newborn screening and the nurses' role [PDF] (https://www.isong.org/resources/Documents/Newborn%20ScreeningThe%20Role%20of%20the%20Nurse%20Updated%20Nov%202020.pdf). (MedlinePlus, 2023).

In Canada, each province is responsible for how it distributes health care funding and programming. Genetic services, including NBS, differ from province to province. The number of conditions screened for ranges from 14-36 (Groulx-Boivin et al., 2024). This creates a lack of equity in healthcare treatment across the country. Ongoing advocacy exists to establish a national NBS program (Canadian MPS Society, 2022).

**Cascade testing** tests family members of an individual with a pathogenic/likely pathogenic variants, usually who is affected by the condition. This process identifies other family members at risk of the hereditary condition (NCI, n.d).

## Examples of genetic diagnostic tests

**Molecular gene tests**: These tests determine the order of DNA building blocks (nucleotides) in an individual's genetic code, a process called DNA sequencing. Molecular tests can also analyze RNA. The purpose of these tests is to identify pathogenic genetic variants. Molecular tests include polymerase chain reaction (PCR), fluorescent in situ hybridization (FISH) and next-generation sequencing (NGS) (MedlinePlus, n.d.-b).

## Targeted single variant testing

Single variant tests look for a specific variant in one gene. The selected variant is known to cause a disorder

(for example, the particular variant in the *HBB* gene (https://medlineplus.gov/genetics/gene/hbb/) that causes sickle cell disease (https://medlineplus.gov/genetics/condition/sickle-cell-disease/)). This type of test is often used to test family members of someone known to have a particular variant to determine whether they have a familial condition (https://medlineplus.gov/genetics/understanding/inheritance/runsinfamily/) (MedlinePlus, n.d.-b).

## Single gene testing

**Single gene tests** –Single gene tests look for any genetic changes in one gene. These tests are typically used to confirm (or rule out) a specific diagnosis, mainly when many variants in the gene can cause the suspected condition (CDC, 2024).

## Genetic panel testing

**Multigene panels** – Panel tests look for variants in more than one gene. This type of test is often used to pinpoint a diagnosis when a person has symptoms that may fit a wide array of conditions or when the suspected condition can be caused by variants in many genes. (For example, there are hundreds of genetic causes of epilepsy) MedlinePlus, n.d.-b).

## Large-scale genomic testing

Two methods, whole exome sequencing and whole genome sequencing, are increasingly used in healthcare and research to identify genetic variations; both methods rely on new technologies that allow rapid sequencing of large amounts of DNA. These approaches are **next-generation sequencing** (or next-gen sequencing) (CDC, 2024).

- **Whole exome sequencing** looks at *all the genes* in the DNA (whole exome) or those related to medical conditions (clinical exome). (MedlinePlus, n.d.-b; CDC, 2024).
- **Whole genome sequencing** is the most significant genetic test and looks at *all of a person's DNA, not just the genes*. (MedlinePlus, n.d.-b; CDC, 2024).

The original sequencing technology, called **Sanger sequencing** (named after the scientist who developed it, Frederick Sanger), was a breakthrough that helped scientists determine the human genetic code, but it was time-consuming and expensive. The Sanger method has been automated to make it faster and is still used in laboratories today to sequence short pieces of DNA, but it would take years to sequence a person's genome. Next-generation sequencing has sped up the process (taking only days to weeks to sequence a human genome) while reducing costs (Medline Plus, n.d.c).

With next-generation sequencing, it is now feasible to sequence large amounts of DNA, for instance, all of an individual's exons, the DNA that provides instructions for making proteins, which are thought to make up 1 percent of a person's genome. Together, all the exons in a genome are known as the **exome.** In whole exome sequencing, variations in the *protein-coding region* of any gene are identified, rather than in only a select few genes. Because most known mutations that cause disease occur in exons, whole exome sequencing is considered an efficient method to identify possible disease-causing mutations (Medline Plus, n.d.c).

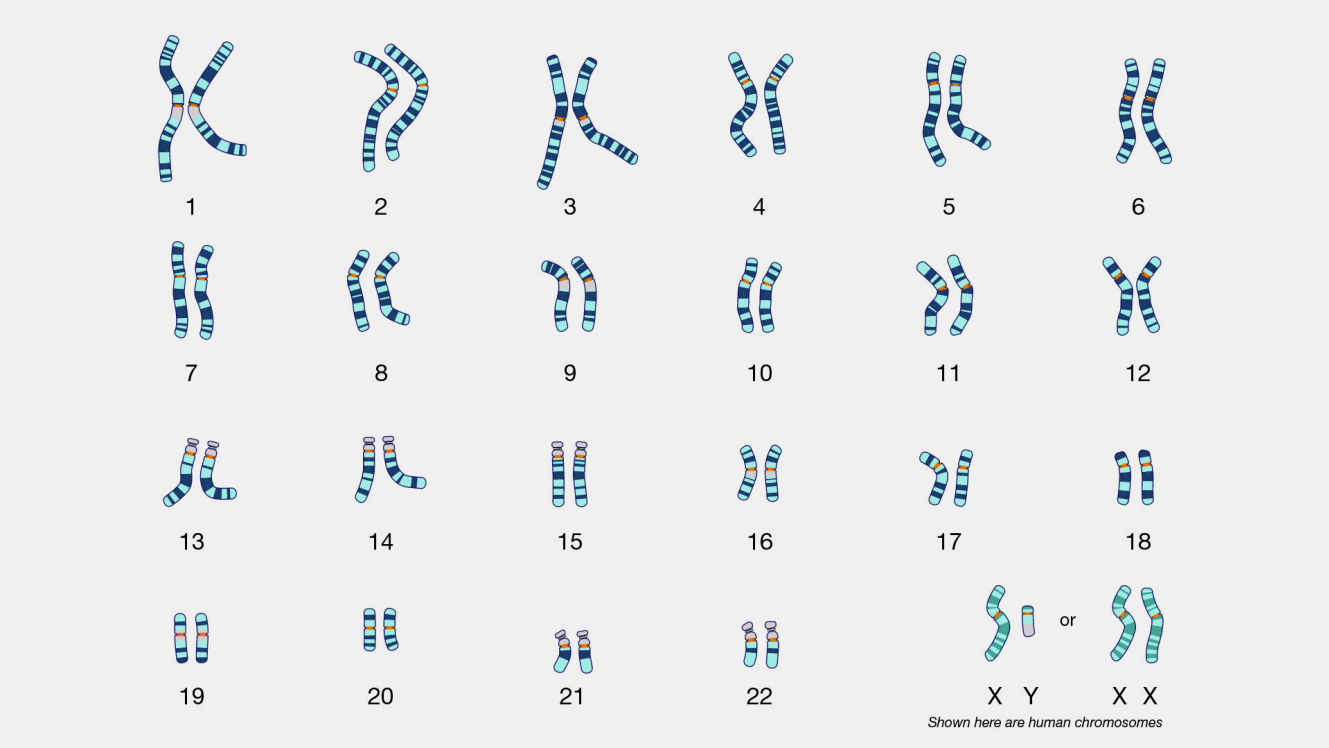
However, researchers have found that DNA variations outside the exons can affect gene activity and protein production and lead to genetic disorders–variations that whole exome sequencing would miss. Whole genome sequencing determines the order of all the nucleotides in an individual's DNA and can determine variations in any part of the genome (Medline Plus, n.d.c).

Whole exome sequencing or whole genome sequencing are tests that analyze the bulk of an individual's DNA to find genetic variations. Whole exome or whole genome sequencing (https://medlineplus.gov/genetics/understanding/testing/sequencing/) is typically used when a single gene or panel testing has not provided a diagnosis or when the suspected condition or genetic cause is unclear. Whole exome or whole genome sequencing is often more cost- and time-effective than performing multiple single gene or panel tests (MedlinePlus, n.d.-b).

**Chromosomal tests**: These tests analyze whole chromosomes or long lengths of DNA to identify large-scale changes, such as an extra or missing copy of a chromosome (trisomy or monosomy, respectively) or abnormalities of large segments of chromosomes, that underlie certain genetic conditions(MedlinePlus, n.d.-b).

A chromosomal microarray is a newer technology that might be recommended for a child with autism spectrum disorder. A karyotype is a high-level genomic test that analyses the number and structure of an individual's chromosomes (GECKO, n.d.-a).

More information on chromosomal microarrays vs karyotyping is available here [PDF] (https://pathwest.health.wa.gov.au/~/media/PathWest/Documents/Our-Services/Clinical-Services/Diagnostic-Genomics/CMA-and-Karyotype-Education-PPT.pdf). Additionally, see GECKO *on the Run:* (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/chromosomal-microarray/gecko-on-the-run-7) Chromosomal microarray – a 2-page, evidence-based summary for healthcare providers. Features a bottom line, red flags to consider microarray testing and genetic referral, what the results mean, and resources.




**Source:** Karyotype from Talking Glossary of Genomic and Genetic Terms Courtesy: National Human Genome Research Institute, PDM with attribution

### Concept in Action

**Watch Chromosomal Microarray Testing (4 mins) from Alberta Health Services on YouTube (https://youtu.be/ZrDANI0KSNU) to learn about chromosomal microarray testing.**

## Other tests

A full description of each of these tests is beyond the scope of this course. However, nurses may encounter these in research papers' methods sections. Therefore, it is beneficial to have a basic overview.

## Gene expression tests

Genes are expressed, or turned on, at different levels in different types of cells. Gene expression tests compare these levels between normal and diseased cells because knowing the difference can provide important

information for treating the disease. For example, these tests can guide chemotherapy treatment for breast cancer (MedlinePlus, n.d.-b).

## Biochemical tests

These tests look at levels or activity of proteins or enzymes produced by genes. Any abnormalities can signify underlying genetic disorders (MedlinePlus, n.d.-b). Metabolomics is a form of biochemical testing where levels of metabolites are measured. Samples such as urine, serum, and plasma can be tested for metabolites. Metabolomics is an emerging area of genetic research. Other forms of biochemical testing include protein assays such as colorimetric assays, immunoassays such as enzyme-linked immuno-absorbent assay (ELISA), mass spectrometry or gel electrophoresis (e.g. Western Blotting).

## Epigenetic biomarkers

Other tests used in a clinical context include those looking for epigenetic markers. This is a rapidly evolving area of medical genetics research. Check out Epi-Sign (https://sadikoviclab.lhsc.on.ca/episign_info.html), used to obtain definitive diagnoses when other methods have returned uncertain results. This test examines DNA methylation patterns (biomarkers) associated with specific genetic disorders.

## What is circulating tumour DNA, and how is it used to diagnose and manage cancer?

Circulating tumour DNA (ctDNA) is found in the bloodstream and refers to DNA from cancerous cells and tumours. Most DNA is inside a cell's nucleus. As a tumour grows, cells die and are replaced by new ones. The dead cells get broken down, and their contents, including DNA, are released into the bloodstream. ctDNA are small pieces of DNA, usually comprising fewer than 200 building blocks (nucleotides) in length.

The quantity of ctDNA varies among individuals and depends on the type of tumour, its location, and the cancer stage of cancerous tumours.

Detection of ctDNA can be helpful in the following cases:

- Detecting and diagnosing a tumour. Because tumour DNA has acquired multiple genetic variants, leading to tumour development, ctDNA is not an exact match to the individual's DNA. Finding DNA with genetic differences aids in tumour detection. Diagnosing the type of tumour using ctDNA can reduce the need to get a tumour tissue sample (tumour biopsy), which can be challenging when a tumour is difficult to access, such as a tumour in the brain or lung.
- Guiding tumour-specific treatment. Analyzing the genome of tumour cells using ctDNA can help doctors determine which treatment will be most effective. However, approval from the U.S. Food and

Drug Administration for ctDNA testing to personalize cancer treatment is limited.

- Monitoring treatment. A decrease in the quantity of ctDNA suggests the tumour is shrinking, and treatment is successful.
- Monitoring periods with no symptoms (remission of cancer). A lack of ctDNA in the bloodstream indicates that the cancer has not returned.

## Clinical versus direct-to-consumer genetic tests

Clinical genetic tests are different from **direct-to-consumer (DTC) genetic tests**. A healthcare provider orders clinical genetic tests for a specific medical reason—an individual cannot order this type of testing. In contrast, anyone can buy DTC tests online (CDC, 2024). Other names for direct-to-consumer genetic testing include DTC genetic testing, direct-access genetic testing, at-home genetic testing, and home DNA testing. Ancestry testing (genealogy testing) is also considered a form of direct-to-consumer genetic testing (MedlinePlus, n.d.-d).

Many companies currently offer direct-to-consumer genetic tests for a variety of purposes. The most popular tests use a limited set of genetic variations to make predictions about certain aspects of health, provide information about common traits, and offer clues about a person's ancestry. The number of companies providing direct-to-consumer genetic testing and the range of health information these tests provide is growing. Because there is currently little regulation of direct-to-consumer genetic testing services, assessing the quality of available services before pursuing any testing (MedlinePlus, n.d.-d).

DTC test results can be used to decide lifestyle choices or identify issues to discuss with a healthcare provider. However, DTC tests cannot determine for sure whether or not the individual will get a disease. Nor should these tests be used alone to make decisions about treatment or medical care or in place of clinical genetic testing. However, patients present to medical professionals with reports generated from DTC testing. Therefore, healthcare providers must be aware that these tests exist and may be sought out by individuals who can pay for them (MedlinePlus, n.d.-d).

For more information, see GECKO *on the run* (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/direct-to-consumer-testing/gecko-on-the-run-9)*: (https://www.geneticseducation.ca/resources-for-clinicians/genomic-technologies/direct-to-consumer-testing/gecko-on-the-run-9)* Direct-to-consumer genomic testing – a 3-page, evidence-based summary for healthcare providers. Features include result interpretation, benefits and limitations of testing, and resources (GECKO, n.d.-d). The National Human Genome Research Institute also has an excellent resource on DTC testing for consumers (https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources/Healthcare-Provider-Direct-to-Consumer-Genetic-Testing-FAQ).

ISONG has a position statement on DTC genetic testing [PDF] (https://www.isong.org/resources/Documents/PS_Direct%20to%20Consumer%20GeneticGenomic%20Testing_September%202022.pdf). It concerns issues of informed consent, misinterpretation of test results, psychosocial concerns, confidentiality,

privacy, and integrity of specimens. The Canadian Medical Association also has a position statement on DTC genetic testing [PDF], (https://www.cma.ca/sites/default/files/2018-11/cma-policy-direct-to-consumer-genetic-testing-pd17-05-e.pdf) which considers the role of government and systems infrastructure in regulating DTC testing.

The Office of the Privacy Commissioner of Canada provides good consumer resources on privacy and DTC testing (https://www.priv.gc.ca/en/privacy-topics/health-genetic-and-other-body-information/02_05_d_69_gen/).

## Attribution & References

Except where otherwise noted, this section is adapted from

- How are genetic screening tests different from genetic diagnostic tests? In *Help Me Understand Genetics* by MedlinePlus, Public Domain
- How is genetic testing done? In *Help Me Understand Genetics* by MedlinePlus, Public Domain
- What is circulating tumour DNA, and how is it used to diagnose and manage cancer? In *Help Me Understand Genetics* by MedlinePlus, National Library of Medicine, Public Domain with attribution
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# 8.4 INTERPRETING GENETIC TEST RESULTS

Genomic testing is becoming more affordable and accessible as it becomes more widely available and utilized in primary care and other non-specialized healthcare settings. However, this shift risks misinterpretation, as genomic reports are often complex, and healthcare providers may need more expertise or resources (GECKO, n.d). Misinterpretation is relatively common and can lead to unnecessary follow-up testing, inappropriate changes to clinical management, or false reassurance (GECKO, n.d.).

## Variant Classification

Previously, pathogenic changes in the genome were called mutations (GECKO, n.d). More than 1% of the general population carries benign changes, which are referred to as *polymorphisms* (GECKO, n.d). Laboratories vary in how and what is reported. However, most accredited/licensed laboratories in Canada follow the American College of Medical Genetics and Genomics (ACMG) guidelines [PDF] (https://www.acmg.net/docs/standards_guidelines_for_the_interpretation_of_sequence_variants.pdf) (Richards et al., 2015). This is a five-tier system of classification of genomic variants. The ACMG classification framework organizes each of the criteria by the type of evidence (e.g. population data, functional data) as well as the strength of that evidence (e.g. very strong, strong, moderate, supporting) (Richards et al., 2015).

The ACMG classifications are recommended for describing pathogenicity in patients with suspected hereditary disorders, primarily Mendelian. This classification system is not meant to apply to somatic variants, pharmacogenomic variants, or complex disorders (Richards et al., 2015).

The five classifications of gene variants are:

- **Pathogenic**: The variant is responsible for causing disease. Ample scientific research supports an association between the disease and the gene variant. These variants are often referred to as mutations.
- **Likely pathogenic**: The variant is probably responsible for causing disease, but there is not enough scientific research to be certain.
- **Variant of uncertain significance (VUS or VOUS)**: The variant cannot be confirmed to play a role in disease development. There may be insufficient scientific research to confirm or refute a disease association or conflicting research.
- **Likely benign**: The variant is probably not responsible for causing disease, but there is not enough scientific research to be certain.
- **Benign**: The variant is not responsible for causing disease. There is ample scientific research to disprove

an association between the disease and the gene variant.

**Source:** Genomic Test Results GECKO on the run by Genetics Education Canada: Knowledge Organization (GECKO), reprinted with permission. See the GECKO website for text-based version (https://geneticseducation.ca/resources-for-clinicians/genomic-technologies/genomic-test-results/gecko-on-the-run).

Evaluation needs to be done for each variant. Just because a gene is associated with a disease does not mean that all variants in that gene are pathogenic. Additionally, a variant must be evaluated for all diseases with which it is thought to be associated. A pathogenic variant for one disease is not necessarily pathogenic for a different disease. It is important to re-evaluate variants periodically; the classification of a variant can change over time as more information about the effects of variants becomes known through additional scientific research.

A positive test result means that the laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the test's purpose, this result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic variant, identify an increased risk of developing a disease (such as cancer), or suggest further testing. Because family members have some genetic material in common, a positive test result may also have implications for certain blood relatives of the person undergoing testing. It is important to note that a positive result of a predictive or presymptomatic genetic test usually cannot establish the exact risk of developing a disorder. Also, healthcare providers typically cannot use a positive test result to predict the course or severity (https://medlineplus.gov/genetics/understanding/consult/prognosis/) of a condition. Rarely test results can be false positive, which occurs when results indicate an increased risk for a genetic condition when the person is unaffected.

A negative test result means that the laboratory did not find a change that affects health or development in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic variant, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration because many tests cannot detect all genetic changes that can cause a particular disorder. Further testing or re-testing at a later date may be required to confirm a negative result. Rarely, test results can be false negative, which occurs when the results indicate a decreased risk or a genetic condition when the person is affected.

In some cases, a test result might not give any useful information. This type of result is called uninformative, indeterminate, inconclusive, or ambiguous. Uninformative test results sometimes occur because everyone has common, natural variations in their DNA, called polymorphisms, that do not affect health. If a genetic test finds a change in DNA that has not been confirmed to play a role in the development of disease, known as a variant of uncertain significance (VUS or VOUS), it can be difficult to tell whether it is a natural polymorphism or a disease-causing variant. For these variants, there may not be enough scientific

research to confirm or refute a disease association or the research may be conflicting. An uninformative result cannot confirm or rule out a specific diagnosis, and it cannot indicate whether a person has an increased risk of developing a disorder. In some cases, testing other affected and unaffected family members can help clarify this type of result.

While many more genetic variants can be identified with whole exome and whole genome sequencing than with select gene sequencing, the significance of much of this information is unknown. Because not all genetic changes affect health, it is difficult to know whether identified variants are involved in the condition of interest. **Secondary findings** are a part of the analysis performed but are not related to the reason the test was performed in the first place (National Society of Genetic Counsellors, 2023). **Incidental findings** are also unrelated to the initial reason for testing but are detected unexpectedly (National Society of Genetic Counsellors, 2023).

## Concept in Action

**Watch this very brief video – Let's talk about incidental findings (3 mins) on Vimeo (https://vimeo.com/451880672)**

In 2013, then again in 2017 and 2021, the American College of Medical Genetics and Genomics (ACMG) recommended that all labs performing whole exome and whole genome sequencing tests report particular secondary findings (https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/), in addition to any variants that are found related to the primary purpose of the testing. In the 2021 updated recommendations, ACMG proposed a list of 81 genes that are associated with a variety of conditions, from cancer to heart disease. The 81 genes for which secondary findings are reported were chosen because they are associated with conditions that have a definable set of clinical features, the possibility of early diagnosis, a reliable clinical genetic test, and effective intervention or treatment. The goal of reporting these secondary findings to an individual is to provide medical benefit by preventing or better managing health conditions. The variants that are reported are known to cause disease. Variants of unknown significance, whose involvement in disease at the current time is unclear, are not reported.

The information provided by secondary findings can be very important because it may help prevent a disease from occurring or guide the management of signs and symptoms if the disease develops or is already present. However, as with any type of medical diagnosis, the news of an unexpected potential health problem may lead to additional health costs and stress for individuals and their families. On the basis of secondary findings, additional testing to confirm results, ongoing screening tests, or preventive care may be advised. Individuals receiving whole exome or whole genome sequencing can choose to "opt out" of analysis of the 81 secondary finding genes and not receive variant results. As whole exome and whole genome sequencing

become more common, it is important for individuals to understand what type of information they may learn and how it can impact their medical care.

## Nursing Implications

Nurses play a pivotal role in supporting patients undergoing genetic testing by providing comprehensive patient education, facilitating informed consent, and fostering shared decision-making. They ensure patients understand the purpose, potential outcomes, and implications of genetic tests, addressing emotional and ethical considerations. Nurses guide patients in evaluating options and preparing for the results, promoting autonomy and informed choices. They collaborate closely with genetic counselors and geneticists, referring patients for specialized consultations when necessary to enhance care quality and optimize health outcomes. This interdisciplinary approach ensures patients receive holistic, informed, and compassionate care throughout the genetic testing process. Nurses need to be aware of the scope, responsibilities, and accountabilities of other members of the genomics healthcare team so they can appropriately refer patients (CDC, 2024).

## The Role of Genetic Counselors

The National Society of Genetic Counselors (National Society of Genetic Counsellors, 2023) recommend individuals have counseling before obtaining genetic testing to plan how results will be returned, including secondary or incidental findings. Genetic counseling before genetic testing can help decide who is the right person in a family to get a genetic test and can help ensure the right tests are ordered. Genetic counseling after genetic testing can help patient's understand their results. Large-scale genetic tests can have findings unrelated to why the test was ordered in the first place.

## Attribution & References

Except where otherwise noted, content on this page is adapted from Do all gene variants affect health and development? , What do the results of genetic tests mean? , What are whole exome sequencing and whole genome sequencing? and What are secondary findings from genetic testing? In *Help Me Understand Genetics* by MedlinePlus, Public Domain

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# 8.5 UNIT SUMMARY AND REVIEW

## Key Takeaways

Genetic testing analyzes DNA, genes, chromosomes, or proteins to identify changes associated with health conditions. It serves various purposes, including predicting disease risk, identifying carriers of genetic conditions, diagnosing disorders, guiding treatment decisions, and informing research. Examples include newborn screening, prenatal testing, carrier screening, pharmacogenomic testing, and diagnostic tests. The benefits include reducing uncertainty about health risks, guiding preventive measures, and aiding treatment planning. However, testing has limitations, such as emotional, financial, and social implications, potential discrimination, and gaps in actionable treatments for identified disorders. Nurses play a critical role in patient education, informed decision-making, and coordination with genetic counsellors.

Genomic testing is becoming more accessible and integrated into primary care, yet its complexity raises challenges, particularly around interpreting results. Canadian laboratories typically classify genomic variants into five categories—pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign—using guidelines like those from the American College of Medical Genetics and Genomics (ACMG). Misinterpreting results can lead to unnecessary follow-up, improper clinical management, or false reassurance. Secondary findings, unrelated to the primary reason for testing but may provide actionable health insights, are increasingly reported in whole exome and genome sequencing. However, they can also pose ethical and emotional challenges. Pre- and post-test counselling is essential to help individuals understand the implications of these findings and plan for their medical care.

## Resource

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## Additional Optional Readings

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2. Smith L. P. (2019). The spectrum of genetic testing. Seminars in Oncology Nursing, 35(1), 11–21. https://doi.org/10.1016/j.soncn.2018.12.008

# Attribution & References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

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# UNIT 9 - PHARMACOGENOMICS

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 9 Contents


- 9.1 Unit Overview
- 9.2 Pharmacogenomics Overview
- 9.3 Genomic Variation in Drug Response
- 9.4 Personalized Drug Therapy
- 9.5 Limitations of Pharmacogenomic Testing
- 9.6 Unit Summary and Review


## Attribution

# 9.1 UNIT OVERVIEW

## Learning Objectives

- Describe how genetic differences influence drug responses.
- Explain the clinical significance of pharmacogenomic testing.
- Explore resources to aid in translating genetic test results into actionable decisions.
- Connect genomic data to real-world applications in drug therapy.
- Describe the limitations of pharmacogenomic testing.

## Outline

Topics covered in this chapter include:

- Pharmacogenomics overview
- Genomic variation in drug response
- Personalized drug therapy
- Limitations of pharmacogenomic testing

## Competencies Nurses will Develop in this Chapter

### ANA (2023):

#### Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential

environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).

### Identification:

- Identifies credible, accurate, appropriate, and current genomic information, resources, services, and technologies specific to given clients.

### Provision of education, care, and support:

- Performs interventions appropriate to clients' genomic health care needs.

## NHS (2023):

### Identify individuals who might benefit from genomic services and information as part of assessing needs and planning care:

- recognizing the critical indicators of a potential genetic condition or clinical situation where genomics-informed healthcare would be appropriate.

### Demonstrate knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

### Apply knowledge, understanding and context of genomic testing and information to underpin care and support for individuals and families before, during and following decision-making:

- including types, uses and limitations of genomic tests to prevent, predict or treat a health condition, and an awareness of the processes for testing and return of results

### Obtain and communicate reliable, current information about genomics for self, patients, families and colleagues:

- using information technologies and other information sources effectively to do so; and
- applying critical appraisal skills to assess the quality of information accessed.

## Key terminology

### Haplotype

A combination of multiple nucleotide changes within a particular gene. Please note that this term can have other meanings.

### Pharmacogenomics

The study of how variation across the genome influences drug response. This term is often used interchangeably with pharmacogenetics or abbreviated to "PGx."

### Star allele

A method of labeling haplotypes in genes (e.g. *2, *3 etc.). Star allele definitions can be found at PharmVar.

# Attribution & References



Except where otherwise noted, this page is adapted from:

- Pharmacogenomics Glossary by PharmGKB, CC BY-SA 4.0

## References

American Nurses Association (ANA). (2023). *Essentials of genomic nursing: Competencies and outcome indicators* (3rd ed.). https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/

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# 9.2 PHARMACOGENOMICS OVERVIEW

## Understanding Pharmacogenomics

The sequence of one's genome can determine how they respond to certain medications? Understanding **pharmacogenomics**, or tailoring a person's medications based on their genome, is only possible by sequencing the genomes of many people and comparing their responses to medicines.

Recall from pharmacology classes that in order for the human body to use some medicines properly (pharmacodynamics), the drug must be distributed to the tissues where it will exert its action and metabolized into an active form. If we want to ensure this happens, it makes sense to target the pathways of our bodies that involve changing the medicine's form or getting medication to the right places. For example, you probably know someone who takes an antidepressant. Many of these medicines get to the right places by interacting with a protein called ABCB1 (http://www.genecards.org/cgi-bin/carddisp.pl?gene=ABCB1), which works like a traffic cop outside your cells. In this analogy, the "traffic" is the movement of drugs into, within, and out of cells, and their distribution to target tissues. This represents the pharmacokinetics (ADME). ABCB1 is a transporter protein that regulates the flow of certain drugs across cell membranes.

