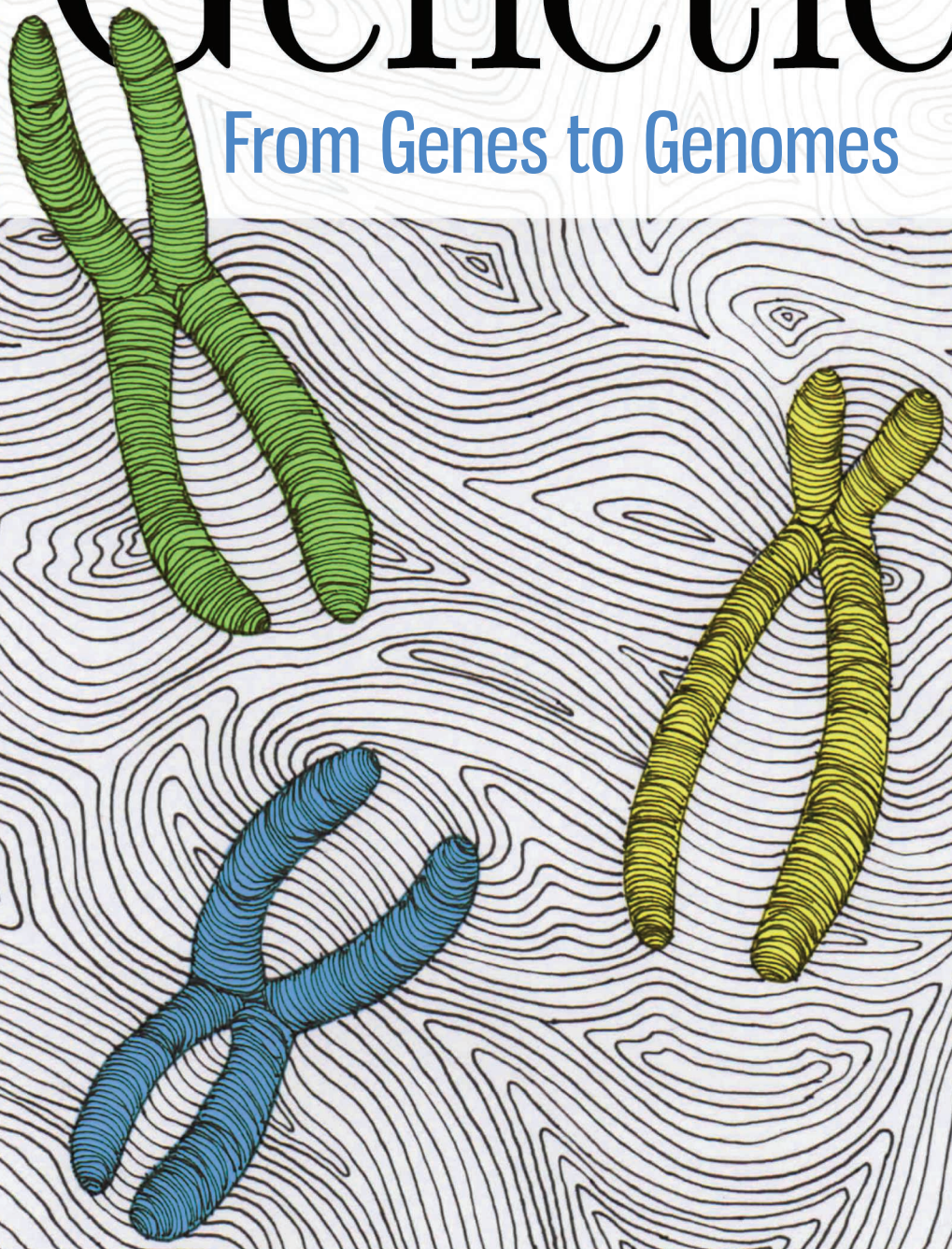
SIXTH EDITION

Genetics

From Genes to Genomes



HARTWELL ~ GOLDBERG ~ FISCHER ~ HOOD

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SIXTH EDITION

Genetics

From Genes to Genomes

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GENETICS: FROM GENES TO GENOMES, SIXTH EDITION

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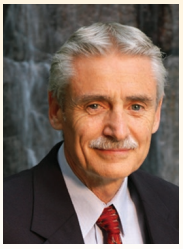


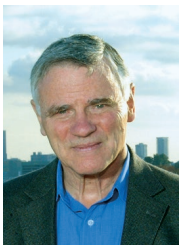
Dr. Leland Hartwell is President and Director of Seattle's Fred Hutchinson Cancer Research Center and Professor of Genome Sciences at the University of Washington.

Dr. Hartwell's primary research contributions were in identifying genes that control cell division in yeast, including those necessary for the division process as well as those necessary for the fidelity of genome reproduction. Subsequently, many of these same genes have been found to control cell division in humans and often to be the site of alteration in cancer cells.

Dr. Hartwell is a member of the National Academy of Sciences and has received the Albert Lasker Basic Medical Research Award, the Gairdner Foundation International Award, the Genetics Society Medal, and the 2001 Nobel Prize in Physiology or Medicine.

Dr. Michael Goldberg is a Professor at Cornell University, where he teaches introductory genetics and human genetics. He was an undergraduate at Yale University and received his Ph.D. in biochemistry from Stanford University. Dr. Goldberg performed postdoctoral research at the Biozentrum of the University of Basel (Switzerland) and at Harvard University, and he received an NIH Fogarty Senior International Fellowship for study at Imperial College (England) and fellowships from the Fondazione Cenci Bolognetti for sabbatical work at the University of Rome (Italy). His current research uses the tools of *Drosophila* genetics and the biochemical analysis of frog egg cell extracts to investigate the mechanisms that ensure proper cell cycle progression and chromosome segregation during mitosis and meiosis.

Dr. Janice Fischer is a Professor at The University of Texas at Austin, where she is an award-winning teacher of genetics and Director of the Biology Instructional Office. She received her Ph.D. in biochemistry and molecular biology from Harvard University, and did postdoctoral research at The University of California at Berkeley and The Whitehead Institute at MIT. In her research, Dr. Fischer used *Drosophila* first to determine how tissue-specific transcription works, and then to examine the roles of ubiquitin and endocytosis in cell signaling during development.



Dr. Lee Hood received an M.D. from the Johns Hopkins Medical School and a Ph.D. in biochemistry from the California Institute of Technology. His research interests include immunology, cancer biology, development, and the development of biological instrumentation (for example, the protein sequencer and the automated fluorescent DNA sequencer). His early research played a key role in unraveling the mysteries of antibody diversity. More recently he has pioneered systems approaches to biology and medicine.

Dr. Hood has taught molecular evolution, immunology, molecular biology, genomics and biochemistry and has co-authored textbooks in biochemistry, molecular biology, and immunology, as well as *The Code of Codes*—a monograph about the Human Genome Project. He was one of the first advocates for the Human Genome Project and directed one of the federal genome centers that sequenced the human genome. Dr. Hood is currently the president (and co-founder) of the cross-disciplinary Institute for Systems Biology in Seattle, Washington.

