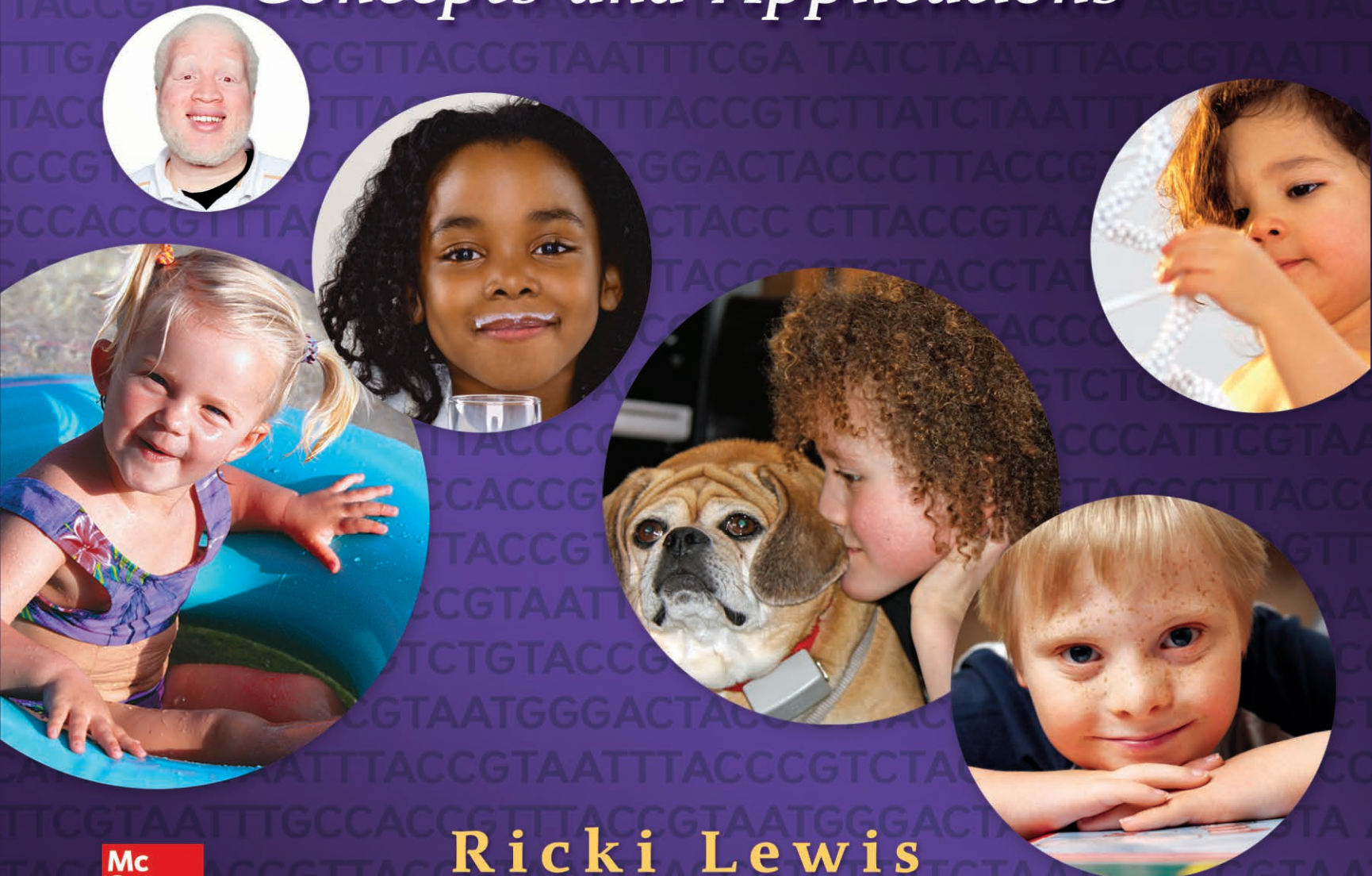
Eleventh Edition

HUMAN GENETICS

Concepts and Applications



Ricki Lewis

Mc Graw Hill Education

eleventh edition

Human Genetics

Concepts and Applications

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HUMAN GENETICS: CONCEPTS AND APPLICATIONS, ELEVENTH EDITION

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About the Author

Ricki Lewis has built an eclectic career in communicating the excitement of genetics and genomics. She earned her Ph.D. in genetics in 1980 from Indiana University. It was the dawn of the modern biotechnology era, which Ricki chronicled in many magazines and journals. She published one of the first articles on DNA fingerprinting in *Discover* magazine in 1988, and a decade later one of the first articles on human stem cells in *The Scientist*.

Ricki has taught a variety of life science courses at Miami University, the University at Albany, Empire State College, and community colleges. She has authored or co-authored several university-level textbooks and is the author of *The Forever Fix: Gene Therapy and the Boy Who Saved It,* as well as an essay collection and a novel. Ricki has been a genetic counselor for a private medical practice since 1984 and is a frequent public speaker. Since 2012, Ricki has written hundreds of news stories for *Medscape Medical News*, articles for *Scientific American* and for several genetic disease organizations, and originated and writes the popular weekly DNA Science blog at *Public Library of Science*.

Ricki teaches an online course on “Genethics” for the Alden March Bioethics Institute of Albany Medical College. She lives in upstate New York and sometimes Martha’s Vineyard, with husband Larry and several felines. Contact Ricki at rickilewis54@gmail.com, or join the discussion on DNA Science at http://blogs.plos.org/dnascience/.

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.

Brief Contents

Contents

Preface

Human Genetics Touches Us All

When I wrote the first edition of this book, in 1992, I could never have imagined that today, thousands of people would have had their genomes sequenced. Nor could I have imagined, when the first genomes were sequenced a decade later, that the process could take under a day, for less than $1,000. Of course, understanding all the information in a human genome will take much longer.

Each subsequent edition opened with a scenario of two students taking genetic tests, which grew less hypothetical and more real over time, even reaching the direct-to-consumer level. This new edition reflects the translation of gene and genome testing and manipulation from the research lab to the clinic.

The eleventh edition opens with "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

Today, human genetics is for everyone. It is about our variation more than about our illnesses, and about the common as well as the rare. Once an obscure science or an explanation for an odd collection of symptoms, human genetics is now part of everyday conversation. At the same time, it is finally being recognized as the basis of medical science, and health care professionals must be fluent in the field's language and concepts. Despite the popular tendency to talk of "a gene for" this or that, we now know that for most traits and illnesses, several genes interact with each other and environmental influences to mold who we are.

What Sets This Book Apart

Current Content

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

- Genetic tests, from preconception to old age
- Disease-in-a-dish stem cell technology
- From Mendel to molecules: family exome analysis
- Allelic diseases: one gene, more than one disease
- Admixture of archaic and modern humans
- Gene silencing and genome editing
- Cancer genomes guide treatment
- The reemergence of gene therapy
- Personal genome sequencing: promises and limitations

The transition of genetics to genomics catalyzed slight reorganization of the book. The order of topics remains, but material that had been boxed or discussed in later chapters because it was once new technology has been moved up as the "applications" become more integrated with the "concepts." The book has evolved with the science.

The Human Touch

Human genetics is about people, and their voices echo throughout these pages. They speak in the narrative as well as in many new chapter introductions, boxes, stories, and end-of-chapter questions and cases.

Compelling Stories and Cases When the parents of children with visual loss stood up at a conference to meet other families with the same very rare inherited disease, Dr. Lewis was there, already composing the opening essay to chapter 5. She knows the little girl in the "*In Their Own Words*" essay in chapter 2 and on the cover with her dog, who is 1 of about 70 people in the world with giant axonal neuropathy. Perhaps there is no more heart-wrenching image of Mendelian inheritance than the chapter 4 opening photo of a daughter and father, who died from Huntington disease within weeks of each other.

Clinical Application of Human Genetics A working knowledge of the principles and applications of human genetics is critical to being an informed citizen and health care consumer. Broad topics of particular interest include

- The roles that genes play in disease risk, physical characteristics, and behavior, with an eye toward the dangers of genetic determinism

- Biotechnologies, including next-generation DNA sequencing, genetic testing, stem cell technology, archaic human genome sequencing, gene therapy, familial DNA searches, exome sequencing, cell-free fetal DNA testing, and personal genome sequencing
- Ethical concerns that arise from the interface of genetic and genomic information and privacy.

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 chapter 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 ("*In Their Own Words,*" "*Clinical Connections,*" "*Bioethics: Choices for the Future,*" "*A Glimpse of History*," and "*Technology Timelines"*). End-of-chapter pedagogy progresses from straight recall to applied and creative questions and challenges.

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!

The genomics of today evolved from the genetics of the twentieth century. *A Glimpse of History* features throughout the book capture key moments in time. *Clinical Connections* bring chapter concepts to patients and health care providers, with thought-provoking questions for discussion. *Key Concepts* after all major sections are now questions.