Given ABCB1's important role in controlling traffic, you might imagine that if someone has a genomic variant that changes the shape or function of their ABCB1 protein, they might have a different response than usual to any number of medicines. We now know that is the case for some antidepressants, as well as other medications (https://www.pharmgkb.org/gene/PA267/clinicalAnnotation) like statins for cholesterol and certain chemotherapy medicines. As a result, at least 18 pharmacogenomic tests for variants in *ABCB1* are listed in the NIH's Genetic Test Registry (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5243%5Bgeneid%5D), suggesting that you be tested for these variants to help determine the correct dose for certain medications.

### Concept in Action

**Concept in Action (text version)**
**Watch Pharmacogenomics: The Right Drug, for the Right Patient, at the Right Dose (2 mins) on YouTube (https://youtu.be/WSf6vyP11aQ) for an overview of how pharmacogenomics helps to tailor drug treatments.**

**Watch Introduction to Pharmacogenomics (10 mins) on YouTube (https://youtu.be/**

**lM7j1v5PInc) from the Pharmacogenomics Knowledgebase (PharmGKB), an NIH-funded resource.**

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# 9.3 GENOMIC VARIATION IN DRUG RESPONSE

Genetic variation affects whether a patient reacts badly to a medicine or how well a patient responds to a medicine by changing a drug's pharmacokinetics (https://www.pharmgkb.org/page/glossary#pharmacokinetics) and pharmacodynamics (https://www.pharmgkb.org/page/glossary#pharmacodynamics). Genetic variation in genes encoding proteins involved in a drug's pharmacokinetics can alter how a drug is metabolized. If a drug is metabolized too quickly, it might be less effective. Alternatively, if the drug is metabolized too slowly, it may build up in the body and cause dangerous side effects.

Genes involved in a drug's pharmacodynamics can encode proteins that the drug may need to bind to to affect the body. Genetic variation can change the structure of a protein, affecting how well the drug binds to the protein. This can change how well the drug works.

Below, find out more about how variation in different types of genes can affect pharmacokinetics and pharmacodynamics:

## Drug transporters

Transporters move molecules in and out of cells. Variation in genes encoding drug transporters can affect their function, changing how well drugs can enter or exit cells and increasing or decreasing drug concentrations in different body parts. If the concentration of the drug at the site of action is too low, the drug may not work as well. If the drug concentration becomes too high, it could cause toxic side effects.

Examples on PharmGKB: *SLCO1B1, (https://www.pharmgkb.org/gene/PA134865839) ABCB1 (https://www.pharmgkb.org/gene/PA267), ABCG2 (https://www.pharmgkb.org/gene/PA390)*

## Drug metabolizing enzymes

Variations in drug-metabolizing enzymes can affect how quickly a drug is broken down in the body. This can have different effects depending on the specific drug. If an active drug is metabolized too quickly, it will be inactivated too quickly and may not work well. If it is metabolized too slowly, toxic concentrations of the

drug might build up. Alternatively, some drugs have to be metabolized to become active. For medications like these, being metabolized too quickly increases the concentrations of active molecules in the body and increases the risk of toxic side effects while being metabolized too slowly can reduce how effective the drug is.

Examples on PharmGKB: *CYP2C9 (https://www.pharmgkb.org/gene/PA126), CYP2D6 (https://www.pharmgkb.org/gene/PA128), CYP2C19 (https://www.pharmgkb.org/gene/PA124), CYP3A5 (https://www.pharmgkb.org/gene/PA131), TPMT (https://www.pharmgkb.org/gene/PA356), UGT1A1 (https://www.pharmgkb.org/gene/PA420)*

## Human leukocyte antigen (HLA) genes

HLA proteins form part of your immune system. Some HLA alleles are associated with an increased risk for an allergic response to certain medications, which can result in severe skin reactions such as Stevens-Johnson syndrome (SJS) (https://www.pharmgkb.org/disease/PA445738) or toxic epidermal necrolysis (TEN) (https://www.pharmgkb.org/disease/PA444059).

Examples on PharmGKB: *HLA-A (https://www.pharmgkb.org/gene/PA35055), HLA-B (https://www.pharmgkb.org/gene/PA35056)*

## Drug targets

Variations in genes coding for proteins which are drug targets can affect how well a drug works by altering the amount of the target protein in the body or by preventing the drug from being able to bind to the protein. For example, the anti-coagulant drug warfarin prevents the vitamin K recycling needed for blood clotting. Warfarin does this by blocking the protein that controls the recycling (VKORC1). Genetic variation that increases or decreases the amount of VKORC1 can affect the dose of warfarin needed to prevent blood clotting.

Examples on PharmGKB: *VKORC1 (https://www.pharmgkb.org/gene/PA133787052), CFTR (https://www.pharmgkb.org/gene/PA109)*

Most work in pharmacogenomics focuses on variation in DNA that is passed down through your family

(germline variation (https://www.pharmgkb.org/page/glossary#germline-variation)). However, somatic variation is also important within pharmacogenomics. Somatic variations are genetic changes that arise spontaneously within cells but are only passed on to other cells and are not passed on to children. Somatic variation is involved in the development of cancer, and some anticancer drugs target specific somatic variations to try to treat the cancer.

### Concept in Action

Review this module, Making SNPs Make Sense, (https://learn.genetics.utah.edu/content/precision/snips/) to learn how single nucleotide polymorphisms (SNPs), which we learned about in an earlier unit, related to pharmacogenomics.

### Read

Saunders, H., Harris, D., & Chirilă, R. M. (2020). Pharmacogenomics: introduction and use in clinical practice. *Romanian Journal of Internal Medicine*, *58*(2), 69-74. https://doi.org/10.2478/rjim-2020-0001

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## References

Whirl-Carrillo, M., Huddart, R., Gong, L., Sangkuhl, K., Thorn, C. F., Whaley, R., & Klein, T. E. (2021). An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. *Clinical Pharmacology and Therapeutics.* https://doi.org/10.1002/cpt.2350

# 9.4 PERSONALIZED DRUG THERAPY

## Clinical Implications of Pharmacogenomics

### What is CPIC®?

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) (http://www.ncbi.nlm.nih.gov/pubmed/?term=21270786)is an international consortium of individual volunteers and a small dedicated staff interested in facilitating pharmacogenetic test use for patient care.

One barrier to implementing pharmacogenetic testing in the clinic is translating genetic laboratory test results into actionable prescribing decisions for affected drugs.

CPIC® aims to address this barrier to the clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines (visit their website to view all CPIC® publications (https://cpicpgx.org/publications/)). CPIC® guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology (https://www.ncbi.nlm.nih.gov/pubmed/27441996), are peer-reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics (http://www.nature.com/clpt/index.html)) with simultaneous posting to cpicpgx.org, where they are regularly updated.

CPIC® started as a shared project between PharmGKB (https://www.pharmgkb.org/) and the Pharmacogenomics Research Network (PGRN) (http://www.pgrn.org/)in 2009. CPIC® guidelines are indexed in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) as clinical guidelines, endorsed (https://cpicpgx.org/endorsements/) by ASHP (https://www.ashp.org/Pharmacy-Practice/Policy-Positions-and-Guidelines/Browse-by-Document-Type/Endorsed-Documents) and ASCPT (https://www.ascpt.org/Resources/Knowledge-Center/Tools-and-resources), and referenced in ClinGen (https://www.clinicalgenome.org/) and PharmGKB (http://www.pharmgkb.org/).

## Guidelines

**Figure 9.1** Pills. Photo by Myriam Zilles, Unsplash license

CPIC (https://cpicpgx.org/)® (http://www.ncbi.nlm.nih.gov/pubmed/?term=21270786) guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A fundamental assumption underlying the CPIC® guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. Several professional societies have endorsed CPIC®'s guidelines, processes and projects.

Each CPIC® guideline adheres to a standard format and includes a standard system for grading levels of evidence linking genotypes to phenotypes (https://cpicpgx.org/levels-of-evidence/), how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation (https://cpicpgx.org/strength-of-recommendations/).

### Exploring CPIC® Guidelines

Visit the CPIC® Guidelines website (https://cpicpgx.org/guidelines/). Under the *Drugs* column, select a drug you provide frequently in clinical practice and explore the associated genes and guidelines. For example, the *CYP2D6* gene is common in several medication pathways, including those for opioids, SSRIs, TCAs, beta-blockers, and more. Variants in this gene can significantly impact how individuals metabolize many medications.

The PharmGKB YouTube channel (https://www.youtube.com/@PharmgkbOrg) has brief videos summarizing CPIC® guidelines for various drugs and genes.

# Examples of Pharmacogenomics in Clinical Practice

## Avoiding adverse drug effects

Healthcare professionals and researchers constantly seek to optimize medical treatments and avoid adverse reactions to treatments, which are estimated to affect between 7 percent and 14 percent of hospitalized patients. This makes adverse reactions a significant cause of added days (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm#ADRs:%20Prevalence%20and%20Incidence) spent in a hospital and the fourth leading cause of death in the United States.

## Stevens-Johnson syndrome

One example of such an adverse reaction is Stevens-Johnson syndrome (SJS), a severe allergic reaction also called "scalded skin syndrome." It can be caused by infections and very common medications like ibuprofen, anti-seizure medicines, or antibiotics. Patients may go from taking two pain pills to ending up in the hospital burn unit fighting for their lives (http://www.nbcnews.com/id/42501090/ns/health-health_care/t/worst-side-effect-youve-never-heard/) if SJS progresses to a worse condition called toxic epidermal necrolysis (TEN). TEN is diagnosed when patients shed at least one-third of their skin off their bodies. Needless to say, anything we can do to prevent this allergic reaction is vitally important.

In Taiwan, married scientists Wen-Hung Chung (a physician) and Shuen-Iu Hung (an immunologist) noticed that SJS/TEN was much more common in patients taking carbamazepine, used to treat epilepsy and seizures, or allopurinol, used to treat gout. They showed that this was due to genomic variants in the *HLA-B* gene (https://ghr.nlm.nih.gov/condition/stevens-johnson-syndrome-toxic-epidermal-necrolysis#genes). Not surprisingly, this gene helps control the immune response. As a result of their work, the country of Thailand has implemented genomic testing (https://www.theatlantic.com/science/archive/2015/10/south-east-asia-genetic-disorder-stevens-johnson-syndrome/408736/) before these medications are prescribed. The results of this "pharmacogenomic test" are used to decide whether it is safe to give a specific patient certain medicines, like carbamazepine or allopurinol. Thailand's government even covers the cost of this testing, and the frequency of SJS/TEN has been drastically reduced. We have since learned that different ancestries are associated with different *HLA-B* genomic variants, so countries may need different approaches (https://www.genome.gov/27560487/research-directions-in-geneticallymediated-stevensjohnson-syndrometoxic-epidermal-necrolysis//research-directions-in-geneticallymediated-stevensjohnson-syndrometoxic-epidermal-necrolysis/) to monitor which medications are most likely to be linked to SJS/TEN.

### Concept in Action

**Watch Pharmacogenomic Testing – Karen's story (3 mins) on YouTube (https://youtu.be/TVZVehYWLYw) for a personal story of Karen's experience with SJS.**

## Mercaptopurine

Although the field is still young, doctors already use pharmacogenomics to treat their patients. Acute lymphoblastic leukemia (ALL) is a type of cancer that mainly affects children and is often treated with the medicine mercaptopurine (https://www.pharmgkb.org/chemical/PA450379).

Children with certain genetic changes in the gene *TPMT* can have a severe reaction to this drug. Doctors will often test for these changes, and if they are present, will give the child a lower dose of mercaptopurine or use a different medicine.

Mercaptopurine belongs to a class of medicines called thiopurines. It is broken down in the body by several proteins, some of which convert mercaptopurine to active molecules that help kill cancer cells. Mercaptopurine is also broken down by a protein called TPMT, encoded for by the *TPMT* gene.

When TMPT breaks down mercaptopurine, it is inactivated. This inactivation prevents dangerous concentrations of active molecules from building up. Changes in the *TPMT* gene, such as the haplotypes *2, *3A or *3C, can reduce or stop the inactivation of mercaptopurine by the TPMT protein. This causes too many active molecules to build up in the body and can lead to a severe decrease in immune system activity, known as myelosuppression. Myelosuppression can be fatal.

Testing for *TPMT* variants is widely available: the Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) provides over 20 laboratories currently offering this test. In Europe, testing before administration of thiopurines is becoming routine clinical practice – a survey in the United Kingdom found that 67% of clinicians ordered a *TPMT* test before prescribing azathioprine, another drug that is broken down by TPMT.

In the United Kingdom, testing for TPMT status is mandatory for children and young adults before treatment on the ALL2011 trial protocol, and the British Association of Dermatologists guidelines for the safe and effective prescribing of azathioprine states that TPMT activity should be checked in all patients before receiving azathioprine. The Clinical Pharmacogenetics Implementation Consortium (CPIC®) has also provided dosing guidance (https://www.pharmgkb.org/guidelineAnnotation/PA166104945) based on the *TPMT* genotype for thiopurines.

## Tamoxifen

We have also learned that a person's genome sequence is not everything regarding

medication responses. The human body is a highly complex machine, and the instructions written in our DNA are just part of the process.

There are some cases, as with the breast cancer treatment tamoxifen, where a small study showed that there might be a relationship between someone's response to the medicine and a variant in the *CYP2D6* gene. However, this finding did not appear true in a larger study involving many more people. That's why, at this time, the U.S. Food and Drug Administration (FDA) labelling for tamoxifen does not recommend *CYP2D6* pharmacogenomic testing. However, the issue is still being reviewed (https://www.ncbi.nlm.nih.gov/books/NBK247013/) as more research is conducted.

Another gene in the same *CYP* family, called *CYP2C19*, has variations which affect how your body can use clopidogrel (https://www.pharmgkb.org/chemical/PA449053) (more commonly known as Plavix), an anticoagulant to prevent blood clots, and thus reduce the risk of stroke heart attack. If an individual has a variant causing malfunction of the *CYP2C19* protein, they cannot process clopidogrel (http://mayoresearch.mayo.edu/center-for-individualized-medicine/cyp2c19-clopidogrel.asp) and either require a different dose or a different medication. As it turns out, these variants in *CYP2C19* are also more common in those with Asian ancestry. Testing for variants in this gene is also not routinely recommended. However, individuals may wish to speak with their healthcare provider about the test if clopidogrel is prescribed, particularly if they have East Asian family members.

## Pharmacokinetic and Pharmacodynamic Pathways

The PharmGKB website has excellent resources for examining the pharmacokinetic and pharmacodynamic pathways of various drugs and their pharmacogenomic associations. Below is an example of two commonly prescribed medications, Amitriptyline and Nortriptyline. Search the PharmGKB Pathways (https://www.pharmgkb.org/pathways) for other drugs of interest. For example, returning to our aminoglycoside ototoxicity example from an earlier unit, review the pathway and pharmacogenomic implications. (https://www.pharmgkb.org/pathway/PA166254101)

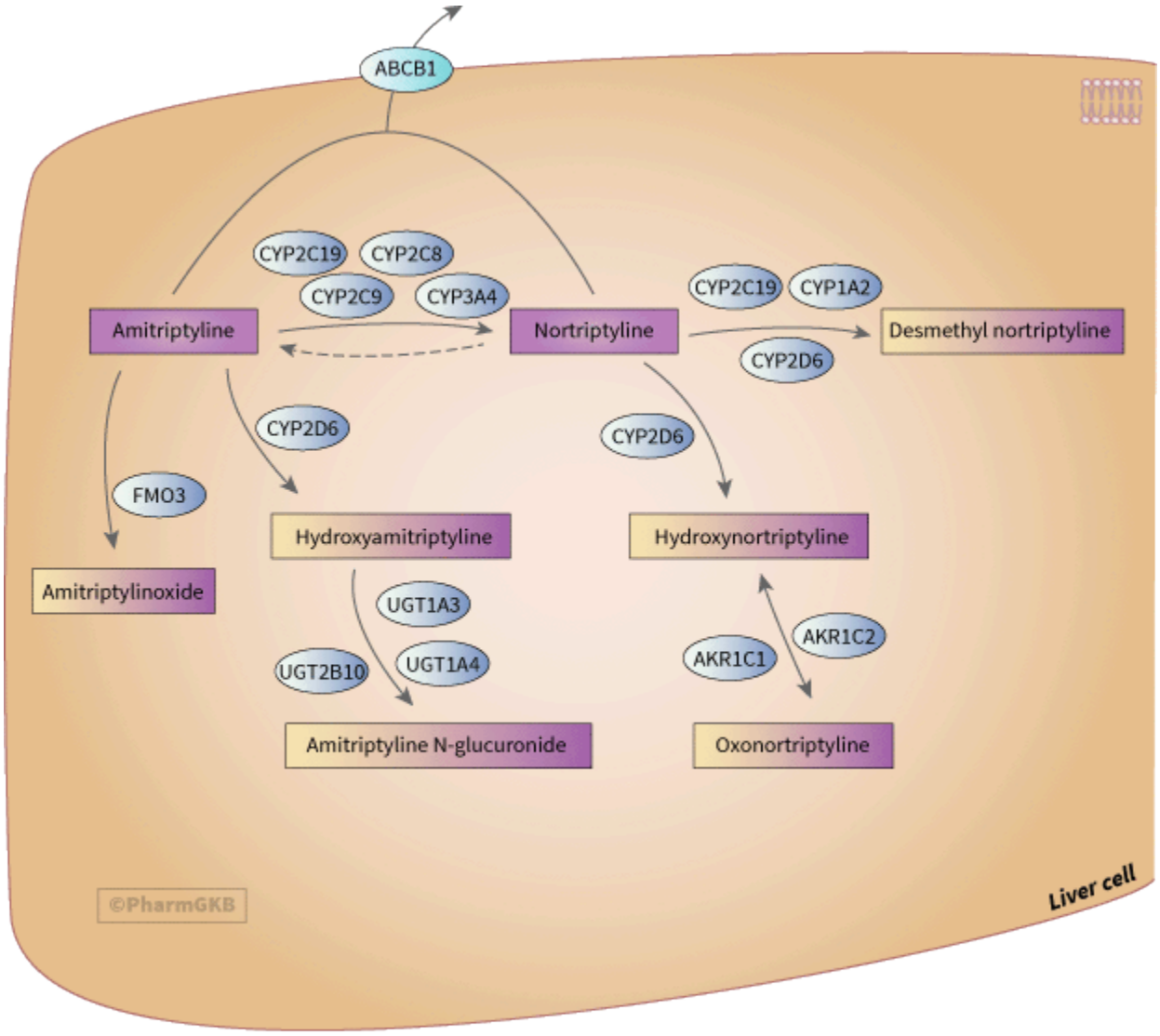


**Figure 9.2** Representation of the candidate genes involved in the metabolism of amitriptyline and nortriptyline in the liver. View the diagram legend. **Source:** PharmGKB, CC BY-SA 4.0

## Background

Amitriptyline and nortriptyline are tricyclic antidepressants initially designed for use in the treatment of depression. Amitriptyline is also used to treat various types of pain, such as fibromyalgia and neuropathic pain [Article:15554244 (https://www.pharmgkb.org/pmid/15554244)]. Nortriptyline is a metabolite of amitriptyline and a drug in its own right [Articles:15554244 (https://www.pharmgkb.org/pmid/15554244), 18359012 (https://www.pharmgkb.org/pmid/18359012)]. Both drugs are non-selective monoamine reuptake inhibitors, preventing the reuptake of norepinephrine and serotonin at nerve terminals via interaction with their respective transporters, *SLC6A2 (https://www.pharmgkb.org/gene/PA310)* and *SLC6A4 (https://www.pharmgkb.org/gene/PA312)*, and potentiating the action of these neurotransmitters. Additional effects and side effects occur due to cross-reactivity with opioid, cholinergic

and adrenergic receptors [Articles:8736630 (https://www.pharmgkb.org/pmid/8736630), 10319193 (https://www.pharmgkb.org/pmid/10319193)].

## Metabolism

Amitriptyline and nortriptyline are readily absorbed in the GI tract and subject to extensive hepatic metabolism, with less than 5% of the drug eliminated unchanged (reviewed in [Article:10319193 (https://www.pharmgkb.org/pmid/10319193)]). The main metabolizing enzymes with clinical significance for amitriptyline are *CYP2C19 (https://www.pharmgkb.org/gene/PA124)* and *CYP2D6 (https://www.pharmgkb.org/gene/PA128)* [Articles:23486447 (https://www.pharmgkb.org/pmid/23486447), 27997040 (https://www.pharmgkb.org/pmid/27997040)]. *CYP2C19 (https://www.pharmgkb.org/gene/PA124)* is the primary enzyme responsible for demethylation at physiological concentrations, while *CYP2D6 (https://www.pharmgkb.org/gene/PA128)* carries out hydroxylation to less active metabolites [Articles:15554244 (https://www.pharmgkb.org/pmid/15554244), 18359012 (https://www.pharmgkb.org/pmid/18359012)]. Hydroxynortriptyline is the most abundant metabolite of both amitriptyline and nortriptyline in humans [Article:10319193 (https://www.pharmgkb.org/pmid/10319193)]. There are two enantiomers of hydroxynortriptyline and the E enantiomer is produced at a rate of around 5 times that of the Z enantiomer [Article:10319193 (https://www.pharmgkb.org/pmid/10319193)]. Methylation of nortriptyline to amitriptyline has been reported in vivo in some case studies. A study that examined metabolite and prescription data from an extensive network of medical centers for whom amitriptyline measurements were available found that approximately 15% of patients receiving nortriptyline had significant levels of amitriptyline (above 28ng/ml) despite not having received the parent drug [Article:16553509 (https://www.pharmgkb.org/pmid/16553509)]. The mechanism for methylation was not elucidated.

## Pharmacogenomics

Many studies have examined variations in drug-metabolizing enzymes for their impact on amitriptyline and nortriptyline pharmacokinetics, with most focusing on *CYP2D6 (https://www.pharmgkb.org/gene/PA128)* and *CYP2C19 (https://www.pharmgkb.org/gene/PA124)*. CPIC guidelines are available for both *CYP2D6* and *CYP2C19* and amitriptyline [Article:23486447 (https://www.pharmgkb.org/pmid/23486447)]. Links to individual papers can be found under the PGx Research tab for amitriptyline and nortriptyline and clinical annotation summaries by haplotype under the Clinical PGx tab.

# Attribution & References

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  CPIC guidelines and content are subject to updates and modifications, and users should refer to cpicpgx.org to confirm they are accessing the most current content
- Amitriptyline and Nortriptyline Pathway, Pharmacokinetics by Carolyn F. Thorn, PharmGKB, CC BY-SA 4.0

# 9.5 LIMITATIONS OF PHARMACOGENOMIC TESTING

## Star Allele System

Many key genes in pharmacogenomics use a 'star allele' (https://www.pharmgkb.org/page/glossary#star-allele) system, where a single star allele (e.g. *3) defines a certain combination of one or more genetic variants found together in that allele. You can find many of these definitions on the PharmVar website (https://www.pharmvar.org/). Genes can have many star alleles; the enzyme *CYP2C9 (https://www.pharmgkb.org/gene/PA126)*, for example, has over 60 known star alleles.'

**Figure 9.3** A person shakes pills from a bottle into their hand. **Source:** Photo by Towfiqu barbhuiya, Unsplash license

Pharmacogenomic tests tend to only test for some of the most common star alleles, meaning that rare alleles will not be detected. Additionally, different tests may test for different alleles. For example, one test may test for the presence of the *2, *3, *5, *8 or *11 alleles of *CYP2C9,* while another may only test for *2 or *3.

If a person has a star allele not detected by the pharmacogenomic test, they default to the *1 allele, which is the 'reference' or 'normal' version of the gene. However, this does not mean that the person definitely has the *1 allele, and there is a significant possibility that they may carry a star allele, which could affect drug response, but the pharmacogenomic test does not detect that.

Some pharmacogenomic tests may test for the presence of a certain star allele by only looking for one particular change found in that star allele rather than all the changes which define the star allele. As some changes can be found in several different star alleles of the same gene, this can confuse which allele is actually present.

Finally, as pharmacogenomics research continues, new star alleles are found, while other star alleles may have their function assignment changed (e.g. an 'uncertain function' star allele may be changed to 'decreased function' based on new evidence). PharmVar is regularly updated with new star alleles and their functions as information becomes available.

To learn more about **star alleles**, **watch the video Haplotypes and Star Alleles (8 mins) on YouTube (https://youtu.be/PcmCohIhWUM)**

## Attribution & References

# 9.6 UNIT SUMMARY AND REVIEW

## Key Takeaways

Pharmacogenomics involves tailoring medications based on a person's genome, which influences drug response and susceptibility to adverse effects. This field relies on sequencing the genomes of many individuals to identify genetic variations that affect drug metabolism (pharmacokinetics) and drug-target interactions (pharmacodynamics). Examples include genomic variants that are linked to severe reactions like Stevens-Johnson syndrome. Guidelines from organizations like CPIC facilitate integrating genetic test results into clinical practice to optimize therapy. Challenges include translating test results into actionable recommendations and addressing variations in testing methods and allele detection.

## Additional Optional Readings

1. Bugada, D., Lorini, L. F., Fumagalli, R., & Allegri, M. (2020). Genetics and opioids: Towards more appropriate prescription in cancer pain. Cancers, 12(7), 1951. https://doi.org/10.3390/cancers12071951
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3. Islam, F., Gorbovskaya, I., & Müller, D. J. (2021). Pharmacogenetic/pharmacogenomic tests for treatment prediction in depression. Advances in Experimental Medicine and Biology, 1305, 231–255. https://doi.org/10.1007/978-981-33-6044-0_13
4. Morris, S. A., Alsaidi, A. T., Verbyla, A., Cruz, A., Macfarlane, C., Bauer, J., & Patel, J. N. (2022). Cost effectiveness of pharmacogenetic testing for drugs with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines: A systematic review. *Clinical Pharmacology and Therapeutics*, *112*(6), 1318–1328. https://doi.org/10.1002/cpt.2754

5. Schuh, M. J., Randles, H., & Crosby, S. (2020). Improving pain management with pharmacogenomics: A general introduction. Journal of Pain & Palliative Care Pharmacotherapy, 34(3), 114–119. https://doi.org/10.1080/15360288.2020.1734140
6. Stocco, G., Lucafò, M., & Decorti, G. (2020). Pharmacogenomics of antibiotics. International Journal of Molecular Sciences, 21(17). https://doi.org/10.3390/ijms21175975

## Attribution and References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

## References

ChatGPT: OpenAI. (2024). *ChatGPT (Version 4.0)* [Large language model]. https://openai.com

# UNIT 10 - ETHICAL, LEGAL, AND SOCIAL ISSUES ARISING FROM GENOMICS

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 10 Contents


- 10.1 Unit Overview
- 10.2 Genetic Discrimination
- 10.3 Eugenics and Scientific Racism
- 10.4 Use of Population Descriptors in Genomics
- 10.5 Nursing Implications
- 10.6 Unit Summary and Review


## Attribution

# 10.1 UNIT OVERVIEW

## Learning Objectives

- Critically assess some of the ethical, legal, and social implications of genomics.
- Evaluate the historical context and origins of eugenics and scientific racism and relate this to contemporary healthcare practices and policies.
- Distinguish between race, ethnicity, and genetic ancestry as applied in biomedical contexts.
- Examine how historical misuse of population descriptors has contributed to health disparities and reinforced inequities in healthcare and genomic research.

## Outline

Topics covered in this chapter include:

- Genetic discrimination
- Eugenics
- Scientific racism
- Population descriptors
- Nursing implications

## Competencies Nurses will Develop in this Chapter

### ANA (2023):

#### Identification:

- Identifies ethical, ethnic or ancestral, cultural, religious, legal, fiscal, and societal issues related to genomic

information and technologies.
- Recognizes issues that undermine the rights of all clients for autonomous, informed genomic-related decision-making and voluntary action.

### Provision of education, care, and support:

- Advocates for autonomous, informed genomic-related decision-making.
- Demonstrates in practice the importance of tailoring genomic information and services that are responsive to the unique attributes of every person.

## NHS (2023):

### Demonstrate effective communication in tailoring genomic information and services to the individual:

- recognizing factors (such as ethnicity, culture, religion, ethical values, developmental stage or language) that may influence the individual's ability to use information and services.