Dr. Hood has received a variety of awards, including the Albert Lasker Award for Medical Research (1987), the Distinguished Service Award from the National Association of Teachers (1998) and the Lemelson/MIT Award for Invention (2003). He is the 2002 recipient of the Kyoto Prize in Advanced Biotechnology—an award recognizing his pioneering work in developing the protein and DNA synthesizers and sequencers that provide the technical foundation of modern biology. He is deeply involved in K–12 science education. His hobbies include running, mountain climbing, and reading.

Brief Contents

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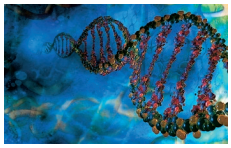
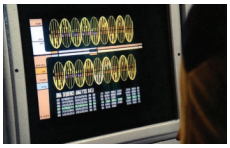


PART III



PART IV

Preface

A Note from the Authors

The science of genetics is less than 150 years old, but its accomplishments within that short time have been astonishing. Gregor Mendel first described genes as abstract units of inheritance in 1865; his work was ignored and then rediscovered in 1900. Thomas Hunt Morgan and his students provided experimental verification of the idea that genes reside within chromosomes during the years 1910–1920. By 1944, Oswald Avery and his coworkers had established that genes are made of DNA. James Watson and Francis Crick published their pathbreaking structure of DNA in 1953. Remarkably, less than 50 years later (in 2001), an international consortium of investigators deciphered the sequence of the 3 billion nucleotides in the human genome. Twentieth century genetics made it possible to identify individual genes and to understand a great deal about their functions.

Today, scientists are able to access the enormous amounts of genetic data generated by the sequencing of many organisms' genomes. Analysis of these data will result in a deeper understanding of the complex molecular interactions within and among vast networks of genes, proteins, and other molecules that help bring organisms to life. Finding new methods and tools for analyzing these data will be a significant part of genetics in the twenty-first century.

Our sixth edition of *Genetics: From Genes to Genomes* emphasizes both the core concepts of genetics and the cutting-edge discoveries, modern tools, and analytic methods that will keep the science of genetics moving forward.

The authors of the sixth edition have worked together in revising every chapter in an effort not only to provide the most up-to-date information, but also to provide continuity and the clearest possible explanations of difficult concepts in one voice.

Our Focus—An Integrated Approach

Genetics: From Genes to Genomes represents a new approach to an undergraduate course in genetics. It reflects the way we, the authors, currently view the molecular basis of life.

We integrate:

- **Formal genetics:** the rules by which genes are transmitted.
- **Molecular genetics:** the structure of DNA and how it directs the structure of proteins.
- **Digital analysis and genomics:** recent technologies that allow a comprehensive analysis of the entire gene set and its expression in an organism.
- **Human genetics:** how genes contribute to health and diseases, including cancer.
- **The unity of life-forms:** the synthesis of information from many different organisms into coherent models.
- **Molecular evolution:** the molecular mechanisms by which biological systems, whole organisms, and populations have evolved and diverged.

The strength of this integrated approach is that students who complete the book will have a strong command of genetics as it is practiced today by both academic and corporate researchers. These scientists are rapidly changing our understanding of living organisms, including ourselves. Ultimately, this vital research may create the ability to replace or correct detrimental genes—those "inborn errors of metabolism," as researcher Archibald Garrod called them in 1923, as well as the later genetic alterations that lead to the many forms of cancer.

The Genetic Way of Thinking

Modern genetics is a molecular-level science, but an understanding of its origins and the discovery of its principles is a necessary context. To encourage a genetic way of thinking, we begin the book by reviewing Mendel's principles and the chromosomal basis of inheritance. From the outset, however, we aim to integrate organism-level genetics with fundamental molecular mechanisms.

Chapter 1 presents the foundation of this integration by summarizing the main biological themes we explore. In Chapter 2, we tie Mendel's studies of pea trait inheritance to the actions of enzymes that determine whether a pea is round or wrinkled, yellow or green, etc. In the same chapter, we point to the relatedness of the patterns of heredity in all organisms. Chapters 3–5 cover extensions to Mendel, the chromosome theory of inheritance, and the fundamentals of gene linkage and mapping. Starting in Chapter 6, we focus on the physical characteristics of DNA, on mutations, and on how DNA encodes, copies, and transmits biological information.

Beginning in Chapter 9, we move into the digital revolution in DNA analysis with a look at modern genetics techniques, including gene cloning, PCR, microarrays, and high-throughput genome sequencing. We explore how bioinformatics, an emergent analytical tool, can aid in discovery of genome features. This section concludes in Chapter 11 with case studies leading to the discovery of human disease genes.

The understanding of molecular and computer-based techniques carries into our discussion of chromosome specifics in Chapters 12–15, and also informs our analysis of gene regulation in Chapters 16 and 17. Chapter 18 describes the most recent technology that scientists can use to manipulate genomes at will – for research and practical purposes including gene therapy. Chapter 19 describes the use of genetic tools at the molecular level to uncover the complex interactions of eukaryotic development. In Chapter 20, we explain how our understanding of genetics and the development of molecular genetic technologies is enabling us to comprehend cancer and in some cases to cure it.

Chapters 21 and 22 cover population genetics, with a view of how molecular tools have provided information on species relatedness and on genome changes at the molecular level over time. In addition, we explain how bioinformatics can be combined with population genetics to understand inheritance of complex traits and to trace human ancestry.

Throughout our book, we present the scientific reasoning of some of the ingenious researchers of the field—from Mendel, to Watson and Crick, to the collaborators on the Human Genome Project. We hope student readers will see that genetics is not simply a set of data and facts, but also a human endeavor that relies on contributions from exceptional individuals.

Student-Friendly Features

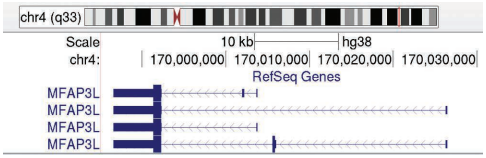
As digital components of the text become more and more crucial, we are very excited that Janice Fischer, a textbook author, is taking on a dual role as Digital Editor! Janice will ensure the important consistency between text and digital.

We have taken great pains to help the student make the leap to a deeper understanding of genetics. Numerous features of this book were developed with that goal in mind.

- ***One Voice Genetics:*** *Genes to Genomes* has a friendly, engaging reading style that helps students master the concepts throughout this book. The writing style provides the student with the focus and continuity required to make the book successful in the classroom.
- ***Visualizing Genetics*** The highly specialized art program developed for this book integrates photos and line art in a manner that provides the most engaging visual presentation of genetics available. Our Feature Figure illustrations break down complex processes into step-by-step illustrations that lead to greater student understanding. All illustrations are rendered with a consistent color theme—for example, all presentations of phosphate groups are the same color, as are all presentations of mRNA.
- ***Accessibility*** Our intention is to bring cutting-edge content to the student level. A number of more complex illustrations are revised and segmented to help the student follow the process. Legends have been streamlined to highlight only the most important ideas, and throughout the book, topics and examples have been chosen to focus on the most critical information.
- ***Problem Solving*** Developing strong problem-solving skills is vital for every genetics student. The authors have carefully created problem sets at the end of each chapter that allow students to improve upon their problem-solving ability.
- ***Solved Problems*** These cover topical material with complete answers provide insight into the step-by-step process of problem solving.
- ***Review Problems*** More than 700 questions involving a variety of levels of difficulty that develop excellent problem-solving skills. The problems are organized by chapter section and in order of increasing difficulty within each section for ease of use by instructors and students. The companion online *Study Guide and Solutions Manual,* completely revised for the 6th edition by Michael Goldberg and Janice Fischer, provides detailed analysis of strategies to solve all of the end-of-chapter problems.