Highlights in the new edition include the following:

Chapter 1 What Is in a Human Genome?
- The story of young Nicholas Volker, near death when exome sequencing led to a diagnosis—and a treatment

Chapter 2 Cells
- The human microbiome

Chapter 3 Meiosis, Development, and Aging
- Progress for progeria
- Maternal and paternal age effects on gametes

Chapter 4 Single-Gene Inheritance
- Family exome analysis solves a medical mystery

Chapter 7 Multifactorial Traits
- Blond hair among the Melanesians
- Smoking-related lung cancer

Chapter 8 Genetics of Behavior
- Genetic risks for posttraumatic stress disorder, depression, autism
- Heritability of intelligence at different ages

Chapter 11 Gene Expression and Epigenetics
- Long noncoding RNAs

Chapter 12 Gene Mutation
- Gonadal mosaicism
- Allelic disease—more common than we thought
- Exon skipping causes and treats disease

Chapter 13 Chromosomes
- Harnessing XIST to silence trisomy 21
- Cell-free fetal DNA for noninvasive prenatal diagnosis

Chapter 15 Changing Allele Frequencies
- The Clinic for Special Children treats the Amish

Chapter 16 Human Ancestry and Evolution
- Updated terminology and evolutionary trees
- Admixture, the Neanderthals, Denisovans, and us
- What makes us human?

Chapter 17 Genetics of Immunity
- Genomic epidemiology tracks an outbreak
- Reverse vaccinology
- Mimicking *CCR5* mutations to prevent HIV infection

Chapter 18 Cancer Genetics and Genomics
- Summary figure of cancer at different levels
- Driver and passenger mutations
- Cancer genomes
- Cell-free tumor DNA
- How *BRCA1* causes cancer

Chapter 19 Genetic Technologies: Patenting, Modifying, and Monitoring DNA
- The Supreme court and DNA patents
- Gene silencing and genome editing

Chapter 22 Genomics
- Genome sequencing and annotation
- Practical medical matters
- Types of information in human genomes
- A gallery of genomes
- Comparative genomics
- Do you want your genome sequenced?

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4.8 Loss-of-function and gain-of-function mutations
7.10 Copy number variants
8.6 Nicotine's effects at the cellular level
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9.17 Replication bubbles
12.5 Allelic disease of connective tissue
12.10 Exon skipping and Duchenne muscular dystrophy
13.14 XIST silences trisomy 21
14.11 Several steps identify STRs
15.13 Antibiotic resistance
16.13 Admixture of haplotypes
16.18 What makes us human?
17.14 Filaggrin and allergy
17.18 Genome sequencing to track outbreaks
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18.13 Cancer chromosomes
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2.2 Stem Cell Sources
3.4 Longevity Genes
7.6 Study Designs for Multifactorial Traits
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22.3 A Gallery of Genomes

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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

Chapter Openers

A GLIMPSE OF HISTORY

The Human Touch

Clinical Connections

In Their Own Words

Bioethics: Choices for the Future

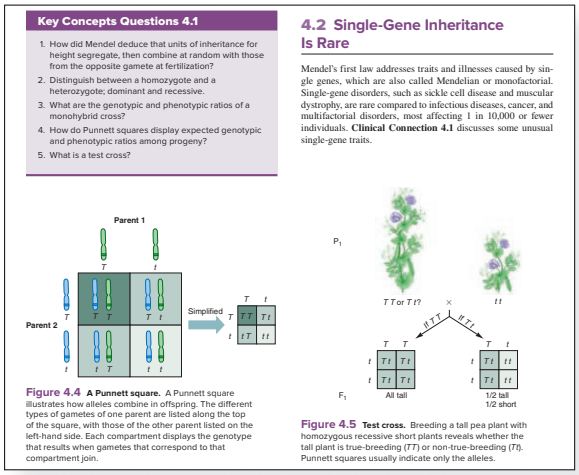
The Lewis Guided Learning System

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.



Key Concepts Questions 4.1

1. How did Mendel deduce that units of inheritance for height segregate, then combine at random with those from the opposite gamete at fertilization?
2. Distinguish between a homozygote and a heterozygote; dominant and recessive.
3. What are the genotypic and phenotypic ratios of a monohybrid cross?
4. How do Punnett squares display expected genotypic and phenotypic ratios among progeny?
5. What is a test cross?

4.2 Single-Gene Inheritance Is Rare

Mendel's first law addresses traits and illnesses caused by single genes, which are also called Mendelian or monofactorial. Single-gene disorders, such as sickle cell disease and muscular dystrophy, are rare compared to infectious diseases, cancer, and multifactorial disorders, most affecting 1 in 10,000 or fewer individuals. **Clinical Connection 4.1** discusses some unusual single-gene traits.

Figure 4.4 A Punnett square. A Punnett square illustrates how alleles combine in offspring. The different types of gametes of one parent are listed along the top of the square, with those of the other parent listed on the left-hand side. Each compartment displays the genotype that results when gametes that correspond to that compartment join.

Figure 4.5 Test cross. Breeding a tall pea plant with homozygous recessive short plants reveals whether the tall plant is true-breeding (*TT*) or non-true-breeding (*Tt*). Punnett squares usually indicate only the alleles.

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 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 tightened for showing utility of a DNA sequence.
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 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: Choices for the Future and **Clinical Connection** boxes include Questions for Discussion.

Who were the little people of Flores?

CHAPTER 16

Human Ancestry and Evolution

Learning Outcomes

16.1 Human Origins
1. How can DNA sequences provide information about our ancestry?
2. Describe our ancestors.
3. What can we learn from indigenous peoples about our origins?

16.2 Methods to Study Molecular Evolution
4. How do chromosome banding patterns and protein sequences reveal evolution?
5. What is a "molecular clock"?
6. How are mitochondrial DNA and Y chromosome sequences used to track human ancestry?
7. Explain how haplotypes provide clues to ancient migrations.

16.3 The Peopling of the Planet
8. What does mitochondrial Eve represent?
9. How did people expand out of Africa?

16.4 What Makes Us Human?
10. How does the human genome differ from the genomes of other primates?
11. What traits are unique to humans?
12. List genes that distinguish us from our closest relatives.

The BIG Picture

Our genes and genomes hold clues to our deep past and our present diversity. How will our species continue to evolve?

The Little Lady of Flores

The Nage people, who live on the island of Flores in Indonesia, speak of the Ebu Gogo, short hairy people thought to be mythical—until a team of Australian and Indonesian archaeologists arrived in 2003. They discovered, 17 feet beneath a cave floor, the near-complete skeleton of a female who fit the legendary description, plus pieces of seven other individuals. The ancient remains represent a people named *Homo floresiensis*.

The little people of Flores were half our height, with a brain about half the size of ours but with well-developed frontal lobes, suggesting that they were smart enough to use tools and fire and to hunt. They must have arrived on the island by raft, so some investigators suggest that the people had a language to coordinate the journey. *Homo floresiensis* had large teeth and feet, no chin, and a receding forehead. The little lady weighed about 55 pounds.

The people may have exhibited "island dwarfism," which is an effect of natural selection on small, isolated island populations. With limited resources, individuals who need less food are more likely to survive to reproduce. Over time under these conditions, average body size decreases. The little people hunted local little elephants.

Evidence indicates that the Flores people lived on the island from 95,000 to as recently as 12,000 years ago, but Portuguese traders report having seen the people as recently as the seventeenth century. Some researchers suggest that they may still exist.

Bioethics: Choices for the Future

Banking Stem Cells: When Is It Necessary?

The parents-to-be were very excited by the company's promise: "Bank your baby's cord blood stem cells and benefit from breakthroughs. Be prepared for the unknowns in life."

The website profiled children saved from certain diseases using stored umbilical cord blood. The statistics were persuasive: More than 70 diseases are currently treatable with cord blood transplants, and 10,000 procedures have already been done.

With testimonials like that, it is little wonder that parents collectively spend more than $100 million per year to store cord blood. The ads and statistics are accurate but misleading, because of what they *don't* say. Most people never actually use the umbilical cord blood stem cells that they store. The scientific reasons go beyond the fact that treatable diseases are very rare. In addition, cord blood stem cells are not nearly as pluripotent as some other stem cells, limiting their applicability. Perhaps the most compelling reason that stem cell banks are rarely used is based on logic: For a person with an inherited disease, *healthy* stem cells are required—not his or her own, which could cause the disease all over again because the mutation is in every cell. The patient needs a well-matched donor, such as a healthy sibling.

Commercial cord blood banks may charge more than $1,000 for the initial collection plus an annual fee. However, the U.S. National Institutes of Health and organizations in many other nations have supported not-for-profit banks for years, and may not charge fees. Donations of cord blood to these facilities are not to help the donors directly, but to help whoever can use the cells.

Commercial stem cell banks are not just for newborns. One company, for example, offers to bank "very small embryonic-like stem cells" for an initial charge of $7,500 and a $750 annual fee, "enabling people to donate and store their own stem cells when they are young and healthy for their personal use in times of future medical need." The cells come from a person's blood and, in fact, one day may be very useful, but the research has yet to be done supporting any use of the cells in treatments.