### Advocate for the rights of all individuals to make informed decisions and act voluntarily:

- understanding the importance of delivering genomic information and counselling fairly, accurately and without coercion or personal bias, to facilitate decision-making and manage expectations;
- recognizing that your values and the values of others may influence the care and support provided during decision-making, and that choices and actions may change over time;
- ensuring that the consent process is person centered; and
- promoting and supporting equitable access to genomic services.

### Apply knowledge, understanding and context of genomic testing and information to underpin care and support for individuals and families prior to, during and following decision-making:

- incorporating awareness of the ethical, legal and social issues related to testing, recording, sharing and storage of genomic information and data; and
- incorporating awareness of the potential physical, emotional, psychological and social consequences of genomic information for individuals, family members and communities.

# Key terminology

## Ethnicity

Refers to a group of people with shared language, religion, customs, beliefs, heritage and history, even though such attributes are not always confined to a single ethnic group. Ethnicity may also refer to groups that are considered indigenous to an area. Ethnicity is not a biological characteristic (NHGRI, 2024).

## Eugenics

Eugenics is a discredited belief that selective breeding for certain inherited human traits can improve the "fitness" of future generations. For eugenicists, "fitness" corresponded to a narrow view of humanity and society that developed directly from the ideologies and practices of racism, colonialism, ableism and imperialism.

## Genetic ancestry

Genetic ancestry refers to information about the people that an individual is biologically descended from, including their genetic relationships. Genetic information can be combined with historical information to infer where an individual's distant ancestors lived.

## Genealogical ancestry

An individuals family origins and ancestral history established through records, family trees, and other forms of documentation tracing lineage and relationships (NHGRI, 2024, para. 10).

## Population descriptors

Population descriptors are ways of describing or distinguishing people from each other based on perceived or actual differences. They capture the various ways in which people can differ from one another. A wide variety of population descriptors are used to describe groups of people in research, healthcare or society. Examples of population descriptors include race, ethnicity, genealogical ancestry, genetic ancestry, Indigenous, primary language spoken, nationality, geographic origin, sex at birth, gender identity, disability status and age. Each population descriptor captures a different aspect of a group or individual. One population descriptor is not enough to fully describe or distinguish any

individual or group. Depending on the situation, some population descriptors may be more relevant than others (NHGRI, 2024).

### Race

Race is a social construct used to group people. Race was constructed as a hierarchal human-grouping system, generating racial classifications to identify, distinguish and marginalize some groups across nations, regions and the world. Race divides human populations into groups often based on physical appearance, social factors and cultural backgrounds.

### Reference populations

To determine genetic ancestry, researchers compare DNA variants in an individual to the frequency of those DNA variants in reference populations – groups of people from around the world who have provided samples of their DNA (NHGRI, 2024. para. 13).

### Scientific racism

Scientific racism is the practice of using data derived from pseudoscience to support racial biases and other forms of discrimination. Leading scientists across scientific institutions in the 19th and early 20th centuries were proponents of such ideologies. By the mid-20th century, data derived from pseudo-science were widely disproven. However, evidence shows that the practice of scientific racism persists in science and research.

## Attribution & References



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- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.

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American Nurses Association (ANA). (2023). *Essentials of genomic nursing: Competencies and outcome*

*indicators* (3rd ed.). https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/

National Human Genome Research Institute (NHGRI). (n.d.). *Talking glossary of genetic and genomic terms*. www.genome.gov

National Human Genome Research Institute (NHGRI). (2024, October 24). *Explainer: Use of population descriptors in genomics.* https://www.genome.gov/about-genomics/policy-issues/population-descriptors-in-genomics

# 10.2 GENETIC DISCRIMINATION

## Ethical, Legal and Social issues

There are a multitude of ethical, legal, and social issues arising from genomic-informed healthcare and research. An entire textbook could be devoted to exploring these ethical issues. While some of these topics have been covered in previous units, as noted in the brackets beside each topic, this course cannot encompass all of them. This chapter intends to build on nursing students' previous studies of legal and ethical issues in healthcare. Some of the ethical issues in genomics include:

- Returning genomic results (5.3, 8.4)
- Predictive testing of minors (5.3, 8.2, 12.4)
- Informed consent (5.3)
- Privacy and confidentiality (8.3)
- Individual vs relational autonomy and the right to know (12.3)
- Genetic discrimination (3.3)
- Data sharing and security (5.3, 13.2)
- Biobanking (5.3)
- Concerns about assistive reproductive technologies (8.3, 12.4, 13.2)
- Gene editing (13.2)
- Eugenics and scientific racism (10.3)
- Population descriptors (10.4)

This unit will specifically focus on genetic discrimination, the dark history of genetics and genomics (eugenics), ongoing scientific racism, and the preferred use of population descriptors. The final section will review implications for nursing, particularly in respect to the nursing Code of Ethics, professional and practice standards, and competencies. The lessons from this unit also apply to other healthcare areas beyond genomics and are rooted in the bioethical principles of autonomy, beneficence, non-maleficence, and justice that nurses learn about in their ethics courses. The Tri-council Policy Statement (TCPS2) was reviewed in chapter 5.3. Recall that chapter 13 of the TCPS2 provides guidance on conducting human genetic research and examines ethical issues in genetic research including biobanking, privacy and confidentiality, vulnerable populations (e.g. predictive testing of children), consent, returning genomic test results (e.g. incidental and secondary findings), and gene transfer.

# Genetic Discrimination

Chapter 3.3 briefly explored how everyday discrimination happens through genetic discourse. The assigned reading for that chapter reviewed the problematic concepts of genetic determinism, essentialism, and reductionism which, when misunderstood or misused, can exacerbate health disparities and perpetuate prejudice. These concepts underlie scientific racism and eugenics due to the misbelief that certain people are advantaged over others due to their 'genetic endowment' or 'good genes'.

In certain cases, genetic information may be misused in ways that impact access to employment, goods, and services. In chapter 8.2, it was mentioned that the possibility of genetic discrimination in employment or insurance is a concern of genetic testing. An example of institutional genetic discrimination is when employers or insurance companies treat people differently based on genetic information that shows a predisposition to an inherited disorder. There are many other forms of individual genetic discrimination. For example, knowledge about carrier status for sickle cell trait is used to select or reject partners for marriage and childbearing. This can make those who carry the trait feel less-than, particularly in cultures where marriage is linked to social status. Fear of discrimination is a common concern among people considering genetic testing" (MedlinePlus, n.d.).

In 2017, parliament passed the Genetic Non-Discrimination Act (GNDA) into law to prevent institutional discrimination based on genetic test results by employers or insurance agencies. Under the GNDA, companies cannot require genetic testing or deny services based on a refusal to obtain testing (Canadian Civil Liberties Association, 2018). Furthermore, a person's genetic test results cannot be collected, used, or disclosed without written consent (Canadian Civil Liberties Association, 2018).

The protections afforded by the act protect individuals being denied goods and services, such as obtaining life or health insurance or entering into contracts, such as employment, based on genetic test results. The complete legislation can be viewed here (https://laws-lois.justice.gc.ca/eng/acts/g-2.5/page-1.html). Nurses should be familiar with the legislation, as patients pursuing genetic testing will likely have questions about what happens to their genetic data, who can access it, and how it can be used. Alaire et al. (2021) found that many Canadian women lacked knowledge or were misinformed about the scope and content of the GNDA, with an average rate of 50.94% correct responses to their questionnaire. Dalpé et al. (2021) analyzed online discussion posts about the GNDA and found that in the forum about fears around the GNDA, 69% of the posts related to avoiding genetic testing.

Several countries have their own form of protection against genetic discrimination and Canada's GNDA is one of the strongest, as it is enforced under the criminal code. Penalties for violation can include fines of up to $1 million dollars or five years imprisonment (Genetic Non-discrimination Act, 2017). However, there is some validity to concerns as there is evidence that some insurance companies have attempted to find loopholes in the legislation (Fernando et al., 2024). The GNDA is not all encompassing and, as genomic sciences advances, the limited frame used by the GNDA to define genetic testing will need to be amended to be more inclusive of other forms of genetic data.

### Read

A news brief on a McGill study (https://www.mcgill.ca/newsroom/channels/news/mcgill-study-finds-some-canadians-may-still-be-risk-genetic-discrimination-despite-new-federal-law-355104) that exposes the ongoing risks of discrimination that are not protected by the GNDA

## Attribution & References

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- Genetic Discrimination section written by Andrea Gretchev, CC BY-NC 4.0

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# 10.3 EUGENICS AND SCIENTIFIC RACISM

## Trigger Warning:

This chapter contains material that may be upsetting or distressing. Contents may include discussion of traumatic experiences related to mental or physical disability, genocide, slavery, and racism.

## Eugenics and Scientific Racism

Genetics has an ugly past – Eugenics. Eugenics is an inaccurate theory linked to historical and present-day forms of discrimination, racism, ableism and colonialism. It has persisted in policies and beliefs worldwide, including in Canada. Have we moved on, or are we just finding different ways to manifest the same thinking?

## Hard Language

In the 21st century, we are accustomed to using vocabulary that is sensitive, respectful, and person-centered regarding physical and mental illnesses and challenges. The language used in the 19th and most of the 20th centuries was far more direct and judgmental. These terms enabled 19th and 20th-century reformers to objectify the individuals they were referring to. Understanding that relationship between language and reform is critical to understanding the attraction and authority of movements like eugenics. The language used in the original source material has been adapted to be more respectful.

**Source:** *Canadian History: Post-Confederation*, CC BY 4.0

## The Big Picture:

- Eugenics is the scientifically inaccurate theory that humans can be improved through selective breeding of populations.
- Eugenicists believed in a prejudiced and incorrect understanding of Mendelian genetics that claimed abstract human qualities (e.g., intelligence and social behaviours) were inherited in a simple fashion. Similarly, they believed complex diseases and disorders were solely the outcome of genetic inheritance.
- The implementation of eugenics practices has caused widespread harm, particularly to populations that are being marginalized.
- Eugenics is not a fringe movement. Starting in the late 1800s, leaders and intellectuals worldwide

perpetuated eugenic beliefs and policies based on common racist and xenophobic attitudes. Many of these beliefs and policies still exist.
- The genomics communities continue to work to scientifically debunk eugenic myths and combat modern-day manifestations of eugenics and scientific racism, particularly as they affect Black, Indigenous, and people of colour, people with disabilities, and LGBTQAI2+ individuals.

Visit the NHGRI website – Eugenics: Its Origin and Development (1883-Present) (https://www.genome.gov/about-genomics/educational-resources/timelines/eugenics). Scroll down to the timeline and use the navigation arrows to learn about some of the more predominant historical examples of eugenics.

## What are eugenics and scientific racism?

**Eugenics** is the scientifically erroneous and immoral theory of "racial improvement" and "planned breeding," which gained popularity during the early 20th century. Eugenicists worldwide believed that they could perfect human beings and eliminate so-called social ills through genetics and heredity. They thought the use of methods such as involuntary sterilization, segregation and social exclusion would rid society of individuals deemed by them to be unfit.

Eugenics can be separated into two equally erroneous categories. Negative eugenics is described above (NIH, 2022). Positive eugenics is the encouragement of reproduction among genetically advantaged people (Thomas et al., 2016). It should be noted that the characteristics that were deemed to be more or less desirable were not determined by genes at all. These were entirely social constructs. Associating these beliefs with science distorts the evidence and undermines the credibility and validity of the findings.

**Scientific racism** is a practice that appropriates the methods and legitimacy of science to argue for the superiority of one race over another. Like eugenics, scientific racism grew out of:

- the misappropriation of revolutionary advances in medicine, anatomy and statistics during the 18th and 19th centuries.
- Charles Darwin's theory of evolution through the mechanism of natural selection.
- Gregor Mendel's laws of inheritance.

Eugenic theories and scientific racism drew support from contemporary xenophobia, antisemitism, sexism, colonialism and imperialism, as well as justifications for slavery.

# How did eugenics begin?

## Listen:

Genetics Unzipped is a great podcast that covers a vast array of topics in genomics. Listen to Living with the Eugenic Past: Michele Goodwin (17:36) (https://geneticsunzipped.com/blog/2022/11/27/adelphi-genetics-michele-goodwin?rq=living%20with%20the%20eugenic). This is one of several talks on the subject from the conference titled the same. Michele Goodwin is a Professor of Law at the Centre for Biotechnology, Global Health Policy Director at the University of California Irvine, and a senior lecturer at Harvard Medical School.

“Her talk focused on how the long shadow of eugenics and white supremacy persists into the present day and remains embedded in contemporary political frameworks, and why this pernicious ideology is taking so long to die” (The Genetics Society, 2022).

Galton defined eugenics as "the study of agencies under social control that may improve or impair the racial qualities of future generations either physically or mentally." Galton claimed that health, disease, and social and intellectual characteristics were based upon heredity and the concept of race.

During the 1870s and 1880s, discussions of "human improvement" and the ideology of scientific racism became increasingly common. So-called experts determined individuals and groups to be superior or inferior. They believed biological and behavioural characteristics were fixed and unchangeable, placing individuals, populations and nations inside that hierarchy.

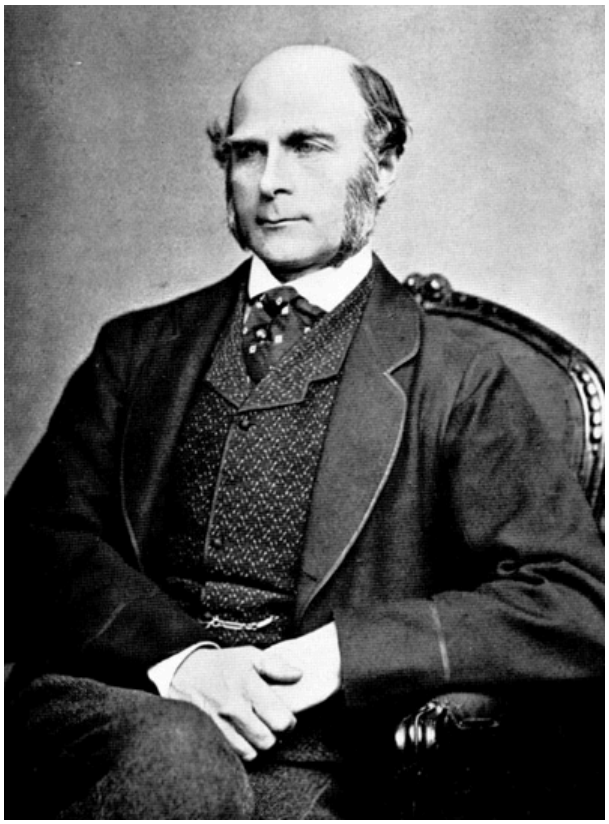

**Figure 10.1** Sir Francis Galton (1822-1911) was a largely self-trained British social scientist, a half-cousin of Charles Darwin, and the figure most readily associated with Eugenics. It is Galton who is credited with coining the dichotomy of nurture vs. nature. **Source:** Francis Galton, 1850s, PDM

## What did eugenics look like across the globe?

By the 1920s, eugenics had become a global movement. There was popular, elite and governmental support for eugenics in Germany, the United States, Great Britain, Italy, Mexico, Canada and other countries. Statisticians, economists, anthropologists, sociologists, social reformers, geneticists, public health officials and members of the general public supported eugenics through various academic and popular literature.

The most well-known application of eugenics occurred in Nazi Germany in the lead-up to World War II and the Holocaust. Nazis in Germany, Austria and other occupied territories euthanized at least 70,000 adults and 5,200 children. They implemented a campaign of forced sterilization that claimed at least 400,000 victims (https://www.ushmm.org/learn/timeline-of-events/1939-1941/euthanasia-killings-continue). This culminated in the near destruction of the Jewish people, as well as an effort to eliminate other marginalized ethnic minorities, such as the Sinti and Roma, individuals with disabilities and LGBTQ+ people.

Slavery and its legacies, fears of "miscegenation, (https://www.britannica.com/topic/miscegenation)" and eugenics were deeply connected in the early 20th century. Prominent American eugenicists expounded on their concerns of "race suicide," or the increasingly differential birthrates between immigrants and non-Nordic races compared to native-born Nordic whites. Eugenicists used these concerns to promote discriminatory policies like anti-immigration and sterilization.

American eugenicists from a variety of disciplines declared specific individuals unfit or anti-social, which resulted in the involuntary sterilization of at least 60,000 people through 30 states' laws by the 1970s.

These eugenicists disproportionately targeted non-white people, particularly those with lower socio-economic status, and people with disabilities during the entirety of the 20th century. Eugenicists were also crucial to the enactment of discriminatory immigration legislation that was passed in 1924 (the Johnson-Reed Act), which completely excluded immigrants from Asia.

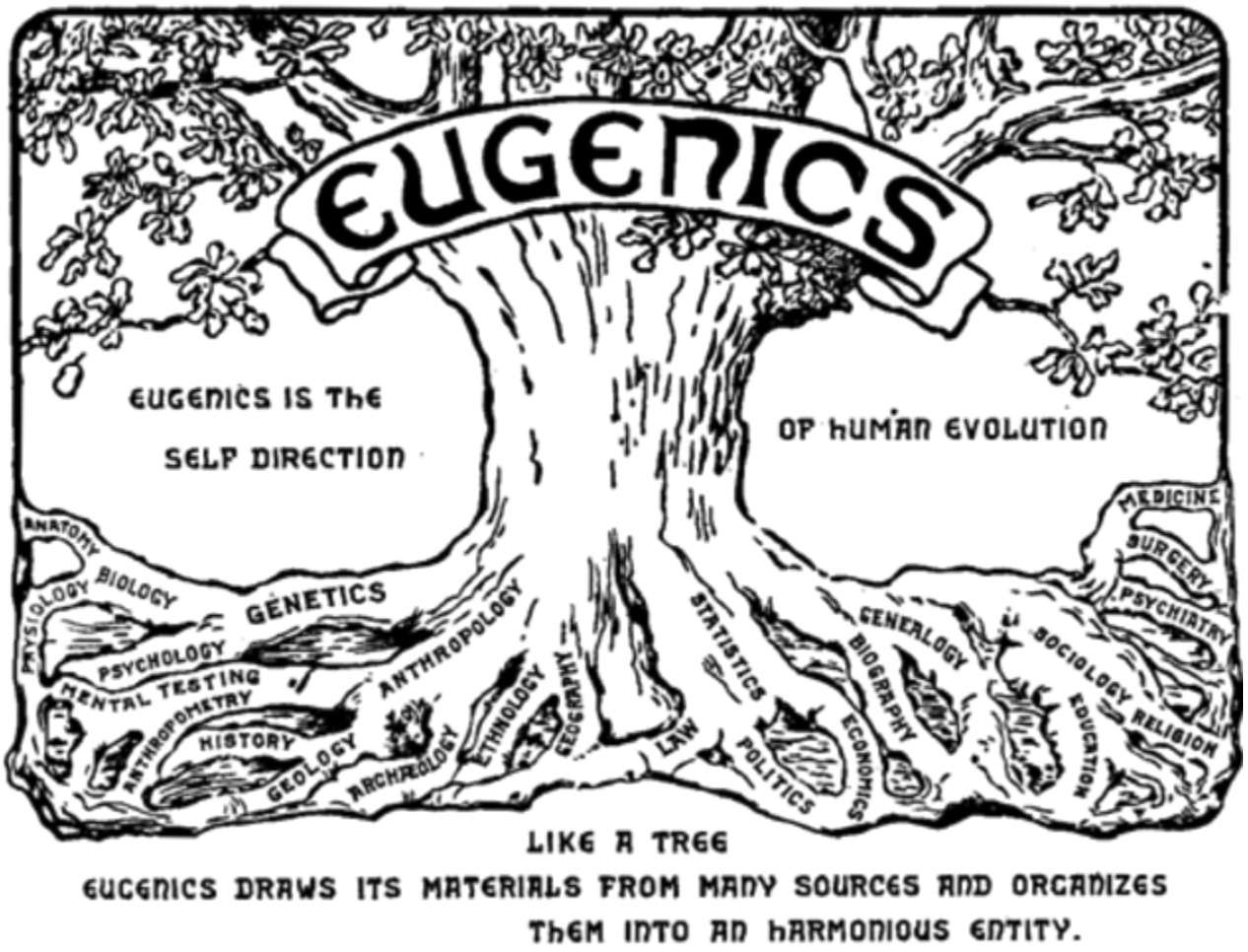


**Figure 10.2** Eugenics Congress logo shows a tree, with the label "Eugenics" across the trunk just before the branches extend out. Label stats that "Eugenics is the self direction of human evolution" and the roots of the tree are labeled with many different areas of study, including biology, genetics, statistics, sociology, etc.. **Source**: Image in the PDM scanned from Harry H. Laughlin, *The Second International Exhibition of Eugenics held September 22 to October 22, 1921, in connection with the Second International Congress of Eugenics in the American Museum of Natural History, New York* (Baltimore: William & Wilkins Co., 1923).


**Figure 10.3** American Eugenics Society photograph of Eugenics Building, Fitter Families Contest, Kansas Free Fair. Staff of Fitter Families Contest, Kansas Free Fair. **Source:** Photo by unknown, courtesy of American Philosophical Society Library (https://diglib.amphilsoc.org/islandora/object/graphics%3A1660), PDM.

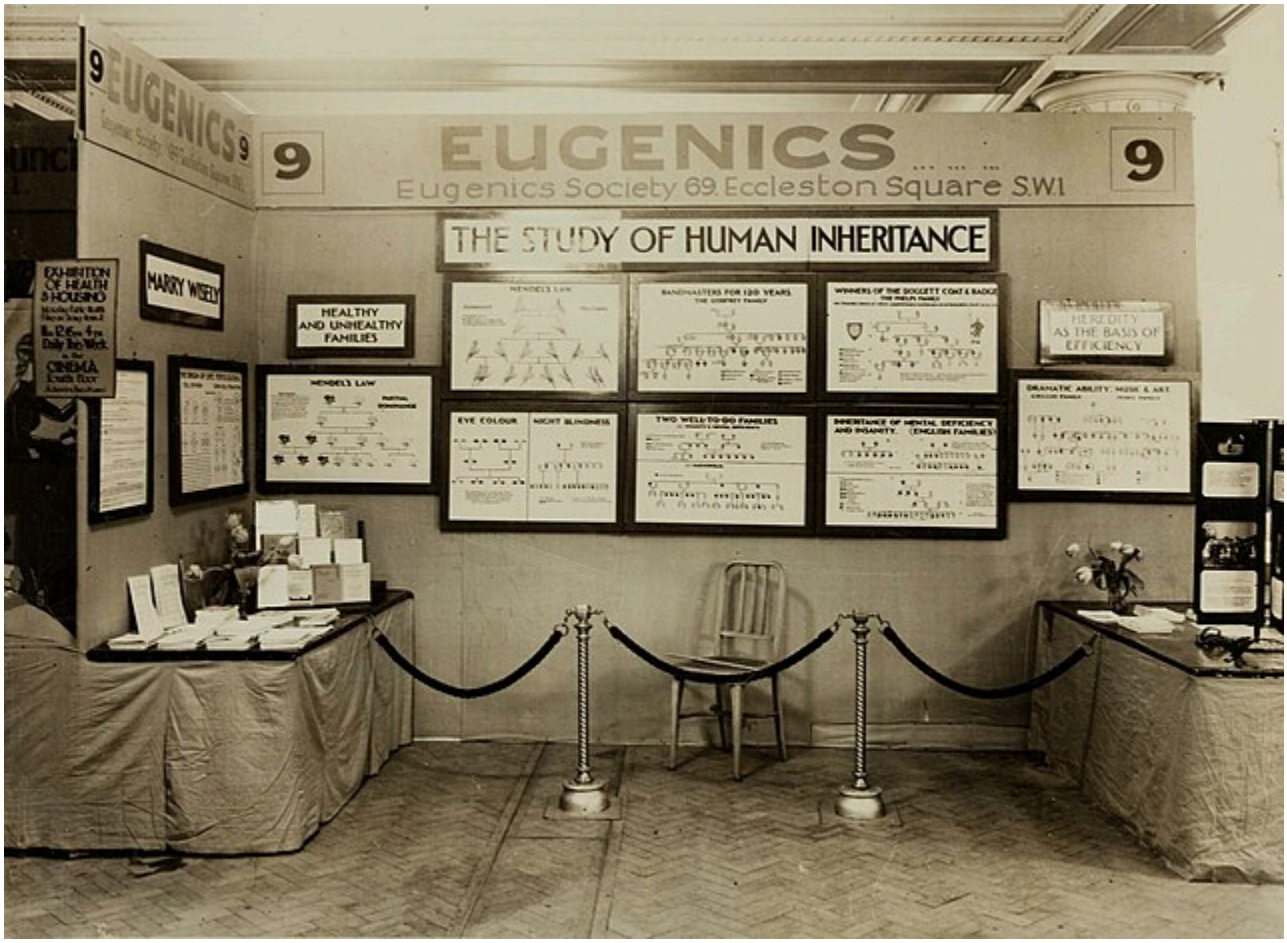


**Figure 10.4** Eugenics Society Exhibit. Image from the Wellcome Library (1930s). **Source:** Photo by Wellcome Library, CC BY 4.0.

## Was there eugenics in Canada?

The Eugenic Archive has a wealth of historical information in an accessible format. Check out this interactive timeline of Eugenics in Canada (https://www.eugenicsarchive.ca/timeline)

The eugenicist strategy has been one of *selective breeding*, but that term does not do it justice. "Selective breeding" invariably involves *selecting in*: that is, encouraging people who were deemed to possess more desirable qualities to have a significant number of children. However, the eugenics message in Canada was more about *selecting out*: to find ways to deter the reproduction of what they regarded as fated populations doomed by their genes to imperil themselves, successive generations, and the nation.

Canada sterilized proportionately fewer people than the United States — the total number is believed to

be slightly more than 3,000 – but record keeping was inconsistent and there is little doubt that an accurate total is unknowable (Hanson and Kind, 2013).


**Figure 10.5** A residential institution for people with mental health challenges at Orillia, ON, ca. 1910.
**Source:** The Asylum, Orillia, ON, about 1910 © McCord Museum (MP-0000.724.13), CC BY-ND.

## Listen:

Judy Lytton is a eugenics survivor and currently is on the Board for the Living Archives in Eugenics in Western Canada. Hear her story (https://www.eugenicsarchive.ca/our-stories?id=531cdbd7132156674b0001f1).

**Figure 10.6** The Provincial  institution for people with mental health challenges in New Westminster, BC, shortly after it was opened in 1878. It would subsequently become known as the Provincial Hospital for the Insane and, from 1950, as Woodlands School. **Source:** Provincial Asylum for the Insane, c. 1878 by S.J. Thompson, Public Domain

## Concept in Action

The eugenics movement in Western Canada and the application of sterilization are discussed by historian of institutionalization Megan Davies (York University).

**Watch Dr. Megan J. Davies Question 9 – Eugenics (5 mins) on YouTube (https://youtu.be/1rzLfGfcwMg)**

# Do eugenics and scientific racism still exist?

While eugenics movements especially flourished during the three decades before the end of World War II, eugenics practices such as involuntary sterilization, forced institutionalization, social ostracization, and stigma were common in many parts of Canada until at least the 1970s and, in some instances, have continued into the present in various forms. Historical injustices also lead people to fear and mistrust government bodies.

Watch Kyle Lillo (https://www.eugenicsarchive.ca/our-stories?id=544724c7d4cf080000000003) describe his concerns about having children. He fears that due to his disability, the government will apprehend his children and deem him unfit to parent.

## Compulsory Sterilization in Canada

Compulsory sterilization in Canada is an ongoing practice that has a documented history in the provinces of Alberta, Saskatchewan, and British Columbia. Sixty Indigenous women in Saskatchewan sued the provincial government, claiming they had been forced to accept sterilization before seeing their newborn babies (Moran, 2016). In June 2021, the Standing Committee on Human Rights in Canada found that compulsory sterilization is ongoing in Canada, and its extent has been underestimated (Government of Canada, 2022). A bill was introduced to Parliament in 2024 to end the practice (Ryckewaert, 2024).