SOLVED PROBLEMS

I. The following figure shows a screen shot from the UCSC Genome Browser, focusing on a region of the human genome encoding a gene called *MFAP3L.* (*Note: hg38* refers to version 38 of the human genome RefSeq.) If you do not remember how the browser represents the genome, refer to the key at the bottom of Fig. 10.3.



Source: University of California Genome Project, https://genome.ucsc.edu

a. Describe in approximate terms the genomic location of *MFAP3L.*

b. Is the gene transcribed in the direction from the centromere-to-telomere or from the telomere-to-centromere?

c. How many alternative splice forms of *MFAP3L* mRNA are indicated by the data?

b. The arrows within the introns of the gene show that the direction of transcription is from the telomere of *4q* toward the centromere of chromosome 4.

c. The data indicate four alternatively spliced forms of the mRNA. In the following parts, we list these as A to D from top to bottom.

d. The data suggest two promoters. One is roughly at position 170,037,000 and allows the transcription of a primary RNA alternatively spliced to produce mRNAs B and D. The other is roughly at position 170,013,000 and leads to the transcription of a primary RNA alternatively spliced to generate mRNAs A and C.

e. The data indicate that the *MFAP3* gene can encode two different but closely related proteins. mRNAs A, B, and C all encode the same protein; mRNA D a slightly larger protein that includes at its N terminus additional amino acids not found in the other protein. Otherwise these two proteins appear to be the same. The ORF that encodes the A B C protein form is about 880 bp long (a rough estimate); this corre-

Changes in the 6th Edition: A Chapter-by-Chapter Summary

The sixth edition has been revised and modernized significantly as compared with the fifth edition. We scrutinized the entire text and clarified the language wherever possible. In total, we created more than 50 new Figures and Tables, and revised more than 100 in addition. We also wrote more than 125 new end-of-chapter problems, and revised many other problems for clarity. The entire *Solutions Manual and Study Guide* was corrected and revised for clarity. We added several new Fast Forward, Genetics and Society, and Tools of Genetics Boxes on modern topics. Chapter 9 in the 5th edition was split into two separate chapters in the 6th edition: Chapter 9 (Digital Analysis of DNA) and Chapter 10 (Genome Annotation).

Along with the numerous text changes, the authors have also spent a great deal of time updating the test bank and question bank content to align more closely to the text. There will also be new video tutorials for difficult concepts in every chapter!

Every chapter of the sixth edition was improved significantly from the fifth edition. The most important changes in the sixth edition are summarized below:

Chapter 3 Extensions to Mendel's Laws
- Relationship between epistasis and complementation explained more clearly.
- Discussion of two-gene versus multifactorial inheritance now separated for clarity.
- Comprehensive Example about dog coat colors expanded to include molecular explanations for the various gene activities.

Chapter 4 The Chromosome Theory of Inheritance
- Figures and text altered to clarify that each chromatid has a centromere.
- New Fast Forward Box: *Visualizing X Chromosome Inactivation in Transgenic Mice*

Chapter 5 Linkage, Recombination, and the Mapping of Genes on Chromosomes
- New Fast Forward Box: *Mapping the Crossovers that Generate Individual Human Sperm*

Chapter 6 DNA Structure, Replication, and Recombination
- Improvements to diagrams of DSB repair model of recombination.
- New section about site-specific recombination.

Chapter 7 Anatomy and Function of Gene: Dissection Through Mutation
- Reorganized and clarified material to separate the discussion of DNA sequence alteration mechanisms from DNA repair mechanisms.

Chapter 9 Digital Analysis of DNA
- Improved depiction of plasmid cloning vectors.
- Renovated explanation of paired-end whole-genome shotgun sequencing.

Chapter 10 Genome Annotation
- Improved depiction of alternative RNA splicing.
- New illustration of consensus amino acid sequences in proteins.
- New material on the evolution of *de novo* genes.

Chapter 12 The Eukaryotic Chromosome
- New material on synthetic yeast chromosomes.

Chapter 15 Organellar Inheritance
- New Fast Forward Box about the Mitchondrial Eve concept.

Chapter 17 Gene Regulation in Eukaryotes
- New Tools of Genetics Box: *The Gal4/UAS$_G$ Binary Gene Expression System*
- New part of Epigenetics section: *Can Environmentally Acquired Traits Be Inherited?*
- New part of Regulation After Transcription section: Trans-*acting Proteins Regulate Translation*

Chapter 18 Manipulating the Genomes of Eukaryotes
- New part of Targeted Mutagenesis section: *CRISPR/Cas9 Allows Targeted Gene Editing in Any Organism*
- New Tools of Genetics Box: *How Bacteria Vaccinate Themselves Against Viral Infections with CRISPR/Cas9*
- New Genetics and Society Box: *Should We Alter the Genomes of Human Germ Lines?*

Chapter 19 The Genetic Analysis of Development
- Comprehensive Example of *Drosophila* body patterning revised to clarify that homeotic genes function within parasegments, and to clarify the concept of a morphogen.

Chapter 20 The Genetics of Cancer
- Clarified the fact that mutation drives cancer progression.
- Improved explanation of driver and passenger mutations.
- Increased coverage of tumor genome sequencing and the heterogeneity of mutations in different individuals with cancers in the same organ.

Chapter 22 The Genetics of Complex Traits
- Revised the section on heritability to clarify: lines of correlation and correlation coefficients; how to use different kinds of human twin studies to estimate the heritability of complex quantitative traits and complex discrete traits.
- New explanation of how to use the chi-square test for independence for GWAS.

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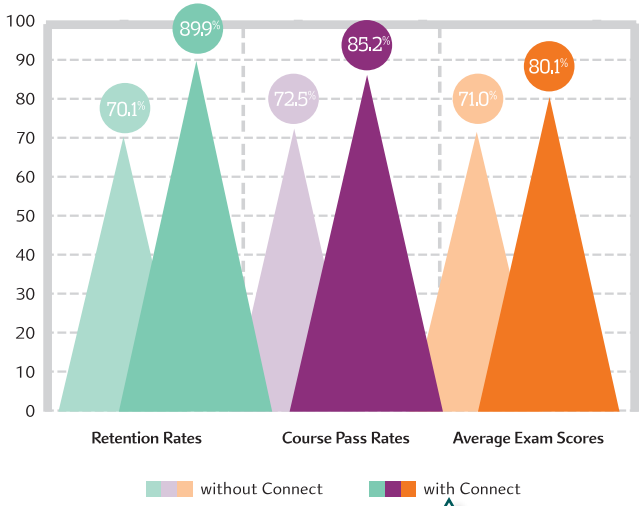