Questions for Discussion

1. Storing stem cells is not regulated by the U.S. government the way that a drug or a surgical procedure is because it is a service that will be helpful for treatments not yet invented. Do you think such banks should be regulated, and if so, by whom and how?
2. What information do you think that companies offering to store stem cells should present on their websites?
3. Do you think that advertisements for cord blood storage services that have quotes and anecdotal reports, but do not mention that most people who receive stem cell transplants do not in fact receive their own cells, are deceptive? Or do you think it is the responsibility of the consumer to research and discover this information?
4. Several companies store stem cells extracted from baby teeth, although a use for such stem cells has not yet been found. Suggest a different way to obtain stem cells that have the genome of a particular child.

Clinical Connection 3.1

When an Arm Is Really a Leg: Homeotic Mutations

Flipping the X ray showed Stefan Mundlos, MD, that his hunch was right—the patient's arms were odd-looking and stiff because the elbows were actually knees! The condition, Liebenberg syndrome (OMIM 186550), had been described in 1973 among members of a five-generation white South African family (**figure 1**). Four males and six females had stiff elbows and wrists, and short fingers that looked strangely out of place. A trait that affects both sexes in every generation displays classic autosomal dominant inheritance—each child of a person with strange limbs had a 50:50 chance of having the condition too.

In 2000, a medical journal described a second family with Liebenberg syndrome. Several members had restricted movements because they couldn't bend their huge, misshapen elbows. Then in 2010, a report appeared on identical twin girls with the curious stiff elbows and long arms, with fingers that looked like toes.

In 2012, Dr. Mundlos noted that the muscles and tendons of the elbows, as well as the bones of the arms, weren't quite right in his patient. The doctor, an expert in the comparative anatomy of limb bones of different animals, realized that the stiff elbows were acting like knees. The human elbow joint hinges and rotates, but the knee extends the lower leg straight out. Then an X-ray scan of the patient's arm fell to the floor. "I realized that the entire limb had the appearance of a leg. Normally you would look at the upper limb X ray with the hand up, whereas the lower limb is looked at foot down. If you turn the X ray around, it looks just like a leg," Dr. Mundlos said.

Genes that switch body parts are termed *homeotic*. They are well studied in experimental organisms as evolutionarily diverse as fruit flies, flowering plants, and mice, affecting the positions of larval segments, petals, legs, and much more. Assignment of body parts begins in the early embryo, when cells look alike but are already fated to become specific structures. Gradients (increasing or decreasing concentrations) of "morphogen" proteins in an embryo program a particular region to develop a certain way. Mix up the messages, and an antenna becomes a leg, or an elbow a knee.

Homeotic genes include a 180-base-long DNA sequence, called the homeobox, which enables the encoded protein to bind other proteins that turn on sets of other genes, crafting an embryo, section by section. Homeotic genes line up on their chromosomes in the precise order in which they're deployed in development, like chapters in an instruction manual to build a body.

The human genome has four clusters of homeotic genes, and mutations in them cause disease. In certain lymphomas, a homeotic mutation sends white blood cells along the wrong developmental pathway, resulting in too many of some blood cell types and too few of others. The abnormal ears, nose, mouth, and throat of DiGeorge syndrome (OMIM 188400) echo the abnormalities in *Antennapedia*, a fruit fly mutant that has legs on its head. Extra and fused fingers and various bony alterations also stem from homeotic mutations.

The search for the mutation behind the arm-to-leg Liebenberg phenotype began with abnormal chromosomes. Affected members of the three known families were each missing 134 DNA bases in the same part of the fifth largest chromosome. The researchers zeroed in on a gene called *PITX1* that controls other genes that in turn oversee limb development. In the Liebenberg families, the missing DNA places an "enhancer" gene near *PITX1*, altering its expression in a way that mixes up developmental signals so that the forming arm instead becomes a leg. Fortunately the condition appears more an annoying oddity than a disease.

Questions for Discussion

1. What is the genotype and phenotype of Liebenberg syndrome?
2. How can homeotic mutations be seen in such different species as humans, mice, fruit flies, and flowering plants?
3. Explain the molecular basis of a homeotic mutation and the resulting phenotype.
4. Name another human disease that results from a homeotic mutation.

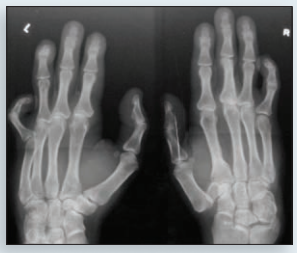


Figure 1 The hands of a person with Liebenberg syndrome resemble feet; the arms resemble legs.

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

Summary

11.1 Gene Expression Through Time and Tissue

1. Changes in gene expression occur over time at the molecular and organ levels. **Epigenetic** changes to DNA alter gene expression, but do not change the DNA sequence.
2. **Proteomics** catalogs the types of proteins in particular cells, tissues, organs, or entire organisms under specified conditions.

11.2 Control of Gene Expression

3. Acetylation of certain histone proteins enables the transcription of associated genes, whereas phosphorylation and methylation prevent transcription. The effect of these three molecules is called **chromatin remodeling.**
4. **MicroRNAs** bind to certain mRNAs, blocking translation.

11.3 Maximizing Genetic Information

5. A small part of the genome encodes protein, but the number of proteins is much greater than the number of genes.
6. Alternate splicing, use of introns, protein modification, and cutting proteins translated from a single gene contribute to protein diversity.

11.4 Most of the Human Genome Does *Not* Encode Protein

7. The non-protein-encoding part of the genome includes viral sequences, noncoding RNAs, **pseudogenes,** introns, **transposons,** promoters and other controls, and repeats.
8. **Long noncoding RNAs** control gene expression.

www.mhhe.com/lewisgenetics11

Answers to all end-of-chapter questions can be found at **www.mhhe.com/lewisgenetics11**. You will also find additional practice quizzes, animations, videos, and vocabulary flashcards to help you master the material in this chapter.

Review Questions

1. Why is control of gene expression necessary?
2. Define *epigenetics*.
3. Distinguish between the type of information that epigenetics provides and the information in the DNA sequence of a protein-encoding gene.
4. Describe three types of cells and how they differ in gene expression from each other.
5. What is the environmental signal that stimulates globin switching?
6. How does development of the pancreas illustrate differential gene expression?
7. Explain how a mutation in a promoter can affect gene expression.
8. How do histones control gene expression, yet genes also control histones?
9. What controls whether histones enable DNA wrapped around them to be transcribed?
10. State two ways that methyl groups control gene expression.
11. Name a mechanism that silences transcription of a gene and a mechanism that blocks translation of an mRNA.
12. Why might a computational algorithm be necessary to evaluate microRNA function in the human genome?
13. Describe three ways that the number of proteins exceeds the number of protein-encoding genes in the human genome.
14. How can alternate splicing generate more than one type of protein from the information in a gene?
15. In the 1960s, a gene was defined as a continuous sequence of DNA, located permanently at one place on a chromosome, that specifies a sequence of amino acids from one strand. List three ways this definition has changed.
16. Give an example of a discovery mentioned in the chapter that changed the way we think about the genome.
17. What is the evidence that some long noncoding RNAs may hold clues to human evolution?

Applied Questions

1. The World Anti-Doping Agency warns against gene doping, which it defines as "the non-therapeutic use of cells, genes, genetic elements, or of the modulation of gene expression, having the capacity to improve athletic performance." The organization lists the following genes as candidates for gene doping when overexpressed:
   Insulin-like growth factor (*IGF-1*)
   Growth hormone (*GH*)

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

Review Questions assess content knowledge.

Applied Questions help students develop problem-solving skills.

Web Activities

1. Gene expression profiling tests began to be marketed several years ago. Search for "Oncotype DX," "MammaPrint," or "gene expression profiling in cancer" and describe how classifying a cancer this way can improve diagnosis and/or treatment. (Or apply this question to a different type of disease.)
2. The government's Genotype-Tissue Expression (GTEx; https://commonfund.nih.gov/GTEx/) project is a database of gene expression profiles of 24 tissues (parts of organs) from 190 people who died while healthy.
   a. What type of data are compared?
   b. Suggest a way that a researcher can use this type of information.
3. Look up each of the following conditions using OMIM or another source, and describe how they arise from altered chromatin: alpha-thalassemia, ICF syndrome, Rett syndrome, Rubinstein-Taybi syndrome.

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. To make a "reprogrammed" induced pluripotent stem (iPS) cell (see figure 2.22), 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?
2. A study investigated "genomic signatures of global fitness" to identify gene expression patterns that indicate that a course of exercise is beneficial. In the study, sixty sedentary women representing different ethnic groups

Web Activities encourage students to use the latest tools and databases in genetic analysis.

