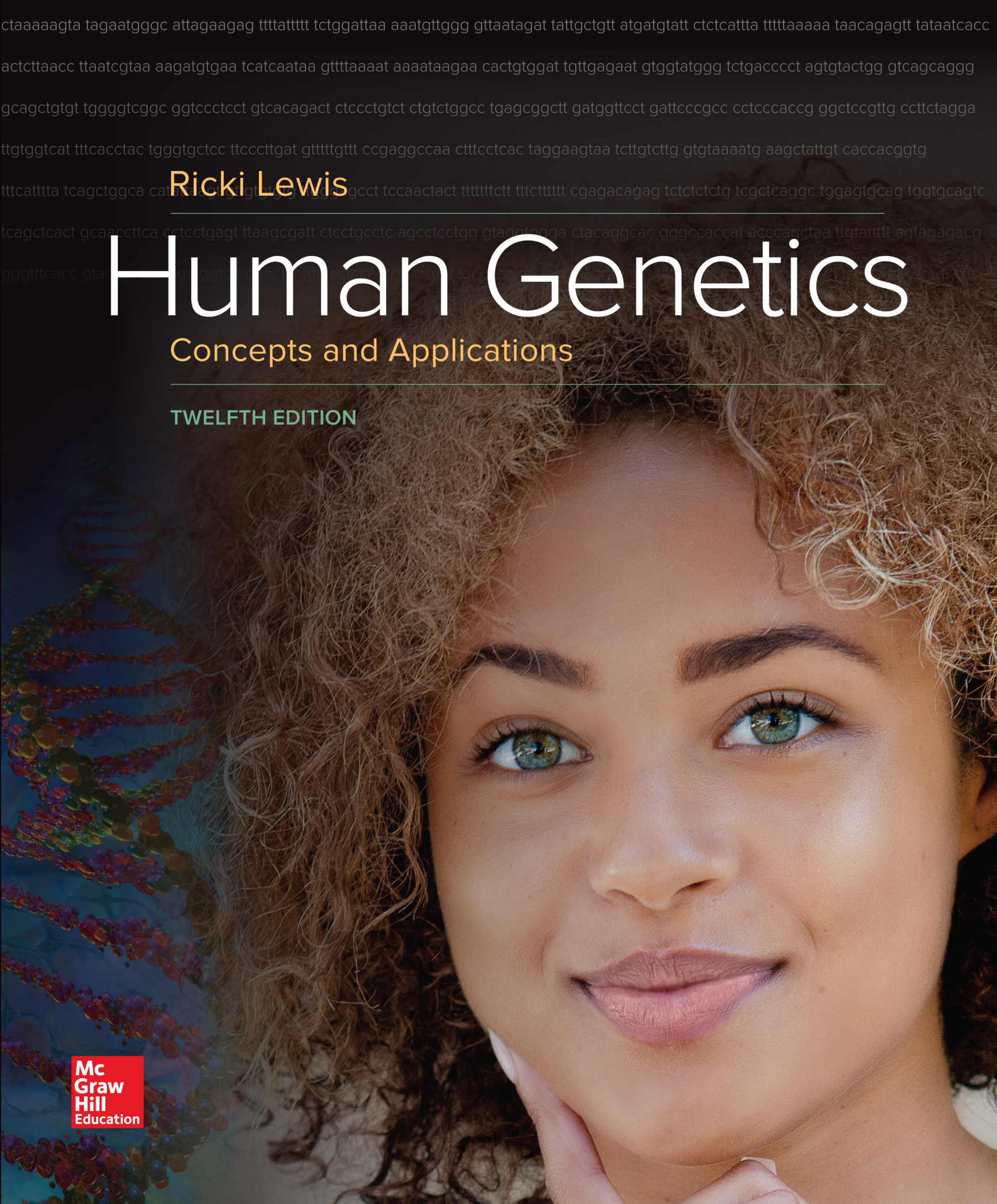
Ricki Lewis

Human Genetics

Concepts and Applications

TWELFTH EDITION



Mc Graw Hill Education

Twelfth Edition

Human Genetics

Concepts and Applications

Ricki Lewis

Genetic Counselor
CareNet Medical Group
Schenectady, New York

Adjunct Assistant Professor of
Medical Education
Alden March Bioethics Institute
Albany Medical College

Writer, Medscape Medical News
Genetic Literacy Project

Blogger, Public Library of Science

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HUMAN GENETICS: CONCEPTS AND APPLICATIONS, TWELFTH EDITION

This book is printed on acid-free paper.

1 2 3 4 5 6 7 8 9 LWI 21 20 19 18 17

ISBN 978-1-259-70093-4
MHID 1-259-70093-3

Portfolio Manager: *Justin Wyatt, Ph.D.*
Senior Product Developer: *Donna Nemmers*
Senior Marketing Manager: *Kelly Brown*
Content Project Managers: *Jane Mohr, Jessica Portz, Christina Nelson, and Sandra Schnee*
Senior Buyer: *Sandy Ludovissy*
Senior Designer: *Tara McDermott*
Content Licensing Specialists: *Lori Hancock and Lori Slattery*
Cover Image: *©Geri Lavrov/Getty Images (woman); ©Adrian Neal/Getty Images (helix model)*
Compositor: *SPi Global*
Typeface: *10/12 STIXMathJax Main*
Printer: *LSC Communications*

Library of Congress Cataloging-in-Publication Data

Names: Lewis, Ricki.
Title: Human genetics : concepts and applications / Ricki Lewis, genetic counselor, CareNet Medical Group, Schenectady, New York; adjunct assistant professor of medical education, Alden March Bioethics Institute, Albany Medical College; writer, Medscape Medical News, Genetic Literacy Project; blogger, Public Library of Science.
Description: Twelfth edition. | New York, NY : McGraw-Hill Education, [2018] | Includes bibliographical references and index.
Identifiers: LCCN 2017016868 | ISBN 9781259700934 (alk. paper)
Subjects: LCSH: Human genetics–Textbooks.
Classification: LCC QH431 .L41855 2018 | DDC 611/.01816—dc23 LC record available at https://lccn.loc.gov/2017016868

mheducation.com/highered

About the Author

Courtesy of Dr. Wendy Josephs

Ricki Lewis has built an eclectic career in communicating the excitement of genetics and genomics, combining skills as a geneticist and a journalist. She currently writes the popular weekly blog, DNA Science, at Public Library of Science (http://blogs.plos.org/dnascience/) and contributes frequent articles to Medscape Medical News and the Genetic Literacy Project. Dr. Lewis has authored or coauthored several university-level textbooks and is the author of the narrative nonfiction book, *The Forever Fix: Gene Therapy and the Boy Who Saved It*, as well as an essay collection, a novel, and a short "basics" book on human genetics. She teaches an online course on "Genethics" for the Alden March Bioethics Institute of Albany Medical College and is a genetic counselor for a private medical practice. Her passion is rare genetic diseases; she writes often about affected families who are pioneering DNA-based treatments.

Dedicated to the families who live with genetic diseases, the health care providers who help them, and the researchers who develop new tests and treatments.

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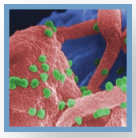

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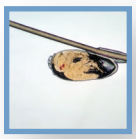

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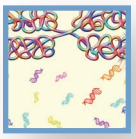

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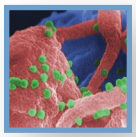

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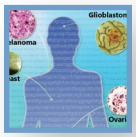

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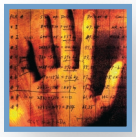

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Preface

Human Genetics Touches Us All

More than a million people have had their genomes sequenced, most of them since the last edition of this book was published in 2014. When I wrote the first edition, the idea to sequence "the" human genome was just becoming reality. The growing field of genomics, of considering all of our genes, is now revealing that we are much more alike than different, yet those differences among 3 million of our 3.2 billion DNA building blocks hold clues to our variation and diversity. It has been a privilege to chronicle the evolution of human genetics, from an academic subfield of life science and a minor medical specialty to a growing body of knowledge that will affect us all.

*The twelfth edition opens with the hypothetical "*Eve's Genome*" and ends with "*Do You Want Your Genome Sequenced?*" In between, the text touches on what exome and genome sequencing have revealed about single-gene diseases so rare that they affect only a single family to clues to such common and complex conditions as intellectual disability and autism. Exome and genome sequencing are also important in such varied areas as understanding our origins, solving crimes, and tracking epidemics. In short, DNA sequencing will affect most of us.*

As the cost of genome sequencing plummets, we all may be able to look to our genomes for echoes of our pasts and hints of our futures—if we so choose. We may also learn what we can do to counter our inherited tendencies and susceptibilities. Genetic knowledge is informative and empowering. This book shows you how and why this is true.

Ricki Lewis

What Sets This Book Apart

Current Content

The exciting narrative writing style, with clear explanations of concepts and mechanisms propelled by stories, historical asides, and descriptions of new technologies reflects Dr. Lewis's eclectic experience as a health and science writer, blogger, professor, and genetic counselor, along with her expertise in genetics. Updates to this edition include

- Children benefiting from genetic technologies
- Cannabidiol to treat genetic seizure disorders
- "Variants of uncertain significance" as test results
- DNA profiling and the Srebrenica genocide
- Steel syndrome in Harlem
- Archaic humans
- Chimeric antigen receptor technology
- Genome editing, gene drives, and synthetic genomes
- Learning from the genomes of the deceased

Connections and Context

For human genome sequence information to be useful, we need to discover all of the ways that genes interact. The patterns with which different parts of the genome touch in a cell's nucleus serves as a metaphor for the new edition of this book. Originally conceived as two-thirds "concepts" followed by one-third "applications," the book has evolved as has the science, with the tentacles of technology no longer constrained to that final third, but touching other chapters, in which the science of genetics becomes applied:

- The very first illustration, figure 1.1, depicts DNA wound around proteins to form a nucleosome, the unit of chromatin. Part of the figure repeats as an inset in figure 11.6, which zooms in on the molecular events as nucleosomes open and close during gene expression.
- The "diagnostic odyssey" of young Millie McWilliams is told in Clinical Connection 1.1. Millie appears again in figure 4.18, in the context of genome sequencing of parent-child trios to track the genetic causes of rare diseases.
- The cell cycle first appears as figure 2.12, then again as figure 2.15 but with the checkpoints added. In figure 18.3, the cell cycle appears yet again in the context of the photo of dividing cancer cells next to it.
- The journey from fertilized ovum to cleavage embryo, then to implantation in the uterine lining, is depicted in figure 3.15. It appears again in figure 21.3 to orient the stages and places of assisted reproductive technologies such as *in vitro* fertilization.