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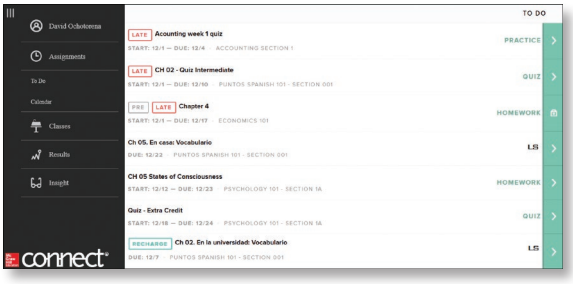

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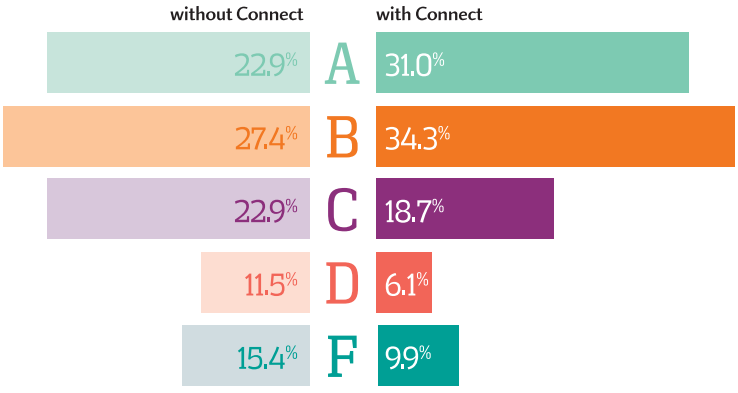

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Guided Tour

Integrating Genetic Concepts

Genetics: From Genes to Genomes takes an integrated approach in its presentation of genetics, thereby giving students a strong command of genetics as it is practiced today by academic and corporate researchers. Principles are related throughout the text in examples, essays, case histories, and connections sections to make sure students fully understand the relationships between topics.

Chapter Outline

Every chapter opens with a brief outline of the chapter contents.

chapter outline

- 18.1 Creating Transgenic Organisms
- 18.2 Uses of Transgenic Organisms
- 18.3 Targeted Mutagenesis
- 18.4 Human Gene Therapy

Learning Objectives

Learning Objectives appear before each section, and are carefully written to clearly outline expectations.

essential concepts

- A wild-type transgene can be inserted into an embryo homozygous for a recessive mutant allele. If the normal phenotype is restored, then the transgene identifies the gene that was mutated.
- The creation of reporter constructs allows easy detection of when and in which tissues a gene is turned on or turned off in eukaryotes.
- Transgenic organisms produce medically important human proteins including insulin, blood clotting factors, and erythropoietin; transgenic crop plants can potentially make ingestible vaccines.
- GM soybeans are resistant to the weed killer glyphosate. Many crops, such as corn, soybean, canola, and cotton have been genetically modified to express Bt protein which discourages insect predation.
- Adding a transgene that carries a disease-causing, gain-of-function allele to a nonhuman animal model allows researchers to observe disease progression and to test possible therapeutic interventions.

18.2 Uses of Transgenic Organisms

learning objectives

1. Describe how transgenes can clarify which gene causes a mutant phenotype.
2. Summarize the use of transgene reporter constructs in gene expression studies.
3. Discuss examples of how transgenic organisms serve to produce proteins needed for human health.
4. List examples of GM organisms and discuss the pros and cons of their production.
5. Explain the use of transgenic animals to model gain-of-function genetic diseases in humans.

Essential Concepts

After each section, the most relevant points of content are now provided in concise, bulleted statements to reinforce crucial concepts and learning objectives for students.

WHAT'S NEXT

Manipulation of the genome is the basis for many of the experimental strategies we will describe in Chapter 19, where we discuss how genetic analysis has been a crucial tool in unraveling the biochemical pathways of development—the process by which a single-celled zygote becomes a complex multicellular organism. Transgenic technology is key to cloning the genes identified in mutant screens that are crucial for regulating development, and also to manipulating these genes in order to understand their precise functions in the organism.

What's Next

Each chapter closes with a What's Next section that serves as a bridge between the topics in the chapter just completed to those in the upcoming chapter or chapters. This spirals the learning and builds connections for students.

New! Exciting Revised Content

Every chapter of the sixth edition has been revised and modernized significantly as compared with the fifth edition. More than 50 new Figures and Tables were created, and more than 100 were revised. More than 125 new end-of-chapter problems were written, and many more revised for clarity. The entire Solutions Manual and Study Guide was updated, corrected, and revised by Michael Goldberg and Janice Fischer. Several new Fast Forward, Genetics and Society, and Tools of Genetics Boxes covering modern topics were created. For breadth and clarity, Chapter 9 in the 5th edition was split into two separate chapters in the 6th edition: Chapter 9 (Digital Analysis of DNA) and Chapter 10 (Genome Annotation).

Figure 6.30 One site-specific recombination mechanism. The Cre and Flp enzymes discussed in the text function as shown. The *red* and *blue* target DNA sequences are identical to each other but are represented in different colors for clarity. These targets are embedded in different DNA molecules (*black* and *gray dots*). The subunits of the recombinase tetramer are *yellow ovals;* this enzyme catalyzes all steps of the reaction. *Black triangles* are sites where recombinase cleaves single-stranded DNA. Note that resolution of the Holliday junction intermediate involves cleavage of the *blue* and *red* DNA strands that were not cleaved initially.

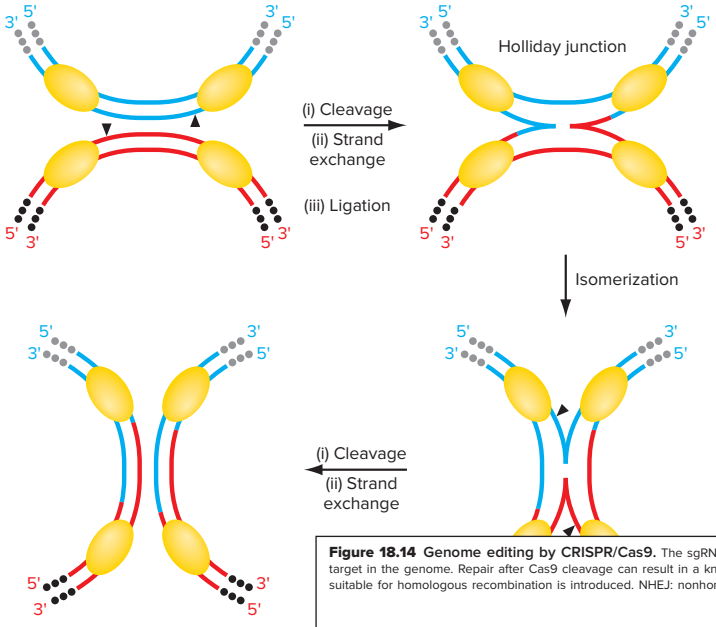
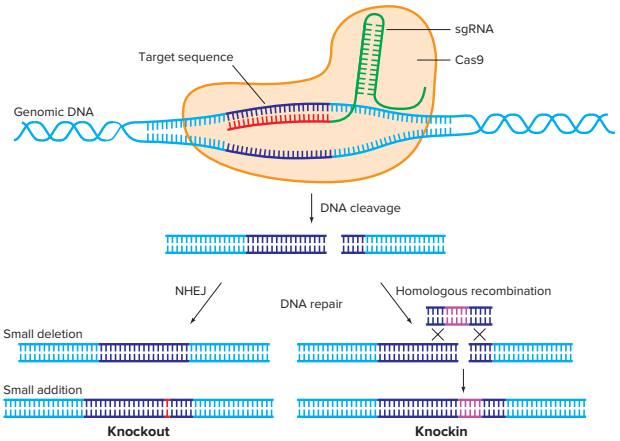


Figure 18.14 Genome editing by CRISPR/Cas9. The sgRNA sequence is designed to bring the Cas9 endonuclease to a specific target in the genome. Repair after Cas9 cleavage can result in a knockout or a knockin, depending on whether or not a DNA fragment suitable for homologous recombination is introduced. NHEJ: nonhomologous end-joining.