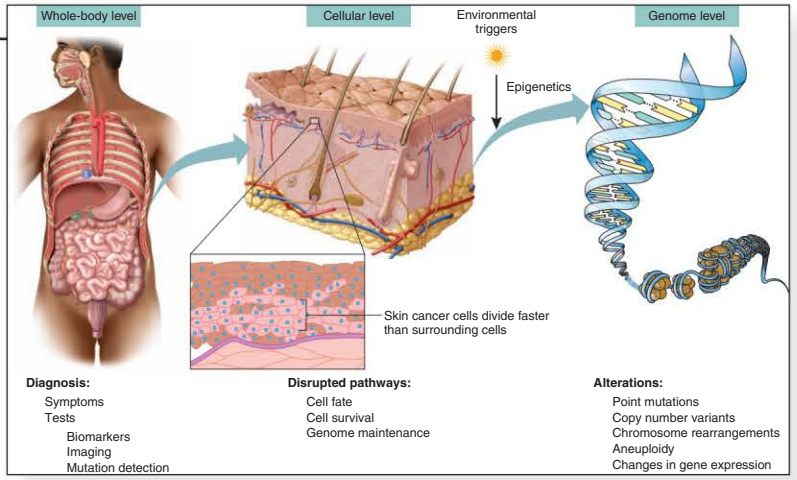
Forensics Focus questions probe the use of genetic information in criminal investigations.

Cases 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

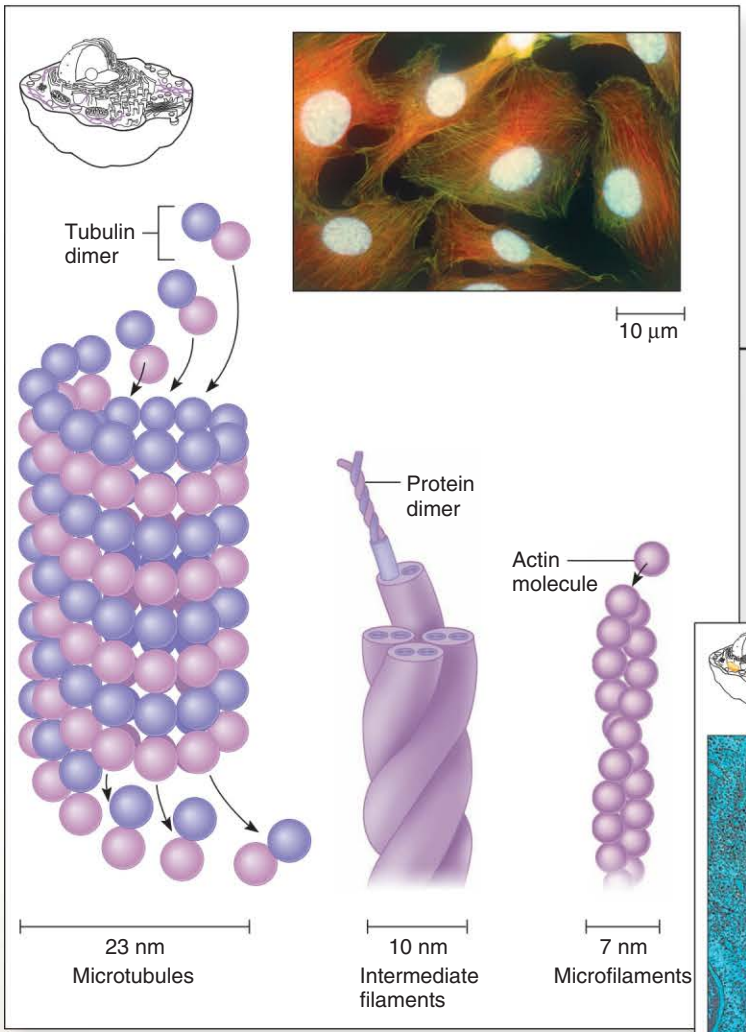
Multilevel Perspective

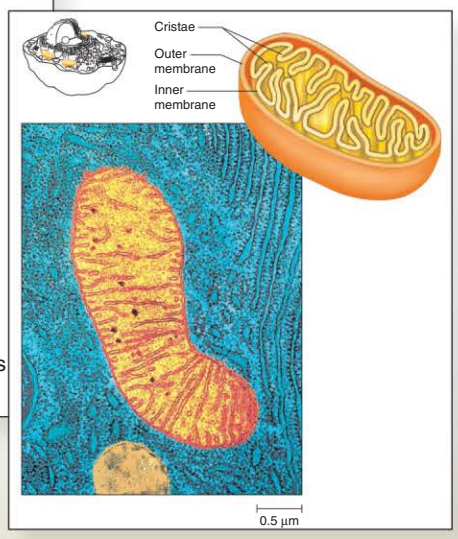
Illustrations depicting complex structures show macroscopic and microscopic views to help students see relationships among increasingly detailed drawings.



Combination Art

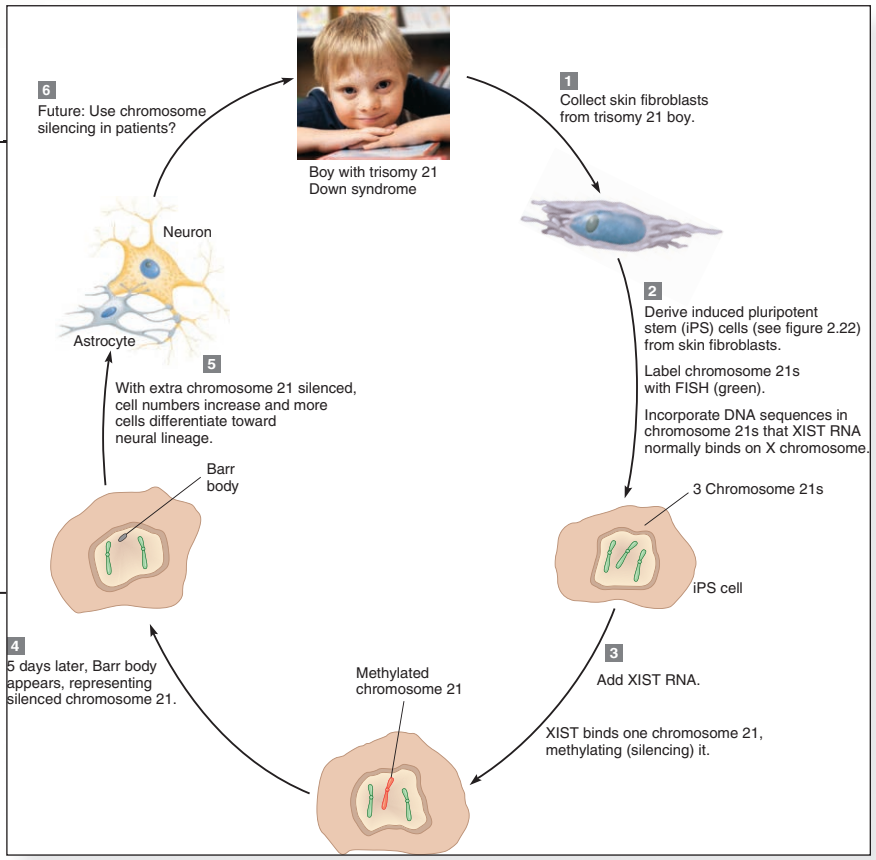
Drawings of structures are paired with micrographs to provide the best of both perspectives: the realism of photos and the explanatory clarity of line drawings.





New Technologies

Stem cells from patients' skin fibroblasts enable researchers to study a disease's beginnings, and may one day lead to new treatments.

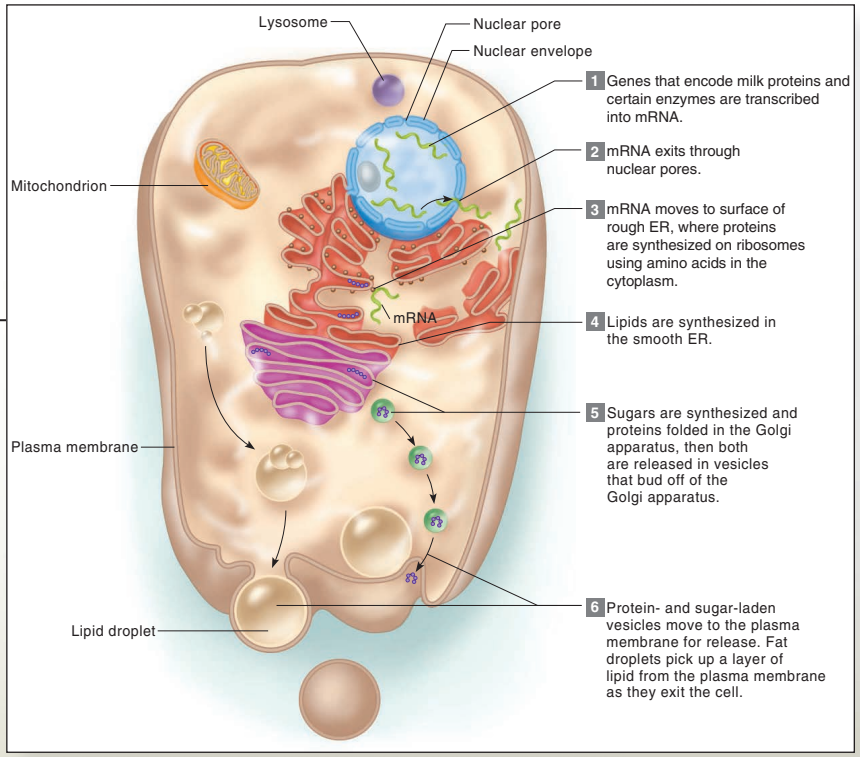


Clinical Coverage

"Mossy foot," or podoconiosis, is common in Ethiopia among people who walk barefoot on volcanic rock and are genetically susceptible to reacting to mineral slivers. The treatment: *shoes*.