- A recurring representation of different-colored shapes moving in and out of an ancestral "population" traces the forces of evolutionary change throughout chapter 15: nonrandom mating (figure 15.2), migration (figure 15.3), genetic drift (figure 15.5), mutation (figure 15.7), and natural selection (figure 15.8), and then all together in figure 15.14.
- Table 20.1 defines and describes all types of genetic testing, with references to their mentions in previous chapters.
- Table 22.2 reviews genomics coverage in other chapters.

The historical roots from which today's genetic technologies emerged appear in *A Glimpse of History* boxes throughout the book.

The chapter and unit organization remain from the eleventh edition, with a few meaningful moves of material to more logical places. The essay on mitochondrial transfer that appeared in the last edition in the context of assisted reproductive technologies in chapter 21 is now with mitochondria, in chapter 5 as a *Bioethics* box. The "diseaseome" that was at the end of chapter 1 is now in chapter 11, in the context of gene expression. Examples of exome and genome sequencing are threads throughout that knit the ongoing transition from genetics to genomics. Chapter 1 is now more molecular in focus because today even grade-schoolers are familiar with DNA. New subheads throughout the book ease understanding and studying.

Changes in terminology reflect the bigger picture of today's genetics. "Abnormal" is now the less judgmental "atypical." Use of the general term "gene variant" clarifies the fuzziness of the distinction between "mutation" and "polymorphism." Both refer to changes in the DNA sequence, but in the past, "mutation" has been considered a rare genetic change and "polymorphism" a more common one. "Gene variant" is a better general term since genome sequencing has revealed that some mutations have no effects in certain individuals—again, due to gene-gene interactions, many as yet unknown.

The Lewis Guided Learning System

Each chapter begins with two views of the content. *Learning Outcomes* embedded in the table of contents guide the student in mastering material. *The Big Picture* encapsulates the overall theme of the chapter. The opening essay and figure grab attention. Content flows logically through three to five major sections per chapter that are peppered with high-interest boxed readings (*Clinical Connections, Bioethics*, *A Glimpse of History*, and *Technology Timelines*). End-of-chapter pedagogy progresses from straight recall to applied and creative questions and challenges, including a question based on the chapter opener. The *Clinical Connections* and *Bioethics* boxes have their own question sets. *Key Concepts Questions* after each major section reinforce learning.

Dynamic Art

Outstanding photographs and dimensional illustrations, vibrantly colored, are featured throughout *Human Genetics: Concepts and Applications*. Figure types include process figures with numbered steps, micro to macro representations, and the combination of art and photos to relate stylized drawings to real-life structures.

New to This Edition

Highlights in the new edition update information and discoveries, ease learning, and conceptually connect chapters. Updates include:

Chapter 1 What Is in a Human Genome?
- How a precision medicine program is integrating human genome information with environmental factors to dissect health and disease, on a population level

Chapter 4 Single-Gene Inheritance
- How genome analysis provides a new view of Mendel's laws

Chapter 8 Genetics of Behavior
- Schizophrenia arises from excess synaptic pruning
- Syndromes that include autism

Chapter 9 DNA Structure and Replication
- More subheads ease learning
- The "loop-ome" brings genes together

Chapter 10 Gene Action: From DNA to Protein
- Why proteins are important

Chapter 12 Gene Mutation
- More subheads to distinguish mutations, polymorphisms, and gene variants
- Figures and discussion on somatic mosaicism
- The famous painting of the "blue people" of Kentucky

Chapter 13 Chromosomes
- Less history, more new technology

Chapter 14 Constant Allele Frequencies and DNA Forensics
- DNA profiling confirms genocide

Chapter 15 Changing Allele Frequencies
- Steel syndrome in East Harlem—how considering population substructure improves health care

Chapter 16 Human Ancestry and Evolution
- Gene flow among archaic and modern humans

Chapter 18 Cancer Genetics and Genomics
- The "3 strikes" to cancer
- Chimeric antigen receptor technology
- Liquid biopsy

Chapter 19 DNA Technologies
- Genome editing and gene drives

Chapter 20 Genetic Testing and Treatment
- Genome editing in research and the clinic
- Gene therapy successes

Chapter 22 Genomics
- Sequencing genomes of the deceased
- Synthetic genomes

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1.3 Gene to protein to person
1.4 A mutation can alter a protein, causing symptoms
1.8 Precision medicine
2.21 The human microbiome
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4.18 Parent and child trios
5.9 Ragged red fibers in mitochondrial disease
8.9 Schizophrenia and overactive synaptic pruning
9.14 DNA looping
11.7 Open or closed chromatin
12.11 The blue people of Kentucky
16.6 Gene flow among archaic and anatomically modern humans
16.9 The dystrophin gene
19.11 CRISPR-Cas9 genome editing
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New Tables

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8.3 Famous People Who Had Autistic Behaviors
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20.3 Pharmacogenetics
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ACKNOWLEDGMENTS

Human Genetics: Concepts and Applications, Twelfth Edition, would not have been possible without the assistance of the editorial and production team: senior brand manager Justin Wyatt, product development director Rose Koos, marketing manager Kelly Brown, content licensing specialists Lori Slattery and Lori Hancock, designer Tara McDermott, senior product developer Donna Nemmers, project managers Jane Mohr and Jessica Portz, copyeditor Carey Lange, and proofreaders Jane Hoover and Sue Nodine. I am also grateful to the dozens of colleagues who have reviewed this textbook over the years and have contributed to its currency and accuracy. Many thanks to the instructors and students who have reached out to me through the years with helpful suggestions and support. Special thanks to my friends in the rare disease community who have shared their stories, and to Jonathan Monkemeyer and David Bachinsky for helpful Facebook posts. As always, many thanks to my wonderful husband Larry for his support and encouragement and to my three daughters and their partners, Emmanuel the future doctor in Africa, my cats, and Cliff the hippo.

This book continually evolves thanks to input from instructors and students. Please let me know your thoughts and suggestions for improvement. (rickilewis54@gmail.com)

Applying Human Genetics

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Courtesy of the Gavin R. Stevens Foundation

Source: Centers for Disease Control and Prevention (CDC)

A GLIMPSE OF HISTORY

3	The first view of sperm
3	Evolution of pregnancy testing
4	Gregor Mendel
5	The murdered Romanovs and mitochondrial DNA
6	Glimpsing the Y chromosome
7	Genetic influence on intelligence of twins
8	Galton's investigation of heredity and intelligence
8	LSD
9	Kary Mullis invents PCR
10	The RNA tie club
10	Discovery of operons in bacteria
12	The discovery of sickled cells
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© Clinic for Special Children, 2013

Courtesy of Lori Sames. Photo by Dr. Wendy Josephs

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The Lewis Guided Learning System

Learning Outcomes preview major chapter topics in an inquiry-based format according to numbered sections.

The Big Picture encapsulates chapter content at the start.

Chapter Openers vividly relate content to real life.

Key Concepts Questions follow each numbered section.

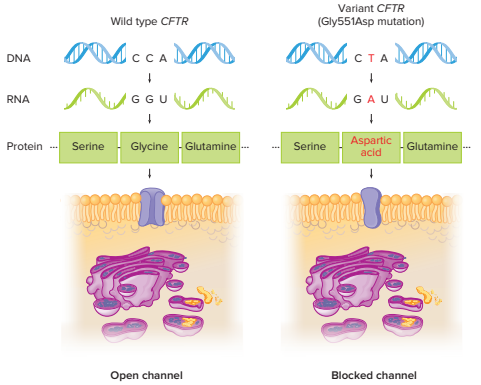
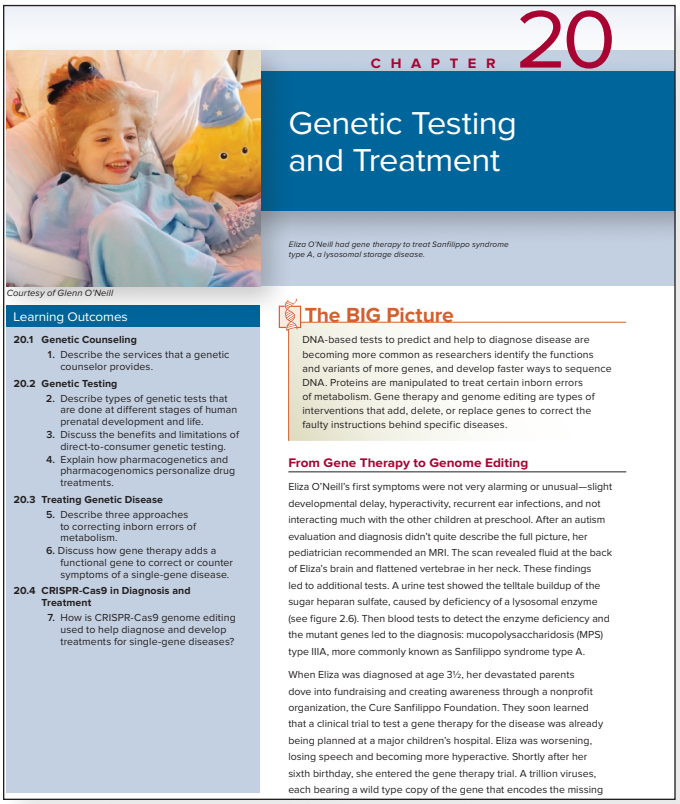


Figure 1.4 **A mutation can alter a protein, causing symptoms.** One type of mutation in the *CFTR* gene replaces one amino acid type (glycine) with another (aspartic acid) at a specific site, altering the encoded protein in a way that closes a type of ion channel that participates in secretion.



Technology Timeline

PATENTING LIFE AND GENES

1790	U.S. patent act enacted. A patented invention must be new, useful, and not obvious.
1873	Louis Pasteur is awarded first patent on a life form, for yeast used in industrial processes.
1930	New plant variants can be patented.
1980	First patent awarded on a genetically modified organism, a bacterium given four DNA rings that enable it to metabolize components of crude oil.
1988	First patent awarded for a transgenic organism, a mouse that manufactures human protein in its milk. Harvard University granted a patent for "OncoMouse," transgenic for human cancer.
1992	Biotechnology company awarded patent for all forms of transgenic cotton. Groups concerned that this will limit the rights of subsistence farmers contest the patent several times.
1996–1999	Companies patent partial gene sequences and certain disease-causing genes for developing specific medical tests.
2000	With gene and genome discoveries pouring into the Patent and Trademark Office, requirements for showing utility of a DNA sequence are tightened.
2003	Attempts to enforce patents on non-protein-encoding parts of the human genome anger researchers who support open access to the information.
2007	Patent requirements must embrace a new, more complex definition of a gene.
2009	Patents on breast cancer genes challenged.
2010	Direct-to-consumer genetic testing companies struggle to license DNA patents for multigene and SNP association tests.
	Patents on breast cancer genes invalidated.
2011	U.S. government considers changes to gene patent laws.
2013	U.S. Supreme Court declares genes unpatentable.