FAST FORWARD

Visualizing X Chromosome Inactivation in Transgenic Mice

Scientists have recently used molecular techniques and transgenic technology (similar to that described in the earlier Fast Forward Box *Transgenic Mice Prove That* SRY *Is the Maleness Factor*) to visualize the pattern of X chromosome inactivation in mice. The researchers generated XX mice containing two different *transgenes* (in this case, genes from a different species). One of these transgenes was a jellyfish gene that specifies green fluorescent protein (GFP); the other was a gene from red coral that makes red fluorescent protein (RFP) **(Fig. A).**

In the XX mice, the GFP gene is located on the X chromosome from the mother, and the RFP gene resides on the X chromosome from the father. Clonal patches of cells are either green or red depending on which X chromosome was turned into a Barr body in the original cell that established the patch **(Fig. B).**

Different XX mice display different green and red patchwork patterns, providing a clear demonstration of the random nature of X chromosome inactivation. The patchwork patterns reflect the cellular memory of which X chromosome was inactivated in the founder cell for each clonal patch. Geneticists currently use these transgenic mice to decipher the genetic details of how cells "remember" which X to inactivate after each cell division.

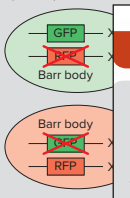


Figure A Cells of transgenic mice glow either green or red in response to X chromosome inactivation. The mouse carries a green (GFP) transgene inserted in the maternal X chromosome (X^M), and a red (RFP) transgene in the paternal X chromosome (X^P). Cells in which X^P is inactivated (*top*) glow green; cells glow red (*bottom*) when X^M is inactivated.

Figure B Heart cells of a transgenic mouse reveal a clonal patchwork of X inactivation. Patches of red or green cells represent cellular descendants of the founders that randomly inactivated one of their X chromosomes.

Fast Forward

This feature is one of the methods used to integrate the Mendelian principles introduced early in the content with the molecular content that will follow.

TOOLS OF GENETICS

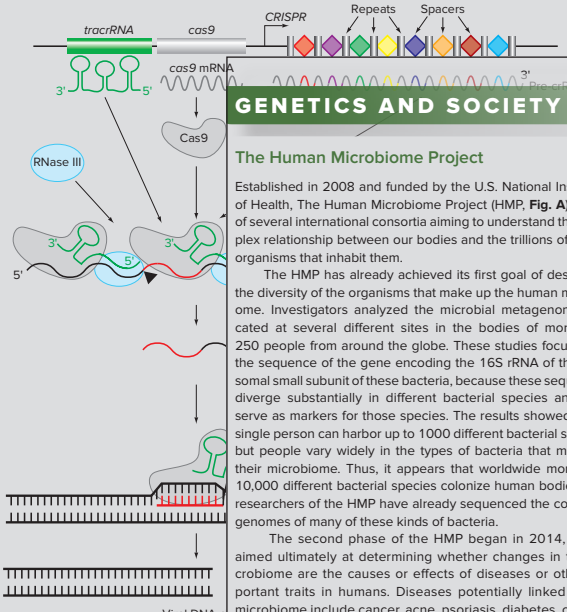
How Bacteria Vaccinate Themselves Against Viral Infections with CRISPR/Cas9

Researchers discovered clustered sequence repeats (CRISPRs) in bacterial genomes as early as 1987. When in 2005 some of these sequences were found to originate from bacteriophage genomes, several astute scientists speculated that CRISPRs might mediate a viral immunity system in bacteria. These ideas were largely ignored for several more years until the mechanism of resistance became clarified. And finally, in 2012–2013, the so-called *CRISPR craze* reached its full bloom when researchers including Feng Zhang, Jennifer Doudna, and Emmanuelle Charpentier developed methods to adapt this viral immunity system to engineer genomes in bacterial cells and in eukaryotic organisms.

At the *CRISPR* locus of bacterial genomes, short direct repeats are interrupted at regular intervals by unique spacer sequences (**Fig. A**). The spacer sequences are fragments of bacteriophage genomes captured by the host cell and integrated into the host genome by the action of two bacterially encoded Cas proteins (Cas1 and Cas2). The repeats within the *CRISPR* arrays are added by these endonucleolytic enzymes during the capture and integration process.

Viral immunity results from steps that begin with transcription of the *CRISPR* array into long RNA molecules called *pre-crRNAs* that are processed into short (24–48 nt) so-called *CRISPR RNAs* (*crRNAs*). In the bacterial species

Figure A The *CRISPR/Cas9* locus vaccinates bacteria against viruses.



Tools of Genetics Essays

Current readings explain various techniques and tools used by geneticists, including examples of applications in biology and medicine.

GENETICS AND SOCIETY

Crowd: © Image Source/Getty Images RF

The Human Microbiome Project

Established in 2008 and funded by the U.S. National Institutes of Health, The Human Microbiome Project (HMP, **Fig. A**) is one of several international consortia aiming to understand the complex relationship between our bodies and the trillions of microorganisms that inhabit them.

The HMP has already achieved its first goal of describing the diversity of the organisms that make up the human microbiome. Investigators analyzed the microbial metagenomes located at several different sites in the bodies of more than 250 people from around the globe. These studies focused on the sequence of the gene encoding the 16S rRNA of the ribosomal small subunit of these bacteria, because these sequences diverge substantially in different bacterial species and thus serve as markers for those species. The results showed that a single person can harbor up to 1000 different bacterial species, but people vary widely in the types of bacteria that make up their microbiome. Thus, it appears that worldwide more than 10,000 different bacterial species colonize human bodies. The researchers of the HMP have already sequenced the complete genomes of many of these kinds of bacteria.

The second phase of the HMP began in 2014, and is aimed ultimately at determining whether changes in the microbiome are the causes or effects of diseases or other important traits in humans. Diseases potentially linked to the microbiome include cancer, acne, psoriasis, diabetes, obesity, and inflammatory bowel disease; some investigators have suggested that the composition of microbiomes could also influence the mental health of their hosts. The first step in these studies will be to establish whether statistical correlations exist between specific kinds of microbial communities and disease states. As one example, one HMP phase II project currently underway is an analysis of vaginal host cells and microbes during pregnancy. Approximately 2000 pregnant women will be studied and their birth outcomes recorded. The goal of this project is to determine if changes in the microbiome correlate with premature birth or other complications of pregnancy.