Process Figures

Complex processes are broken down into a series of numbered smaller steps that are easy to follow. Here, organelles interact to produce and secrete a familiar substance—milk (figure 2.6).



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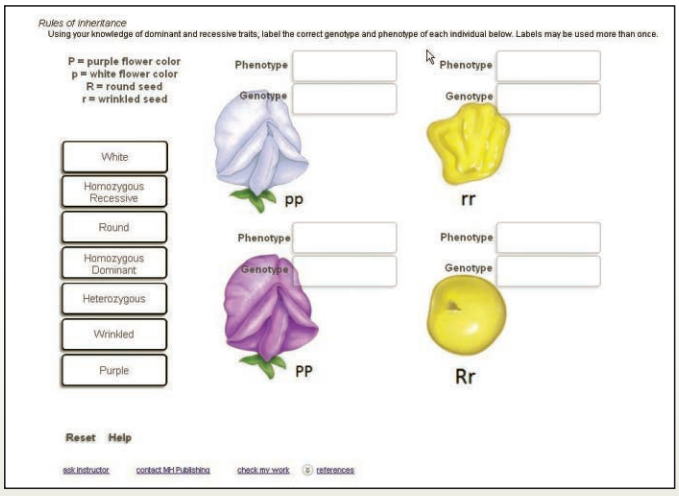

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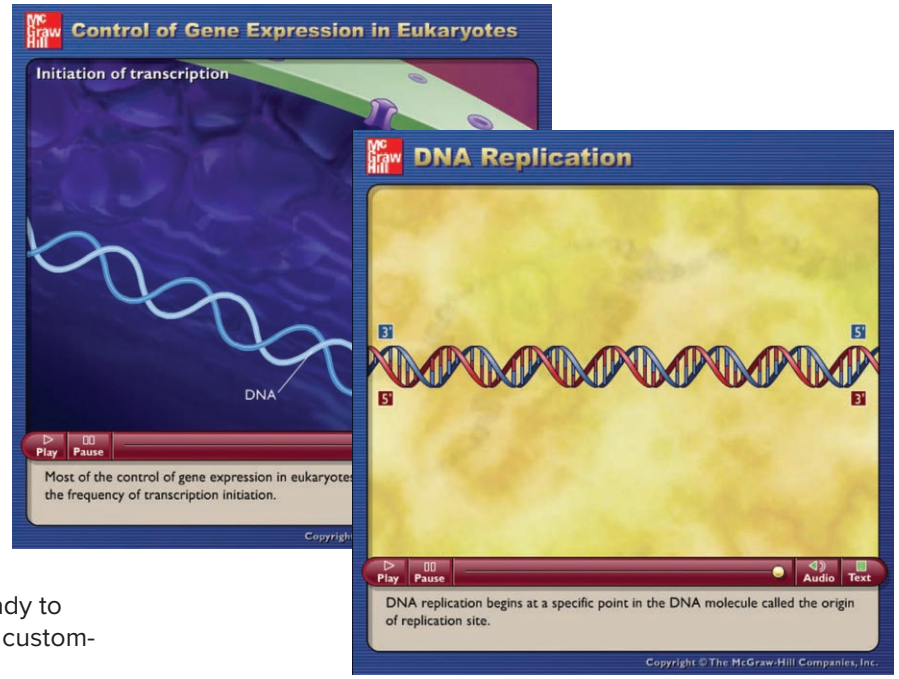

Computerized Test Bank written by Ricki Lewis!

The author has rewritten and expanded the test bank to include many more cases and problems. Terms match those used in the text, and the questions follow the order of topics within the chapters. This comprehensive bank of questions is provided within a computerized test bank powered by McGraw-Hill's flexible electronic testing program EZ Test Online. EZ Test Online allows you to create paper and online tests or quizzes in this easy-to-use program!

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Case Workbook to Accompany Human Genetics by Ricki Lewis

For those who enjoy learning and teaching from cases, *In the Family: A Case Workbook to Accompany Human Genetics, Eleventh Edition,* bases questions on a multigenerational blending of three core families. Each chapter in the workbook corresponds to a textbook chapter and highlights a section of the overall connected pedigree. The casebook is a fun, highly innovative way to apply genetics concepts. Through the narrative and dialog style of the workbook, readers will come to know the various family members, while learning genetics.

PART 1 Introduction

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

CHAPTER 1

What Is in a Human Genome?

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. Describe the levels of genetics, from nucleic acids to chromosomes, to cells, body parts, families, and populations.
5. Explain how genetics underlies evolution.

1.3 Applications of Genetics and Genomics

6. Provide examples of how genetics is used in identification of people and in health care.

1.4 A Global Perspective on Genomes

7. How can investigating genomes extend 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 reflects how we are biologically related to one another.

Eve's Genome

A baby is born. A few drops of blood from her heel are placed into a small device that within hours 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.

Sequencing the first human genome took 15 years; now it takes hours. Eve's genome sequence holds clues to her current and future health, as well as to her ancestry. Past, present, and future are encoded in nature's informational molecule, deoxyribonucleic acid, or DNA—with room for environmental influences.

Eve's genome indicates overall good genetic health. She has a mild clotting disorder 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 one day 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. 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 her mother comes from, 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.

Over the next few years sequencing of our genomes, or perhaps relevant parts of them, will become routine in health care. 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. Sometimes people confuse genetics with genealogy, which considers relationships but not traits. Because some genetic tests can predict illness, genetics has also been compared to fortune-telling. 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 the freckles and red hair of the young man in **figure 1.1**, 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 a combination of genetic and environmental influences. Attributing some behavioral traits to genetics, such as sense of humor, fondness for sports, and whether or not one votes, are oversimplifications.

Over the past few years, genetics has exploded from a mostly academic discipline and a minor medical specialty dealing mostly with very rare diseases, to a part of everyday discussion. Personal genetic information is accessible and we are learning the contribution of genes to the most common traits and disorders. Many physicians are taking continuing medical education courses to learn how to integrate genetic and genomic testing into clinical practice.

Like all sciences, genetics has its own vocabulary. Many terms may be familiar, but actually have precise technical definitions. "It's in her DNA," for example, usually means an inborn trait, not a specific DNA sequence. This chapter introduces terms and concepts that are explained in detail in subsequent chapters.

Figure 1.1 Inherited traits. This young man owes his red hair, fair skin, and freckles to a variant of a gene that encodes a protein (the melanocortin 1 receptor) that controls the balance of pigments in his skin.

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.

The complete set of genetic instructions characteristic of an organism, including protein-encoding genes and other DNA sequences, constitutes a **genome**. Researchers concluded sequencing the human genome in 2003. Nearly all of our cells contain two copies of the genome. Researchers 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. Comparing and analyzing genomes, which constitute the field of **genomics,** reveals 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, 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** was founded 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, beginning with the story of how DNA sequencing saved a boy's life, on page 10.

Key Concepts Questions 1.1

1. Distinguish between genetics and heredity.
2. Distinguish between a gene and a genome.
3. What is 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 1.2**).

The Instructions: DNA, Genes, Chromosomes, and Genomes

DNA resembles a spiral staircase or double helix. The "rails," or backbone, consist of alternating chemical groups (sugars and phosphates) that are the same in all DNA molecules. The "steps" of the DNA double helix hold the information because they are pairs of four types of building blocks, or bases, whose sequence varies from molecule to molecule (**figure 1.3**). The bases are adenine (A) and thymine (T), which attract each other, and cytosine (C) and guanine (G), which attract each other. The information is in the sequences of A, T, C, and G. The two strands of the double helix are oriented in opposite directions, like two snakes biting each other's tails.

The chemical structure of DNA enables it both to perpetuate itself when a cell divides and to provide the cell with information used to manufacture proteins. Each consecutive three DNA bases is a code for a particular amino acid, and amino acids are the building blocks of proteins.

In DNA replication, the chains of the helix part and each half builds a new partner chain by pulling in free DNA bases—A and T attracting and C and G attracting. To produce protein, a process called transcription copies the sequence of part of one strand of a DNA molecule into a related molecule, messenger **ribonucleic acid** (**RNA**). Each three RNA bases in a row then attract another type of RNA that functions as a connector, bringing in a particular amino acid. The amino acids align, forming a protein. Building a protein is called translation. Proteins provide the traits associated with genes, such as blood clotting factors. **Figure 1.4** is a conceptual look ahead to chapter 10, which presents these complex processes in detail.