Over 9,000 Indigenous People in British Columbia were surveyed and interviewed in an inquiry into racism and discrimination in BC's healthcare system. The In Plain Sight Report (https://engage.gov.bc.ca/app/uploads/sites/613/2020/11/In-Plain-Sight-Full-Report-2020.pdf) summarized the findings, which included examples of forced sterilization of Indigenous women in Canada.

With the completion of the Human Genome Project (HGP) and, more recently, advances in genomic screening technologies, there is some concern about whether generating an increasing amount of genomic information in the prenatal setting would lead to new societal pressures to terminate pregnancies where the fetus is at heightened risk for genetic disorders, such as Down Syndrome and spina bifida.

The possible genomic-based screening of embryos for behavioural, psychosocial and intellectual traits would be reminiscent of the history of eugenics in its attempt to eliminate specific individuals.

In fact, some geneticists view both genomic screening and genetic counselling as an extension of eugenics.

Human enhancement through consensual gene editing has also been described as the new eugenics. Despite its basis in science and

### Optional Video

Watch the Eugenics Crusade on AppleTV or Prime Video for a

deeper dive into Eugenic history.

Honeycutt, C., De La Uz, R., & Ferrari, M. (October 16, 2018). The eugenics crusade: What's wrong with perfect? (https://www.pbs.org/wgbh/americanexperience/films/eugenics-crusade/) PBS. USA: 42nd Parallel Films.

being consensual, it has underpinnings of the historical examples of eugenics – the pursuit of a superior being at the expense of those considered inferior.

## How can nurses address eugenics and scientific racism?

Nurses can commit to interrogating the legacies of eugenics and scientific racism to further develop ethical and equitable uses of genomics. Understanding the history of eugenics, including forced sterilizations and discriminatory practices, helps healthcare providers recognize the deep-seated mistrust some patients may have toward medical institutions. This awareness can guide providers in delivering trauma-informed care. By integrating these practices, healthcare providers can create a safer, more supportive environment for all patients, particularly those who have experienced trauma. This history emphasizes the potential for misuse of genetic information and reinforces the need for nurses to remain vigilant against discrimination and stigmatization based on genetic traits. Nurses can integrate this knowledge and awareness into practice to ensure genomic services are provided ethically, equitably, and inclusively.

It is also crucial that nurses critically evaluate medical literature to identify scientific racism, and challenge unscientific medical practices such as the misrepresentation of race as a biological variable rather than a social construct.

### Read:

Dordunoo, D., Abernethy, P., Kayuni, J., McConkey, S., & Aviles-G, M. L. (2022). Dismantling "race" in health research. *Canadian Journal of Nursing Research, 54*(3), 239-245. https://doi.org/10.1177/08445621221074849

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Questions for Reflection

1. What can nurses do to avoid making assumptions about their patients based on skin colour or perceived racial background?
2. How can nurses identify and address the impacts of racism, including frequency, intensity, and duration of racist encounters in their patients' lives when assessing their health and planning their care?
3. Why do the authors propose using the term *racism* instead of *race* as a variable in health research and practice and how would this help quantify the social determinants of health that are related to racism?

## Attribution & References

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- How can nurses address eugenics and scientific racism? Written by Andrea Gretchev is licensed under a CC BY 4.0 International License

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# 10.4 USE OF POPULATION DESCRIPTORS IN GENOMICS

## Population Descriptors

Appropriate use of **population descriptors** is a critical scientific issue that is important for advancing genomic research and improving healthcare across human populations. Given the ethical, legal and social implications of their historical and current use, thoughtful use by researchers and other interested parties is essential.

The inaccurate belief that human populations are biologically distinct has contributed to harm, such as justifying eugenics through the practice of scientific racism, and marginalizing groups. In turn, misapplication of concepts of population groups has contributed to health disparities, alienated marginalized groups from research participation, and led to harmful stereotypes that have reinforced inequities.

More work is needed to educate researchers, clinicians, policymakers, and the public on the distinctions between race, ethnicity, and genetic ancestry and advance the use of population descriptors in genomics and biomedical research.

The National Academies of Sciences, Engineering and Medicine (NASEM) assessed the methods, benefits and challenges in a review of the use of population descriptors in genomics research. The NASEM Report (https://www.nationalacademies.org/our-work/use-of-race-ethnicity-and-ancestry-as-population-descriptors-in-genomics-research) includes 13 recommendations to transform how population descriptors are used in human genetics and genomics research.

## Types of population descriptors

Population descriptors are ways of describing or distinguishing people from each other based on perceived or actual differences. They capture the various ways in which people can differ from one another.

A wide variety of population descriptors describe groups of people in research, healthcare or society. Examples of population descriptors include race, ethnicity, skin colour, genealogical ancestry, genetic ancestry, Indigenous, primary language spoken, nationality, geographic origin, sex at birth, gender identity, disability status and age. Each population descriptor captures a different aspect of a group or individual. One population descriptor cannot fully describe or distinguish any individual or group. Depending on the situation, some population descriptors may be more relevant than others.

People commonly use population descriptors and their corresponding categories or numerical scales to

describe themselves and others. For example, we use categories like female, male or intersex when referring to the biological sex assigned at birth (Phenex Toolkit, 2024-a). We use numerical values like months and years when referring to age. We also use categories like newborn, adolescent or older adult.

Researchers in genomics and healthcare also use population descriptors and corresponding categories to describe who is participating in a research study, what groups are being compared as part of the study and to whom their study findings may apply. These are collectively referred to as demographics. Researchers can obtain information about population descriptors in many ways, for instance, by asking participants how they identify, looking in an electronic medical record, using data from a prior research study that was shared, or searching public records. Researchers may also assign a population descriptor to an individual or group using a specific analytical approach, such as using statistics to look at the frequency of DNA variants across the genome.

The definitions, measurements, uses, and interpretations of population descriptors have varied over time across users and worldwide. Human rights movements or social and political action can bring about such changes. In addition, new scientific discoveries or knowledge, such as in the fields of genomics, archaeology or social science, can lead to changes. New scientific discoveries and well-established facts present an opportunity to improve our understanding of human genetic variation and our knowledge of what types of differences between or across groups may be important for health. For example, the first modern humans lived somewhere in Africa approximately 300,000 years ago (Hublin et al., 2017), and physical barriers to the migration of humans, such as oceans and mountains, led to geographical differences in the frequency of genetic variants we see within and between populations (Rosenberg, 2011).

While we're often searching for differences, we must remember that human beings are far more similar than they are different. When identifying groups that differ genetically, researchers have found that **most of the variation occurs *within* groups of people rather than between them**. This means that nearly all differences are not specific to a group. Instead, they are sometimes found at different frequencies between groups.

## Understanding genetic ancestry, race, and ethnicity

### Concept in Action

Watch **this video** from the Canadian Nursing and Genomics Steering Committee on the intersection of genomics, social determinants of health, race and racism for an description and illustration of how these concepts impact nursing practice.

There is not one agreed-upon definition for these terms. The descriptions below highlight key differences across them.

## Genetic ancestry

**Genetic ancestry** refers to the biological relationships between individuals resulting from inheriting common ancestors' DNA. These common ancestors are tied to their geographical origins from many centuries ago when long-distance travel was extremely difficult. Parents do not pass down all their DNA to their children. Therefore, **genealogical ancestry** and genetic ancestry can be different. Genetic ancestry is based on a statistical measure of genetic similarity across individuals.

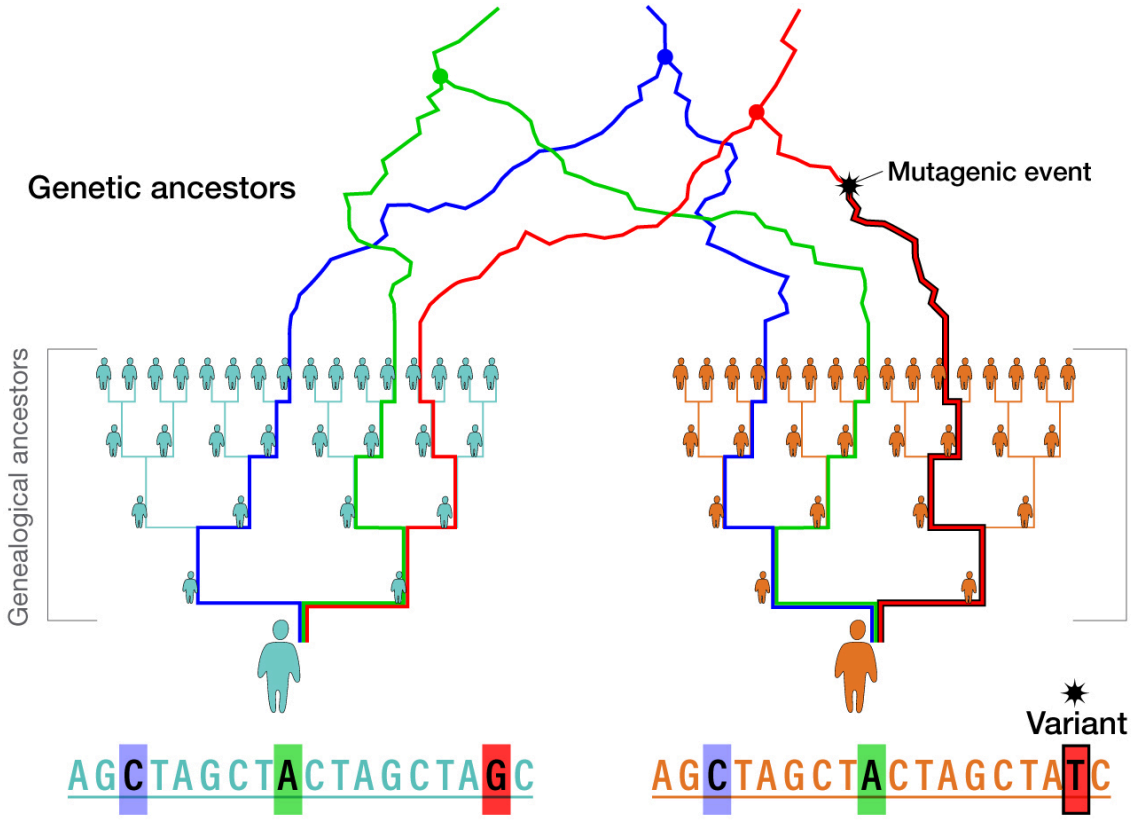


**Figure 10.7** Genetic ancestry refers to the bits of DNA a person or group has inherited over time from prior generations. **Source:** National Human Genome Research Institute, PDM with attribution.

**Figure 10.8** Race is a population descriptor with multiple definitions. Race has been used to group humans into a hierarchical system that identifies, distinguishes and marginalizes some groups across nations, regions and the world. **Source:** National Human Genome Research Institute, PDM with attribution.

## Race

People created the concept of race. **Race** typically divides human populations into groups based on perceived physical appearance (such as skin colour), social factors and cultural backgrounds (NHGRI, 2022). Race has been used to inappropriately group people into a hierarchical system to "establish and justify systems of power, privilege, disenfranchisement and oppression" (National Museum of African American History and Culture, n.d.-b, para. 1).

## Ethnicity

**Ethnicity** refers to a group of people with shared language, religion, customs, beliefs, heritage and history, even though such attributes are not always confined to a single ethnic group. Ethnicity may also refer to groups that are considered indigenous to an area. Ethnicity is not a biological characteristic.

**Figure 10.9** Ethnicity refers to a group of people with a shared language, religion, customs, beliefs and history. **Source:** National Human Genome Research Institute, PDM with attribution.

## How well can researchers determine genetic ancestry?

Methods for estimating genetic ancestry are evolving. To determine an individual's genetic ancestry, researchers compare DNA variants in that individual to the frequency of those DNA variants in groups of people from around the world who have provided samples of their DNA. These groups of people form what is referred to as **reference populations.** Genetic ancestry is estimated using statistical techniques and is typically based on some measure of genetic similarity. An individual with a collection of genetic variants that appear in the highest frequency within a reference population is estimated to have ancestors from that reference population. Individuals may have a collection of genetic variants that appear in more than one reference populations, which indicates they likely have ancestors from more than one group. Some have argued that instead of thinking about genetic ancestry as broad groups or categories, genetic ancestry should be considered a continuum.

Currently, genomic researchers do not have DNA samples from many groups of people around the world, which means genetic ancestries for some geographical locations cannot be estimated accurately. In addition, as mentioned above, scientists use reference datasets to calculate ancestries. Genetic ancestry estimations can differ from one analysis to another due to differences in the frequencies of genetic variants in the datasets used. Furthermore, when someone is estimated to have ancestors from more than one group, researchers sometimes lump individuals together into a single group to simplify analyses. Therefore, determining genetic ancestry is a statistical estimate based on available data and is inconsistent across studies. More recently, companies offering ancestry-related services directly to consumers have combined genetic ancestry information with family history information.

### Read

Cerdeña, J. P., Grubbs, V. & Non, A.L. (2022). Genomic supremacy: the harm of conflating genetic ancestry and race. *Human Genomics, 16*(18), 1-5. https://doi.org/10.1186/s40246-022-00391-2

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## A closer look: Genetic ancestry and identification

Regardless of the outcome of a genetic ancestry test, people will choose how they want to be identified by others. DNA, social factors, personal or familial preferences, or lived experiences may inform these choices.

### How do I identify?

Imagine your friend received an ancestry test for the holidays and was surprised by some results. After taking the test, your friend had a primary care appointment with a new doctor. When completing the required forms, they answered questions about their race and ethnicity differently than in the past based on the latest information provided in their ancestry test. While their physical body and health status did not change, their social identity did change. People vary in their response to ancestry testing. For some, the outcome may lead to an identity change. For others, they may maintain their original identity (Roth & Ivemark, 2018).

But how meaningful is this change for healthcare decision-making? An estimate of genetic ancestry (not race) can be informative for some conditions. For example, some heritable cancers are more common in certain groups than others. Should self-identified race or ethnicity change a doctor's decision about medical treatment? The answer can depend on a variety of factors.

## How am I identified?

As another example, the U.S. government has changed the reporting of race and ethnicity over time, with categories being renamed, merged, removed or expanded (United States Census Bureau, 2015). Was this change due to new information about how people differ genetically or biologically? No. The change was made to reflect better perceptions of growing diversity across groups in the country, better reflect how different people identify themselves and improve the quality of available demographic data. The way people self-identify can change in their lifetime or across generations, along with the questions and forms intended to capture this information.

# Are population descriptors social constructs?

A social construct is an idea or collection of ideas created, agreed upon, accepted, or acknowledged by groups of people in a society. Social constructs offer ways to organize, explain or make sense of the world. Many population descriptors are social constructs. A socially constructed population descriptor can change and be used and defined differently in different parts of the world (National Museum of African American History and Culture, n.d.-a).

Race and ethnicity are social constructs. There is no clear or consistent way to place people into racial or ethnic groups using biology or innate characteristics. For example, people of similar skin colour or hair texture have been defined as being of different races. Skin colour variation has arisen from people adapting to varying levels of sun exposure (Jablonski & Chaplin, 2010), and people of similar skin colour may have very little in common genetically.

For centuries, definitions of race and ethnicity were overly simplistic, unscientific, unethical and regularly used to support colonialism, slavery, imperialism, scientific racism and eugenics. Race has been used to group people into a hierarchical system that identifies, distinguishes and marginalizes some groups across nations, regions and the world. Race also has been used to "establish and justify systems of power, privilege, disenfranchisement and oppression" (National Museum of African American History and Culture, n.d.-b).

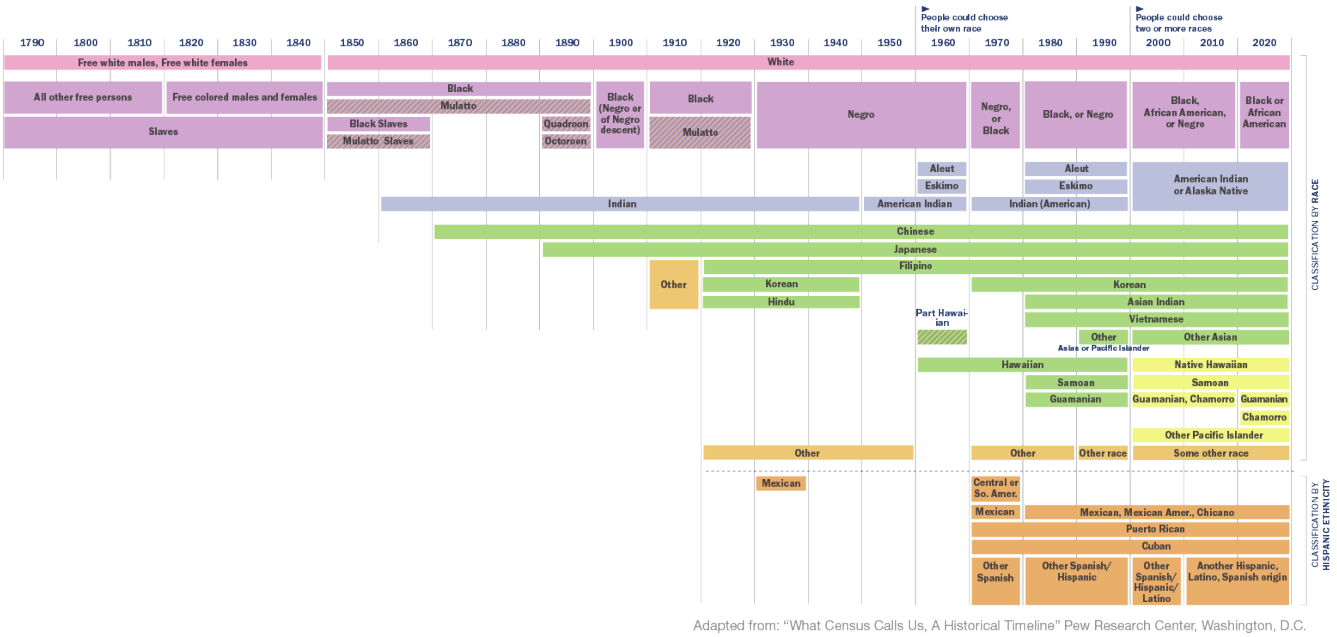
The U.S. federal government notes that the race and ethnicity categories established by the Office of Budget and Management (OMB) are sociopolitical constructs and do not attempt to define race and ethnicity biologically or genetically. Furthermore, these categories reflect a social definition of race and ethnicity recognized in the U.S. and do not conform to biological, anthropological or genetic criteria (United States Office of Management and Budget, 1997).

While genetic ancestry involves analyzing DNA variants and is tied to biology, as described above, the availability of reference populations can influence the ancestral group(s) a person is categorized into. Scientists must decide what level of resolution they will use to group people and what terms they will use to label these genetic ancestry groups. The categories that result when calculating genetic ancestry are sometimes aligned with social constructs of race and ethnicity. Broad genetic ancestry categories are sometimes labelled using the

continents from where people are believed to have origins or roots, such as African, European, and Asian. In this way, descriptors for race, ethnicity and genetic ancestry are often intertwined and misused. Because of these factors, some have described genetic ancestry as socially constructed, too (Dauda et al., 2023).

## How are population descriptors used?

The categories used to describe racial and ethnic groups around the world vary. Different ways of categorizing race and ethnicity arise from various historical and modern-day experiences. Some of these experiences include colonization, forced and voluntary migration, racial or ethnic stratification and governance systems. For example, Australia's census form (Australian Bureau of Statistics, 2021) in 2021 asked residents to indicate whether they are "of Aboriginal or Torres Strait Islander origin" and to indicate their "ancestry" using no more than two categories. Some of the ancestry categories included "English," "Italian," "Chinese," "Maori," and "Australian South Sea Islander." There is no mention of "race" on the 2021 form, but it did appear in prior years (Australian Bureau of Statistics, 2011). In some countries, language spoken, origins, or religion matter more than race or ethnicity. France and Italy are examples of countries that do not include race or ethnicity in their census. Some have argued that including race and ethnicity on censuses is essential for understanding and addressing inequities or racism.




Adapted from: "What Census Calls Us, A Historical Timeline" Pew Research Center, Washington, D.C.

**Figure 10.10** Racial categories changed over time due to shifts in scientific, political and social thinking about race and ethnicity. According to Pew Research Center (2020), "this graphic displays the different race, ethnicity and origin categories used in the U.S. decennial census, from the first one in 1790 to the latest count in 2020. The category names often changed from one decade to the next, in a reflection of current politics, science and public attitudes. For example, "colored" became "black," with "Negro" and "African American" added later. The term "Negro" was dropped for the 2020 census. Through 1950, census-takers commonly determined the race of the people they counted. From 1960 on, Americans could choose their own race. Starting in 2000, Americans could include themselves in more than one racial category. Before that, many multiracial people were counted in only one racial category" (para. 1). Visit the Pew Research Centre version for an expanded copy in PDF. **Source:** Adapted from "What Census Calls Us, A Historical Timeline" Pew Research Center, Washington, D. C. by National Human Genome Research Institute, used with permission.

When the U.S. government established racial categories around 1790, they were tied to colonialism and flawed science. They were used in population surveys for taxation, government representation, counting enslaved persons and maintaining power (Diamond, 2020). The names and number of categories changed over time due to shifts in scientific, political and social thinking about race and ethnicity (United States Census Bureau, 2015).

The major categories used in the U.S. 2020 Census (U.S. Census Bureau, 2020) included Hispanic, Latino or Spanish for ethnicity, and White, Black or African American, American Indian or Alaskan Native and Asian or Pacific Islander.

In addition to their use in the census, race and ethnicity have been used to measure racial and ethnic health disparities and track progress in reducing inequalities. Race and ethnicity are also commonly used as a **proxy** (Proxy, n.d.). These uses may be helpful for research and public health, especially when other data are unavailable.

## Why should we be intentional about how population descriptors are used in genomics research and healthcare?

Advances in genomic medicine greatly amplify the urgency of ensuring the field exemplifies scientific and social accuracy in all our work. Simply stated, the design of some genomic research studies has exacerbated scientific flaws due to how data are being analyzed, interpreted, reported and aligned across data sets. In no small part, this is because of how we *misuse* population descriptors.

Race and ethnicity are not valid or reliable proxies for genetic ancestry. In addition, genetic ancestry is a poor proxy for the geographic area where someone is from, where they currently live or things that may be part of their surrounding environment. Relying on race, ethnicity or genetic ancestry as a proxy for something not measured in research often hides underlying biological, environmental or social factors that may contribute to health and disease. In healthcare, race and ethnicity have been improperly treated as biological or innate characteristics.

In society, there are tangible and measurable impacts of one's racial or ethnic identity on health, wellness and status in the United States, whether self-identified or assigned by someone else. Thus, race and ethnicity may help examine social or political issues, document racial/ethnic health disparities, explore the impact of racial bias in health service delivery (Smedley et al., 2003) and monitor diversity, equity and inclusion efforts (https://diversity.nih.gov/about-us/population-underrepresented) within the biomedical workforce. Directly measuring and analyzing social determinants of health (SDOH), such as racism, violence, access to nutritious food or safe water, or exposure to trees and nature, would improve the rigour and usefulness of research. A growing collection of SDOH measures is available in a toolkit for researchers (PhenX Toolkit, 2024-b).

In all types of research, when using population descriptors, researchers should be clear and transparent about which population descriptor(s) they are using, how they are measured and why they were chosen. Researchers should have a reasonable hypothesis for why specific descriptors may or may not be important to their research questions. Research should use labels and categories that accurately reflect what is being measured. Researchers should carefully consider whether race, ethnicity or genetic ancestry directly causes the health differences across individuals or groups. If proxies are used in research because data of interest are unavailable or cannot be collected, then the challenges and limitations of doing so should be acknowledged.

## A closer look: Measuring "race" in heart disease research

Imagine three different studies that look at the severity of heart disease among people living in three different regions of the United States. "Race" is one of several variables analyzed in each study:

- The first study measures race by asking participants to select a category that best describes their race by

checking a box on a form.

- The second study measures race by asking each participant for a saliva sample and using genetic analysis to group study participants into different races.
- The third study uses the birth certificates of participants and their parents to assign a race to each participant.

All three studies use similar labels — Black, White, Native American, Hispanic, Asian and Other — when reporting their findings of heart disease across groups. After completing their analysis, all three studies conclude that "race" is a key factor in the severity of heart disease.

In this scenario, the same population descriptor and group labels are used in each study, but their measurements are different and range from self-reporting to DNA analysis to using vital records. In the second study, race and genetic ancestry appear to be merged as if they are similar or equal. We don't know from this scenario why each study is including race as a variable. The reasons may be varied.


**Figure 10.11** In this scenario, three different approaches are used to measure "race," including self-reported race, DNA analysis and vital records. **Source:** National Human Genome Research Institute, PDM with attribution.

Suppose studies are unclear or inconsistent in the labels, definitions, measurements or justifications used for population descriptors in research. Our ability to advance science and improve health outcomes is compromised. For example, when research approaches are not specified, it is hard to repeat a study to confirm its accuracy or to see if the same outcome occurs in a different population or part of the world. Furthermore, broad categories for genetic ancestry can obscure DNA variation relevant to understanding certain health conditions (Rotimi & Jorde, 2010).

Poor use of population descriptors can also cause harm to communities. Findings from such studies are more likely to be misinterpreted and misused. For example, readers may believe there is something biological about race when a study uses DNA analysis to analyze "race" differences. Over the last seven decades, various population descriptors have been used in genomic research studies and have varied (Ganguly, 2021).

Using population descriptors in genomic and biomedical research is a critical scientific issue with varied ethical, legal and social implications (ELSI). NHGRI will continue focusing on this issue to promote the ethical, responsible and scientifically rigorous advancement of genomic science, genomic medicine and ELSI research. NHGRI is also focusing on this issue to:

- Recognize that people have been and continue to be harmed by the misuse of race in genomic research and the misinterpretation of research findings.
- Avoid repeating mistakes of the past, which have caused immediate and long-lasting harm to minoritized and disenfranchised groups here in the U.S. and worldwide.
- Earn the public's trust by ensuring that researchers thoughtfully consider whether, when and how to use population descriptors and ensure they are used ethically.
- Build and maintain trust in science among those we hope will participate in genomic research.
- Ensure a more complete understanding of the diversity across people who participate in research.
- Ensure that all populations benefit from advances in genomic and biomedical research.
- Improve health equity and eliminate disparities in genomic medicine.

## Looking forward

Understanding the true role of genomics in health and wellness will require careful attention to the full spectrum of potential contributing factors, including genomic, biological or clinical traits; components of the natural, built or social environment in which people live; and more significant systemic or structural issues. Clarity and specificity around population descriptors used in genomic research can improve the scientific integrity of research while also showing respect for the people represented in genomic research.

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# 10.5 NURSING IMPLICATIONS

## Implications for Nursing Practice

Each province and territory in Canada has a nursing regulatory body that sets out the professional and practice standards and entry-level competencies. These are based on the Canadian Nursing Associations (CNA) *Framework for the Practice of Registered Nurses in Canada* (2015). Nurses practicing in genomics apply these standards to ethical issues as they arise. These standards and competencies promote the provision of safe, ethical, compassionate, competent, and evidence-informed nursing care. Nurses must consider issues around consent, privacy, and confidentiality when working with clients and families receiving genomic services. Trauma-informed practices are a vital component of genomic nursing care, particularly given historical harms related to genetics and genomics. Establishing a therapeutic nurse-client relationship can help build trust and promote informed decision-making.

The CNA Code of Ethics (the Code) provides a framework to guide nurses in navigating ethical dilemmas and decision-making that align with professional values and principles. In addition, the Code promotes equity and addresses social determinants of health by encouraging nurses to challenge systems of oppression, discrimination, and inequity in healthcare. The Code Recognizes the importance of culturally safe care, particularly in addressing the health needs of Indigenous peoples and other communities that experience disproportionate burdens. Thus, the Code can serve as a resource for nurses to address ethical issues arising from genomics-informed nursing. The previous version of the Code (CNA, 2008) included mention of genetic endowment as a health determinant (Puddester et al., 2023). Additionally, the document noted that advances in genetics and genomics impact healthcare system transformation in Canada (Puddester et al., 2023). The absence of any mention of genetics or genomics in the current (CNA, 2017) version of the Code is concerning, given the mainstreaming of genetics and genomics in medicine.