Of course, the existence of any correlations found between microbiomes and disease does not prove cause or effect. But even if bacteria correlated with a disease state do not cause the disease, the existence of the correlation could be useful as a way to diagnose certain conditions. Nevertheless, the most exciting

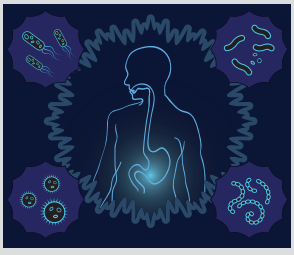


Figure A
© Anna Smirnova/Alamy RF

an effect? One method is to investigate in detail how the biological properties of the microbiome and the host might be changed by the interactions of bacteria and the humans they colonize. Thus, scientists will characterize whether and how the transcriptomes and proteomes of the bacteria and human cells are changed by bacterial colonization of human organs. These studies will further delve into *metabolomics* (characterizing metabolites in the human bloodstream).

A second and even more powerful method for establishing the cause and effect of microbiome changes is the use of *germ-free mice* raised in sterile environments. Surprisingly, germ-free mice can survive although they are not normal: they have altered immune systems, poor skin, and they need to eat more calories than do normal mice to maintain a normal body weight. Researchers can populate germ-free mice with a single bacterial species or a complex microbial community, and thus determine how microbiomes influence physiological states. Problem 8 at the end of this chapter will allow you to explore this approach by discussing an experiment recently performed with germ-free mice that asks if the microbiome plays a causal role in obesity.

If microbial communities indeed contribute to disease states in humans, then future treatments might aim to alter resident microbiomes. Thus, the flip side of the HMP is to in-

Genetics and Society Essays

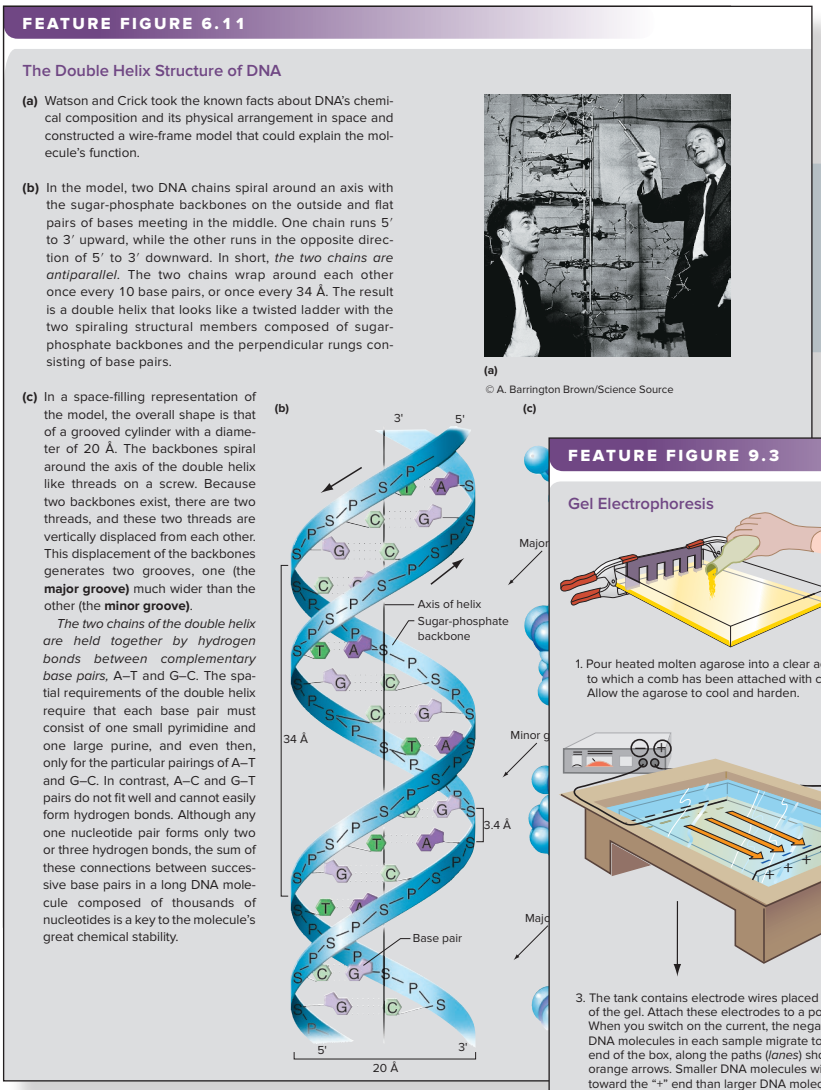
Dramatic essays explore the social and ethical issues created by the multiple applications of modern genetic research.

Visualizing Genetics

Full-color illustrations and photographs bring the printed word to life. These visual reinforcements support and further clarify the topics discussed throughout the text.

Feature Figures

Special multipage spreads integrate line art, photos, and text to summarize in detail important genetic concepts.



FEATURE FIGURE 6.11

The Double Helix Structure of DNA

(a) Watson and Crick took the known facts about DNA's chemical composition and its physical arrangement in space and constructed a wire-frame model that could explain the molecule's function.

(b) In the model, two DNA chains spiral around an axis with the sugar-phosphate backbones on the outside and flat pairs of bases meeting in the middle. One chain runs 5′ to 3′ upward, while the other runs in the opposite direction of 5′ to 3′ downward. In short, *the two chains are antiparallel*. The two chains wrap around each other once every 10 base pairs, or once every 34 Å. The result is a double helix that looks like a twisted ladder with the two spiraling structural members composed of sugar-phosphate backbones and the perpendicular rungs consisting of base pairs.

(c) In a space-filling representation of the model, the overall shape is that of a grooved cylinder with a diameter of 20 Å. The backbones spiral around the axis of the double helix like threads on a screw. Because two backbones exist, there are two threads, and these two threads are vertically displaced from each other. This displacement of the backbones generates two grooves, one (the **major groove)** much wider than the other (the **minor groove)**.

The two chains of the double helix are held together by hydrogen bonds between complementary base pairs, A–T and G–C. The spatial requirements of the double helix require that each base pair must consist of one small pyrimidine and one large purine, and even then, only for the particular pairings of A–T and G–C. In contrast, A–C and G–T pairs do not fit well and cannot easily form hydrogen bonds. Although any one nucleotide pair forms only two or three hydrogen bonds, the sum of these connections between successive base pairs in a long DNA molecule composed of thousands of nucleotides is a key to the molecule's great chemical stability.

(a)

© A. Barrington Brown/Science Source

(b) **(c)**

3′ 5′ Axis of helix Sugar-phosphate backbone 34 Å 3.4 Å Base pair 5′ 3′ 20 Å

FEATURE FIGURE 9.3

Gel Electrophoresis

1. Pour heated molten agarose into a clear acrylic plate to which a comb has been attached with clamps. Allow the agarose to cool and harden.

2. Remove the comb; shallow wells will be left in the gel. Remove the gel from the acrylic plate and transfer it to a tank containing a buffered solution. Use a micropipette to load a different DNA sample into each well of the gel. Each sample contains a blue dye to make it easier to see. One sample should contain DNA molecules of known length to serve as size markers.

3. The tank contains electrode wires placed along each end of the gel. Attach these electrodes to a power supply. When you switch on the current, the negatively charged DNA molecules in each sample migrate toward the "+" end of the box, along the paths (*lanes*) shown by the orange arrows. Smaller DNA molecules will move faster toward the "+" end than larger DNA molecules.