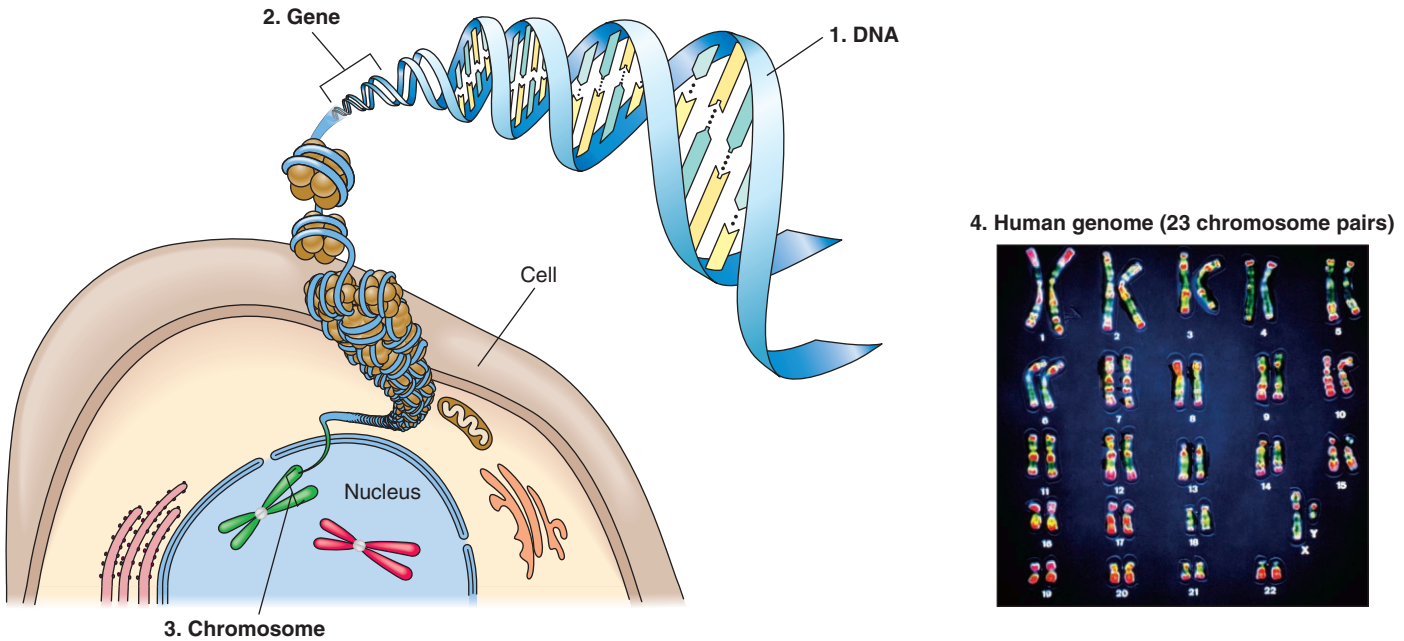

Figure 1.2 **Levels of genetics.** Genetics can be considered at several levels, from DNA, to genes, to chromosomes, to genomes, to the more familiar individuals, families, and populations. (A gene is actually several hundred or thousand DNA bases long.)

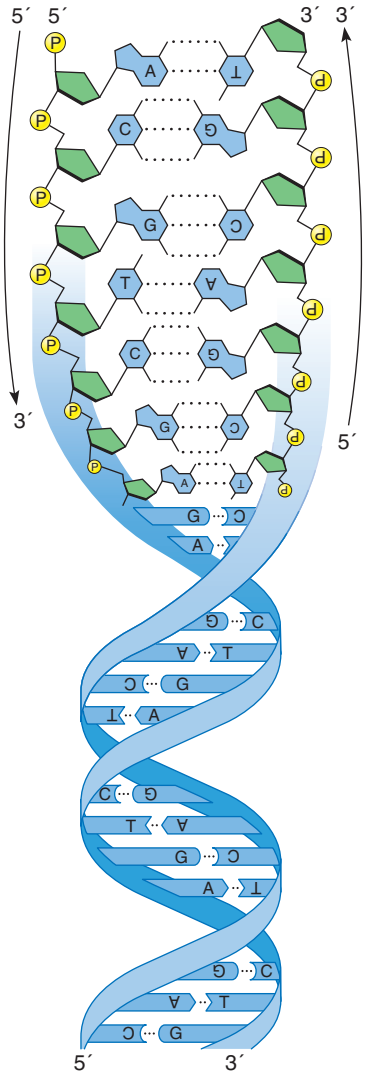

Figure 1.3 **The DNA double helix.** The 5′ and 3′ labels indicate the head-to-tail organization of the DNA double helix. A, C, T, and G are bases. S stands for sugar and P for phosphate.

A genome's worth of DNA is like a database that is accessed to run the cell. Different types of cells have different protein requirements. A muscle cell has abundant contractile proteins, but a skin cell contains mostly scaly proteins called keratins. A cell's protein production can change as conditions change. A cell lining the stomach, for example, would produce more protein-based digestive enzymes after a meal than when a person hasn't eaten in several hours.

The human genome has about 20,325 protein-encoding genes, and these DNA sequences comprise the **exome**. A database called Online Mendelian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/omim) describes the few thousand genes known to cause disorders or traits.

Protein-encoding genes account for only about 1.5 percent of the human genome. The rest includes many DNA sequences that assist in protein synthesis or turn protein-encoding genes

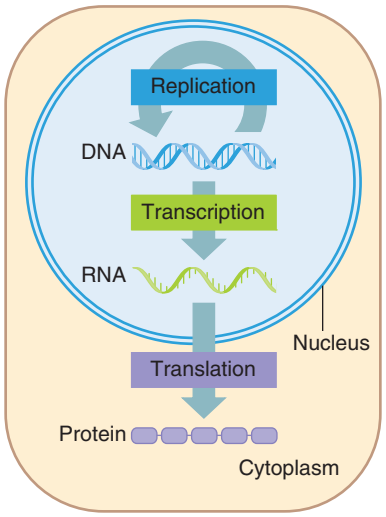

Figure 1.4 **The language of life:** DNA to RNA to protein.

on or off. The ongoing effort to understand what individual genes do is termed annotation.

The same protein-encoding gene may vary slightly in base sequence from person to person. These gene variants are called **alleles**. The changes in DNA sequence that distinguish alleles arise by a process called **mutation**. A "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. For example, a mutation makes a person's cells unable to manufacture a surface protein that binds HIV. These people are resistant to HIV infection. Many mutations have no visible effect because they do not change the encoded protein in a way that affects its function, just as a minor spelling error does not obscure the meaning of a sentence.

DNA molecules are very long. They wrap around proteins and wind tightly, forming rod-shaped structures called **chromosomes**. The DNA of a chromosome is continuous, but it includes hundreds of genes among other sequences.

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

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

A trait caused by a single gene is termed Mendelian. Most traits are **multifactorial traits,** which means that they

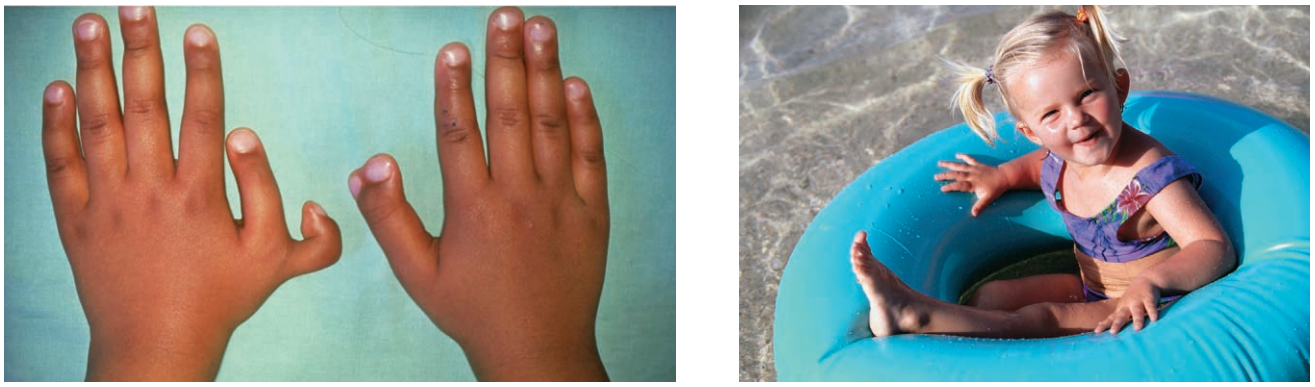

Figure 1.5 **Mendelian versus multifactorial traits.** **(a)** Polydactyly—extra fingers and/or toes—is a Mendelian trait (single-gene). **(b)** Hair color is multifactorial, controlled by at least three genes plus environmental factors, such as the bleaching effects of sun exposure.