In-Chapter Review Tools, such as Key Concepts Questions, summary tables, and timelines of major discoveries, are handy tools for reference and study. Most boldfaced terms are consistent in the chapters, summaries, and glossary.

Bioethics and **Clinical Connection** boxes include Questions for Discussion.

Clinical Connection 1.1

Genome Sequencing Ends a Child's "Diagnostic Odyssey"

Millie McWilliams was born September 2, 2005. At first, Millie seemed healthy, lifting her head and rolling over when most babies do. "But around 6 months, her head became shaky, like an infant's. Then she stopped saying 'dada'," recalled her mother Angela.

By her first birthday, Millie couldn't crawl or sit, and her head shaking had become a strange, constant swaying. She had bouts of irritability and vomiting and the peculiar habit of biting her hands and fingers. In genetic diseases, odd habits and certain facial features can be clues. None of the many tests, scans, and biopsies that Millie underwent led to a diagnosis.

By age 6, Millie had lost the ability to speak, was intellectually disabled, and confined to a wheelchair, able to crawl only a few feet. Today she requires intensive home-based therapies. But Millie can communicate with her parents. "She likes to look at what she wants, with an intense stare," said Angela. She loves country music and Beyoncé, and every once in awhile something funny will happen and she'll break into a big smile.

Millie's pediatrician, Dr. Sarah Soden, suggested that genome sequencing, already being done at the medical center where Millie receives care, might explain the worsening symptoms (**figure 1A**). So the little girl and her parents had their genomes sequenced in December 2011. Dr. Soden's team identified a suspicious mutation, but the gene had never been linked to a childhood disease.

In February 2013, a medical journal published a report about four children with mutations in this gene who had symptoms strikingly like those of Millie. An answer had finally emerged: Millie has Bainbridge-Ropers syndrome. Even her facial structures—arched eyebrows, flared nostrils, and a high forehead—matched, as well as the hand-biting symptom.

Millie is missing two DNA bases in the gene *ASXL3*. DNA bases are "read" three at a time to indicate the amino acids in a protein, so missing two bases garbled the code, leading to tiny, nonfunctional proteins for that particular gene. Somehow the glitch caused the symptoms. Because Millie's father Earl and Angela do not have the mutation, it originated in either a sperm or an egg that went on to become Millie.

Figure 1A Dr. Sarah Soden examines Millie McWilliams. Genome sequencing identified the cause of Millie's intellectual disability, lack of mobility, and even her hand-biting. *Courtesy of Children's Mercy Kansas City*

So far a few dozen individuals have been diagnosed with Bainbridge-Ropers syndrome, and families have formed a support group and Facebook page. Although there is no treatment yet, the families are happy to have an answer, because sometimes parents blame themselves. Said Angela, "It was a relief to finally put a name on it and figure out what was actually going on with her, and then to understand that other families have this too. I've been able to read about her diagnosis and what other kids are going through."

Questions for Discussion

1. Millie has a younger brother and an older sister. Why don't they have Bainbridge-Ropers syndrome?
2. Would exome sequencing have discovered Millie's mutation?
3. Find a Facebook page for families that have members with a specific genetic disease and list topics that parents of affected children discuss.
4. Do you think it is valuable to have a diagnosis of a condition that has no treatment? Why or why not?

Clinical Connection boxes discuss how genetics and genomics impact health and health care.

Summary

7.1 Genes and the Environment Mold Traits

1. **Multifactorial** traits reflect influences of the environment and genes. A **polygenic** trait is determined by more than one gene and varies continuously in expression.
2. Single-gene traits are rare. For most traits, many genes contribute to a small, but not necessarily equal, degree.

7.2 Polygenic Traits Are Continuously Varying

3. Genes that contribute to polygenic traits are called **quantitative trait loci.** The frequency distribution of phenotypes for a polygenic trait forms a bell curve.

7.3 Methods to Investigate Multifactorial Traits

4. **Empiric risk** measures the likelihood that a multifactorial trait will recur based on **incidence.** The risk rises with genetic closeness, severity, and number of affected relatives.
5. **Heritability** estimates the proportion of variation in a multifactorial trait due to genetics in a particular population at a particular time. The **coefficient of relatedness** is the proportion of genes that two people related in a certain way share.
6. Characteristics shared by adopted people and their biological parents are mostly inherited, whereas similarities between adopted people and their adoptive parents reflect environmental influences.
7. **Concordance** measures the frequency of expression of a trait in both members of MZ or DZ twin pairs. The more influence genes exert over a trait, the higher the differences in concordance between MZ and DZ twins.
8. **Genome-wide association studies** correlate patterns of genetic markers (**single nucleotide polymorphisms** and/or **copy number variants**) to increased disease risk. They may use a **cohort study** to follow a large group over time, or a **case-control study** on matched pairs.
9. An **affected sibling pair study** identifies homozygous regions that may include genes of interest. **Homozygosity mapping** identifies mutations in genome regions that are homozygous because the parents shared recent ancestors.

7.4 A Closer Look: Body Weight

10. Leptin and associated proteins affect appetite. Fat cells secrete leptin in response to eating, which decreases appetite.
11. Populations that switch to a high-fat, high-calorie diet and a less-active lifestyle reveal effects of the environment on body weight.

Review Questions

1. Explain how Mendel's laws apply to multifactorial traits.
2. Choose a single-gene disease and describe how environmental factors may affect the phenotype.
3. Explain the difference between a Mendelian multifactorial trait and a polygenic multifactorial trait.
4. Do all genes that contribute to a polygenic trait do so to the same degree?
5. Explain why the curves shown in figures 7.2, 7.3, and 7.4 have the same bell shape, even though they represent different traits.
6. How can skin color have a different heritability at different times of the year?
7. Explain how the twins in figure 7.4 can have such different skin colors.
8. In a large, diverse population, why are medium brown skin colors more common than very white or very black skin?
9. Which has a greater heritability—eye color or height? State a reason for your answer.
10. Describe the type of information resulting from a(n)
    a. empiric risk determination.
    b. twin study.
    c. adoption study.
    d. genome-wide association study.
11. Name three types of proteins that affect cardiovascular functioning and three that affect body weight.
12. What is a limitation of a genome-wide association study?
13. Explain how genome sequencing may ultimately make genome-wide association studies unnecessary.

Applied Questions

1. "Heritability" is often used in the media to refer to the degree to which a trait is inherited. How is this definition different from the scientific one?
2. Would you take a drug that was prescribed to you based on your race? Cite a reason for your answer.
3. The incidence of obesity in the United States has doubled over the past two decades. Is this due more to genetic or environmental factors? Cite a reason for your answer.
4. One way to calculate heritability is to double the difference between the concordance values for MZ versus DZ twins. For multiple sclerosis, concordance for MZ twins is 30 percent, and for DZ twins, 3 percent. What is the heritability? What does the heritability suggest about the

Each chapter ends with a point-by-point **Summary**.

Review Questions assess content knowledge.

Applied Questions help students develop problem-solving skills. The first question in this section relates back to the chapter opener.

Forensics Focus

1. Establishing time of death is critical information in a murder investigation. Forensic entomologists can estimate the "postmortem interval" (PMI), or the time at which insects began to deposit eggs on the corpse, by sampling larvae of specific insect species and consulting developmental charts to determine the stage. The investigators then count the hours backwards to estimate the PMI. Blowflies are often used for this purpose, but their three larval stages look remarkably alike in shape and color, and development rate varies with environmental conditions. With luck, researchers can count back 6 hours from the developmental time for the largest larvae to estimate the time of death.

   In many cases, a window of 6 hours is not precise enough to narrow down suspects when the victim visited several places and interacted with many people in the hours before death. Suggest a way that gene expression profiling might be used to more precisely define the PMI and extrapolate a probable time of death.

Case Studies and Research Results

1. Kabuki syndrome is named for the resemblance of an affected individual to a performer wearing the dramatic makeup used in traditional Japanese theater called Kabuki. The face has long lashes, arched eyebrows, flared eyelids, a flat nose tip, and large earlobes. The syndrome is associated with many symptoms, including developmental delay and intellectual disability, seizures, a small head (microcephaly), weak muscle tone, fleshy fingertips, cleft palate, short stature, hearing loss, and heart problems. Both genes associated with the condition result in too many regions of closed chromatin. Drugs that inhibit histone deacetylases (enzymes that remove acetyl groups from histone proteins) are effective. Explain how the drugs work.
2. To make a "reprogrammed" induced pluripotent stem (iPS) cell (see figure 2.20), researchers expose fibroblasts taken from skin to "cocktails" that include transcription factors. The fibroblasts divide and give rise to iPS cells, which, when exposed to other transcription factors, divide and yield daughter cells that specialize in distinctive ways that make them different from the original fibroblasts. How do transcription factors orchestrate these changes in cell type?
3. Using an enzyme called DNAse 1, researchers can determine which parts of the genome are in the "open chromatin" configuration in a particular cell. How could this technique be used to develop a new cancer treatment?

Forensics Focus questions probe the use of genetic information in criminal investigations.

Case Studies and Research Results use stories based on accounts in medical and scientific journals; real clinical cases; posters and reports from professional meetings; interviews with researchers; and fiction to ask students to analyze data and predict results.

Dynamic Art Program

Multilevel Perspective

Illustrations depicting complex structures show microscopic and macroscopic views to help students see relationships among increasingly detailed drawings.

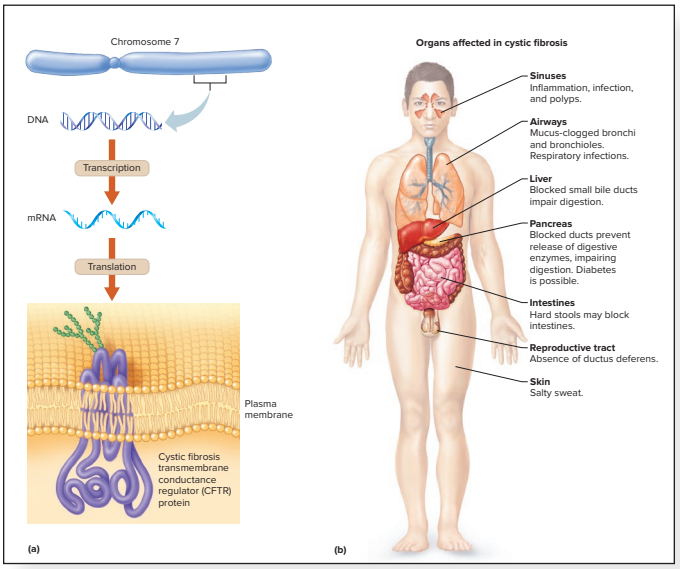


Figure 1.3 From gene to protein to person.