The following article explores how the American Nurses Association (ANA) Code of Ethics can be applied to genomics nursing, emphasizing the ethical responsibilities of nurses working in this rapidly evolving area. The article explains how the core principles of the ANA code – including respect for persons, beneficence, justice, and the nurse's duty to advocate for patients – are applicable to genetic/genomic nursing. Additionally, it highlights the importance of informed consent, ensuring patients understand complex genetic information, and the need to protect patient privacy and confidentiality.

Although the ANA Code of Ethics only applies to American nurses, there are many similarities to the CNA Code of ethics. While both the CNA and ANA Codes of Ethics align in their commitment to patient care, advocacy, and professional integrity, the CNA Code reflects Canada's focus on global health, cultural safety, and reconciliation with Indigenous communities. In contrast, the ANA Code addresses issues relevant

to the U.S., such as privatized healthcare and disaster response. These distinctions highlight how each code adapts ethical nursing principles to meet the specific needs of their populations and healthcare systems.

The article below focuses on the nurse's role in patient education, advocacy, and addressing health disparities related to access to genetic services. While the specific context is American, the ethical considerations and the role of the nurse outlined in this article can be readily related to the CNA code of ethics and to the practice of nursing in Canada.

## Read

Tluczek, A., Twal, M. E., Beamer, L. C., Burton, C. W., Darmofal, L., Kracun, M., Zanni, K. L., & Turner, M. (2019). How American nurses association code of ethics informs genetic/genomic nursing. *Nursing ethics*, *26*(5), 1505-1517. https://doi.org/10.1177/0969733018767248



## Questions for Reflection

While reading the above article, consider the following questions:

1. How can nurses ensure truly informed consent when patients may have limited health literacy? Consider the challenges nurses face in conveying complicated genetic concepts, such as DNA, variants, and inheritance patterns.
2. How can nurses balance the patient's right to know with the right not-to-know, particularly in cases where genetic findings may have no clear treatment?
3. In what ways can nurses advocate for equitable access to genetic/genomic services and address potential health disparities? Given that genetic technologies and information are not always equally available or accessible to all populations, what steps can nurses take to ensure that all patients receive appropriate genetic services?
4. What strategies can nurses use to protect patient privacy and confidentiality in the age of electronic health records and increased genetic testing?

5. How does having knowledge and awareness of the eugenic past contribute to trauma-informed care and ensuring a safe practice environment?

## Position Statements

A position statement is a strategic tool used to define and communicate an organization's perspective on a topic, provide guidance, and advocate for change. It is essential for influencing practice, shaping policy, and fostering awareness and alignment on critical issues.

The International Society of Nurses in Genetics (ISONG) have issued policy statements that align with nurses responsibilities related to ethical issues arising from genomics. Note that these are also founded on nursing guidance from the United States, therefore, should be read with a critical view to their relevance in the Canadian context.

Briefly review the following documents:

- Access to Genomic Healthcare: The Role of the Nurse [PDF] (https://www.isong.org/resources/Documents/PS_Access%20to%20Genomic%20Healthcare_November%202021.pdf)
- Privacy and Confidentiality of Genetic Information: The Role of the Nurse [PDF] (https://www.isong.org/resources/Documents/ISONG%20Position%20Statement_Privacy%20and%20Confidentiality%20of%20Genetic%20Information%20approved%20May%201%202018.pdf)
- Informed Decision-Making and Consent Related to Genetic Testing (Clinical and Research): The Role of Nursing [PDF] (https://www.isong.org/resources/Documents/Informed%20decision%20making%20position%20statement%20approved%20Dec%202018.pdf)

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# 10.6 UNIT SUMMARY AND REVIEW

## Key Takeaways

Genomic healthcare and research raise numerous ethical, legal, and social issues, such as privacy and confidentiality, informed consent, genetic discrimination, and the implications of gene editing and biobanking. Addressing these concerns requires careful consideration of justice, equity, and access to ensure ethical and fair practices. Protections like Canada's Genetic Non-Discrimination Act (GNDA) aim to safeguard against misuse of genetic data.The history of eugenics highlights its scientifically flawed and discriminatory roots, which have caused widespread harm through practices like forced sterilization, segregation, and social exclusion. Eugenics gained global traction in the 20th century, driven by racist, ableist, and colonial ideologies, influencing policies in countries such as Nazi Germany, the United States, Canada, and beyond. While the most infamous applications include Nazi racial policies and sterilizations targeting marginalized groups, eugenics also shaped immigration and public health policies in the U.S. and Canada, with Indigenous populations disproportionately affected. Modern concerns center on the potential for new genomic technologies to revive eugenic-like practices, emphasizing the need for ethical vigilance in genomics research and healthcare

Population descriptors, such as race, ethnicity, skin colour, and genetic ancestry, are essential yet complex tools in genomics and healthcare research. Historically, their misuse has justified eugenics through the practice of scientific racism, and marginalized groups, contributing to health disparities and social inequities. The National Academies of Sciences, Engineering, and Medicine (NASEM) has issued recommendations to transform how these descriptors are applied in research, emphasizing the importance of understanding their distinctions and implications.

Descriptors like race and ethnicity are social constructs, often conflated with genetic ancestry, a biological measure based on inherited DNA. While genetic ancestry provides insights into human migration and variation, most genetic differences occur within populations rather than between them. Misinterpretation of these terms can reinforce stereotypes and inequities. Effective use of

population descriptors requires researchers and healthcare providers to consider their relevance and limitations, acknowledging their social, historical, and scientific contexts. Greater education and precision in their application are needed to ensure ethical and equitable practices in research and healthcare.

The Canadian Nurses Association (CNA) Code of Ethics provides a foundational framework to guide nurses in navigating ethical challenges, including those related to equity, culturally safe care, and social determinants of health. The integration of principles from both the CNA and American Nurses Association (ANA) Codes of Ethics emphasizes the ethical responsibilities of nurses in informed consent, patient advocacy, education, and addressing disparities in access to genetic services, which are critical to ensuring equitable and patient-centered care in the genomic era.

## Resource

Dordunoo, D., Villeneuve, M., Hamza, A., Guest, T., Etowa, J., Bourque Bearskin, M. L., Magassa, Y., Markin, M., Bosco, C., Song, C., Hubert, J., Wonsiak, T., & Bailey, C. (2024, June). *Racism and discrimination among nurses in Canada and the impacts of the COVID-19 Pandemic: A scoping review*. Canadian Nurses Association. https://www.casn.ca/wp-content/uploads/2024/07/CNA_Racism_Discrimation_Nurses_E.pdf

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## Attribution & References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

## References

ChatGPT: OpenAI. (2024). *ChatGPT (Version 4.0)* [Large language model]. https://openai.com

# UNIT 11 - APPLICATION OF THEORY IN PRACTICE PART 2

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 11 Contents


- 11.1 Unit Overview
- 11.2 Application of Theory in Practice – Case Studies
- 11.3 Group Discussion


## Attribution

# 11.1 UNIT OVERVIEW

## Learning Objectives

- Apply course content to practice scenarios

Practice questions and case studies are provided for independent practice for students to apply what they have learned thus far in the course. Please see Blackboard for the group discussion assignment for this week which will also provide an opportunity to apply learning.

## Attribution

# 11.2 APPLICATION OF THEORY IN PRACTICE - CASE STUDIES

## Pediatric Genetic Disorders

Rady Children's Institute for Genomic Medicine has three pediatric case studies. Watch a vignette, follow the patient through their trajectory, or read the full story if you prefer print.

- Mario (https://radygenomics.org/case-studies/marios-story/) – a stomachache turns into a serious heart condition. Genome sequencing identifies the cause.
- Hudson (https://radygenomics.org/case-studies/hudsons-story/) – quick deterioration leads to respiratory distress and a genetic diagnosis.
- Fitz (https://radygenomics.org/case-studies/fitzs-story/) – newborn screening reveals Severe Combined Immunodeficiency (SCID)

## Pharmacogenomics

### Pharmacogenomics Exercises

**Pharmacogenomics exercises (text version)**

1. Match the words to the correct blanks to complete the sentences:
   **Words:** pharmacodynamics, pharmacogenomics, pharmacokinetics
   The study of the absorption, distribution, metabolism and excretion of drugs is called **[Blank a]**.
   The study of the biochemical and physiological effects of drugs and their mechanism of action is called **[Blank b]**.
   **Check your answer in footnote**[1]

2. Sara is a 17-year-old patient who comes to the clinic today after struggling with a number of symptoms for 2 months. She reports sad and lonely feelings daily, an inability to leave her bed, poor appetite, and a 10 lb weight loss. She has not had suicidal tendencies.Sara meets with the clinic's psychiatrist for 1 hour who conducts a number of diagnostic tests and inquires more about her symptoms. The psychiatrist diagnoses Sara with major depressive disorder (or depression). The doctor recommends weekly behavioral therapy with the clinic's psychologist and discussed medication options with Sara. The prescriber is considering treating with Citalopram (Celexa).**Q: How does this drug work to treat this disease?** Hint: pharmacodynamics; use the Drugs with Variant Annotations (https://www.pharmgkb.org/annotatedDrugs) database from PharmGKB.

    a. By blocking dopamine reuptake to increase dopamine levels in the brain
    b. By inhibiting serotonin reuptake, leading to increased levels of the neurotransmitter in the synaptic cleft
    c. By increasing norepinephrine release at the synaptic cleft
    d. By acting as an antagonist at glutamate receptors to decrease excitatory neurotransmission

    **Check your answer in footnote**[2]

3. **Key pharmacogene for citalopram: *CYP2C19* – Metabolized by the liver**You recommend preemptive testing of Sara's CYP2C19 genotype before initiating therapy with citalopram. In the meantime, you have the genotypes of Sara's parents in the electronic medical records. Parent 1 (male): *1/*2 Parent 2 (female): *2/*3Q: What genotypes are possible for Sara based on parental genotypes (Hint: there are four correct answers)?

    a. *1/*2
    b. *2/*2
    c. *1/3
    d. *2/*3
    e. *1/*1
    f. *3/*3

---

1. **Blank a** – pharmacokinetics; **Blank b** – pharmacodynamics

2. b. By inhibiting serotonin reuptake, leading to increased levels of the neurotransmitter in the synaptic cleft

**Check your answer in footnote**[3]

4. Sara's genotype for *CYP2C19*: *2/*3
   **True or false?** her phenotype would be "normal metabolizer." Use PharmGKB (https://www.pharmgkb.org/haplotype/PA165980635/variantAnnotation) to find the answer.
   **Check your answer in footnote**[4]

**Activity source:** Adapted from Engaging Students in Pharmacogenetics: Patient Case Studies Using the PharmGKB Website, CC BY-NC-SA 4.0

# Various Additional Case Studies for Practice

Select a case study on a topic of interest from below or work through them all.

## Case #1

Read Sally's story of survivor's guilt (http://www.tellingstories.nhs.uk/index.php/joys-story?id=243) – growing up with cystic fibrosis in the family.

### Question for reflection – Sally's story

1. Can you think of reasons why parents would and would not want to talk to their children about genetic conditions in the family? Use cystic fibrosis (an autosomal recessive condition) as an example. Consider the taboo that surrounds the issue of talking about a dead child with others outside the family.

3. a, b, c and d are all possible.

4. False. She would be a poor metabolizer and the drug dose should be reduced or another drug selected

2. What sort of information/ resources could a nurse pass on to the family to help them learn and understand about cystic fibrosis and their own risk?
3. What could the nurse offer to parents in case they might want to tell their children about their own risk?
4. Discuss the role hospital-based health care staff might play in supporting siblings of children with life-limiting conditions.

**Source:** Questions based on Sally's Story In *Telling stories: Understanding real life genetics* © National Genetics and Genomics Education Centre (NHS).

## Case #2

Read Eve's story (http://www.tellingstories.nhs.uk/index.php/joys-story?id=287) about her son's chromosomal condition mosaic ring 22 trisomy.

### Question for reflection – Eve's Story

1. Eve describes some of the anxieties she and her husband have about Caleb's health and care needs and how they worry about his future. Consider what it must be like for a parent with anxieties and concerns over their child's long-term health needs and what the psychosocial impact on the family might be. How might a healthcare professional be able to support parents in this situation?
2. Eve has found support groups such as Unique and Chromosome 22 Central and Contact a Family to be a great source of help. Think about the role support organizations can play in helping families like Eve's. How might they be able to provide a different kind of support to that of a healthcare professional?
3. Eve explains that the geneticist tried to explain Caleb's rare chromosomal condition to her and her husband by writing on paper and showing diagrams to help with the explanation. Reflect on your own practice as a healthcare professional. Have you experienced a situation where you had to explain a complex clinical or scientific concept to an individual? How did

you go about it? Did you check that the individual had understood the explanation? Was there anything further you could have done to improve the explanation? Were there any other resources you could have used?

**Source:** Questions based on Eve's story In *Telling stories: Understanding real life genetics* © National Genetics and Genomics Education Centre (NHS).

## Case #3

Read Joy's story (http://www.tellingstories.nhs.uk/index.php/cancer/38-joys-story) about her experience with a *BRCA2* gene variant and the impact on her family.

### Question for reflection – Joy's story

1. Joy describes how she feels about her sons' decision not to be tested, saying "It's their decision. I would like to know, if there was a way I could have the test done on their behalf and know the result without telling them, that obviously would satisfy my wants, you know, of the knowledge, but they decide and so their decision we have to wait..."
    - Discuss the ethical issues that would arise if a mother could learn the genetic status of her adult children without their consent?
2. What further family history questions might you want to ask someone like Joy when discussing a family history?
3. Would you know how to refer someone to your local genetics service or where to find out information about this?
4. Joy talks about the implications that having a BRCA2 gene alteration has for her three sons. Search the internet to find out what you can about familial breast cancer in men, including what the incidence is, what the increased risk of developing breast cancer would be in a man with a BRCA2 gene alteration, and whether a BRCA2 gene alteration is also associated with an increased risk of developing other types of cancer in males. The Macmillan website has

specific webpages on breast cancer in men (http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Breastmale/Breastcancerinmen.aspx) that you might like to refer to.

**Source:** Questions based on Joy's story In *Telling stories: Understanding real life genetics* © National Genetics and Genomics Education Centre (NHS).

## Attribution & References



## References

Mosquera, A. M., & Aleksunes, L. M. (2023). Engaging students in pharmacogenetics: Patient case studies using the PharmGKB website. *CourseSource*, *10*, 10.24918/cs.2023.10. https://doi.org/10.24918/cs.2023.10

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# 11.3 GROUP DISCUSSION

## Assignment – Group Discussion

This week students will engage in group discussions on Blackboard. Students will be randomly assigned to groups. See the Blackboard course shell for assignment directions and rubric. Students may also want to use this unit and unit 11 to work on their case study assignment.

## Attribution

# UNIT 12 - GENOMICS APPLICATIONS

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 12 Contents


- 12.1 Unit overview
- 12.2 Global health and genomics
- 12.3 Cancer genomics
- 12.4 Genomics applications by specialty
- 12.5 Unit summary and review


## Attribution

# 12.1 UNIT OVERVIEW

## Learning Objectives

- Identify the direct and indirect health consequences of environmental phenomena such as climate change, pollution, and natural disasters.
- Briefly explore the relevance of genomics to oncology.
- Distinguish between types of genomic variants in cancer.
- Examine various way genomics aids diagnosis and treatment in different medical specialties

## Outline

Topics covered in this chapter include:

- Global health and genomics
- Cancer genomics
- Genomics applications by specialty

## Competencies Nurses will Develop in this Chapter

### ANA (2023):

#### Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).

### Identification:

- Identifies credible, accurate, appropriate, and current genomic information, resources, services, and technologies specific to given clients.

### Provision of education, care, and support:

- Performs interventions appropriate to clients' genomic health care needs.

## NHS (2023):

### Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the key indicators of a potential genetic condition, or clinical situation where genomics-informed healthcare would be appropriate;
- recognizing the importance of family history in assessing predisposition to a genetic condition;
- based on an awareness of the care pathways relevant to your role that incorporate genomics services and information; and
- taking appropriate and timely action to seek assistance from and refer individuals to genomics specialists, other specialists and peer support resources.

### Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

### Apply knowledge, understanding and context of genomic testing and information to underpin care and support for individuals and families prior to, during and following decision-making:

- including types, uses and limitations of genomic tests to prevent, predict or treat a health condition, and an awareness of the processes for testing and return of results;
- recognizing that decision-making and testing in some situations may be time-critical; and
- incorporating awareness of the potential physical, emotional, psychological and social consequences of genomic information for individuals, family members and communities.

### Examine your own competency of practice on a regular basis:

- recognizing areas where professional development related to genomics would be beneficial;

- maintaining awareness of clinical developments in genomics that are likely to be of most relevance to your area of practice, seeking further information on a case-by-case basis; and
- based on an understanding of the boundaries of your professional role in delivering genomic healthcare including the referral, provision or follow-up to genomic services.

### Provide ongoing nursing care and support to patients, carers, families and communities with genomic healthcare needs:

- being responsive to changing needs through the life-stages and during periods of uncertainty; and
- demonstrating awareness about how a genomic test result can have implications for family members and might impact on family dynamics.

## Key terminology

### Circulating tumour DNA (ctDNA)

As cancer cells grow very fast and die, they release some of their DNA into the bloodstream. We now have tests that are sensitive enough to detect and sequence these pieces of ctDNA in the bloodstream separately from the normal DNA of the patient – this is called a "liquid biopsy" (NHGRI, n.d.a).

### BRCA1/2

BRCA1 and BRCA2 are the first two genes found to be associated with inherited forms of breast cancer and ovarian cancer. People with mutations in either BRCA1 or BRCA2 have a much higher risk for developing breast, ovarian or other types of cancer than those without mutations in the genes. Both BRCA1 and BRCA2 normally act as tumor suppressors, meaning they help to regulate cell division. Most people have two active copies of these genes. When one of the two copies becomes inactive due to an inherited mutation, a person's cells are left with only one copy. If this remaining copy also becomes inactivated, then uncontrolled cell growth results, which leads to breast, ovarian or other types of cancer.

## Attribution & References



Except where otherwise noted, this page is adapted from:

- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.

## References

American Nurses Association (ANA). (2023). *Essentials of genomic nursing: Competencies and outcome indicators* (3rd ed.). https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/

National Human Genome Research Institute (NHGRI). (n.d.a). *Cancer genomics*. https://www.genome.gov/dna-day/15-ways/cancer-genomics

National Human Genome Research Institute (NHGRI). (n.d.b). *Talking glossary of genetic and genomic terms*. https://www.genome.gov/genetics-glossary

# 12.2 GENOMICS AND GLOBAL HEALTH

## How the Environment and Genetics Shape Health Outcomes

In Unit Three, we examined the interplay between the environment and genetics in shaping health outcomes. The evidence for climate change is undeniable, as demonstrated by the increasing frequency and intensity of forest fires, floods, warming oceans, hurricanes and weather terms that have become a part of our vernacular like heat domes, atmospheric rivers, and cyclone bombs. These events have profound direct effects on environmental health and biodiversity which, in turn, impact human physical, mental, and social health. Additionally, indirect effects emerge through exposure to environmental toxins such as pollution and forest fire smoke, disruptions to the food chain, and the rising costs of essential goods. Global pandemics, often exacerbated by environmental degradation and changes in human-animal interactions, further illustrate the far-reaching health consequences of a disrupted ecosystem. Our ecosystem is an interconnected system, and when one link is disrupted, the consequences ripple broadly across all aspects of life.

**Watch GenARCC | Will Canadian species be able to adapt to climate change? (5 mins) on YouTube (https://youtu.be/pKGzvffK6uA)**

### Read

The following article examines the role of genetic variation and environmental exposures, such as toxicants, pollution, and viruses, in disease pathogenesis. Applied examples include Chron's disease and cystic fibrosis. Genomics offers tremendous potential for global public health but there are also significant challenges to overcome.

Virolainen, S. J., VonHandorf, A., Viel, K. C. M. F., Weirauch, M. T., & Kottyan, L. C. (2023). Gene-environment interactions and their impact on human health. *Genes and immunity*, *24*(1), 1–11. https://doi.org/10.1038/s41435-022-00192-6

OPEN ACCESS ONLINE

In 2022, the World Health Organization (WHO) Science Council produced a report (https://www.who.int/publications/i/item/9789240052857) containing 15 recommendations for WHO to promote the current and future use of genomic technologies for global health.

Some examples of ways in which genomics is used for global health include:

- Genomic surveillance for pathogens with pandemic and epidemic potential (https://www.who.int/initiatives/genomic-surveillance-strategy)
- Using genomic surveillance to track MRSA "superbugs" (https://www.yourgenome.org/theme/using-genomic-surveillance-to-track-mrsa-superbugs/)
- Using phylogenetics (the study of evolutionary relationships between organisms) to track disease outbreaks (https://www.yourgenome.org/theme/using-phylogenetics-to-track-disease-outbreaks/)
- Examining genetic and environmental factors influencing health disparities (https://globalgenomics.med.upenn.edu/)
- Using genomics to understand malaria (https://www.yourgenome.org/theme/using-genomics-to-understand-malaria/)

## Concept in Action

**Watch how genomic surveillance can be used to track diseases with pandemic potential in COVID-19 Genomic Surveillance (5 mins) on YouTube (https://youtu.be/hiX7jvdE8KI)**

To effect change, global health must be addressed at the policy level. Genomics-informed global health research can provide evidence for policy development to address the impacts of climate change on the health of populations through monitoring and mitigating environmental health risks. Genomic surveillance can be utilized to track pathogens as part of a pandemic preparedness public health strategy. Genomic sciences can help to identify genetic and environmental factors that contribute to health disparities in order to promote greater health equity. Additionally, developing policies that recognize the interconnectedness of the environment and human health can help reduce environmental degradation and associated health risks.

# Attribution & References

# 12.3 CANCER GENOMICS

## Proto-oncogenes

Recall from chapter 2.4 that control of cell division involves many different genes. Some of these genes act as signaling molecules to activate normal progression through the cell cycle. Think of oncogenes as the "accelerators" of cell growth and proliferation. One of the pre-requisites for cancer occurs when one or more of these activators of cell division become altered. Proto-oncogenes are normal genes that, when altered, become oncogenes and contribute to cancer as they code for positive cell-cycle regulators.

## Tumour Suppressor Genes

Tumor suppressor genes act like the "brakes" of the cell cycle, preventing uncontrolled growth and promoting repair. More than 30 genes, including *BRCA1* and *p53*, are classified as tumor suppressors. These genes repair DNA, induce apoptosis, and prevent abnormal cell division. Loss-of-function variants in these genes contribute to cancer progression, and both alleles must be varied (loss of heterozygosity) for abnormal growth to proceed.

### Why is genomics important in cancer care?

***Cancer is a disease of the genome.*** It occurs when variants in the genome result in uncontrolled cell growth and division. These genomic variants can be inherited from a parent or acquired at some point during a person's lifetime. Most cancers are caused by acquired genomic variants. In around 5%-10% of cases, the individual has inherited a variant that greatly increases their chances of developing cancer.

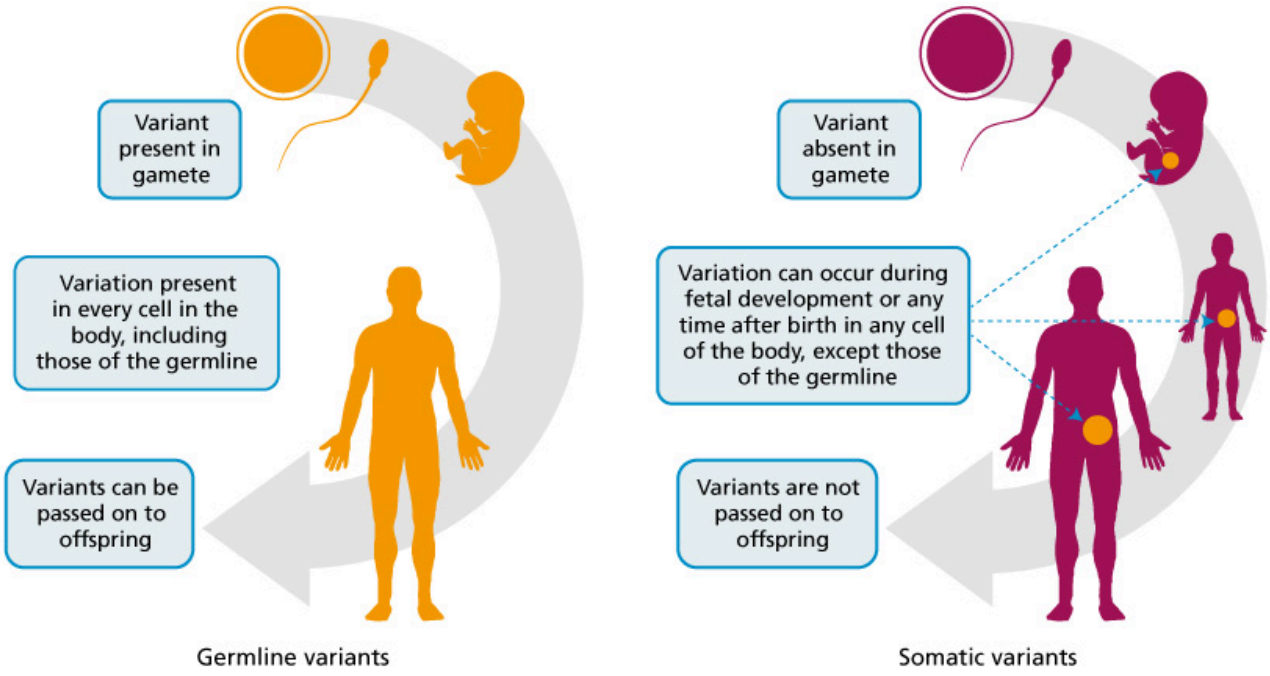


**Figure 12.1.** Inherited (germline) genomics variants vs acquired (somatic) variants. **Germline variants:** Variant present in gamete. Variation present in every cell in the body, including those of the germline. Variants can be passed on to offspring. **Somatic variants:** Variant is absent in gamete. Variation can occur during fetal development or any time after birth in any cell of the body, except those of the germline. Variants are not passed on to offspring. **Source:** Genomics Education Programme, CC BY-NC 4.0.

Cancer care has rapidly evolved, particularly over the last 15-20 years. View genomics milestones in oncology (http://media.mycrowdwisdom.com.s3.amazonaws.com/ons/_ACTIVE/MILESTONES/story.html) using this Genomic Milestones interactive site.

# Two kinds of cancer variants

## Inherited variants

Inherited genomic variants are also called germline variants. For an individual with a cancer predisposing germline variant (i.e. known to be pathogenic or likely pathogenic) each cell in their body already has an altered copy (see ch. 8.4 – Interpreting Genetic Tests) . This significantly increases their lifetime risk of cancer.

A patient with this type of variant may be offered additional screening or prophylactic surgery. For example, patients with particular *BRCA1* and *BRCA2* gene variants that are known to be pathogenic or likely pathogenic may opt for enhanced breast screening protocols, preventative medications, and reproductive health planning and counselling. An additional option is to have a preventative mastectomy or oophorectomy.

It is also important to consider the implications for the patient's family, as appropriate testing (cascade testing) can identify other at-risk relatives who may be able to take measures to reduce their chance of developing cancer. Therefore, not only do nurses need to consider the autonomy of their patient, but their relational autonomy, including their networks and relationships that factor into their decision-making.

## Acquired variants

Acquired genomic variants are called somatic variants, and these variants are present only in cancer cells. These variants are not inherited and cannot be passed on to any children.

Somatic variants can be the result of exposure to environmental factors, such as ultraviolet light, smoking, radiation and alcohol, or they can be entirely random. Each time a cell divides, errors might be introduced. While there are many mechanisms within the cell to correct these errors, occasionally they are missed.

## Is cancer hereditary?

The term hereditary cancer is a bit misleading. It is important to note that not all cancers are hereditary and for those that are, cancer itself cannot be inherited. Specifically, somatic variants in tumour cells are not passed down to offspring. However, an inherited germline genetic variant ***increases the risk of developing certain types of cancer*** because at birth they have inherited one altered "copy" of the cancer causing gene. Inheriting a variant does not guarantee that person will develop cancer. However, their risk is increased over those without the specific variant for particular types of cancer.