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 confer susceptibility to fractures, as 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." Because of the role of the environment, some genetic test results given before symptoms are present indicate risks, not a diagnosis. A doctor might discuss the results of a test finding an inherited susceptibility to a form of breast cancer as, "You have a 45 percent chance of developing this form of cancer," not "You will get cancer."

Genetic determinism may be harmful or helpful, depending on circumstance. As part of social policy, genetic determinism can be disastrous. An assumption that one group of people is genetically less intelligent than another can lead to lowered expectations and/or 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 give us more control over health outcomes by influencing noninherited factors, such as diet and exercise habits.

The Body: Cells, Tissues, and Organs

A human body consists of approximately 37 trillion cells. All cells except red blood cells contain the entire 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 both inside and outside the body.

Like the Internet, a genome contains a wealth of information, but only some of it need be accessed. 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 complete genomes. Groups of differentiated cells assemble and interact with each other and the nonliving material that they secrete to form aggregates called tissues.

The body has four basic tissue types, composed of more than 290 types of cells (see figure 2.2). Tissues intertwine and layer to form the organs of the body, which in turn connect into organ systems. The stomach shown at the center of **figure 1.6**, 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. **Table 1.1** describes tissue types.

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 half of his or her gene variants in common with each parent and each sibling, 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

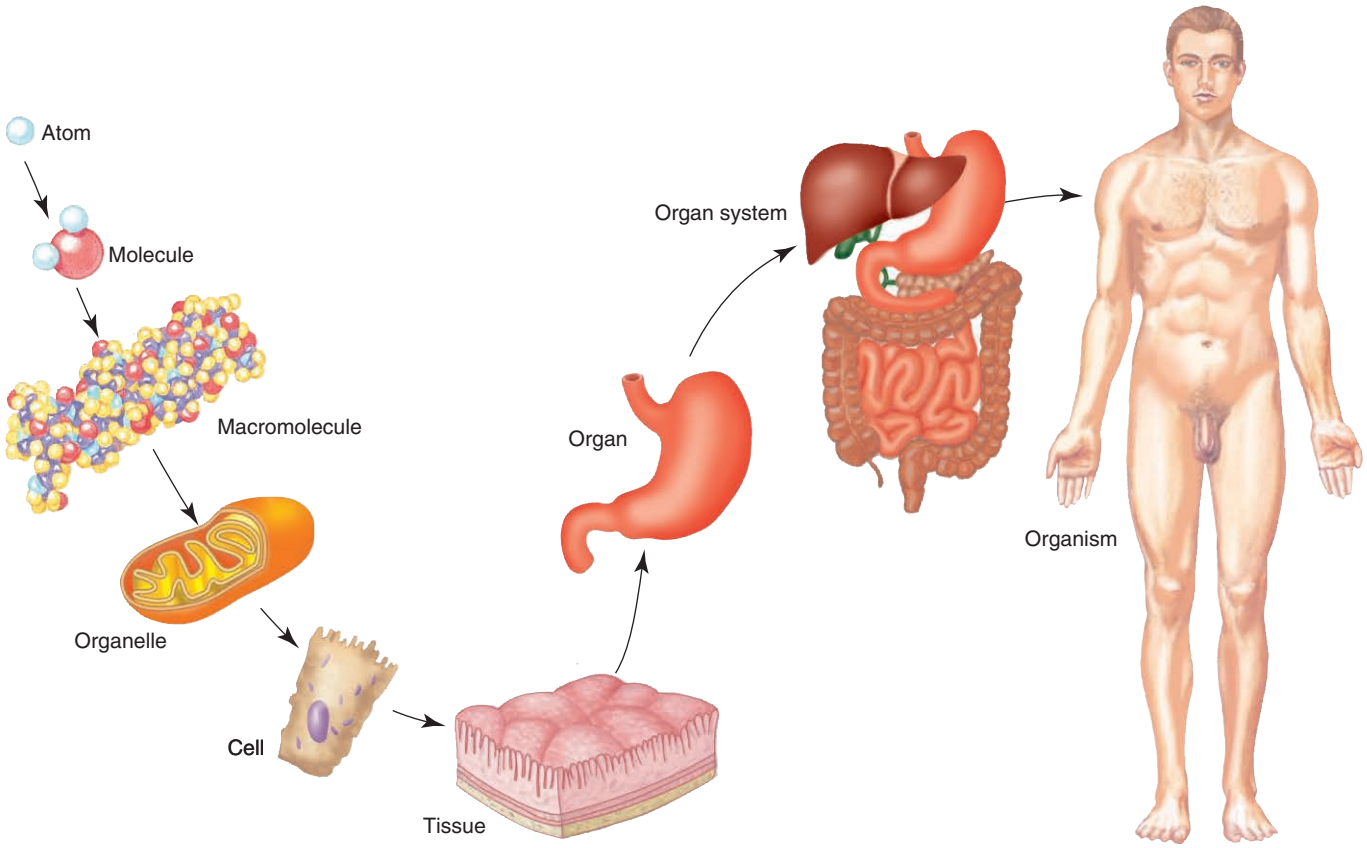

Figure 1.6 **Levels of biological organization.**

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 more obvious 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 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. All life is related, and different species use the same basic set of genes that makes life possible.

Both the evolution of species and family patterns of inherited traits show divergence from shared ancestors. This idea is based on logic. 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.

Genome sequence comparisons reveal more about evolutionary relationships than comparing 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 than in the overall sequence. Learning the functions of the human-specific genes may explain the differences between us and them—such as our lack of hair and use of spoken language. Figure 16.8 highlights some of our distinctively human traits.

Table 1.1 **Tissue Types**

Tissue	Function/Location/Description
Connective tissues	A variety of cell types and materials around them that protect, support, bind to cells, and fill spaces throughout the body; include cartilage, bone, blood, and fat
Epithelium	Tight cell layers that form linings that protect, secrete, absorb, and excrete
Muscle	Cells that contract, providing movement
Nervous	Neurons transmit information as electrochemical impulses that coordinate movement and sense and respond to environmental stimuli; neuroglia are cells that support and nourish neurons

Comparisons of people at the genome level reveal that 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. What are the levels of genetic information?
2. Explain how the DNA molecule carries information.
3. Explain how a gene can exist in more than one form.
4. Distinguish between Mendelian and multifactorial traits.
5. Explain how gene expression underlies formation of the human body.
6. Distinguish between genotype and phenotype; dominant and recessive.
7. How can comparing DNA sequences reveal 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. A direct-to-consumer genetic testing company used its clients' information to discover a new gene that causes Parkinson disease, for example. Thinking about genetics evokes fear, hope, anger, and wonder, depending upon context and circumstance. Following are glimpses of applications of genetics that are explored more fully in subsequent chapters.

Establishing Identity

A technique called DNA profiling compares DNA sequences among individuals to establish or rule out identity, relationships, or ancestry. DNA profiling has varied applications, in humans and other species.

Forensic science is the collecting of physical evidence of a crime. Comparing DNA samples from evidence at crime scenes to 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. For example, analyzing DNA sequences revealed horsemeat in meatballs sold at a restaurant chain, cheap fish sold as gourmet varieties, and worms in cans of sardines.

Figure 1.7 DNA reveals and clarifies history. After DNA evidence showed that Thomas Jefferson likely fathered a son of his slave, descendants of both sides of the family met.

DNA analysis can clarify details of history. A famous case confirmed that Thomas Jefferson had children with his slave Sally Hemings. The president was near Hemings 9 months before each of her seven children were born, and the children looked like 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 revealed the presence of the microorganism that causes malaria. The child king 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 fall from a chariot, as had been thought. His tomb included a cane and drugs, supporting the diagnosis based on DNA evidence.

Health Care

Looking at diseases from a genetic point of view is changing health care. Many diseases, not just inherited ones, are now viewed as the consequence of complex interactions among genes and environmental factors. Even the classic single-gene diseases are sensitive to the environment. A child with cystic fibrosis (OMIM 219700), for example, is more likely to suffer frequent respiratory infections if she regularly breathes second-hand smoke. In the opposite situation, whether or not a person is susceptible to a mostly environmentally caused condition depends upon genetics. **Figure 1.8** shows the feet of a young person with podoconiosis, also known as "mossy foot." The swollen, itchy, painful bumps result from walking barefoot on damp, red volcanic rock that contains microscopic slivers

Figure 1.8 **A gene-environment interaction.** Podoconiosis ("mossy foot") is a painful foot condition that develops in genetically susceptible individuals who walk barefoot on hard, volcanic rock that contains slivers of minerals. It is common in parts of Ethiopia.

of minerals. In the 15 countries that have the volcanic rock, 10 to 20 percent of the people have the painful foot disease. They share a pattern of gene variants that affects the immune response, causing extreme inflammation in response to irritation. In general, inherited differences in immunity are one of several reasons why some people are more susceptible to contracting certain infections than others, discussed in chapter 17.