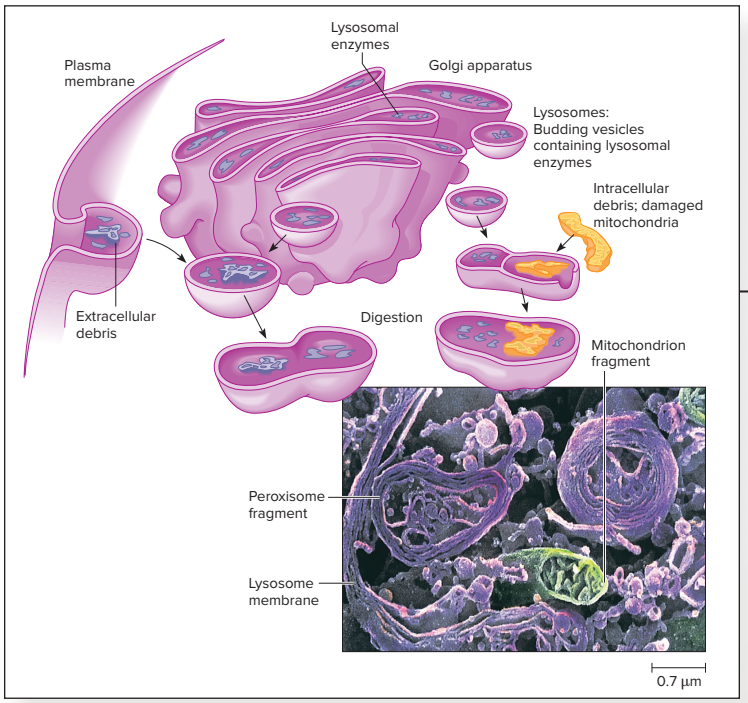


Figure 2.6 Lysosomes are trash centers.
© Prof. P. Motta & T. Naguro/SPL/Science Source

Combination Art

Drawings of structures are paired with micrographs to provide the best of both perspectives: the realism of photos and the explanatory clarity of line drawings.

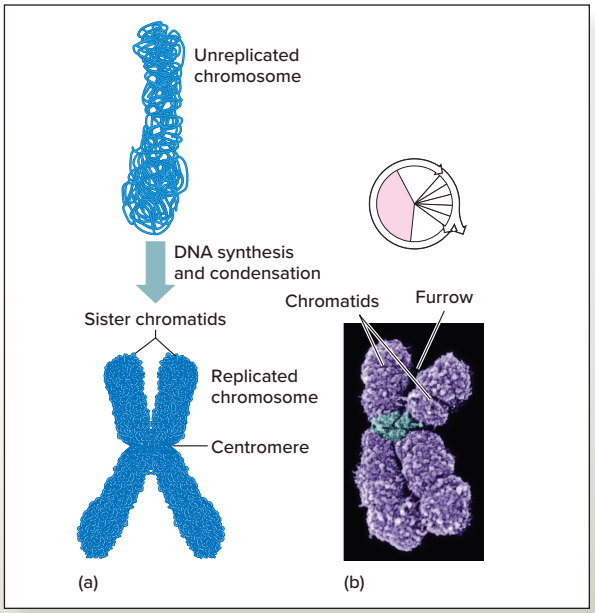


Figure 2.13 Replicated and unreplicated chromosomes. *(b): © SPL/ Science Source*

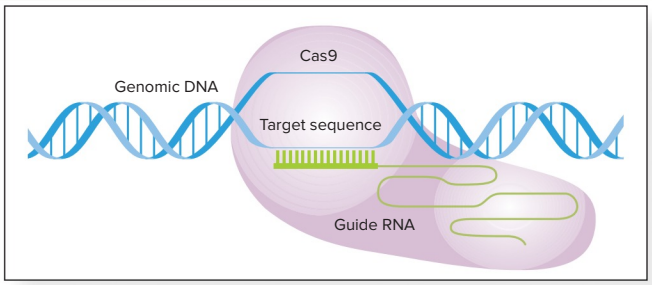


Figure 19.11 **CRISPR-Cas9.**

New Technologies

Genome editing can replace mutant genes with wild type alleles to counter disease or "drive out" pest populations.

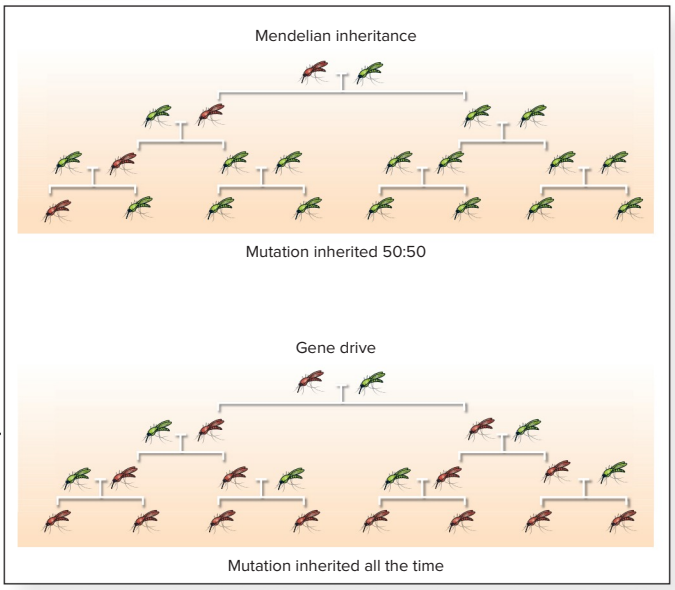


Figure 19.12 **A gene drive.**

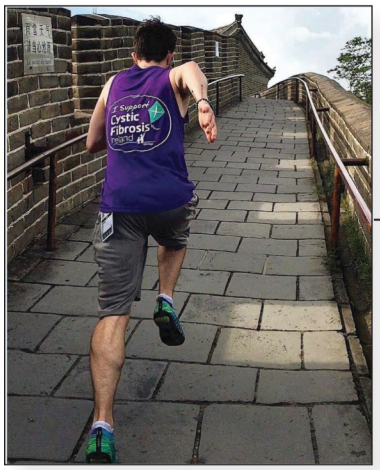


Figure 4A **Regular exercise helps many people who have cystic fibrosis.** *Courtesy of Evan Scully*

Clinical Coverage

Evan Scully controls his cystic fibrosis with an exercise schedule of running, gym workouts, and yoga.

Process Figures

Complex processes are broken down into a series of numbered smaller steps that are easy to follow. Here, cancer evolves from an initial breakthrough "driver" mutation through additional mutations as the tumor expands and invades healthy tissue (figure 18.10).

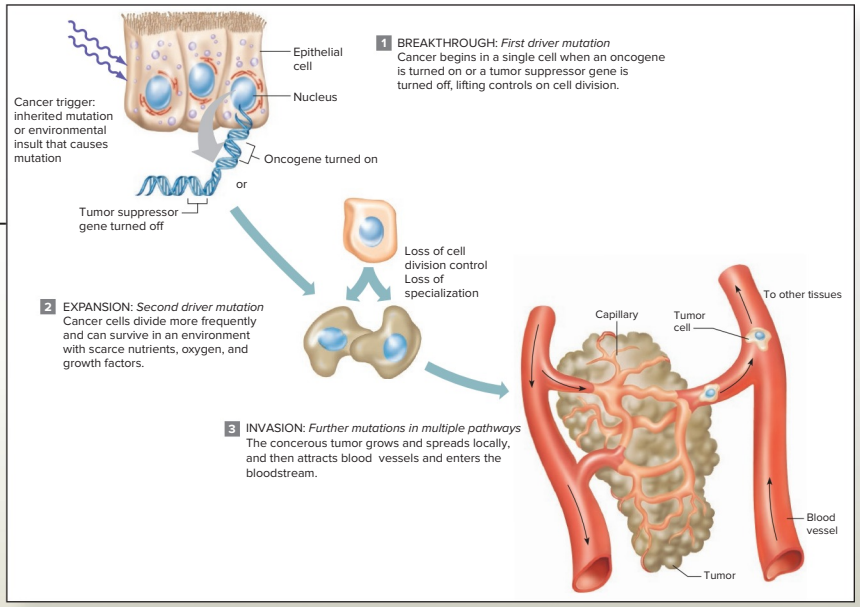


Figure 18.10 **The "three strikes" of cancer.**

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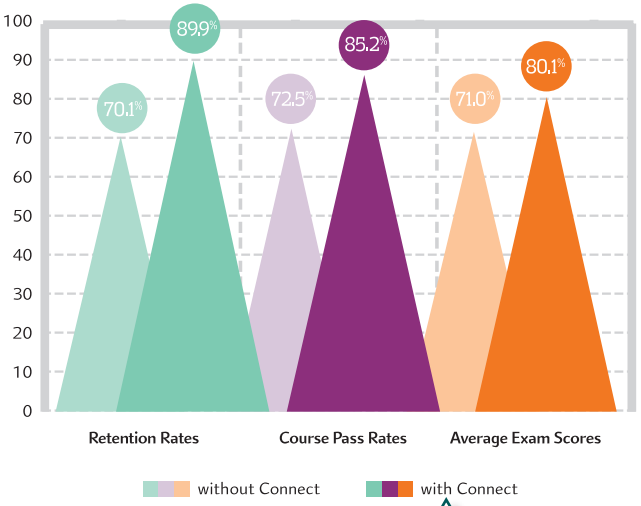

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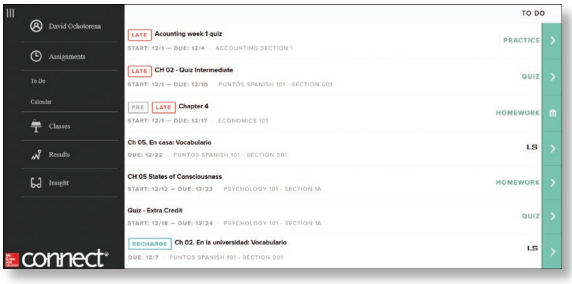

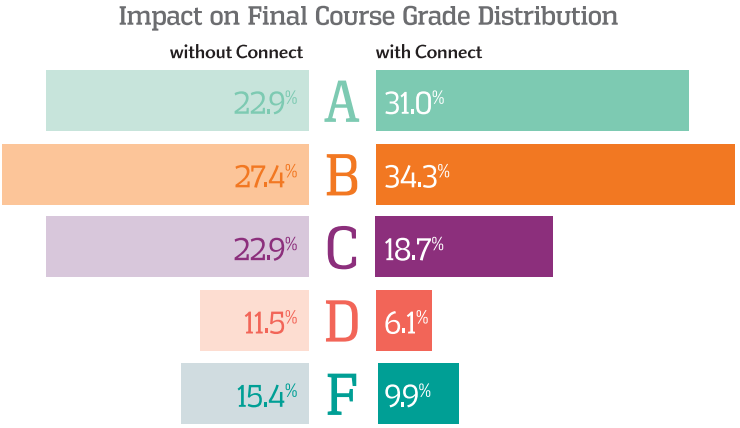

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PART 1 Introduction

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CHAPTER 1

What Is in a Human Genome?