For example, if a parent passes a *BRCA1* or *BRCA2* gene variant to their child, the child will have a much higher risk of developing breast and several other cancers. That's why cancer sometimes appears to run in families.

**Watch Genomics in Medical Specialties – Oncology: Cancer Treatment (3 mins) on YouTube (https://youtu.be/Putm4DHuj84)**

# Blood Tests to Detect Cancer

Did you know that we are increasingly able to detect cancers by testing just a blood sample? Or that we are moving toward treating cancers not by where they are found in the body, but by how their genomes have changed? Cancer is caused by changes in an individual's genome, but advances in DNA sequencing technology are leading to a new understanding of cancer and new ways for diagnosing and treating many types of cancer.

Cancer is a group of genetic diseases that result from changes in the genome of cells in the body, leading them to grow uncontrollably. These changes involve DNA variants in the genome. Our cells are constantly finding and fixing variants that occur in our genome as the cells divide over and over again. But on rare occasions, some variants slip through our cells' repair machinery, and those variants can lead to cancer. The Human Genome Project has allowed us to establish what "normal" usually looks like for a human genome, so that we can now tell when changes in our genome have taken place that lead to cancer.

Large projects around the world, like The Cancer Genome Atlas (https://cancergenome.nih.gov/) in the United States and the Catalogue of Somatic Mutations (http://cancer.sanger.ac.uk/cosmic) (COSMIC) in the United Kingdom, have now determined the genome sequences of thousands of cancer samples of many cancer types. These projects have shown that some cancers have variants in the same group of genes, even though they may have started in completely different tissues. Many of the variants activate genes that normally promote cell growth or break genes that normally prevent cell growth. If we know more about the specific variants that led to someone's cancer, no matter what tissue it was located in, then we can look for more specific and effective treatments for their cancer.

Unfortunately, some cancers are harder to evaluate because looking at their genomes would require difficult and painful biopsies or operations where tiny parts of the cancer tissue are removed for study. This also makes it harder for clinicians to monitor how treatment is working for some cancers because repeated biopsies are just not possible. Recent breakthroughs now allow the detection of **circulating tumour DNA** (or ctDNA (https://www.labroots.com/videos/3156/liquid-biopsy-when-blood-reveals-cancer-s-story)) in the blood of patients instead of directly sampling the tumour. As cancer cells grow very fast and die, they release some of their DNA into the bloodstream. We now have tests that are sensitive enough to detect and sequence these pieces of ctDNA in the bloodstream separately from the normal DNA of the patient – this is called a "liquid biopsy."

Although liquid biopsies are not yet in widespread use for cancer detection, improvements are being made all the time that move us closer to the routine use of ctDNA tests (http://www.cnn.com/2018/01/19/health/cancer-blood-test-study/index.html). One of the current approved uses for ctDNA is to test progression of non-small cell lung cancer (http://www.phgfoundation.org/documents/developing-effective-ctdna-services-for-lung-cancer.pdf) by looking for specific variants in the *EGFR* gene over time. Liquid biopsies (http://www.phgfoundation.org/documents/developing-effective-ctdna-services-for-lung-cancer.pdf) can point to who will likely relapse after treatment, by detecting DNA with *EGFR* variants that is circulating in the blood, sometimes better and more quickly than the now-used standard imaging techniques. The CHARM study is ongoing in five Canadian provinces. Visit their website cfDNA in Hereditary and High-Risk Malignancies (CHARM) study (https://charmconsortium.ca/about/). This is an excellent example of research revolutionizing how hereditary cancer syndromes can be managed in practice. Their aim is to to develop a blood test to predict cancer development in carriers of cancer predisposition genes including *BRCA1, BRCA2, PALB2* (hereditary breast and ovarian cancer) *CDH1* (hereditary diffuse gastric cancer)

*MLH1, MSH2, MSH6, PMS2, EPCAM* (Lynch syndrome) *TP53* (Li-Fraumeni syndrome) using circulating tumour DNA. On an international level, the CASCADE (https://swisscascade.ch/en/home/) study aims to provide support and care coordination to families with pathogenic variants connected to breast and ovarian cancer and to Lynch syndrome.

## Refining treatment

Some genomic variants within the cancer genome can be used to work out the most appropriate treatment for the patient. Some variants can make the person more, or less, likely to respond well to particular treatments.

For example, tumours with certain variants in the *EGFR* gene respond well to EGFR-inhibitor drugs, but those without such variants do not. So two people with the same diagnosis of breast cancer may have different treatments based on the genomic information from their tumour.

Novel treatments can also be identified by sequencing (https://www.genomicseducation.hee.nhs.uk/glossary/sequencing/) the tumour's genome.

Listen to specialist registrar Dr Alison Berner discuss the impact this is having on patients. **Watch The Realisation of Personalised Medicine (3 mins) on Vimeo (https://vimeo.com/336816796).**

By far, most cancers are not inherited, but there are a few examples of inherited cancers like Lynch syndrome (also known as hereditary non-polyposis colorectal cancer). This disorder is due to inherited variants in any of five different genes (https://ghr.nlm.nih.gov/condition/lynch-syndrome#genes), and leads to an increased risk of different types of cancers, most often in the colon. Breast cancer is another example; again most cases are not inherited, but men or women who have inherited variants in the *BRCA1* or *BRCA2* genes have a much higher chance for developing breast cancer than other people.

**Table 12.1. High and moderate-penetrance genes in breast and gynecologic cancer Source: National Cancer Institute (NCI) (2024).**

| High penetrance breast and/or gynecologic cancer susceptibility genes | Moderate-penetrance genes associated with breast and/or gynecologic cancers |
|---|---|
| *BRCA1* and *BRCA2* | Fanconi anemia genes |
| Lynch Syndrome | *CHEK2* |
| Li-Fraumeni Syndrome (LFS) | *ATM* |
| *PTEN* Hamartoma Tumor Syndromes (Including Cowden Syndrome) | *RAD51* |
| Hereditary Diffuse Gastric Cancer (HDGC) | *SMARCA4* |
| Peutz-Jeghers Syndrome (PJS) | – |
| *PALB2* | – |
| De Novo Pathogenic Variant Rate | – |

As we learn more about the genomic changes predisposing a person to cancer, we have been able to make screening tests available to many more people. The specific DNA sequences of the *BRCA1* and *BRCA2* genes were even the subject of a legal case (https://en.wikipedia.org/wiki/Association_for_Molecular_Pathology_v._Myriad_Genetics,_Inc.)that went all the way to the United States Supreme Court, who ruled that the sequences of your genes could not be patented. Before this ruling, only one company could provide *BRCA1* or *BRCA2* testing in the United States, but now there are a number of companies who can help if you'd like to have genomic testing for hereditary causes of breast cancer.

Tom explains what genetic testing means to him and how he benefited from the information it provided.

**Watch Tom's story: Genomic testing and treatment for Lynch syndrome (3 mins) on YouTube.**

## Appropriate Referrals

Oncology nurses are often a primary point of contact for oncology patients. Oncology nurses collect comprehensive health histories including family histories that may include findings indicative of possible hereditary cancer predisposition. The Oncology Nursing Society (ONS) has created this excellent handout *Why it is Important to know if Your Patient's Cancer is Hereditary,* (https://www.ons.org/clinical-tools/resources/when-refer-genetics-professional-quick-guide) which details the hereditary and red flag indicators

that the patient would benefit from further consultation for genetic testing (click the link then click "download .pdf). Oncology nurses should become familiar with the protocols in their jurisdiction about how to initiate referrals for further consultation or genetic testing when they find health assessment data suggestive of a possible hereditary cancer predisposition.

# Oncology Resources

This unit provided a brief introduction to oncology genomics, as within this practice context genomics is extensively integrated. Nurses working in oncology need more than a foundational level of genomic literacy. There are ample professional development opportunities available for nurses wishing to learn more about this important area of genomics nursing.

## Nursing organizations

- The Oncology Nursing Society (ONS) have a wealth of professional development resources for oncology nurse members, including a Genomics and Precision Oncology Learning Library (https://www.ons.org/genomics-and-precision-oncology-learning-library).
- The Canadian Association of Nurses in Oncology also has numerous resources for Canadian oncology nurses, including a Genomics Oncology Nursing Special Interest Group (https://www.cano-acio.ca/page/genomics).

**Student membership is free** for both of these organizations!

- Linkage (LInking Nursing Knowledge And GEnomics) has online learning modules (https://linkage.trubox.ca/learning-modules/module-4/), including one on cancer genomics.

## Oncology Genomics

- The National Comprehensive Cancer Network (NCCN) provides an excellent clinical resource Guidelines for Treatment by Cancer Type (https://www.nccn.org/guidelines/category_1), and cancer Detection, Prevention, and Risk Reduction (https://www.nccn.org/guidelines/category_2).
- My Cancer Genome (https://www.mycancergenome.org/) offers genetically-informed cancer medicine resources including current information on variants, therapeutic implications, and clinical trials.
- The National Cancer Institute has a cancer genetics overview for healthcare professionals (https://www.cancer.gov/publications/pdq/information-summaries/genetics/overview-hp-pdq).

# Attribution & References



## References

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# 12.4 GENOMICS APPLICATIONS BY SPECIALTY

While numerous practice areas are still progressing toward widespread integration of genomics into routine medical practices, certain specialties have seen more substantial advancements, often due to greater research funding or the strategic prioritization of genomics implementation. While the previous chapter focused on oncology as a leading example where the integration of genomics is well-established and extensively applied, key resources and emerging practices in each of these other five practice areas are provided to highlight the growing prevalence of genomics: pediatrics, maternity/obstetrics, mental health, neurology, and cardiology. It should be noted that the relevance of genomics is not limited to these practice areas.

## Pediatrics

Units three and four briefly introduced a number of genetic conditions that manifest in childhood, along with early adverse experiences and their influence on the epigenome.

Recent advances in genomics mean that increasing numbers of children and their families can benefit from genomic testing. Testing can provide new diagnoses, shape management decisions, guide treatment options and provide valuable information.

Many genomic conditions affect early development, leading to congenital structural malformations and/or neurodevelopmental delay. This means that individuals with genomic conditions will commonly present in childhood.

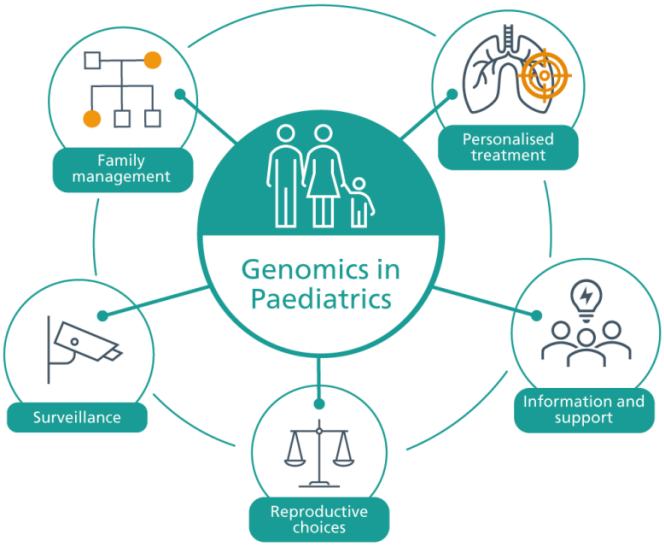


**Figure 12.2.** Examples of genomics in pediatric practice include family management, personalised treatment, information and support, reproductive choices and surveillance. **Source:** Genomics Education Programme, CC BY-NC 4.0

Identifying a diagnosis can help patients and their families in a wide variety of ways. Some examples are outlined below.

## Information and support

Having a genomic diagnosis often allows the patient and their family – as well as other healthcare professionals – to learn more about their condition, understand the health implications in the short and long term, and access family support groups, which may be helpful from both an emotional and an educational perspective. Support groups often inform their members about developments in the field, including research and clinical trials.

## Surveillance

Some pediatric genomic conditions are associated with specific health complications, such as an increased risk of developing early childhood tumours. For some of these complications, specific surveillance guidelines have been developed and published; this means that if the genomic condition is diagnosed early on, the child will have timely access to a condition-specific surveillance program that could improve their healthcare outcomes by identifying and enabling management of complications (which may include personalized treatments) at an early stage.

## Personalized treatment

In some cases, a genomic diagnosis provides access to personalized treatment. Some examples of this are outlined below.

- The use of commonly-used drugs proven to be particularly effective in a specific genomic condition. For example, the anticonvulsant retigabine (ezogabine) has particular efficacy in treating epilepsy caused by loss-of-function variants in the *KCNQ2* gene.
- The avoidance of certain medications. For example, some babies (1 in 500) are born with a particular genetic variant that means that administering the antibiotic gentamicin will cause irreversible hearing loss; however, new technologies have enabled clinicians to test for this genetic variant with a single cheek swab, which has a 15-minute turnaround time for results and means that use of gentamicin can be avoided where necessary.
- The use of targeted therapies – many of which are in development – such as enzyme replacements, dietary restrictions or gene therapies. For example, patients with spinal muscular atrophy are now benefiting from treatment with nusinersen (widely marketed as Spinraza (https://www.spinraza.com/)), a drug that is delivered directly to the central nervous system to target an underlying cause of motor neuron degeneration.

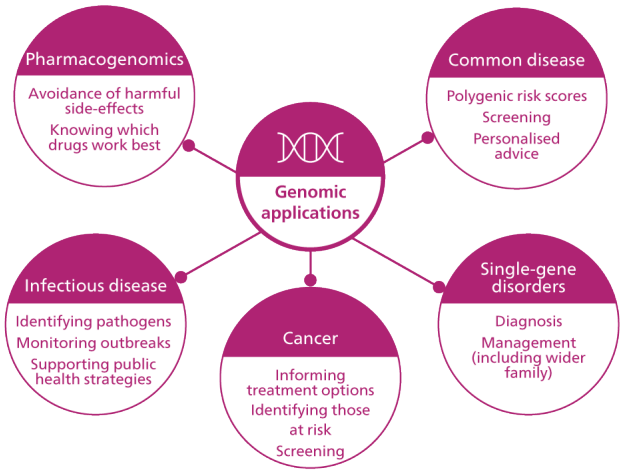


**Figure 12.3.** Genomic applications appears in a circle in the centre. Branching off from this is pharmacogenomics, common disease, single-gene disorders, cancer, and infectious disease. **Source:** Genomics Education Programme, CC BY-NC 4.0

## Family management and reproductive choices

Because we share some of our DNA with people to whom we are genetically related, genomic conditions can have implications for our family members. This means that we must consider the inheritance pattern of any genomic diagnosis. It may be appropriate to offer parental testing, which helps to clarify any inheritance patterns and potential risks to immediate family members. For some conditions, it may be appropriate to offer cascade testing to the wider family.

Where there is a significant chance of future pregnancies being affected by the same genomic condition, some couples may wish to make complex, personal reproductive choices that may include a normal pregnancy (sometimes with additional scans or screening), use of donated sperm, egg and/or embryo, adoption, prenatal diagnosis or pre-implantation genetic diagnosis (PGD). Prenatal diagnosis is usually performed through chorionic villus sampling between 11 and 14 weeks of pregnancy. PGD is an IVF-based technique in which embryos are screened and only those without the familial genomic variant are transferred into the womb. In these scenarios, your role as a pediatrician would be to refer your patients to the appropriate specialist team – be it genetic counselling, fetal and women's health or clinical genetics.

Finally, children with a genomic condition may be anxious about and want to discuss the implications of their diagnosis for any future children they themselves may have. An understanding of the inheritance patterns of genomic conditions will help you, as a pediatrician, to have those conversations with affected children.

The number of ways in which genomics can be applied in pediatrics will only increase with time. Take a look at the diagram below to find out some of the ways in which genomics is already being used to improve pediatric patient outcomes.

### Case Example: Bardet-Biedl Syndrome

- Antenatally, George was found to have an echogenic kidney (a kidney that appears bright in an ultrasound, indicating a possible condition). He was also born with an extra fifth digit (a condition known as polydactyly), and was consequently referred to the clinical genetics team.

- When George was reviewed by the clinical genetics team as a baby, results of microarray testing and a postnatal renal ultrasound scan were both normal.
- George was followed up by the clinical genetics team until the age of two. There were no further suspicions of a genetic disorder, so he was discharged back to pediatric care, where he was later managed for developing obesity and mild learning difficulties.
- Due to evolving genomic technologies, George was then recruited into a research study into early-onset obesity by his pediatrician.
- Two years later, the research study found two variants in George's *BBS5* gene, indicating a diagnosis of autosomal recessive Bardet-Biedl syndrome (BBS).
- As well as presenting a cause for George's polydactyly, obesity and learning difficulties, this new diagnosis had important implications for his management and prognosis. Sadly, most individuals with BBS become blind by their second or third decade of life.
- George was referred back to the clinical genetics team for further support and counselling about the condition, while his pediatrician made clinical referrals to the ophthalmology, audiology, endocrinology and renal teams for surveillance of his syndromic manifestations.

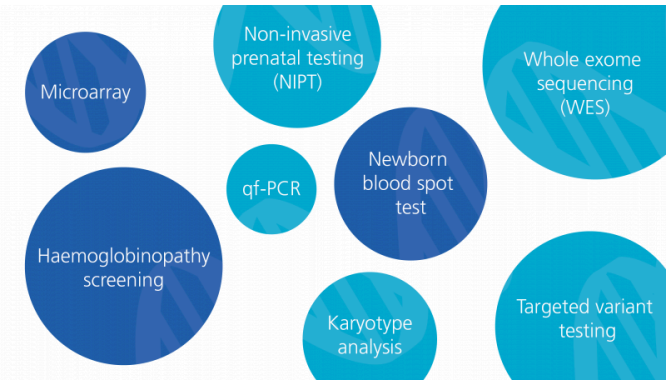


**Figure 12.4**. Genomics testing used in pregnancy and family planning. Various circles containing the names of genomics tests used in pregnancy and family planning including: microarray, non-invasive prenatal testing, hemoglobionopathy screening, newborn blood spot test, qf-PCR, whole exome sequencing, targeted variant testing, and karyotype analysis.
**Source:** Genomics Education Programme, CC BY-NC 4.0

## Maternity

Genomics will continue to play more of a role in the diagnosis, management and treatment pathways for parents and their babies. Expectant parents need nurses who are knowledgeable, confident and competent so it's paramount to ensure your genetics and genomics knowledge and skills are up to date with the latest developments. This will allow them to make choices with conviction and courage. Information is easier than ever to access online and people are now more aware about genomics – they could even know something that the nurse does not. Be prepared for questions and know where you can find accurate answers.

There is some overlap between maternity and pediatric specialties, depending on when a genetic condition is suspected or diagnosed. Nurses may care for patients at any point in their family planning or pregnancy journey, depending on their context of practice. Pre-natal, antenatal, and postnatal screening was briefly covered in unit eight. This will not be revisited here except to mention that it is nurses that typically obtain

specimens for genetic screening in these contexts. To provide appropriate informed consent, nurses must know what the tests might reveal and the risks and benefits of testing.

Some types of tests are indeed ***genetic***, because they test for a condition by looking for a variation in a specific gene. ***Genomics,*** however, describes how we interpret and act on information from the whole genome, or any part of it. The National Genomic Test Directory (https://www.england.nhs.uk/publication/national-genomic-test-directories/) refers to all tests as 'genomic' and we will do the same throughout this resource.

Look at the graphic to see the names of some genomic tests used in family planning or pregnancy. There is more information available here (https://www.genomicseducation.hee.nhs.uk/genomics-in-healthcare/genomics-in-midwifery/#toggle-id-7).

Our understanding of genomic information is increasing all the time. In addition, family histories change, and new information may alter clinical management or genetic risk assessment. If an expectant parent says something like "no-one was interested about this in my last pregnancy," consider revisiting this information – there could be cause for referral to clinical genetics for further testing. It is also always worth taking another look at a family history, especially if the previous genomics consultation was several years ago.

**Figure 12.5.** Pregnancy. Photo shows a pregnant individual's abdomen with hands making a heart sign over the abdomen. **Source:** Photo by Ignacio Campo, Unsplash license.

Referrals for genomic counselling or testing should be made at the earliest possible opportunity as the test results can provide information that can have a considerable impact on care. Some genomic tests can take several weeks to come back, so a fast referral is crucial. It is important to 'think genomics' whenever you ask about a personal, obstetric and family history, and to take timely, appropriate action if you notice a red flag.

Nurses working in labour and delivery may experience some of the following circumstances that require genomic literacy:

- A nurse could be the first to notice signs and symptoms that may indicate the baby has a genetic condition.
- A nurse could be involved in the delivery of a baby that was diagnosed with a genetic condition during the pregnancy or that has been identified as having a higher chance of having a condition, based on a screening test result or because of the family history.
- Nurses might be caring for an expectant parent who has a genetic condition themselves, meaning they are at higher risk during labour.

**Table 12.2 Genetic conditions and the ways in which they can affect the pregnancy:**

| Condition | How it can affect the pregnancy |
|---|---|
| Loeys-Dietz or vascular Ehlers Danlos syndrome | Increased risk of uterine/vascular rupture. |
| Cystic fibrosis or sickle cell disease | Increased risk of complications around labour. |
| MCADD | Dietary considerations. Also has a considerable impact on neonatal care for the baby after birth (see our case study: Sara's story). |
| Haemophilia (carrier) | Increased risk of port-partum haemorrhage due to changes in factor VIII levels. |
| Marfan syndrome | Increased risk of complications around labour |
| Epidermolysis bullosa (EB) | Potential for huge changes in care and management, both during the pregnancy and neonatally. Read more in this document: 'Epidermolysis bullosa (EB) – information for pregnancy and childbirth' [PDF] |
| Factor V Leiden | Increased risk of clotting disorders in pregnancy, and of miscarriage. Autosomal dominant condition. |

- Nurses could be involved in the delivery of a baby following termination of pregnancy, or a stillborn baby due to genomic complications.

# Mental health

## The challenge of the mind

Throughout the history of psychiatry, researchers have tried but failed to find any physical basis for the strikingly abnormal experiences and behaviours of patients with severe mental illness.

There are no blood tests or brain scans that can help us understand the nature of mental illness. Diagnoses are based on patterns in the clinical presentation, such as mood changes, delusions or ritualistic checking, and medications are prescribed on an empirical basis: we know that they work (sometimes with a surprising level of effectiveness), but we don't really know why.

Mental illnesses are especially difficult to research because invasive investigations of the brain are not possible in the way they are for other organs. Even when physiological differences *can* be measured, it is often impossible to distinguish whether these are causes or effects of mental illness.

## Hope through research

It's now believed that our genes could well play a part in our susceptibility to any given illness, and the effect of genetics on the risk of schizophrenia and bipolar disorder are well evidenced and substantial.

Genomic research offers the hope of better understanding the root causes of mental illness: by finding specific genes which are involved in these devastating illnesses, we might gain some understanding of the pathological processes leading to their development and ultimately develop better treatments.

**Figure 12.6** A colourful, computer-generated image of a brain in hues of blue, pink, and purple. **Source:** Photo by Milad Fakurian, Unsplash license

## CNVs in schizophrenia

The discovery with the most immediate clinical relevance relates to schizophrenia. Research has found that some patients with the condition have a chromosomal abnormality called a copy number variant (CNV) – where there is either an extra copy of part of the chromosome (a duplication) or a part that is missing completely (a deletion).

There are around 12 known locations on the chromosome where a CNV results in a substantially increased risk of schizophrenia – perhaps a thirty-fold or more increase above the background risk of 1%. If such a CNV is present in a person with schizophrenia, then it would be reasonable to say that the CNV had 'caused' the illness.

## Wider implications

Typically, a CNV will impact several different genes and it has proved difficult to identify which of these are specifically responsible for increasing risk. Nevertheless, discovering that a patient carries a CNV has important implications:

- Validation: Finding a CNV can provide the patient and those around them with a clear, concrete explanation for why they have become unwell. For many people, it can be difficult to accept that mental illness is real, and finding a definitive cause can help the person to understand and accept that their condition is valid and deserving of treatment.
- Associated conditions: As well as being the primary cause of a condition like schizophrenia, some CNVs

are also associated with increased risk of additional physical health conditions. Finding a CNV therefore presents an opportunity to investigate, and possibly discover, an illness that was previously undiagnosed.

- Impact on family: Any genetic diagnosis can also have implications for family members, and younger siblings of patients with schizophrenia often express anxiety that they may also develop the illness. If the patient carries a CNV but the sibling does not, then they can be reassured that they are at no increased risk.

The proportion of people with schizophrenia in which a CNV is found is small – around 2% – but since the identification of a CNV has important implications for them and their family, and since the test is simple and inexpensive, some psychiatrists argue that testing for CNVs should be routine for those with a new diagnosis.

## Individual genes

It is known that when the function of certain genes is disrupted by variants in a person's DNA, the risk of schizophrenia can rise. However, implicating individual genes has proved challenging, and the first to be identified, *SETD1A*, did not provide insights into how its disruption might lead to schizophrenia, as had been hoped.

In 2019, research by an international collaboration called SCHEMA (https://www.sciencedirect.com/science/article/abs/pii/S0924977X17305096?via%3Dihub), analyzed thousands of exomes, and identified a handful of genes where loss of function substantially affects schizophrenia risk – with some genes appearing to be linked to disease processes.

The clearest example relates to a particular receptor molecule for the neurotransmitter glutamate. It was already known that drugs blocking this receptor, as well as a syndrome called autoimmune encephalitis where antibodies attack the receptor, could cause symptoms that are similar to schizophrenia. Researchers have now demonstrated that variants that disrupt a gene coding for this receptor also increase schizophrenia risk. Thus, pharmacological, immune and genetic results all suggest that impaired functioning of this glutamate receptor can increase the risk of developing psychotic symptoms and other problems associated with schizophrenia.

These findings offer an opportunity to try to develop better drug treatments which might modify receptor functioning and lessen symptoms.

## Where we are now

Psychiatric genomics is a burgeoning area of research and ever-expanding clinical application. For example, the Psychiatric Genomics Consortium (https://pgc.unc.edu/) is a collaboration of over 800 international scientists working with the pooled data of almost 1 million participants to uncover the role of genetics in psychiatric disorders. Some other fascinating areas of implementation in this practice context include:

PharmGKB (https://www.pharmgkb.org/page/DrugUseAndAddiction) provides evidence-based

information and CPIC guidelines on pharmacogenomics for drugs, genes, and phenotypes involved in substance use disorder.

In this recent study published in November 2024, researchers used machine learning (AI) to detect complex structural variations in the genome that likely contribute to psychiatric disease.

The Mayo Clinic has a Psychiatric Genomics and Pharmacogenomics Program (https://www.mayo.edu/research/centers-programs/psychiatric-genomics-pharmacogenomics-program/focus-areas) that focuses on bipolar disorder, alcohol use disorder, and psychiatric pharmacogenomics.

Discoveries of genetic causes of disordered eating has led to advances in treatment and hope for patients who have been unsuccessful with more traditional therapies.

# Neurology

Rapid advances in technology and understanding mean that genomic testing is becoming much more integral to the field of neurology. Understanding the control of gene expression in the brain is central to understanding normal brain function, and increasingly neurological disease.

As genomic technology is enabling progress in our understanding of the etiology of disease, it is enabling the development of new targeted therapies. Rapid progress in clinical trials and drug development are expected over the next few years. There are now trails underway for Parkinson's disease and motor neurone disease, for example, targeting specific genes such as *LRRK2* and *C9orf72*.