Because genes instruct cells to manufacture specific proteins, inherited diseases can result from altered proteins or too little or too much of a protein, or proteins made at the wrong place or time. Genes also affect how people respond to particular drugs. For example, inheriting certain gene variants can make a person's body very slow at breaking down an anti-clotting drug, or extra sensitive to the drug. The person bleeds profusely at the same dose that most patients tolerate. Identifying individual drug reactions based on genetics is a growing field called pharmacogenetics. Tests based on pharmacogenetics can prevent adverse reactions or indicate that a particular drug will or will not work in a particular individual. Some physicians use these tests to prescribe antidepressants, anti-clotting drugs, chemotherapies, and cholesterol-lowering drugs.

Single-Gene Diseases

Inherited illness caused by a single gene differs from other types of illnesses in several ways (**table 1.2**). In families, we can predict inheritance of a single-gene disease by knowing exactly how a person is related to an affected relative. In contrast, an infectious disease requires that a pathogen pass from one person to another, which is much less predictable.

A second distinction of single-gene disorders is that tests can sometimes predict the risk of developing symptoms. This is possible because all cells harbor the mutation. A person with a family history of Huntington disease (HD; OMIM 143100), for example, can have a blood test that detects the mutation at any age, even though symptoms typically do not occur until early middle age, and the disease affects the brain, not the blood. Inheriting the HD mutation predicts illness with near certainty. For many conditions, predictive power is much lower. For example, inheriting one copy of a particular variant of a gene called *APOE* raises risk of developing Alzheimer disease by threefold, and inheriting two copies raises it 15-fold. But without absolute risk estimates and no treatments for this disease, would you want to know if you have a high risk of developing it?

A third feature of single-gene diseases is that they may be much more common in some populations than others. Genes do not like or dislike certain types of people; rather, mutations stay in certain populations because we have children with people like ourselves. While it might not seem politically correct to offer a "Jewish genetic disease" screen, it makes biological and economic sense—several disorders are much more common in this population. A fourth characteristic of a genetic disease is that it may be "fixable" by altering the abnormal instructions.

A Genomic View Connects Diseases

"Gene expression" refers to whether a gene is "turned on" or "turned off" from being transcribed and translated into protein. Tracking gene expression in cells can reveal new information about diseases. It can show that diseases with different symptoms actually share the same underlying genetic defect, or that conditions with similar symptoms have different causes at the molecular level.

Figure 1.9 shows part of a huge disease map called the "diseasome." It connects diseases that share genes that have altered expression. Some of the links and clusters are well known, such as obesity, hypertension, and diabetes. Others are surprises, such as Duchenne muscular dystrophy (DMD; see figure 2.1) and heart attacks. The muscle disorder has no treatment, but heart attack does—researchers are now testing cardiac drugs on boys with DMD. In other cases, the association of a disease with genes whose expression goes up or down can suggest targets for new drugs.

The diseases in figure 1.9 are well known. Thousands of people have illnesses that their health care providers cannot diagnose, because the collection of symptoms does not match any known disease. A technology called exome sequencing is helping many of these patients finally learn the cause of their conditions.

Table 1.2 **How Single-Gene Diseases Differ from Other Diseases**

1. Risk can be predicted for family members.
2. Predictive (presymptomatic) testing may be possible.
3. Different populations may have different characteristic disease frequencies.
4. Correction of the underlying genetic abnormality may be possible.

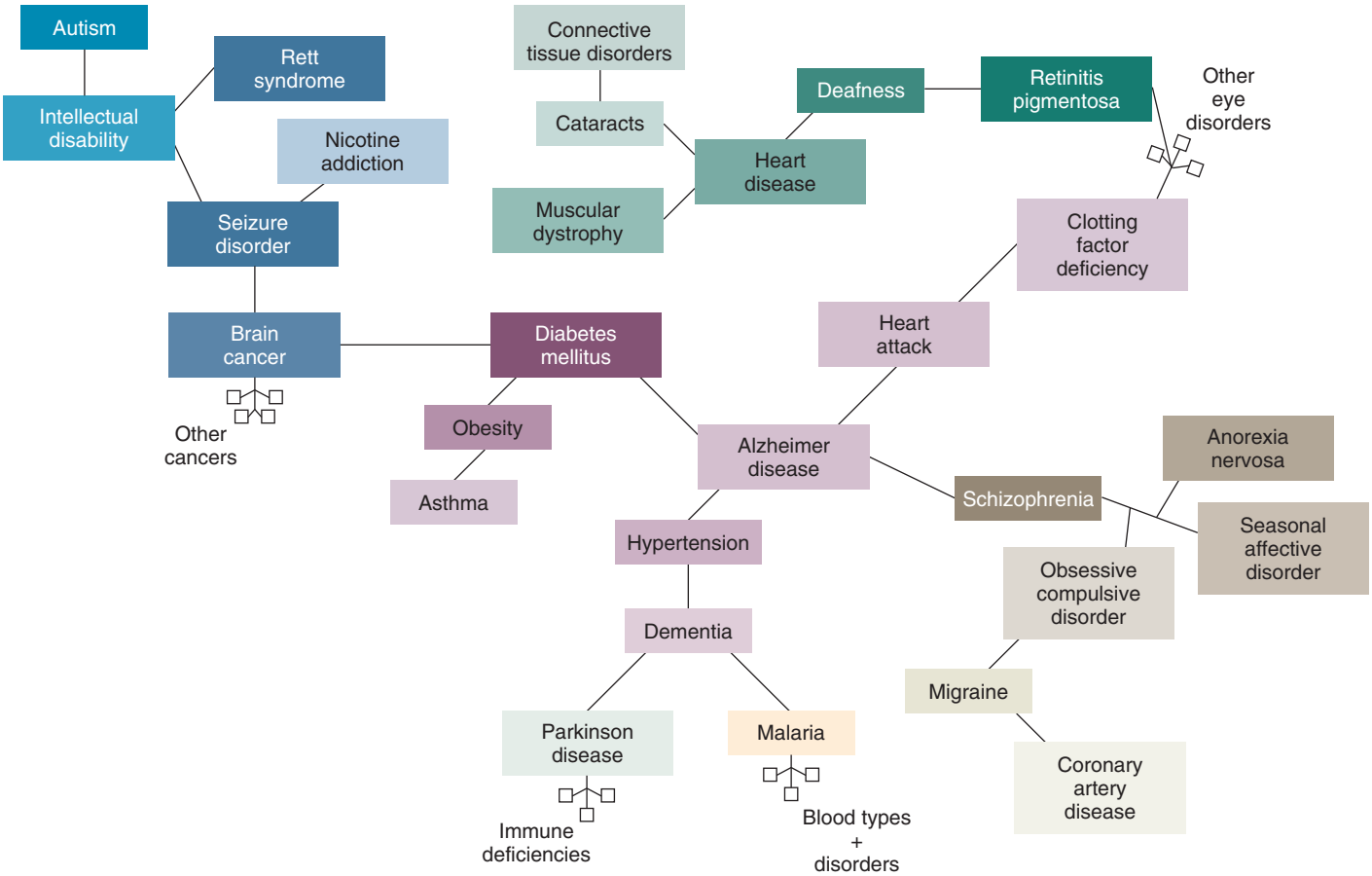

Figure 1.9 **Part of the diseasome.** This tool links diseases by shared gene expression. That is, a particular gene may be consistently overexpressed or underexpressed in two diseases, compared to the healthy condition. The lines refer to at least one gene connecting the disorders depicted in the squares. The conditions are not necessarily inherited because gene expression changes in all situations. For example, Alzheimer disease is linked to heart attack because in both conditions cholesterol builds up. Finding diseasome links can suggest existing drugs to "repurpose" to treat different illnesses. The cholesterol-lowering statin drugs are being tested on Alzheimer patients, for example. (Based on the work of A-L Barabási and colleagues.)

Exome sequencing reveals mutations in the protein-encoding part of an individual's genome. Powerful algorithms search the data for variants in genes that might explain the symptoms. **Clinical Connection 1.1** on page 10 describes the case of Nicholas Volker, one of the first patients to receive a diagnosis thanks to exome sequencing. It saved his life.

Key Concepts Questions 1.3

1. What are some uses of DNA profiling?
2. How can inheriting certain gene variants raise the risk of developing an illness without actually causing it?
3. How are single-gene diseases different from other types of diseases?
4. How do gene expression profiling and exome sequencing help us to better understand health and diseases?

1.4 A Global Perspective on Genomes

We share the planet with many thousands of other species. We aren't familiar with many of Earth's residents because we can't observe their habitats, or we can't grow them in laboratories. "Metagenomics" is a field that is revealing and describing much of the invisible living world by sequencing all of the DNA in a particular habitat. Such areas range from soil, to an insect's gut, to garbage, to a volume of captured air over a polluted city. Metagenomics studies are showing how species interact, and may yield new drugs and reveal novel energy sources.

Metagenomics researchers collect and sequence DNA, then consult databases of known genomes to imagine what the organisms might be like. The first metagenomics project described life in the Sargasso Sea. This 2-million-square-mile oval area off the coast of Bermuda has been thought to lack life beneath its thick cover of seaweed, which is so abundant that Christopher Columbus thought he'd reached land when