A child's genome holds information on her health, where she came from, and what she might experience and achieve—but the environment is very important too in guiding who she is and will become.

Learning Outcomes

1.1 Introducing Genes and Genomes

1. Explain what genetics is and what it is not.
2. Distinguish between gene and genome.
3. Define *bioethics*.

1.2 Levels of Genetics and Genomics

4. List the levels of genetics.
5. Explain how DNA is maintained and how it provides the information to construct a protein.
6. Explain how a mutation can cause a disease.
7. Define *exome*.
8. Distinguish between Mendelian and multifactorial traits.
9. Explain how genetics underlies evolution.

1.3 Applications of Genetics and Genomics

10. List some practical uses of DNA information.
11. Explain how DNA information can be considered with other types of information to learn about maintaining health and treating disease.
12. Distinguish between traditional breeding and genetically modifying organisms.
13. Describe a situation in which exome sequencing can be useful.

1.4 A Global Perspective on Genomes

14. Explain how investigating genomes extends beyond interest in ourselves.

The BIG Picture

The human genome is a vast store of information encoded in the sequence of building blocks of the molecule deoxyribonucleic acid (DNA). Genetic information affects our health and traits, and holds clues to how we are biologically related to one another.

Eve's Genome

A baby is born. Drops of blood from her heel are placed into a small device that sends personal information into her electronic medical record. The device deciphers the entire sequence of DNA building blocks wound into the nucleus of a white blood cell. This is Eve's genome. Past, present, and future are encoded in nature's master informational molecule, deoxyribonucleic acid, or DNA—with room for environmental influences.

Eve's genome indicates overall good genetic health. She has a mild clotting disease that the nurse suspected when two gauze patches were needed to stop the bleeding from the heel stick. Two rare variants of the gene that causes cystic fibrosis (CF) mean that Eve is susceptible to certain respiratory infections and sensitive to irritants, but her parents knew that from prenatal testing. Fortunately the family lives in a rural area far from pollution, and Eve will have to avoid irritants such as smoke and dust.

The inherited traits that will emerge as Eve grows and develops range from interesting to important. Her hair will darken and curl, and genes that contribute to bone development indicate that she'll have a small nose, broad forehead, and chiseled cheekbones. If she follows a healthy diet, she'll be as tall as her parents. On the serious side, Eve has inherited a mutation in a gene that greatly raises her

risk of developing certain types of cancers. Her genes predict a healthy heart, but she might develop diabetes unless she exercises regularly and limits carbohydrates in her diet.

Many traits are difficult to predict because of environmental influences, including experiences. What will Eve's personality be like? How intelligent will she be? How will she react to stress? What will be her passions?

Genome sequencing also reveals clues to Eve's past, which is of special interest to her father, who was adopted. She has gene variants common among the Eastern European population of her mother's origin, and others that match people from Morocco. Is that her father's heritage? Eve is the beautiful consequence of a mix of her parents' genomes, receiving half of her genetic material from each.

Do you want to know the information in your genome?

1.1 Introducing Genes and Genomes

Genetics is the study of inherited traits and their variation. Genetics is not the same as genealogy, which considers relationships but not traits. Because some genetic tests can predict illness, genetics has also been compared to fortunetelling. However, genetics is a life science. **Heredity** is the transmission of traits and biological information between generations, and genetics is the study of how traits are transmitted.

Inherited traits range from obvious physical characteristics, such as freckles and red hair, to many aspects of health, including disease. Talents, quirks, personality traits, and other difficult-to-define characteristics might appear to be inherited if they affect several family members, but may reflect shared genetic and environmental influences. Attributing some traits to genetics, such as sense of humor or whether or not one votes, are oversimplifications. These connections are associations, not causes.

Over the past decade, genetics has exploded from a mostly academic discipline and a minor medical specialty dealing with rare diseases, to the new basis of some fields, such as oncology (cancer care). Genetics is a part of everyday discussion. Personal genetic information is accessible, and we are learning the contribution of genes to the most common traits and diseases. Many health care providers are learning how to integrate DNA information into clinical practice.

Like all sciences, genetics has its own vocabulary. Some technical terms and expressions may be familiar, but actually have precise scientific definitions. Conversely, the language of genetics sometimes enters casual conversation. "*It's in her DNA,*" for example, usually means an inborn trait, not a specific DNA sequence. The terms and concepts introduced in this chapter are explained and explored in detail in subsequent chapters.

Genes are the units of heredity. Genes are biochemical instructions that tell **cells**, the basic units of life, how to manufacture certain proteins. These proteins, in turn, impart or control the characteristics that create much of our individuality. A gene consists of the long molecule **deoxyribonucleic acid (DNA)**. The DNA transmits information in its sequence of four types of building blocks, which function like an alphabet.

The complete set of genetic instructions characteristic of an organism, including protein-encoding genes and other DNA sequences, constitutes a **genome**. Nearly all of our cells contain two copies of the genome. Following a multi-year, international effort, researchers published the deciphered sequences of the first human genomes, in 2003. However, scientists are still analyzing what all of our genes do, and how genes interact and respond to environmental stimuli. Only a tiny fraction of the 3.2 billion building blocks of our genetic instructions determines the most interesting parts of ourselves—our differences. Analyzing and comparing genomes, which constitute the field of **genomics**, reveal how closely related we are to each other and to other species.

Genetics directly affects our lives and those of our relatives, including our descendants. Principles of genetics also touch history, politics, economics, sociology, anthropology, art, the law, athletics, and psychology. Genetic questions force us to wrestle with concepts of benefit and risk, even tapping our deepest feelings about right and wrong. A field of study called **bioethics** began in the 1970s to address moral issues and controversies that arise in applying medical technology. Bioethicists today confront concerns that arise from new *genetic* technology, such as privacy, use of genetic information, and discrimination. Essays throughout this book address bioethical issues.

Key Concepts Questions 1.1

1. Distinguish between genetics and heredity.
2. Distinguish between a gene and a genome.
3. Describe the type of information that the DNA sequence of a gene encodes.
4. Define *bioethics.*

1.2 Levels of Genetics and Genomics

Genetics considers the transmission of information at several levels. It begins with the molecular level and broadens through cells, tissues and organs, individuals, families, and finally to populations and the evolution of species (**figure 1.1**).

Instructions and Information: DNA

DNA resembles a spiral staircase or double helix. The "rails," or backbone, consist of alternating chemical groups (sugars and phosphates) and are the same in all DNA molecules.

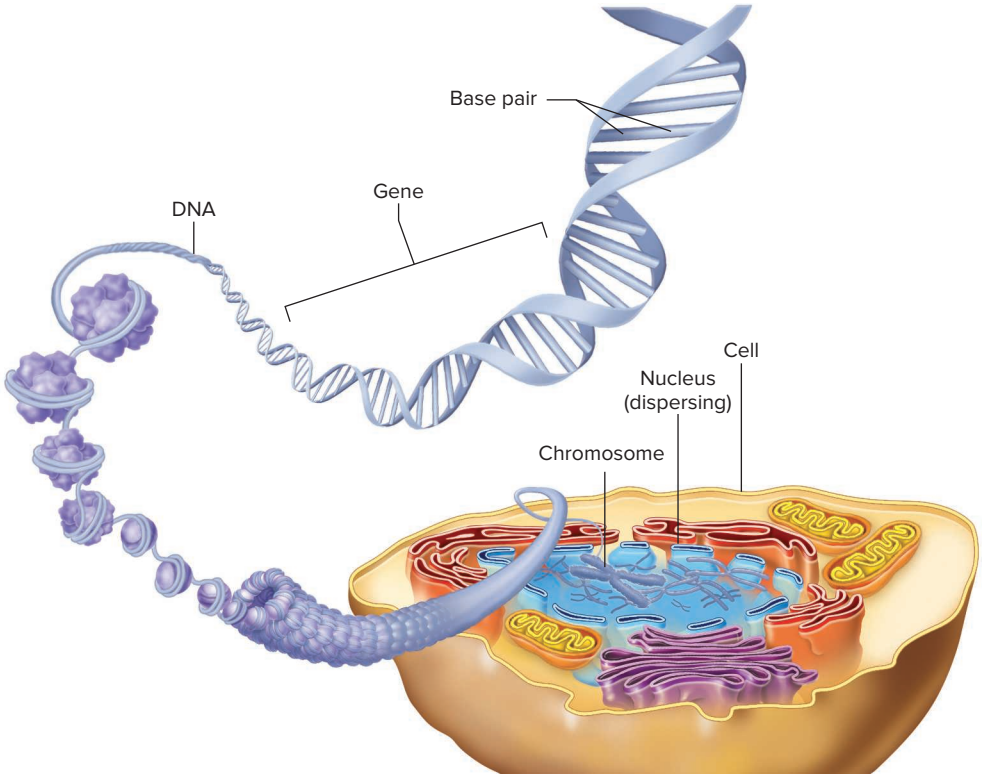


Figure 1.1 **Levels of genetics.** Genetics can be considered at several levels, from DNA, to genes, to chromosomes, to genomes, to the more familiar individuals, families, and populations.

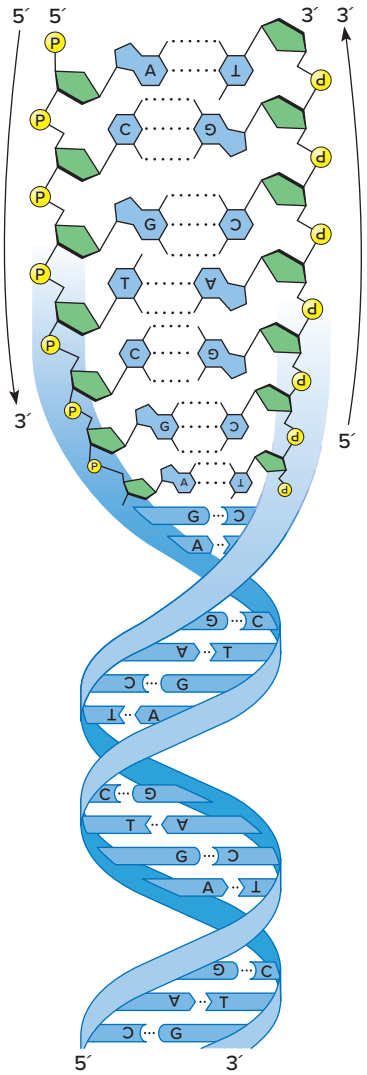


Figure 1.2 **The DNA double helix.** The 5' and 3' labels indicate the head-to-tail organization of the DNA double helix. A, C, T, and G are bases. S stands for sugar and P for phosphate. The green five-sided shapes represent the sugars.