## How is genomics used in neurology?

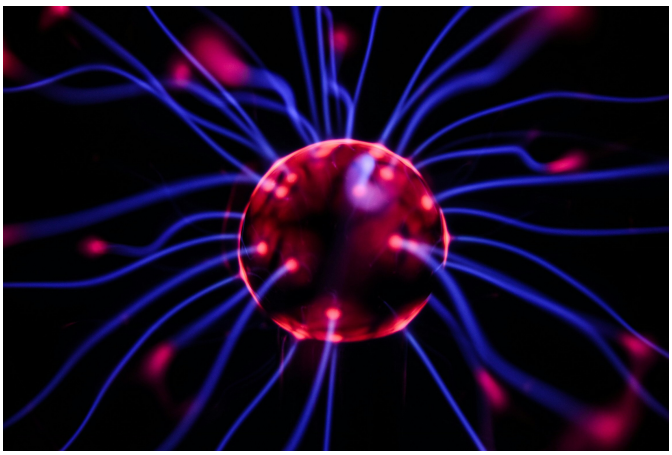

**Figure 12.7.** Photo by Josh Riemer on Unsplash

### Diagnosis

Genomic testing is particularly useful in the diagnosis of familial and early-onset neurodegenerative diseases, for example ataxia, hereditary spastic paraparesis and some forms of dementia and Parkinson's. Disorders such as epilepsy can have a single genetic variant in about 30% of affected individuals (Jain et al., 2019), and more is becoming known about the genetics of neurodevelopmental disorders such as autism (Aldridge et al., 2024).

## Predictive testing

Genomic test results can impact whole families. If variants are found early, it can enable better clinical management for the whole family and enable individuals to consider their options for the future. For example, identification of the Huntington's gene mutation in a family with Huntington disease enables the counselling of other family members for risk-management including possible predictive testing and referral to relevant clinical trials.

## Targeted treatment

In some instances, a precise genetic diagnosis means an individual can access gene-directed therapies which have a good chance of benefiting them.

### Case Example: SMA

An example is the treatment of spinal muscular atrophy (SMA) with Nusinersin. It is hoped that other gene-directed therapies will soon be available.

- SMA is a rare, severely life-limiting and ultimately fatal neuromuscular condition which causes most affected children to die from respiratory failure within the first three years of life.
- Until 2016, there was no treatment for SMA and management in severe cases was with palliative care.
- SMA is caused by mutations in the *SMN* gene, leading to loss of the SMN1 protein.
- In 2016, the therapy Nusinersin was introduced. Nusinersin works by upregulating a 'back-up' copy of the gene, *SMN2*.
- As a result of the availability of this therapy, children with a diagnosis who previously would have had a very limited life expectancy are able to lead much more normal lives.
- Although the long term effects of the treatment are not known, it is clear that it has a dramatic effect on both quality of life and life expectancy for affected children.

It is hoped that many more treatments, based on similar mechanisms, will be developed now that wider access to genomic technology and genomic data is possible.

## Clinical trails and drug development

The identification of the genetic cause(s) of a disease makes it easier to develop targeted therapies. For example:

- The identification of mutations in the synuclein gene in Parkinson's disease, and identifications and mutations in the *APP* and presenilin genes in Alzheimer's disease (https://www.genetics.edu.au/SitePages/Alzheimer-disease.aspx), have allowed for the development of animal models. These animal models have been used to develop antibody-based treatments for these diseases, and those antibody treatments are now in clinical trials. Updates can be found on the Alzoforum website (https://www.alzforum.org/).
- Several years ago, the gene most commonly associated with motor neurone disease – the *C9orf72* gene – was identified. A gene therapy trial is now in progress, looking to turn off the abnormal gene and potentially provide a treatment for affected patients (see 'Genomics in Practice' example below).

The widespread availability and relative accessibility of genomic testing will result in more trials, more patients being eligible for and recruited to trials, and, as a result, more rapid progress in the area of targeted treatments.

## Cardiology

The field of cardiology is increasingly influenced by advances in genomics, which can be used in diagnosis, treatment and management in a number of ways. Health professionals in cardiovascular medicine are increasingly likely to encounter genetic and genomic information and should be aware of how to deal with it.

As well as a role in rarer, inherited cardiac conditions, genomics is increasingly going to have a role in assessment and management of common cardiovascular diseases such as hypertension and coronary disease.

Genomic research directly identifies genes and pathways underpinning disease that may represent new therapeutic targets. Genetics and genomics also have an important and growing role in patient stratification.

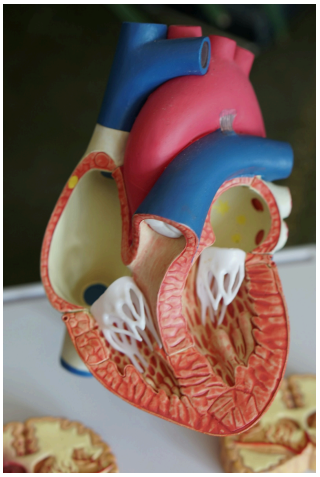

**Figure 12.8.** A plastic model of a heart, cut in half, displaying the four chambers, pulmonary, tricuspid and mitral valves, superior vena cava, pulmonary artery and aorta. **Source:** Photo by Robina Weermeijer, Unsplash license

### Families with inherited cardiac conditions (ICC)

Most ICCs are autosomal dominant, meaning that immediate family members have a 50% chance of inheriting the same condition. Cascade testing can be used to determine the risk to the patient's family members.

## Treatment and management of cardiac conditions

For some inherited cardiac conditions, treatment can be refined when we understand the precise molecular basis of an individual's condition. For example, those with inherited arrhythmia may receive treatment tailored to the genetic cause.

Increasingly, other cardiological treatment can be chosen in accordance with an individual's genetics. For example, genetic testing can determine whether an individual will be resistant to clopidogrel, or has an elevated risk of developing statin myopathy.

Genetic information can be used to intervene early. For example, adopting a favourable lifestyle has been shown to reduce coronary disease risk by around 50% even in the presence of a high genetic predisposition.

To read some examples of Canadian nurses conducting research on the psychosocial aspects of participating in predictive genetic testing for cardiovascular conditions or living with autosomal dominant cardiac conditions, read Manuel and Brunger (2015) (https://journals.sagepub.com/doi/full/10.1177/2333393616674810)and Manuel and Brunger (2014) (https://doi.org/10.1007/s10897-014-9733-4).

## New therapies

Understanding the genetic basis of disease can give us an insight into the molecular mechanisms and pathways involved, which can allow us to develop new treatment strategies. For example, specific disease-modifying targeted therapies are in phase 3 trials in both dilated and hypertrophic cardiomyopathies.

Inherited conditions can serve as genetic models for more common forms of disease. For example, PCSK9 inhibitors – a new class of lipid lowering therapy – were developed as a result of studies into familial hypercholesterolaemia.

New genome technologies are also offering the promise of new therapies through gene repair or replacement. Additional resources for cardiogenomics include GECKO (https://www.geneticseducation.ca/resources-for-clinicians/cardiogenomics) and the University of Ottawa Heart Clinic (https://www.ottawaheart.ca/heart-condition/inherited-cardiac-conditions-genetic-disorders).

# Attribution & References

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# 12.5 UNIT SUMMARY AND REVIEW

## Key Takeaways

This unit explored the interaction between environmental and genetic factors in shaping health outcomes, emphasizing the undeniable evidence of climate change and its direct and indirect impacts on physical, mental, and social health. Climate-related phenomena like forest fires, floods, and warming oceans have profound effects, including exposure to toxins, food chain disruptions, and economic challenges. Global pandemics, driven by environmental degradation, further highlight the interconnected nature of ecosystems. The WHO's 2022 report outlines recommendations for leveraging genomic technologies in global health, including pathogen surveillance, tracking antimicrobial resistance, studying disease outbreaks, and addressing health disparities through genomics.

The molecular and genomic underpinnings of cancer were explored, highlighting two physiological processes of cancer development: growth signal autonomy and insensitivity to growth inhibitory signals. Oncogenes, like *ras*, act as accelerators of cell division when altered by a variant, while tumor suppressor genes, such as *p53* and *BRCA1*, serve as brakes but can promote cancer when inactivated. Most cancers arise from acquired somatic mutations, although germline variants, like those in *BRCA1* or Lynch syndrome genes, can elevate cancer risk. That is to say cancer cannot be inherited – one can inherit an increased risk of developing particular cancers. Advances in genomics, such as liquid biopsies and tumor genome sequencing, are transforming cancer detection, monitoring, and treatment. Nurses play a vital role in recognizing hereditary cancer risks, facilitating referrals, and advancing genomic literacy within oncology care.

The integration of genomics into clinical practice is advancing across several specialties, with oncology leading the way and growing applications in pediatrics, maternity, mental health, neurology, and cardiology, as examples. In these practice areas, genomic testing aids in diagnosis, guides treatments, and enables personalized interventions. It also facilitates family planning through cascade testing and genetic counseling. In psychiatry, genomic research has deepened

understanding of mental illnesses like schizophrenia and informed targeted therapeutic approaches. As genomics becomes more central to healthcare, practitioners must develop genomic literacy to meet evolving patient needs effectively.

## Optional Additional Readings


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## Attribution & References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

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# UNIT 13 - THE FUTURE OF GENOMICS AND NURSING

## Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev


Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

## Unit 13 Contents


- 13.1 Unit Overview
- 13.2 Gene Editing
- 13.3 Other Genomic Technologies
- 13.4 Health System Readiness for the Genomic Era
- 13.6 Unit Summary and Review


## Attribution

# 13.1 UNIT OVERVIEW

## Learning Objectives

- Identify current and emerging gene therapies
- Explore ethical issues involving gene therapy and regulatory oversight
- Compare somatic-cell and germ-line gene therapy
- Examine additional biotechnologies that can contribute to health and wellness
- Envision the future of genomics nursing in the context of Canada's readiness for genomics integration

## Outline

Topics covered in this chapter include:

- Gene editing
- Other genomic technologies
- Health system readiness for the genomic era

## Competencies Nurses will Develop in this Chapter

### ANA (2023):

#### Identification:

- Identifies credible, accurate, appropriate, and current genomic information, resources, services, and technologies specific to given clients.
- Identifies ethical, ethnic or ancestral, cultural, religious, legal, fiscal, and societal issues related to genomic

information and technologies.

# NHS (2023):

## Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the key indicators of a potential genetic condition, or clinical situation where genomics-informed healthcare would be appropriate; and
- recognizing the importance of family history in assessing predisposition to a genetic condition.

## Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

## Apply knowledge, understanding and context of genomic testing and information to underpin care and support for individuals and families prior to, during and following decision-making:

- incorporating awareness of the ethical, legal and social issues related to testing, recording, sharing and storage of genomic information and data.

## Examine your own competency of practice on a regular basis:

- recognizing areas where professional development related to genomics would be beneficial;
- maintaining awareness of clinical developments in genomics that are likely to be of most relevance to your area of practice, seeking further information on a case-by-case basis; and
- based on an understanding of the boundaries of your professional role in delivering genomic healthcare including the referral, provision or follow-up to genomic services.

## Obtain and communicate reliable, current information about genomics, for self, patients, families and colleagues:

- using information technologies and other information sources effectively to do so;
- applying critical appraisal skills to assess the quality of information accessed; and
- ensuring the information is appropriate for the intended audience.

# Key terminology

## Bio-hacking

A movement in which people are experimenting with biotechnology research and development methods outside of traditional research institutions (Parker et al., 2016).

## CRISPR

CRISPR (short for "clustered regularly interspaced short palindromic repeats") is a technology that research scientists use to selectively modify the DNA of living organisms. CRISPR was adapted for use in the laboratory from naturally occurring genome editing systems found in bacteria.

## Gene drives

A natural phenomenon whereby the inheritance of a particular gene or set of genes is favorably biased, resulting in the increase in its frequency in the population. Gene drives can arise through a variety of mechanisms, and scientists have proposed using gene editing to engineer gene drives for specific purposes (Parker et al., 2016).

## Gene therapy

Gene therapy is a technique that uses a gene(s) to treat, prevent or cure a disease or medical disorder. Often, gene therapy works by adding new copies of a gene that is broken, or by replacing a defective or missing gene in a patient's cells with a healthy version of that gene. Both inherited genetic diseases (e.g., hemophilia and sickle cell disease) and acquired disorders (e.g., leukemia) have been treated with gene therapy.

## Genetically modified organisms

GMO (short for "genetically modified organism") is a plant, animal or microbe in which one or more changes have been made to the genome, typically using high-tech genetic engineering, in an attempt to alter the characteristics of an organism. Genes can be introduced, enhanced or deleted within a species, across species or even across kingdoms. GMOs may be used for a variety of purposes, such as making human insulin, producing fermented beverages and developing pesticide resistance in crop plants.

### Germline gene therapy

Alteration of a germline cells using gene therapy. These changes can be passed on to offspring, leading to unintended consequences for future generations (Parker et al., 2016).

### Off-target effects

Potential alterations induced by CRISPR that are unintended, such as changing a beneficial gene, altering its product (Parker et al., 2016).

### Recombinant DNA technology

Recombinant DNA technology involves using enzymes and various laboratory techniques to manipulate and isolate DNA segments of interest. This method can be used to combine (or splice) DNA from different species or to create genes with new functions. The resulting copies are often referred to as recombinant DNA. Such work typically involves propagating the recombinant DNA in a bacterial or yeast cell, whose cellular machinery copies the engineered DNA along with its own.

### Transgenic

Transgenic refers to an organism or cell whose genome has been altered by the introduction of one or more foreign DNA sequences from another species by artificial means. Transgenic organisms are generated in the laboratory for research purposes.

## Attribution & References



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- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.
- 12.4 Gene Therapy In *Microbiology* by Nina Parker, Mark Schneegurt, Anh-Hue Thi Tu, Philip Lister and Brian M. Forster, CC BY 4.0. Access for free at *Microbiology (OpenStax) (https://openstax.org/books/microbiology/pages/1-introduction)*

Definitions adapted from the two sources and combined.

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# 13.2 GENE EDITING

## Genetic Engineering

Many types of genetic engineering have yielded clear benefits with few apparent risks. Few would question, for example, the value of our now abundant supply of human insulin produced by genetically engineered bacteria. However, many emerging applications of genetic engineering are much more controversial, often because their potential benefits are pitted against significant risks, real or perceived. This is certainly the case for gene therapy, a clinical application of genetic engineering that may one day provide a cure for many diseases but is still largely an experimental approach to treatment.

Historically, clinical trials have shown the clear hazards of attempting genetic manipulation in complex multicellular organisms like humans. In some patients, the use of an adenovirus vector can trigger an unanticipated inflammatory response from the immune system, which may lead to organ failure. Moreover, because viruses can often target multiple cell types, the virus vector may infect cells not targeted for the therapy, damaging these other cells and possibly leading to illnesses such as cancer. Another potential risk is that the modified virus could revert to being infectious and cause disease in the patient. Lastly, there is a risk that the inserted gene could unintentionally inactivate another important gene in the patient's genome, disrupting normal cell cycling and possibly leading to tumor formation and cancer. Because gene therapy involves so many risks, candidates for gene therapy need to be fully informed of these risks before providing informed consent to undergo the therapy.

### Case in Point: Gene Therapy Gone Wrong

The risks of gene therapy were realized in the 1999 case of Jesse Gelsinger, an 18-year-old patient who received gene therapy as part of a clinical trial at the University of Pennsylvania. Jesse received gene therapy for a condition called ornithine transcarbamylase (OTC) deficiency, which leads to ammonia accumulation in the blood due to deficient ammonia processing. Four days after the treatment, Jesse died after a severe immune response to the adenovirus vector (Sibbald, 2001).

Until that point, researchers had not really considered an immune response to the vector to be a legitimate risk, but on investigation, it appears that the researchers had some evidence suggesting that this was a possible outcome. Prior to Jesse's treatment, several other human patients had suffered side effects of the treatment, and three monkeys used in a trial had died as a result of inflammation

and clotting disorders. Despite this information, it appears that neither Jesse nor his family were made aware of these risks when they consented to the therapy. Jesse's death was the first patient death due to a gene therapy treatment and resulted in the immediate halting of the clinical trial in which he was involved, the subsequent halting of all other gene therapy trials at the University of Pennsylvania, and the investigation of all other gene therapy trials in the United States. As a result, regulation and oversight of gene therapy in general was reexamined, resulting in new regulatory protocols that are still in place today.

**Source:** Sibbald, B.. (2001). Death but one unintended consequence of gene-therapy trial. *Canadian Medical Association Journal,* 164(11), 1612–1612. https://pmc.ncbi.nlm.nih.gov/articles/PMC81135/

No discussion of gene editing would be complete without introducing CRISPR. Genome editing (also called gene editing) is a group of technologies that give scientists the ability to change an organism's DNA. These technologies allow genetic material to be added, removed, or altered at particular locations in the genome. Several approaches to genome editing have been developed. A well-known one is called CRISPR-Cas9, which is short for clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9. The CRISPR-Cas9 system has generated a lot of excitement in the scientific community because it is faster, cheaper, more accurate, and more efficient than other genome editing methods.

CRISPR-Cas9 was adapted from a naturally occurring genome editing system that bacteria use as an immune defense. When infected with viruses, bacteria capture small pieces of the viruses' DNA and insert them into their own DNA in a particular pattern to create segments known as CRISPR arrays. The CRISPR arrays allow the bacteria to "remember" the viruses (or closely related ones). If the viruses attack again, the bacteria produce RNA segments from the CRISPR arrays that recognize and attach to specific regions of the viruses' DNA. The bacteria then use Cas9 or a similar enzyme to cut the DNA apart, which disables the virus.

Researchers adapted this immune defense system to edit DNA. They create a small piece of RNA with a short "guide" sequence that attaches (binds) to a specific target sequence in a cell's DNA, much like the RNA segments bacteria produce from the CRISPR array. This guide RNA also attaches to the Cas9 enzyme. When introduced into cells, the guide RNA recognizes the intended DNA sequence, and the Cas9 enzyme cuts the DNA at the targeted location, mirroring the process in bacteria. Although Cas9 is the enzyme that is used most often, other enzymes (for example Cpf1) can also be used. Once the DNA is cut, researchers use the cell's own DNA repair machinery to add or delete pieces of genetic material, or to make changes to the DNA by replacing an existing segment with a customized DNA sequence.

Genome editing is of great interest in the prevention and treatment of human diseases. Currently, genome editing is used in cells and animal models in research labs to understand diseases. Scientists are still working to determine whether this approach is safe and effective for use in people.

## CRISPR – Applications in Humans

Applications of CRISPR in humans include treatment for sickle cell disease, (https://ghr.nlm.nih.gov/condition/sickle-cell-disease) which causes severe pain and premature death in millions of people worldwide. Scientists use CRISPR to treat sickle cell disease by removing blood stem cells from a patient with sickle cell disease, editing the genome of those cells to remove the sickle cell mutation, and then re-insert the modified cells into the person's bone marrow.

Another CRISPR application now entering human clinical trials aims to combat human immunodeficiency virus (or HIV) infection (https://www.drugtargetreview.com/news/145203/eliminating-the-hiv-virus-from-infected-cells-with-crispr-cas/). HIV enters human white blood cells and then alters those cells' genomes. Then, it makes copies of itself to infect the person's immune system, making them vulnerable to other infections. CRISPR is now being investigated for use in either cutting out the HIV-derived DNA from the genome as well as engineering a person's genome so that HIV cannot enter their cells. However, it is important to stress that these techniques are still relatively new and very much still in testing mode.

### Concept in Action

## Oversight of Gene Therapy

Presently, there is significant oversight of gene therapy clinical trials. In the US, at the federal level, three agencies regulate gene therapy in parallel: the Food and Drug Administration (FDA), the Office of Human Research Protection (OHRP), and the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH). Along with several local agencies, these federal agencies interact with the institutional review board to ensure that protocols are in place to protect patient safety during clinical trials. Compliance with these protocols is enforced mostly on the local level in cooperation with the federal agencies. Gene therapies are currently under the most extensive federal and local review compared to other types of therapies, which are more typically only under the review of the FDA. Some researchers believe that these extensive regulations actually inhibit progress in gene therapy research. In 2013, the Institute of Medicine (now the National Academy of Medicine) called upon the NIH to relax its review of gene therapy trials in most cases (Grens, 2013). However, ensuring patient safety continues to be of utmost concern.

In Canada, gene therapy products are regulated in the same way as other pharmaceuticals, under the *Food and Drugs Act* and *Food and Drug Regulations* (Jorgensen et al., 2024). Gene therapy products are classified by Health Canada as biologic drugs, which are under the purview of the Health Canada (HC) Biologic and Radiopharmaceutical Drugs Directorate (Jorgensen et al., 2024). Gene therapy products qualify for expedited

approval via HC Notice of Compliance with Conditions (NOC/c), approving drugs that have evidence of potential to treat serious life-threatening or life-limiting conditions, subject to further testing. As such, these drugs are usually not subject to phase 3 clinical trials (Jorgensen et al., 2024).

As of June 6, 2024, there were ten approved gene therapy products in Canada, including treatments targeting rare and severe conditions such as blood cancers and spinal muscular atrophy (Jorgensen et al., 2024). Six of these are CAR-T therapies for blood cancer treatment and the other four are AAV-based therapies that restore gene function (Jorgensen et al., 2024). As of November 21, 2024, there were 41 FDA-approved gene and cell therapies in the US, including treatment for several types of cancer, Duchenne muscular dystrophy, hemophilia A and B, type 1 diabetes, spinal muscular atrophy, and sickle cell disease (USFDA, 2024).

In 2024 Health Canada approved CASGEVY® (exagamglogene autotemcel), an autologous CRISPR-Cas9 genome-edited hematopoietic stem cell therapy to treat sickle cell disease (SCD). This is the first CRISPER-based gene editing therapy approved in Canada. For those who qualify, this will bring relief for this severely debilitating and progressive disease. However, the cost of these medications is exorbitant and it is unclear in the long term whether provincial healthcare plans or insurance companies will continue to pay. CASGEVY, for example, costs $2.2 million for a one-time treatment (Watt, 2024). According to Watt (2024), LENMELDY is one of the most expensive at $4.25 million per dose. However, the cost of managing SCD using other previously existing therapies, including hospital stays for crisis management, is comparable, if not more (Watt, 2024).

## Ethical Concerns

Beyond the health risks of gene therapy, the ability to genetically modify humans poses a number of ethical issues related to the limits of such "therapy." While current research is focused on gene therapy for genetic diseases, scientists might one day apply these methods to manipulate other genetic traits not perceived as desirable, which brings us back to the discussion on eugenics. This raises questions such as:

- Which genetic traits are worthy of being "corrected"?
- Should gene therapy be used for cosmetic reasons or to enhance human abilities?
- Should genetic manipulation be used to impart desirable traits to the unborn?
- Is everyone entitled to gene therapy, or could the cost of gene therapy create new forms of social inequality?
- Who should be responsible for regulating and policing inappropriate use of gene therapies?

### What are off-target effects?

There are concerns that CRISPR might inadvertently alter regions of the genome other than the intended

ones. These are called "**off-target effects**." The worry is that CRISPR could change a beneficial gene, such as disabling a tumor-suppressing gene or activating one that causes cancer. Another concern is that because no two people's genomes are identical, identifying off-target effects in individuals may be impossible. Researchers attempt to predict where in the genome off-target effects might occur using web-based algorithms, but there are concerns that this approach is not accurate enough.

In May 2017, an article published in the journal Nature Methods (http://www.nature.com/nmeth/journal/v14/n6/full/nmeth.4293.html) reported an alarming number of off-target mutations in mice whose genomes had been edited using CRISPR. However, experts voiced skepticism (https://geneticliteracyproject.org/2017/06/02/crispr-study-reporting-off-target-mutations-draws-skepticism-researchers/) of the finding because only two mice were edited and unusual methods used. Scientists are attempting to address these concerns by developing more precise variants of the Cas9 enzyme used in the CRISPR system. Some of these enzymes have been shown to improve targeting in human tissue in the lab. Researchers have also focused on developing methods to more efficiently locate off-target mutations in the animals they study.

## Somatic vs. Germline Editing

The ability to alter reproductive cells using gene therapy could also generate new ethical dilemmas. To date, the various types of gene therapies have been targeted to somatic cells, the non-reproductive cells within the body. Because somatic cell traits are not inherited, any genetic changes accomplished by somatic-cell gene therapy would not be passed on to offspring. However, should scientists successfully introduce new genes to germ cells, the resulting traits could be passed on to offspring. This approach, called **germ-line gene therapy**, could potentially be used to combat heritable diseases, but it could also lead to unintended consequences for future generations. Moreover, there is the question of informed consent, because those impacted by germ-line gene therapy are unborn and therefore unable to choose whether they receive the therapy. For these reasons, the U.S. government does not currently fund research projects investigating germ-line gene therapies in humans.

### Ethical Issues Spotlight

In 2018, Chinese researcher He Jiankui edited twin embryos using CRISPER to disable the CCR5 gene to make them immune to HIV infection and transplanted them into a human uterus. He only announced his work to the world once the twins were born. As a result, the Chinese government arrested him and he served jail time. There was immense backlash following his announcement among the scientific community. This expedited the conversation around the ethical issues on the use of this technology.

### Read this short article that highlight the concerns

Bai, N. (2018, November 30). *What's so controversial about the first gene-edited babies? Experts explain*. University of California San Francisco. https://www.ucsf.edu/news/2018/11/412461/whats-so-controversial-about-first-gene-edited-babies-experts-explain


Following the announcement about the work of He Jiankui, in 2019, scientists called for a five-year global moratorium on all clinical uses of human germline editing (Ladner et al., 2019). The aim was to allow for a period of discussion about the potential medical, societal, and ethical issues germline editing might pose. This was to be followed by a period where nations would choose how to proceed and whether they would continue to impose a ban. The hope was for transparency and open communication amongst the scientific community. The ban did not apply to research using germline editing, provided there was no transfer of embryos to a human uterus (Ladner et al., 2019). In Canada, the TCPS2 guidelines, article 13.7, section G, addresses research involving gene transfer. It directs readers to the *Assisted Human Reproduction Act* which prohibits altering the human genome or in vitro embryo such that the alteration can be passed on to subsequent generations (Government of Canada, 2022). While there are no laws or regulations in many countries prohibiting germline editing, the moratorium is strictly voluntary. It has now been five years and, despite the potential ethical issues remaining, there is discussion that South Africa might be the first country to accept germline editing (https://www.nature.com/articles/d41586-024-03643-4).

## What are gene drives?

A **gene drive** is a natural phenomenon whereby the inheritance of a particular gene or set of genes is favorably biased, resulting in the increase in its frequency in the population. Gene drives can arise through a variety of mechanisms, and scientists have proposed using gene editing to engineer gene drives for specific purposes. These include preventing the spread of insects that carry pathogens, such as mosquitoes that transmit malaria, dengue, Zika and other diseases.

Here is how it works: This system uses genetically modified male mosquitos to deliver new genes along with a mechanism for copying the new sequences from one member of a chromosome pair to the other. In other words, a mosquito larva has a gene that came only from its father, yet has it as both a paternal and maternal copy. Thus, even a recessive gene will manifest its trait in all offspring. Furthermore, the offspring will spread the gene and trait to their own offspring. Since mosquitoes have a short life cycle, this means that in the course of just a summer, we could alter almost the entire population of a particular mosquito species in

say the Brazilian rain forest, possibly wiping out the Zika disease. In August 2016 the U.S. Food And Drug Administration (FDA) issued a "Finding of No Significant Impact (https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm490246.htm)" to biotech company Oxitec's plan to release genetically modified male Aedes aegypti mosquitoes into the Florida Keys.

Engineered gene drives have also been proposed (https://geneticliteracyproject.org/2017/11/16/saving-galapagos-gene-drives-help-rid-invasive-pests/) to control invasive species, such as rodents that eat the eggs of endangered bird species in New Zealand, and for eliminating herbicide and pesticide resistance in crops.

Concerns about gene drives (https://geneticliteracyproject.org/2017/11/17/gene-drive-trials-risky-field-studies/) include the possibility that a mutation could happen during the engineered gene drive, which could spread unwanted traits with the drive. The spread of some other disease could be unexpectedly facilitated. Or the elimination of a link in the food chain could harm the local ecology. It's also plausible that something could happen akin to the introduction of rabbits in 19th century Australia (http://www.nma.gov.au/online_features/defining_moments/featured/rabbits_introduced), where the population exploded, due to lack of predators, with major consequences for the ecosystem. There are also worries that an engineered gene drive could move beyond its target population, causing unintended impacts on other species and ecosystems.