4. Remove the gel from the tank. Incubate in a solution containing ethidium bromide (which binds to DNA), then wash with water to remove excess dye from the gel.

5. Expose the gel to ultraviolet (UV) light. DNA molecules will fluoresce as orange bands because the ethidium bromide bound to the DNA absorbs UV photons and gives off photons in the visible red range. You can estimate the size of the DNA molecules in the unknown samples by comparing their migration in the gel with that of the size markers (*standards*) in the lane at the left.

Standard Human A B Lambda C D E Plasmid F G H Well Kb 20 10 7 5 4 3 2 1.5 1 0.7 0.5 0.4 0.3 0.2 Direction of electrophoresis

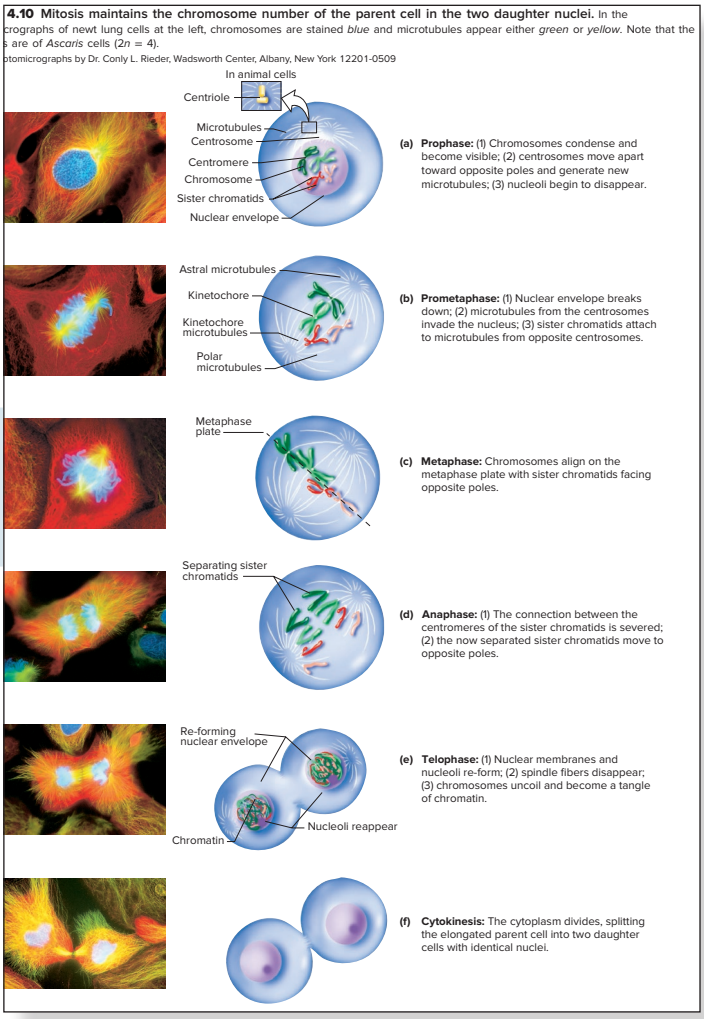
(5): © Lee Silver, Princeton University

Separating DNA molecules according to their size by agarose gel electrophoresis. To prepare an agarose gel with wells for samples, you pour the gel as shown in Step 1. You then transfer the gel to a tank containing a buffered solution with ions that allow current to flow, and load DNA samples in the wells (Step 2). You then connect the gel tank to a power supply and allow electrophoresis to run from 1 to 20 hours (depending on the DNA size and the voltage; Step 3). After incubating the gel with the fluorescent dye ethidium bromide (Step 4), you then expose the gel to UV light (Step 5). DNA molecules will appear as orange bands because they bind to the fluorescent dye.

Step 5 shows actual results from gel electrophoresis; because black-and-white film was used, DNA appears white rather than orange. The standard lane at left has DNA fragments of known sizes. Human genomic DNA was cut with *Eco*RI in lane A and with *Rsa*I in lane B. Smears containing hundreds of thousands of fragments are produced with an average size of about 4.1 kb for *Eco*RI and 256 bp for *Rsa*I. In C, D, and E, the chromosome of bacteriophage λ was cut with *Hin*dIII, *Eco*RI, and *Rsa*I, respectively. The sizes of the fragments in any one lane add up to 48.5 kb, the size of the viral genome. In F, G, and H plasmid DNA of total length 6.9 kb was cut with the same three enzymes. Note that the larger the genome analyzed, the more fragments are produced; moreover, the more bases in the restriction enzyme recognition site, the larger is the average size of the fragments produced.

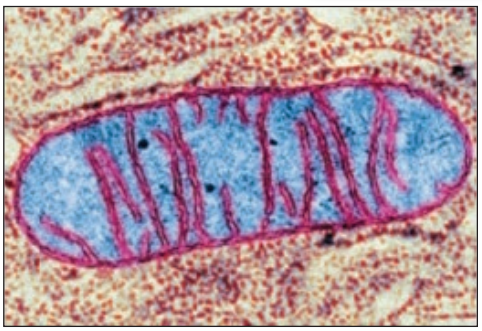
Process Figures

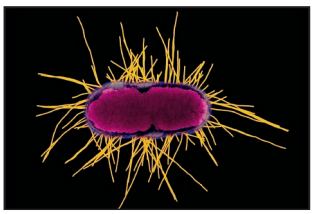
Step-by-step descriptions allow the student to walk through a compact summary of important details.

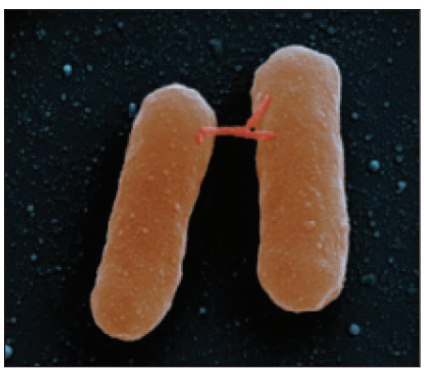


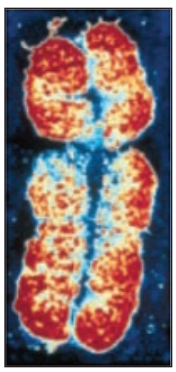
Micrographs

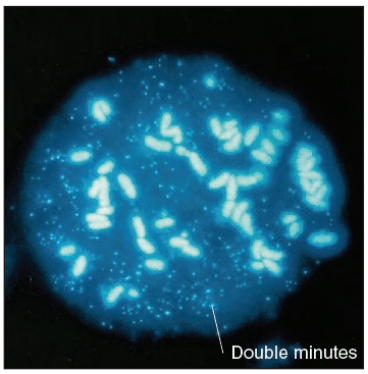
Stunning micrographs bring the genetics world to life.