The two strands of the double helix are oriented in opposite directions, like two snakes biting each other's tails. The "steps" of the DNA double helix are pairs of the four types of building blocks, or **nitrogenous bases**: **adenine** (A) and **thymine** (T), which attract each other, and **cytosine** (C) and **guanine** (G), which attract each other (**figure 1.2**). The information that a DNA molecule imparts is in the sequences of A, T, C, and G.

The chemical structure of DNA gives the molecule two key abilities that are essential for the basis of life: DNA can both perpetuate itself when a cell divides and provide information to manufacture specific proteins. Each set of three consecutive DNA bases is a code for a particular amino acid, and amino acids are the building blocks of proteins.

Accessing genetic information occurs in three processes: replication of DNA, transcription of RNA from the information in DNA, and translation of protein from RNA. Chapter 10 discusses these complex processes in detail.

In **DNA replication**, the chains of the double helix untwist and separate, and then each half builds a new partner chain from free DNA bases. A and T attract and C and G attract. Then **transcription** copies the sequence of part of one strand of a DNA molecule into a related molecule, messenger **ribonucleic acid (RNA)**. In **translation**, each three RNA bases in a row attract another type of RNA that functions as a connector, bringing in a particular amino acid. The amino acids align and link like snap beads, forming a protein. The inherited disease cystic fibrosis (CF) illustrates how proteins provide the traits associated with genes. The protein that is abnormal in CF works like a selective doorway in cells lining the airways and certain other body parts, thickening secretions when it doesn't work properly (**figure 1.3**).

A change in a gene, or **mutation**, can have an effect at the whole-person level, such as causing a disease. **Figure 1.4** depicts the effect of a mutation in the gene that causes CF when mutant, which is called *CFTR* (cystic fibrosis transmembrane conductance regulator). A change of a "C" in the DNA sequence at a specific location in the gene to a "T" inserts the amino acid aspartic acid rather than the amino acid glycine as the protein forms. The resulting protein cannot open to the cell's surface, removing channels for certain salt components, causing the symptoms described in figure 1.3.

The human genome has about 20,325 protein-encoding genes, and these DNA sequences comprise the **exome**. Protein-encoding genes account for only about 1.5 percent of the human genome, yet this portion accounts for about 85 percent of

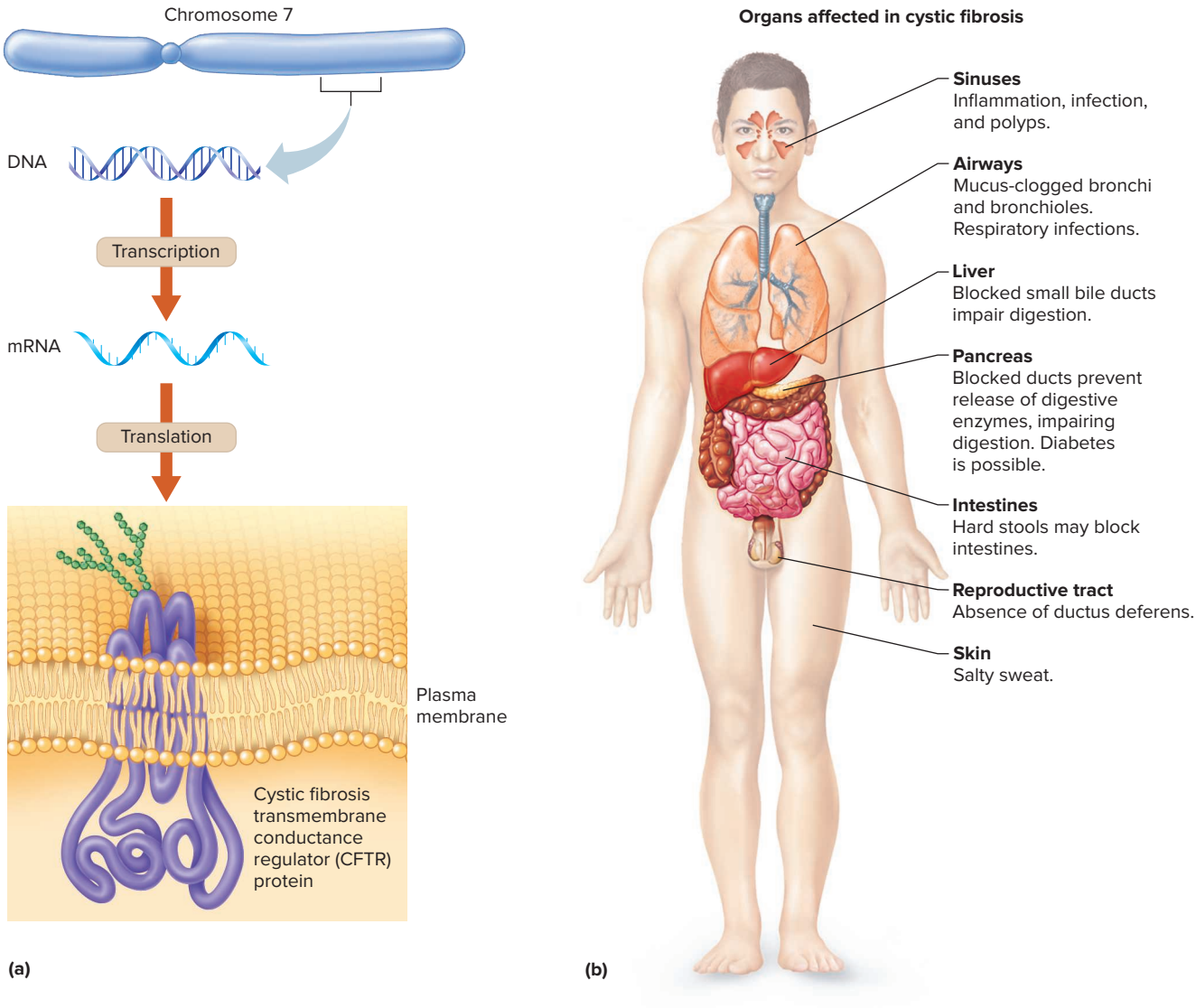


Figure 1.3 **From gene to protein to person.** **(a)** The gene encoding the CFTR protein, causing cystic fibrosis when in a variant form (a mutation), is part of the seventh largest chromosome. CFTR normally folds into a channel that regulates the flow of salt components (ions) into and out of cells lining the respiratory tract, pancreas, intestines, and elsewhere. **(b)** Cystic fibrosis causes several symptoms.

(Source: Data from "Reverse genetics and cystic fibrosis" by M. C. Iannuzi and F. S. Collins. *American Journal of Respiratory Cellular and Molecular Biology* 2:309–316 [1990].)

known genetic diseases. The rest of the genome includes many DNA sequences that assist in protein synthesis or turn protein-encoding genes on or off. The ongoing effort to understand what individual genes do is termed *annotation*.

The same protein-encoding gene may vary slightly in DNA base sequence from person to person. These gene variants are called **alleles**. The changes in DNA sequence that distinguish alleles arise by mutation. (The word "mutation" is also used as a noun to refer to the changed gene.) Once a gene mutates, the change is passed on when the cell that contains it divides. If the change is in a sperm or egg cell that becomes a fertilized egg, it is passed to the next generation.

Some mutations cause disease, and others provide variation such as freckled skin. Mutations can also help. One rare mutation makes a person's cells unable to manufacture a surface protein that binds HIV. These people are resistant to HIV infection. Mutations that have no detectable effect because they do not change the encoded protein in a way that affects its function are sometimes called gene variants. They are a little like a minor spelling error that does not obscure the meaning of a sentence.

The DNA sequences of the human genome are dispersed among 23 structures called **chromosomes**. When a cell is dividing, the chromosomes wind up so tightly that they can be seen under a microscope when stained, appearing rod shaped. The DNA of a chromosome is continuous, but it includes hundreds of genes, plus other sequences.

A human **somatic cell** (non-sex cell) has 23 pairs of chromosomes. Twenty-two of these 23 pairs are **autosomes**, which do not differ between the sexes. The autosomes are numbered from 1 to 22, with 1 being the largest. The other two chromosomes, the X and the Y, are **sex chromosomes**.

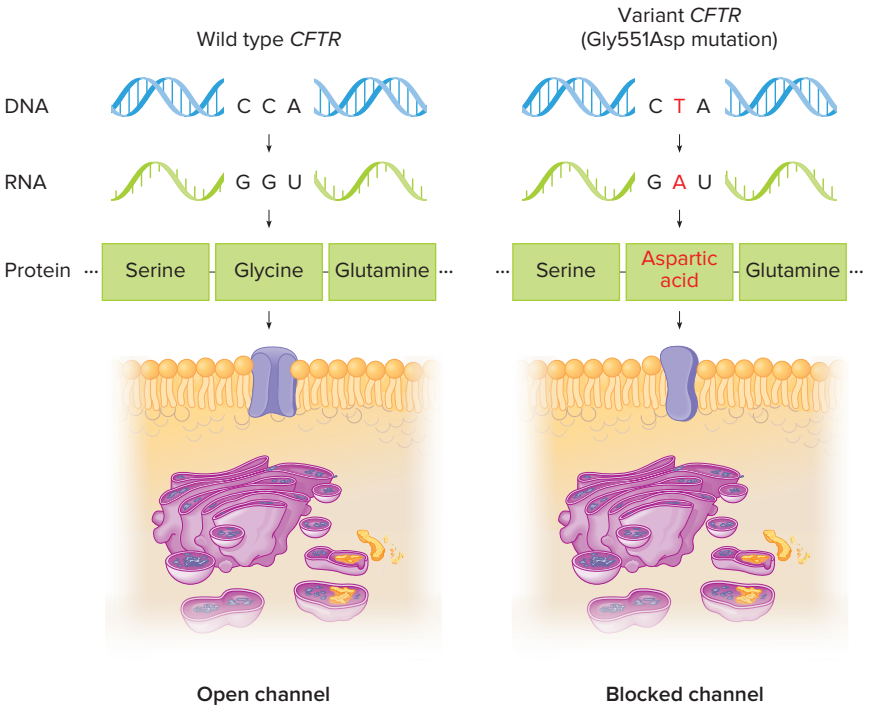


Figure 1.4 **A mutation can alter a protein, causing symptoms.** One type of mutation in the *CFTR* gene replaces one amino acid type (glycine) with another (aspartic acid) at a specific site, altering the encoded protein in a way that closes a type of ion channel that participates in secretion.