Anti-biotechnology activists including Vandana Shiva, Jane Goodall and David Suzuki have advocated against the use of gene drives. In August 2017, they joined with other radical environmental groups (https://globaljusticeecology.org/30-environmental-leaders-say-no-to-gene-drives-in-conservation/) to issue a well-publicized opposition statement [PDF] (http://www.etcgroup.org/files/files/final_gene_drive_letter.pdf) to gene drive technology, writing:

*Given the obvious dangers of irretrievably releasing genocidal genes into the natural world, and the moral implications of taking such action, we call for a halt to all proposals for the use of gene drive technologies, but especially in conservation.*

In 2016, the National Academy of Sciences issued its wide-ranging review of dozens of studies, Report on Gene Drives in Non-Human Organisms [PDF] (https://www.nap.edu/resource/23405/Gene-Drives-Brief.pdf), which outlined a number of potential risks but urged more research and gave a cautious green light to "highly controlled field trials." Some studies have come to different conclusions, among them: researchers at the University of California, San Diego and colleagues at Harvard created a mathematical model (https://www.nytimes.com/2017/11/16/science/gene-drives-crispr.html) for CRISPRs likely success, concluding the a gene drive could be remarkably aggressive in the wild, spreading a new gene beyond its targeted population—possibly meaning that experiments in the real world are too risky on a case by case basis at this stage in the technology's development.

If you are interested in learning how CRISPR-Cas9 is being used by consumers and bio-hackers,

## What is "bio-hacking" and "DIY-bio?"

Do-it-yourself biology, also called "**biohacking**" or "DIY bio," is a movement in which people are experimenting with biotechnology

research and development methods outside of traditional research institutions. Some "biohackers" are trying to make these methods easier and more accessible, so that even non-scientists can use them. Because of its relative ease to deploy, CRISPR experiments can be performed even by high school students.

watch this fascinating and horrifying documentary on Netflix – Unnatural Selection (https://www.netflix.com/ca/title/80208910)

One of the most accessible forms of biohacking is through engineering microorganisms or plants. Experiments range from using plasmids to create fluorescent bacteria, controlling gene expression using light in bacteria and even using CRISPR to engineer the genomes of bacteria or yeast. Some biohackers have begun selling kits that allow you to use CRISPR at home (https://geneticliteracyproject.org/2017/11/09/crispr-home-easy-hack-dna/). One kit, created as part of an Indiegogo crowd-funding project, was sold for $130 by biohacker Josiah Zayner.

## The Future of CRISPR

Despite the serious ethical challenges, CRISPR/Cas 9 is a promising technology to treat a multitude of conditions.

### Concept in Action

Watch this brief Ted Talk given by Nobel Prize recipient Jennifer Doudna, the scientist credited with CRISPR's creation, speak about how metagenomics and CRISPR are being combined to create a new field of science called Precision Microbiome editing. This could provide a transformative solution targeting the microbiome to treat diseases and disorders such as asthma, obesity, diabetes, Alzheimer's and climate change.

**Watch CRISPR's Next Advance is Bigger Than You Think | Jennifer Doudna | TED (8 mins) on YouTube (https://youtu.be/HANo__Z8K6s)**

## Attribution & References

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- Genome Editing and Human Disease from What are genome editing and CRISPR-Cas9? In *Help Me Understand Genetics* Courtesy of MedlinePlus from the National Library of Medicine, Public Domain with attribution

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# 13.3 OTHER GENOMIC TECHNOLOGIES

It is easy to see how biotechnology can be used for medicinal purposes. Knowledge of the genetic makeup of our species, the genetic basis of heritable diseases, and the invention of technology to manipulate and fix mutant genes provides methods to treat diseases. Biotechnology in agriculture can enhance resistance to disease, pests, and environmental stress to improve both crop yield and quality. Genomic technologies have the potential to transform the future of health and healthcare.

## Production of Vaccines, Antibiotics, and Hormones

Traditional vaccination strategies use weakened or inactive forms of microorganisms or viruses to stimulate the immune system. Modern techniques use specific genes of microorganisms cloned into vectors and mass-produced in bacteria to make large quantities of specific substances to stimulate the immune system. The substance is then used as a vaccine. In some cases, such as the H1N1 flu vaccine, genes cloned from the virus have been used to combat the constantly changing strains of this virus.

Antibiotics kill bacteria and are naturally produced by microorganisms such as fungi; penicillin is perhaps the most well-known example. Antibiotics are produced on a large scale by cultivating and manipulating fungal cells. The fungal cells have typically been genetically modified to improve the yields of the antibiotic compound.

**Recombinant DNA technology** was used to produce large-scale quantities of the human hormone insulin in *E. coli* as early as 1978. Previously, it was only possible to treat diabetes with pig insulin, which caused allergic reactions in many humans because of differences in the insulin molecule. In addition, human growth hormone (HGH) is used to treat growth disorders in children. The HGH gene was cloned from a cDNA (complementary DNA) library and inserted into *E. coli* cells by cloning it into a bacterial vector.

## Transgenic Animals

Although several recombinant proteins used in medicine are successfully produced in bacteria, some proteins need a eukaryotic animal host for proper processing. For this reason, genes have been cloned and expressed in animals such as sheep, goats, chickens, and mice. Animals that have been modified to express recombinant DNA are called **transgenic animals**. Several human proteins are expressed in the milk of transgenic sheep and goats. In one commercial example, the FDA has approved a blood anticoagulant protein that is produced in the milk of transgenic goats for use in humans. Mice have been used extensively for expressing and studying the effects of recombinant genes and mutations.

**Figure 13.1** It can be seen that two of these mice are transgenic because they have a gene that causes them to fluoresce under a UV light. The non-transgenic mouse does not have the gene that causes fluorescence. **Source:** Moen et al., CC BY 2.0)

## Cloning

The term cloning describes a number of different processes that can be used to produce genetically identical copies of a biological entity. The copied material, which has the same genetic makeup as the original, is referred to as a clone. Researchers have cloned a wide range of biological materials, including genes, cells, tissues and even entire organisms, such as a sheep.

### Do clones ever occur naturally?

Yes. In nature, some plants and single-celled organisms, such as bacteria (https://www.genome.gov/Glossary/?id=15), produce genetically identical offspring through a process called asexual reproduction. In asexual reproduction, a new individual is generated from a copy of a single cell from the parent organism.

Natural clones, also known as identical twins, occur in humans and other mammals. These twins are produced when a fertilized egg splits, creating two or more embryos that carry almost identical DNA (https://www.genome.gov/Glossary/?id=48). Identical twins have nearly the same genetic makeup as each other, but they are genetically different from either parent.

## What are the types of artificial cloning?

There are three different types of artificial cloning: gene cloning, reproductive cloning and therapeutic cloning.

Gene cloning produces copies of genes or segments of DNA. Reproductive cloning produces copies of whole animals. Therapeutic cloning produces embryonic stem cells for experiments aimed at creating tissues to replace injured or diseased tissues.

Gene cloning, also known as DNA cloning, is a very different process from reproductive and therapeutic cloning. Reproductive and therapeutic cloning share many of the same techniques, but are done for different purposes.

## How are genes cloned?

Researchers routinely use cloning techniques to make copies of genes that they wish to study. The procedure consists of inserting a gene from one organism, often referred to as "foreign DNA," into the genetic material of a carrier called a vector. Examples of vectors include bacteria, yeast cells, viruses or plasmids, which are small DNA circles carried by bacteria. After the gene is inserted, the vector is placed in laboratory conditions that prompt it to multiply, resulting in the gene being copied many times over.

## How are animals cloned?

In reproductive cloning, researchers remove a mature somatic cell (http://www.genome.gov/Glossary/?id=186), such as a skin cell, from an animal that they wish to copy. They then transfer the DNA of the donor animal's somatic cell into an egg cell, or oocyte, that has had its own DNA-containing nucleus removed.

Researchers can add the DNA from the somatic cell to the empty egg in two different ways. In the first method, they remove the DNA-containing nucleus of the somatic cell with a needle and inject it into the empty egg. In the second approach, they use an electrical current to fuse the entire somatic cell with the empty egg.

In both processes, the egg is allowed to develop into an early-stage embryo in the test-tube and then is implanted into the womb of an adult female animal.

Ultimately, the adult female gives birth to an animal that has the same genetic make up as the animal that donated the somatic cell. This young animal is referred to as a clone. Reproductive cloning may require the use of a surrogate mother to allow development of the cloned embryo, as was the case for the most famous cloned organism, Dolly the sheep.

## What animals have been cloned?

Over the last 50 years, scientists have conducted cloning experiments in a wide range of animals using a variety of techniques. In 1979, researchers produced the first genetically identical mice by splitting mouse embryos in the test tube and then implanting the resulting embryos into the wombs of adult female mice. Shortly after that, researchers produced the first genetically identical cows, sheep and chickens by transferring the nucleus of a cell taken from an early embryo into an egg that had been emptied of its nucleus.

It was not until 1996, however, that researchers succeeded in cloning the first mammal from a mature (somatic) cell taken from an adult animal. After 276 attempts, Scottish researchers finally produced Dolly, the lamb from the udder cell of a 6-year-old sheep. Two years later, researchers in Japan cloned eight calves from a single cow, but only four survived.

Besides cattle and sheep, other mammals that have been cloned from somatic cells include: cat, deer, dog, horse, mule, ox, rabbit and rat. In addition, a rhesus monkey has been cloned by embryo splitting.

## Have humans been cloned?

Despite several highly publicized claims, human cloning still appears to be fiction. There currently is no solid scientific evidence that anyone has cloned human embryos.

In 1998, scientists in South Korea claimed to have successfully cloned a human embryo, but said the experiment was interrupted very early when the clone was just a group of four cells. In 2002, Clonaid, part of a religious group that believes humans were created by extraterrestrials, held a news conference to announce the birth of what it claimed to be the first cloned human, a girl named Eve. However, despite repeated requests by the research community and the news media, Clonaid never provided any evidence to confirm the existence of this clone or the other 12 human clones it purportedly created.

In 2004, a group led by Woo-Suk Hwang of Seoul National University in South Korea published a paper in the journal *Science* in which it claimed to have created a cloned human embryo in a test tube. However, an independent scientific committee later found no proof to support the claim and, in January 2006, *Science* announced that Hwang's paper had been retracted.

From a technical perspective, cloning humans and other primates is more difficult than in other mammals. One reason is that two proteins essential to cell division, known as spindle proteins, are located very close to the chromosomes in primate eggs. Consequently, removal of the egg's nucleus to make room for the donor nucleus also removes the spindle proteins, interfering with cell division. In other mammals, such as cats, rabbits and mice, the two spindle proteins are spread throughout the egg. So, removal of the egg's nucleus does not result in loss of spindle proteins. In addition, some dyes and the ultraviolet light used to remove the egg's nucleus can damage the primate cell and prevent it from growing.

## What are the potential applications of cloned animals?

Reproductive cloning may enable researchers to make copies of animals with the potential benefits for the fields of medicine and agriculture.

For instance, the same Scottish researchers who cloned Dolly have cloned other sheep that have been genetically modified to produce milk that contains a human protein essential for blood clotting. The hope is that someday this protein can be purified from the milk and given to humans whose blood does not clot properly. Another possible use of cloned animals is for testing new drugs and treatment strategies. The great advantage of using cloned animals for drug testing is that they are all genetically identical, which means their responses to the drugs should be uniform rather than variable as seen in animals with different genetic make-ups.

After consulting with many independent scientists and experts in cloning, the U.S. Food and Drug Administration (FDA) decided in January 2008 that meat and milk from cloned animals, such as cattle, pigs and goats, are as safe as those from non-cloned animals. The FDA action means that researchers are now free to using cloning methods to make copies of animals with desirable agricultural traits, such as high milk production or lean meat. However, because cloning is still very expensive, it will likely take many years until food products from cloned animals actually appear in supermarkets.

Another application is to create clones to build populations of endangered, or possibly even extinct, species of animals. In 2001, researchers produced the first clone of an endangered species: a type of Asian ox known as a guar. Sadly, the baby guar, which had developed inside a surrogate cow mother, died just a few days after its birth. In 2003, another endangered type of ox, called the Banteg, was successfully cloned. Soon after, three African wildcats were cloned using frozen embryos as a source of DNA. Although some experts think cloning can save many species that would otherwise disappear, others argue that cloning produces a population of genetically identical individuals that lack the genetic variability necessary for species survival.

Some people also have expressed interest in having their deceased pets cloned in the hope of getting a similar animal to replace the dead one. But as shown by Cc the cloned cat, a clone may not turn out exactly like the original pet whose DNA was used to make the clone.

## What are the potential drawbacks of cloning animals?

Reproductive cloning is a very inefficient technique and most cloned animal embryos cannot develop into healthy individuals. For instance, Dolly was the only clone to be born live out of a total of 277 cloned embryos. This very low efficiency, combined with safety concerns, presents a serious obstacle to the application of reproductive cloning.

Researchers have observed some adverse health effects in sheep and other mammals that have been cloned. These include an increase in birth size and a variety of defects in vital organs, such as the liver, brain and heart. Other consequences include premature aging and problems with the immune system. Another potential

problem centers on the relative age of the cloned cell's chromosomes. As cells go through their normal rounds of division, the tips of the chromosomes, called telomeres, shrink. Over time, the telomeres become so short that the cell can no longer divide and, consequently, the cell dies. This is part of the natural aging process that seems to happen in all cell types. As a consequence, clones created from a cell taken from an adult might have chromosomes that are already shorter than normal, which may condemn the clones' cells to a shorter life span. Indeed, Dolly, who was cloned from the cell of a 6-year-old sheep, had chromosomes that were shorter than those of other sheep her age. Dolly died when she was six years old, about half the average sheep's 12-year lifespan.

## What is therapeutic cloning?

Therapeutic cloning involves creating a cloned embryo for the sole purpose of producing embryonic stem cells with the same DNA as the donor cell. These stem cells can be used in experiments aimed at understanding disease and developing new treatments for disease. To date, there is no evidence that human embryos have been produced for therapeutic cloning.

The richest source of embryonic stem cells is tissue formed during the first five days after the egg has started to divide. At this stage of development, called the blastocyst, the embryo consists of a cluster of about 100 cells that can become any cell type. Stem cells are harvested from cloned embryos at this stage of development, resulting in destruction of the embryo while it is still in the test tube.

## What are the potential applications of therapeutic cloning?

Researchers hope to use embryonic stem cells, which have the unique ability to generate virtually all types of cells in an organism, to grow healthy tissues in the laboratory that can be used replace injured or diseased tissues. In addition, it may be possible to learn more about the molecular causes of disease by studying embryonic stem cell lines from cloned embryos derived from the cells of animals or humans with different diseases. Finally, differentiated tissues derived from ES cells are excellent tools to test new therapeutic drugs.

## What are the potential drawbacks of therapeutic cloning?

Many researchers think it is worthwhile to explore the use of embryonic stem cells as a path for treating human diseases. However, some experts are concerned about the striking similarities between stem cells and cancer cells. Both cell types have the ability to proliferate indefinitely and some studies show that after 60 cycles of cell division, stem cells can accumulate mutations that could lead to cancer. Therefore, the relationship between stem cells and cancer cells needs to be more clearly understood if stem cells are to be used to treat human disease.

## What are some of the ethical issues related to cloning?

Gene cloning is a carefully regulated technique that is largely accepted today and used routinely in many labs worldwide. However, both reproductive and therapeutic cloning raise important ethical issues, especially as related to the potential use of these techniques in humans.

Reproductive cloning would present the potential of creating a human that is genetically identical to another person who has previously existed or who still exists. This may conflict with long-standing religious and societal values about human dignity, possibly infringing upon principles of individual freedom, identity and autonomy. However, some argue that reproductive cloning could help sterile couples fulfill their dream of parenthood. Others see human cloning as a way to avoid passing on a deleterious gene that runs in the family without having to undergo embryo screening or embryo selection.

Therapeutic cloning, while offering the potential for treating humans suffering from disease or injury, would require the destruction of human embryos in the test tube. Consequently, opponents argue that using this technique to collect embryonic stem cells is wrong, regardless of whether such cells are used to benefit sick or injured people.

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# 13.4 HEALTH SYSTEM READINESS FOR THE GENOMIC ERA

## Nursing & The Future of Genomics

The future of genomics in healthcare is poised to transform the prevention, diagnosis, and treatment of diseases through precision medicine. As healthcare evolves to integrate these technologies, nurses will play a pivotal role as educators, advocates, and leaders. They will guide patients in understanding genetic information, support informed decision-making, and bridge the gap between complex genomic data and patient-centred care. Additionally, nurses will contribute to interdisciplinary teams by addressing ethical considerations, ensuring equitable access to genomic interventions, and fostering genomic literacy within healthcare systems. Their holistic perspective positions them as vital contributors to the equitable implementation of genomics in improving population health outcomes.

**Watch The Future of Genomics (1 mins) on YouTube (https://youtu.be/Ghkrzc0QxrA)**

## What will the future of genomics look like?

Watch Siddhartha Mukherjee, biologist, physician, and Pulitzer Prize-winning author of the Gene: An Intimate History, describe 10 bold predictions for the future of genomics.

Note: This is an amazing book that everyone should read! There is also a full length PBS series by Ken Burns based on the book by Mukherjee (https://www.pbslearningmedia.org/resource/the-gene-full-film/the-gene-intimate-history/).

**Watch The Future of Genomics: 10 Bold Predictions (4 mins) on YouTube (https://youtu.be/5kAL11m_fwM)**

Visit the NHGRI website for an interactive web-based application detailing the NHGRI 2020 Strategic Vision (https://www.genome.gov/2020SV). You can also access the full document in .pdf format [PDF]

(https://www.genome.gov/sites/default/files/media/files/2022-11/Strategic-vision-for-improving-human-health-at-The-Forefront-of-Genomics.pdf).

## Canada's Readiness for Genomics Integration

In this course, we have discussed the benefits of genomics, alongside the challenges associated with its implementation. In 2021, Canada committed $400 million dollars to the Pan-Canadian Genomics Strategy (PCGS), aiming to position Canada as a global leader in genomics innovation (Government of Canada, 2023). To guide this initiative, the government engaged interested parties to identify strategic priorities, resulting in publishing a consultation paper (https://ised-isde.canada.ca/site/genomics/en/consultation-paper-developing-pan-canadian-genomics-strategy).

The consultation paper (Government of Canada, 2023) outlines that a major challenge to genomics integration lies in the fragmentation of genomics services due to federated health systems, which hinder a unified national approach. Addressing these gaps requires enhanced coordination and collaboration across jurisdictions. Building a robust genomics workforce is also critical, involving initiatives to develop expertise, create employment opportunities, and attract and retain top talent. Furthermore, the standardization and secure sharing of genomic data across regions must be prioritized to maximize the utility of genomics research. The Global Alliance for Genomics and Health (GA4GH, n.d) provides a framework for responsible sharing of genomic and health-related data (https://www.ga4gh.org/framework/). Additionally, the World Health Organization (2024) just released guidance for human genome data collection, access, use and data sharing (https://www.who.int/publications/i/item/9789240102149).Overcoming barriers in transitioning genomics technologies from research to commercialization, including pharmaceuticals, is essential for Canada to lead in the genomic era. Finally, the integration of genomics across diverse sectors—such as healthcare, environmental stewardship, and the food industry—will be pivotal in realizing the full potential of genomics in advancing Canadian society (Government of Canada, 2023). The Canadian Institutes of Health Research strategic plan Sequencing Our Future: 2020-2027, (https://cihr-irsc.gc.ca/e/52973.html) mentioned in a previous unit, also commits to enabling genomic medicine through research, including streamlining data access through developing a Canadian Human Genome Library (https://genomelibrary.ca/). Husereau et al. (2023) evaluated Canada's readiness to adopt widespread genomic testing through a comprehensive literature review and interviews with key informants. Their analysis assessed the healthcare system against established readiness conditions, revealing that Canada remains in the early stages of preparing for a genomic future. Among the provinces examined by the authors (British Columbia, Alberta, Ontario, Quebec, and Nova Scotia), Alberta and Quebec have made the most significant strides in genomics integration, attributed to their establishment of centralized laboratories and service organizations, which mitigate fragmentation within these provinces. In contrast, provinces with multiple health authorities face heightened challenges in coordinating genomic services. These findings align with priorities identified in the consultation paper and underscore the need for provider education and navigation tools to facilitate integration into healthcare

systems. A major barrier highlighted is funding, which will require substantial attention to ensure successful implementation (Husereau et al., 2023).

## Attribution & References



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# 13.6 UNIT SUMMARY AND REVIEW

## Key Takeaways

Genetic engineering has produced significant benefits, such as insulin production, but applications like gene therapy remain controversial due to significant risks and ethical issues. Gene therapy shows potential to cure diseases but has faced challenges, including immune reactions to viral vectors, off-target effects, and tumor risks, as highlighted by the 1999 case of Jesse Gelsinger, whose death spurred stricter regulations.

Advancements in genome editing, particularly CRISPR-Cas9, have revolutionized DNA manipulation by enabling precise, efficient, and cost-effective edits. Adapted from bacterial immune systems, CRISPR-Cas9 introduces targeted DNA cuts, allowing researchers to modify genetic material. Applications include promising but experimental treatments for conditions such as sickle cell disease and HIV, though these approaches remain under evaluation for safety and efficacy in humans.

Biotechnology has broad applications in medicine, leveraging genetic knowledge and technology to address challenges such as disease treatment. In medicine, biotechnology enables the production of vaccines, antibiotics, and hormones, often using recombinant DNA technology and genetically engineered microorganisms or transgenic animals. For example, insulin and human growth hormone are now produced in bacteria, while transgenic animals produce complex proteins for therapeutic use.

The integration of genomics into healthcare is set to revolutionize disease prevention, diagnosis, and treatment through precision medicine, with nurses playing critical roles as educators, advocates, and leaders in supporting patient understanding and equitable implementation. In Canada, efforts to advance genomics include the Pan-Canadian Genomics Strategy and strategic initiatives to address challenges such as service fragmentation, workforce development, and data standardization. Alberta and Quebec have made notable progress through centralized services, but funding and coordination remain significant barriers nationally. Continued investment in

infrastructure, education, and collaboration is essential to fully realize the potential of genomics in healthcare and beyond.

Genomics is reshaping healthcare by enabling personalized approaches to patient care. As genomics becomes integral to healthcare practice, nurses must adapt by acquiring the knowledge and skills necessary to provide safe, equitable, and accessible care. This book has equipped readers with foundational genomic literacy, emphasizing the significance of genetic, environmental, and lifestyle factors in disease susceptibility and progression. By understanding the interconnection of these factors and integrating evidence-based, genomics-informed practices, nurses can assess risks, interpret data, and advocate for personalized care strategies. Furthermore, the text highlights the critical role of nurses within interdisciplinary teams, advancing the delivery of genomic services and fostering improved health outcomes for individuals and populations through advocacy and policy. The hope is that this book empowers nursing professionals to participate as leaders in the evolution of genomics-integration for precision healthcare.

## Attribution and References

- Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.
- Closing summary written by Andrea Gretchev.

## References

ChatGPT: OpenAI. (2024). *ChatGPT (Version 4.0)* [Large language model]. https://openai.com

# APPENDIX

# APPENDIX A: GENETIC AND GENOMIC ONLINE RESOURCES

## Compilation of Genetic and Genomic Online Resources

- **OMIM**: OMIM: Online Mendelian Inheritance in Man (https://omim.org/) – A comprehensive database of human genes and genetic phenotypes, focusing on the relationship between genotype and phenotype.
- **The Human Protein Atlas**: The Human Protein Atlas (https://www.proteinatlas.org/)– Provides detailed information on the tissue and cell distribution of proteins in the human body.
- **GeneCards**: GeneCards (https://www.genecards.org/)– An integrated database offering comprehensive information on all annotated and predicted human genes.
- **ClinGen**: ClinGen (https://www.clinicalgenome.org/)– Defines the clinical relevance of genes and variants for use in precision medicine and research.
- **ClinVar**: ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/)– Archives and aggregates information about relationships among genomic variation and human health.
- **GeneReviews**: GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/)– Provides expert-authored, peer-reviewed disease descriptions focusing on diagnosis, management, and genetic counseling.
- **NIH Gene**: NIH Gene (https://www.ncbi.nlm.nih.gov/genbank/)– A searchable database of genes, focusing on genomes that have been completely sequenced.
- **Human Disease Genes**: Human Disease Genes (https://humandiseasegenes.nl/)– Offers professional information about genes and their clinical consequences.
- **ExpressAnalyst**: ExpressAnalyst (https://expressanalyst.ca/) – A web-based platform for gene expression data analysis.
- **Reactome**: Reactome (https://reactome.org/)– A free, curated database of biological pathways.
- **Comparative Toxicogenomics Database**: Comparative Toxicogenomics Database (https://ctdbase.org/about/) – Provides information on the effects of environmental chemicals on human health.
- **National Comprehensive Cancer Network**: NCCN (https://www.nccn.org/)– Provides guidelines and resources for cancer care.
- **National Library of Medicine (Gene)**: NLM Gene (https://www.ncbi.nlm.nih.gov/) – Offers access to a wide range of biomedical and genomic information.

- **The Expression Atlas**: The Expression Atlas (https://www.ebi.ac.uk/gxa/home) – Provides information on gene expression patterns under different biological conditions.
- **Ensembl**: Ensembl (https://useast.ensembl.org/index.html)– A genome browser for vertebrate genomes.
- **Gene Omnibus**: Gene Omnibus (https://www.ncbi.nlm.nih.gov/genbank/)– A repository for gene expression data.
- **NCBI Genome Data Viewer**: NCBI Genome Data Viewer (https://www.ncbi.nlm.nih.gov/genbank/)– A genome browser for visualizing genomic data.
- **UCSC Genome Browser**: UCSC Genome Browser (https://genome.ucsc.edu/cgi-bin/hgGateway)– A tool for exploring the human genome.
- **SFARI Gene**: SFARI Gene (https://gene.sfari.org/) – A database for autism research.
- **PhenX Toolkit**: PhenX Toolkit (https://www.phenxtoolkit.org/) – A repository of standardized measurement protocols.
- **Gabriella Miller Kids First Data Resource Center**: Kids First Data Resource Center (https://d3b.center/kidsfirst/) – Provides biospecimens and genetic data related to pediatric cancer and structural birth defects.
- **Health and Retirement Study**: Health and Retirement Study (https://hrs.isr.umich.edu/about) – A longitudinal study of health and economic conditions in older adults.
- **MetaboAnalyst**: MetaboAnalyst (https://www.metaboanalyst.ca/) – A tool for metabolomics data analysis.
- **Plink**: Plink (https://zzz.bwh.harvard.edu/plink/) – A toolset for whole-genome association analysis.
- **Plink 1.9 Update**: Plink 1.9 Update (https://www.cog-genomics.org/plink/) – An updated version of the Plink toolset.
- **IGV Integrative Genomics Viewer**: IGV (https://software.broadinstitute.org/software/igv/) – A tool for interactive exploration of large genomic datasets.
- **GeneMania**: GeneMania (https://genemania.org/) – A tool for predicting gene function and gene-gene interactions.
- **Cytoscape**: Cytoscape (https://cytoscape.org/) – A software platform for visualizing complex networks.
- **OpenEpi.com**: OpenEpi.com (https://www.openepi.com/Menu/OE_Menu.htm) – Provides statistical calculators for epidemiology.
- **Coriell Institute**: Coriell Institute – A biobank for human cells and DNA.
- **NHANES**: NHANES – A program of studies designed to assess the health and nutritional status of adults and children in the United States.
- **Pharmacogenomics**:
    - CPIC (https://cpicpgx.org/guidelines/) – Provides guidelines for pharmacogenomics.
    - PharmGKB (https://www.pharmgkb.org/) – A resource for pharmacogenomics knowledge.
    - PharmVar (https://www.pharmvar.org/) – A database of pharmacogenetic variants.

- **Cancer/Control Data Sets**:
  - GTEx (https://gtexportal.org/home/) – Provides data on gene expression and regulation in multiple human tissues.
  - cBioPortal (https://www.cbioportal.org/) – A resource for exploring cancer genomics data.
- **miRNA**:
  - miRDB – A database for miRNA target prediction.
  - miRBase – A database of published miRNA sequences and annotations.
  - miRNet – A tool for miRNA network analysis.
  - TargetScan – A tool for predicting biological targets of miRNAs.

# UPDATE & CHANGE LOG

## January 10, 2024

- First publication – view this version of the book in Print PDF or Digital PDF version