The Y chromosome bears genes that determine maleness. In humans, a female has two X chromosomes and a male has one X and one Y chromosome. Charts called **karyotypes** display the chromosome pairs from largest to smallest.

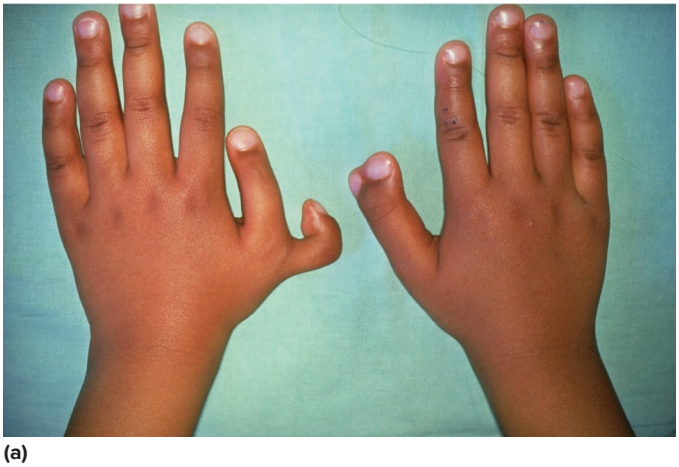
To summarize, a human somatic cell has two complete sets of genetic information (genomes). The protein-encoding genes are scattered among 3.2 billion DNA bases in each set of 23 chromosomes.

A trait caused predominantly by a single gene is termed Mendelian. Most characteristics are **multifactorial traits**, which means that they are determined by one or more genes and environmental factors (**figure 1.5**). The more factors that contribute to a trait or illness—inherited or environmental—the more difficult it is to predict the risk of occurrence in a particular family member. The bone-thinning condition osteoporosis illustrates the various factors that can contribute to a disease. Several genes elevate osteoporosis risk by conferring susceptibility to fractures, but so do smoking, lack of weight-bearing exercise, and a calcium-poor diet.

Environmental effects on gene action counter the idea of "genetic determinism," that "we are our genes." This idea may be harmful or helpful. As part of social policy, genetic determinism can be disastrous. Assuming that one group of people is genetically less intelligent than another can lower expectations and even lead to fewer educational opportunities for people perceived as inferior. Environment, in fact, has a large impact on intellectual development. On the other hand, knowing the genetic contribution to a trait can provide information that can help a health care provider select a treatment most likely to work, with minimal adverse effects.

The Body: Cells, Tissues, and Organs

A human body consists of approximately 30 trillion cells. All somatic cells except red blood cells contain two copies of the genome, but cells differ in appearance and activities because they use only some of their genes. Which genes a cell uses at any given time depends upon environmental conditions inside and outside the body.



(a)

(b)

Figure 1.5 **Mendelian versus multifactorial traits.** **(a)** Polydactyly—extra fingers and/or toes—is a Mendelian trait (single gene). **(b)** Hair color is multifactorial, controlled by at least three genes plus environmental influences, such as the bleaching effects of sun exposure. *(a): © Lester V. Bergman/Getty Images; (b): © Steve Mason/Getty RF*

Like the Internet, a genome contains a wealth of information, but only some of it is needed in a particular cell under particular circumstances. The use, or "expression," of different subsets of genes to manufacture proteins drives the **differentiation**, or specialization, of distinctive cell types. An adipose cell is filled with fat, but not the contractile proteins of muscle cells. Both cell types, however, have two complete genomes. Groups of differentiated cells assemble and interact with each other and the nonliving materials that they secrete to form aggregates called **tissues**. Table 2.1 lists the four basic tissue types, which are composed of more than 290 types of cells.

Tissues intertwine and layer to form organs, which connect into organ systems. The stomach, for example, is a sac made of muscle that also has a lining of epithelial tissue, nervous tissue, and a supply of blood, which is a type of connective tissue. Many organs include rare, unspecialized **stem cells**. A stem cell can divide to yield another stem cell and a cell that differentiates. Stem cells provide a reserve supply of cells that enable an organ to grow and repair damage.

Relationships: From Individuals to Families

Two terms distinguish the alleles that are *present* in an individual from the alleles that are *expressed*. The **genotype** refers to the underlying instructions (alleles present), whereas the **phenotype** is the visible trait, biochemical change, or effect on health (alleles expressed). Alleles are further distinguished by how many copies are necessary to affect the phenotype. A **dominant** allele has an effect when present in just one copy (on one chromosome), whereas a **recessive** allele must be present on both chromosomes of a pair to be expressed.

Individuals are genetically connected into families. A person has approximately half of his or her gene variants in common with each parent, sibling, and offspring, and one-quarter with each grandparent. First cousins share one-eighth of their gene variants. Charts called **pedigrees** depict the members of a family and indicate which individuals have particular inherited traits.

The Bigger Picture: From Populations to Evolution

Above the family level of genetic organization is the population. In a strict biological sense, a population is a group of individuals that can have healthy offspring together. In a genetic sense, a population is a large collection of alleles, distinguished by their frequencies. People from a Swedish population, for example, would have a greater frequency of alleles that specify light hair and skin than people from a population in Nigeria, who tend to have dark hair and skin. All the alleles in a population constitute the **gene pool**. (An individual does not have a gene pool.)

Population genetics is applied in health care, forensics, and other fields. It is also the basis of evolution, which is defined as changing allele frequencies in populations. These small-scale genetic changes underlie the species distinctions we most often associate with evolution.

Comparing DNA sequences for individual genes, or the amino acid sequences of the proteins that the genes encode, can reveal how closely related different types of organisms are. The assumption is that the more similar the DNA sequences are, the more recently two species diverged from a shared ancestor, and the more closely related they are. This is a more plausible explanation than two species having evolved similar or identical gene sequences coincidentally. The same logic applies to family patterns of inherited traits. It is more likely that a brother and sister share approximately half of their gene variants because they have the same parents than that half of their genetic material is identical by chance.

More information is available in full genome sequences than in single genes. Humans, for example, share more than 98 percent of the DNA sequence with chimpanzees. Our genomes differ from theirs more in gene organization and in the number of copies of genes. Learning the functions of the human-specific genes may explain the differences between us and them—such as our sparse body hair and use of spoken language. Figure 16.8 highlights some of our distinctively human traits.

At the genome level, we are much more like each other genetically than are other mammals. Chimpanzees are more distinct from each other than we are! The most genetically diverse modern people are from Africa, where humanity arose. The gene variants among different modern ethnic groups include subsets of our ancestral African gene pool.

Key Concepts Questions 1.2

1. List and define the levels of genetic information.
2. Explain how DNA carries and maintains information.
3. Explain how a mutation can cause a disease.
4. Explain how a gene can exist in more than one form.
5. Distinguish between Mendelian and multifactorial traits.
6. Explain how gene expression underlies composition of the human body.
7. Distinguish between genotype and phenotype; dominant and recessive.
8. Explain how comparing DNA sequences can clarify evolutionary relationships.

1.3 Applications of Genetics and Genomics

Genetics is impacting many areas of our lives, from health care choices, to what we eat and wear, to unraveling our pasts and guiding our futures. "Citizen scientists" are discovering genetic information about themselves while helping researchers compile databases that will help many.

Thinking about genetics evokes fear, hope, anger, and wonder, depending upon context and circumstance. Following are a few eclectic uses of DNA information, then glimpses of applications of genetics and genomics that are explored more fully in subsequent chapters:

- Identifying which of several pets produced feces, so a stool sample can be brought to a veterinarian to diagnose the sick animal
- Predicting shelf life of fruits and vegetables, detecting spoiled meat, identifying allergens, and indicating degree of fermentation in cheese
- Identifying victims of human trafficking at transportation centers by comparing the DNA of suspected victims to DNA from concerned relatives
- Detecting disease-causing mutations or abnormal chromosome numbers in a fetus from DNA in a pregnant woman's blood
- Performing rapid diagnosis of an infectious disease on the battlefield
- Creating a tree of life depiction of how all species are related
- Selecting crops and show animals for breeding
- Choosing people to date
- Detecting tiny amounts of DNA in fur, feathers, or feces of rare or elusive species to sequence their genomes and learn more about them (**figure 1.6**)

Establishing Identity

A technique called **DNA profiling** compares DNA sequences among individuals to establish or rule out identity, relationships, or ancestry. The premise is that the more DNA sequences two individuals share, the more closely related they are.

DNA profiling has varied applications, in humans and other species. The term is most often used in the context of forensic science, which is the collecting of physical evidence of a crime. Comparing DNA collected at crime scenes to DNA in samples from suspects often leads to convictions, and also to reversing convictions erroneously made using other forms of evidence.

DNA profiling is useful in identifying victims of natural disasters, such as violent storms and earthquakes. In happier circumstances, DNA profiles maintained in databases assist adopted individuals in locating blood relatives and children of sperm donors in finding their biological fathers and half-siblings.

Another use of DNA profiling is to analyze food, because foods were once organisms, which have species-specific DNA sequences. Analyzing DNA sequences revealed horsemeat in meatballs sold at a restaurant chain, cheap fish sold as gourmet varieties, and worms in cans of sardines.

Illuminating History

DNA analysis is a time machine of sorts. It can connect past to present, from determining family relationships to establishing geographic origins of specific populations. DNA evidence is perhaps most interesting when it contradicts findings from anthropology and history. Consider three examples, from most recent to most ancient.

DNA analysis confirmed that Thomas Jefferson had children with his slave Sally Hemings. The president was near Hemings 9 months before each of her seven children was born, and the children resembled him. Male descendants of Sally Hemings share an unusual Y chromosome sequence with the president's male relatives. His only son with his wife died in infancy, so researchers deduced the sequence of the president's Y chromosome from descendants of his uncle. Today the extended family holds reunions (**figure 1.7**).

DNA testing can provide views into past epidemics of infectious diseases by detecting genes of the pathogens. For example, analysis of DNA in the mummy of the Egyptian king Tutankhamun, who died in 1323 B.C.E. at age 19, revealed DNA

(a)

(b)

Figure 1.6 DNA is used to study endangered and difficult-to-capture animals. The field of conservation genomics collects and analyzes DNA from fur, feathers, and feces. The approach is used to study the American pika **(a)** and a rare subspecies of panther **(b)** that lives in isolated areas of southeast Russia and northeast China. *(a): Source: Jim Peaco/National Park Service; (b): © Destinyweddingstudio/Shutterstock*

Figure 1.7 DNA reveals and clarifies history. After DNA evidence showed that Thomas Jefferson likely fathered children with his slave Sally Hemings, confirming gossip of the time, descendants of both sides of the family met, and continue to do so. *© Leslie Close/AP Images*

from the microorganism that causes malaria. He likely died from complications of malaria following a leg fracture from weakened bones, rather than from intricate murder plots, a kick from a horse, or a fall from a chariot, as had been thought. His tomb included a cane and drugs, supporting the diagnosis based on DNA evidence.

The Basque people, who have a distinct language, live on the coastal border of France and Spain. The 700,000 modern Basques had long been thought to descend from hunter-gatherers who lived in the area about 7,500 years ago, before the first farmers arrived. DNA told a different story. Researchers compared the genome sequences of bones from eight Basque farmers who had lived in a cave in northern Spain from 5,500 to 3,500 years ago to genomes from other skeletons representing several European hunter-gatherers and early farming groups, as well as to modern Europeans. While the ancient farmers had genomes representing many groups, including those of hunter-gatherers, the Basques indeed have a unique genome—but one that descends from the earliest farmers, not from hunter-gatherers. Apparently their uniqueness today is due to their self-imposed isolation as the rest of Europe interbred.

Precision Medicine

In several nations, people are volunteering to have their genomes sequenced to learn more about health and disease. The DNA data are considered along with other types of information that can impact health, such as environmental exposures, exercise, diet, lifestyle factors, and the many microbes that live in and on the human body, collectively termed the **microbiome** (**figure 1.8**). In the United States, a precision medicine initiative is tracking 1 million volunteers who are having their genomes sequenced and providing as much information about their lives as possible.

On a smaller scale, a precision medicine approach consults DNA information to select drugs that are most likely to work and least likely to have side effects in a particular individual. This strategy, called **pharmacogenetics**, is already used to guide prescription of more than 150 drugs. Some highly effective new drugs that collectively treat a variety of conditions, from cystic fibrosis to cancers, are targeted to patients who have specific mutations in specific genes.

Healthy people have much to contribute to precision medicine by helping researchers identify gene variant combinations that contribute to wellness and longevity. Consider one participant's story:

My grandmother, mother, and myself all look at least 15 years younger than we are. My mother and I have absolutely no health concerns and have vital signs that are also indicative of people 15 to 20 years younger. I'm 46 and my mother is 64. I know there are world record holders who have amazingly long life spans, too, and other families with characteristics of slower aging, like my own. Maybe there is something in our DNA that delays aging?

The initiative in the United States, and efforts elsewhere such as the United Kingdom's 100,000 Genomes Project, are involving the general population in collecting information that will improve health care for many. For example, imagine identifying a group of people who all have a mutation known to cause a specific disease, but some of them do not have the disease. Something in the environment or that the protected people are doing might explain their health, and the finding used to develop treatments.

Genetic Modification

Genetic modification means altering a gene or genome in a way that does not occur in nature, such as giving a carrot a gene from a green bean that isn't part of the carrot genome. Traditional agriculture and animal breeding do not result in "genetically modified organisms" (GMOs) because they select traits within one species.

In health care, GMOs in the form of bacteria bearing human genes have provided many drugs, such as insulin and clotting factors, since the 1970s. Foods are genetically modified to be more nutritious, easier to cultivate, or able to grow in the presence of herbicides and pesticides. In the United States, more than 90 percent of the crops of corn, soybeans, and cotton are GMOs and the public has been eating them for more than a quarter century. However, some GMO foods have been failures. The "Flavr Savr" tomato, for example, was genetically modified to have a longer shelf life, but it had a terrible taste!

Genetically modified crops and drugs have been available for many years. A newer technology, **genome editing**, can replace, remove, or add specific genes into the cells of any organism (**figure 1.9**). Researchers are using genome-editing techniques experimentally to alter individual somatic cells growing in laboratory glassware, and genome editing may one day be used to treat certain inherited diseases. However, in the meantime, many researchers have agreed not to edit the genomes of human gametes (sperm or eggs) or fertilized eggs, which would create a genetically modified human. The most talked-about genome-editing tool is CRISPR-Cas9, but similar technologies

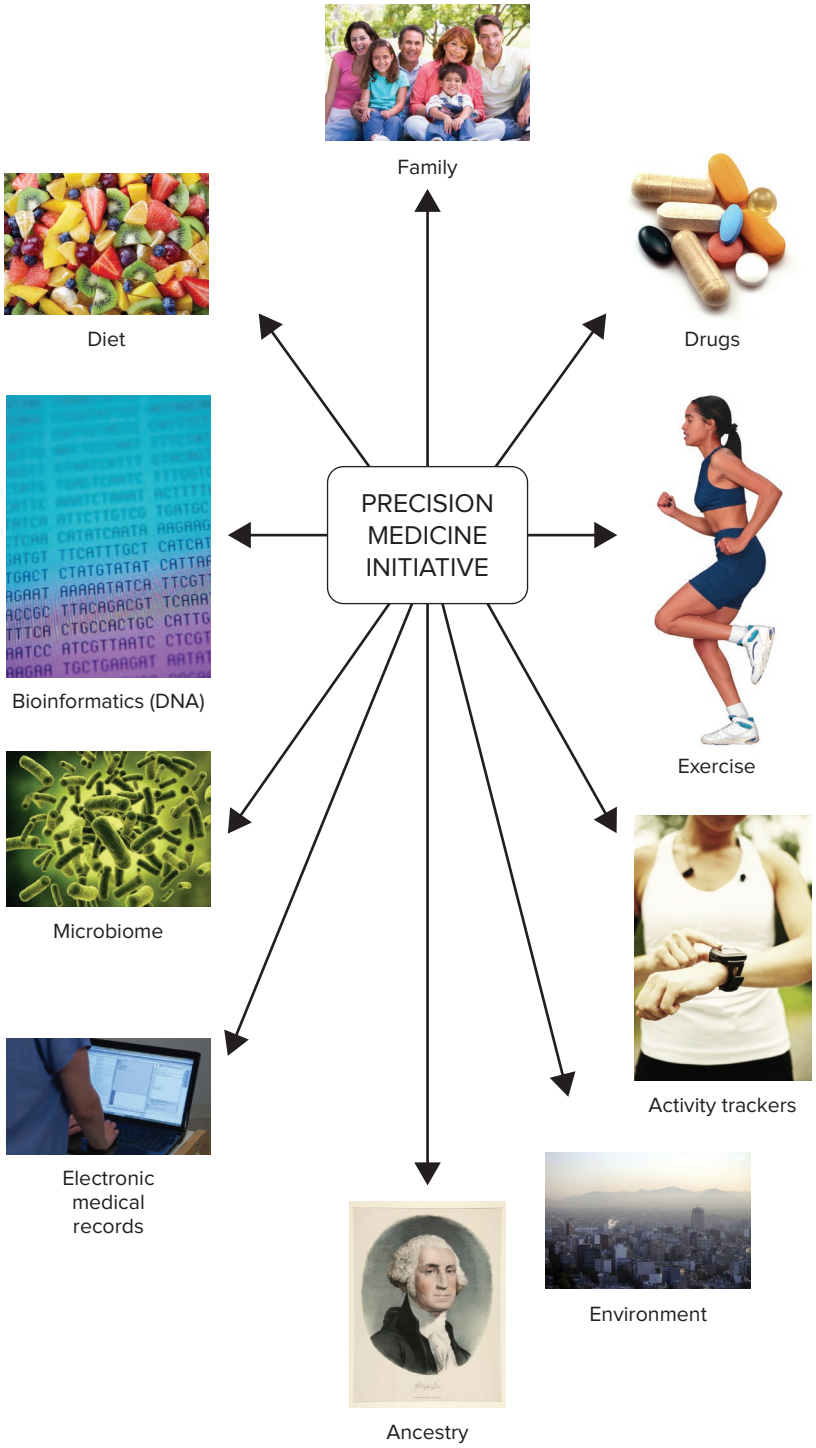


Figure 1.8 **Precision medicine.** In the United States, researchers are analyzing the genome sequences of 1 million citizens with other sources of "big data," such as electronic medical records, diet, exercise, family history and ancestry, the microbiome, and environmental exposures. *(Family): © Stockbroker/Alamy; (Drugs): © Dan Wilkie/Getty Images; (Exercise): © Glyn Jones/Corbis; (Activity trackers): © Disuke Martis /Getty Images; (Environment): © Phototreat/Getty Images; (Ancestry): Courtesy Yale University Library; (Electronic medical records): © McGraw-Hill Higher Education, Inc.; (Microbiome): © Disuke Martis/Getty Images; (Bioinformatics (DNA)): © Getty/Stockphoto; (Diet): © Babaz/Shutterstock*

Figure 1.9 **Genome editing.** CRISPR-Cas9 is one genome-editing technique. It uses a protein (Cas9) that functions much like a wrench, along with RNA molecules (CRISPRs) that guide the tool to a specific site in a genome. Genome editing enables researchers to add, delete, or replace specific DNA sequences in the cells of any type of organism. *Ernesto del Aguilo, III, NHGRI*

have been used since 2009, and the idea to edit the genome has been discussed since the 1980s.

Exome Sequencing

Exome sequencing determines the order of the DNA bases of all parts of the genome that encode proteins—that is, about 20,325 genes. The information is compared to databases that list many gene variants (alleles) and their associations with specific phenotypes, such as diseases. Exome sequencing is valuable after more conventional tests, such as tests for single gene diseases and chromosome abnormalities, do not explain a person's symptoms.

The information in an exome sequence can be lifesaving. For example, it showed that a 2-year-old boy who had severe eating difficulties and was very thin had a mutation known to cause Marfan syndrome, although he didn't have the characteristic long limbs and fingers that might have alerted a doctor. However, one symptom of Marfan syndrome is an enlarged aorta, the largest artery, and often this is not obvious until the aorta bursts and the person dies. After exome sequencing revealed a Marfan mutation, an ultrasound scan indeed showed a bulge in the wall of the aorta near the boy's heart, which could have resulted in his sudden death. Doctors successfully patched the bulging blood vessel.

Exome sequencing is particularly valuable in identifying extremely rare diseases—swiftly. In the past, parents of children with very unusual symptoms referred to the multiyear effort to find a physician who recognized the disease as a "diagnostic odyssey," in reference to Homer's epic poem about Greek hero Odysseus' 10-year journey home. Most diagnostic odysseys for genetic diseases took 5 years or longer. With exome as well as full genome sequencing, diagnosis can take just hours. **Clinical Connection 1.1** describes how genome sequencing led to diagnosis of a rare genetic disease in a child.