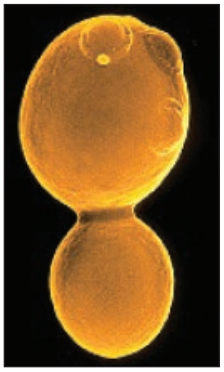


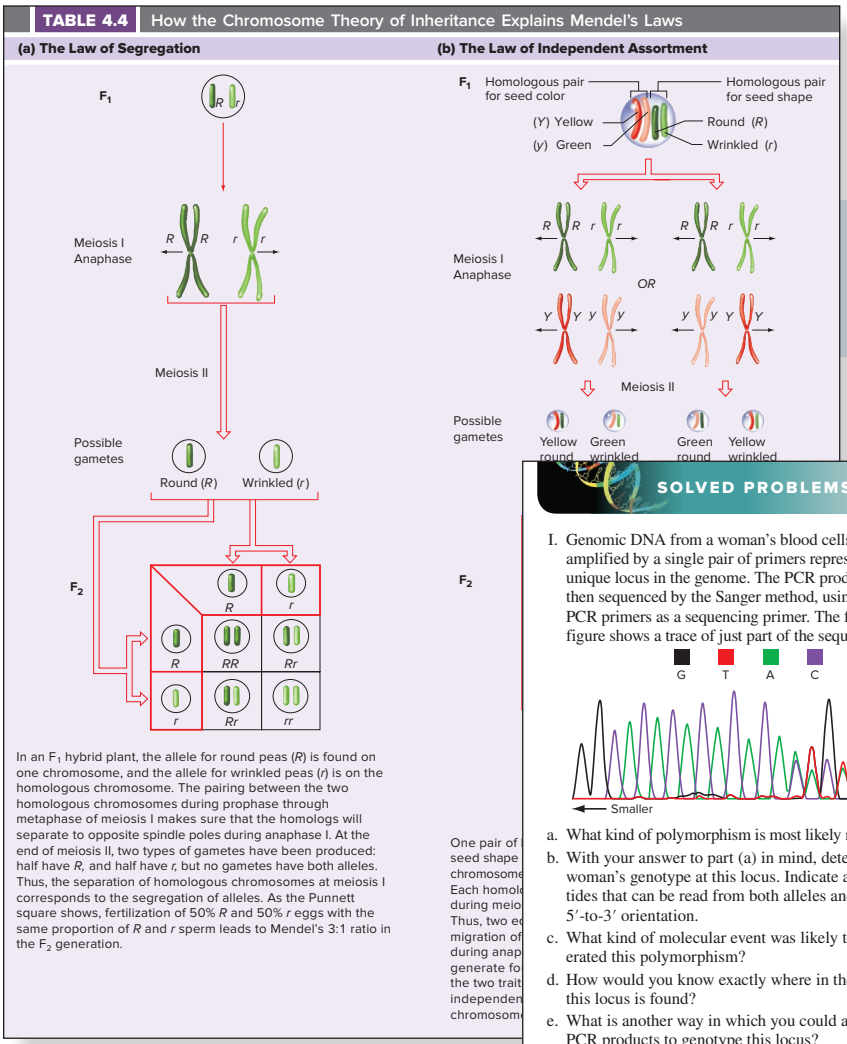






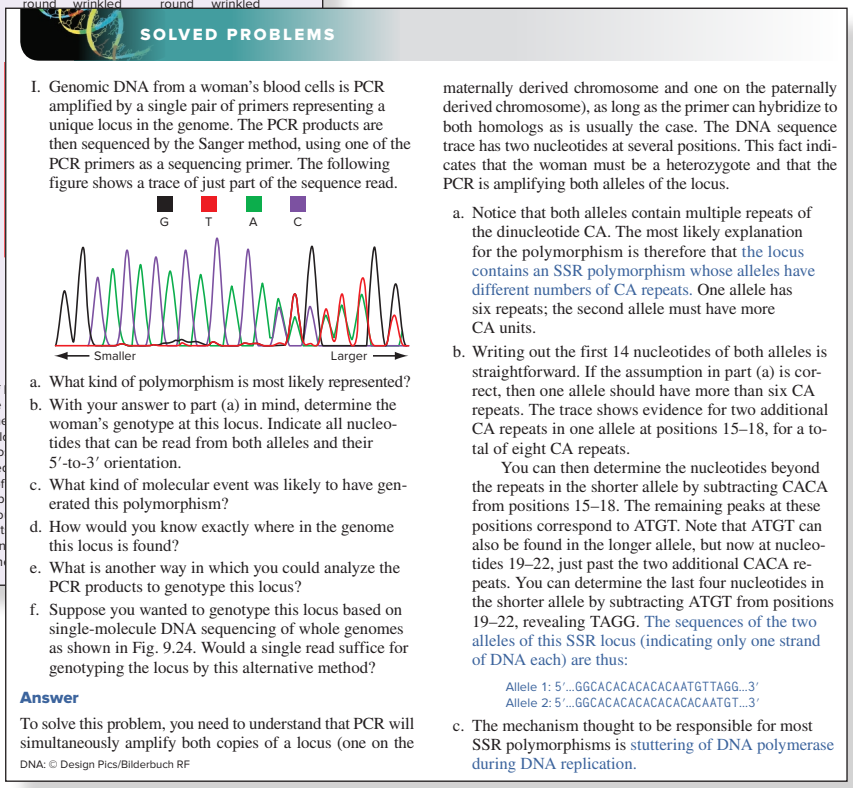






Comparative Figures

Comparison illustrations lay out the basic differences of often confusing principles.



Solving Genetics Problems

The best way for students to assess and increase their understanding of genetics is to practice through problems. Found at the end of each chapter, problem sets assist students in evaluating their grasp of key concepts and allow them to apply what they have learned to real-life issues.

Review Problems

Problems are organized by chapter section and in order of increasing difficulty to help students develop strong problem-solving skills. The answers to select problems can be found in the back of this text.

Solved Problems

Solved problems offer step-by-step guidance needed to understand the problem-solving process.

Acknowledgements

The creation of a project of this scope is never solely the work of the authors. We are grateful to our colleagues who answered our numerous questions, or took the time to share with us their suggestions for improvement of the previous edition. Their willingness to share their expertise and expectations was a tremendous help to us.

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chapter 1

Genetics: The Study of Biological Information

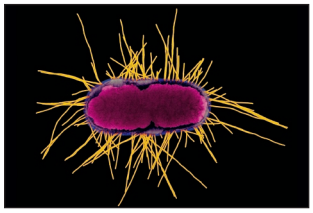
Information can be stored in many ways, including the patterns of letters and words in books and the sequence of nucleotides in DNA molecules.

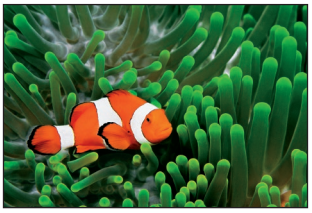
chapter outline

GENETICS, THE SCIENCE of heredity, is at its core the study of biological information. All living organisms—from single-celled bacteria and protozoa to multicellular plants and animals—must store and use vast quantities of information to develop, survive, and reproduce in their environments (**Fig. 1.1**). Geneticists examine how organisms use biological information during their lifetimes and pass it on to their progeny.

This book introduces you to the field of genetics as currently practiced in the early twenty-first century. Several broad themes recur throughout this presentation. First, we know that biological information is encoded in *DNA*, and that the *proteins* responsible for an organism's many functions are built from this code. Second, we have found that all living forms are related at the molecular level. With the aid of high-speed computers and other technologies, we can now study *genomes* at the level of DNA sequence. These new methods have revealed that genomes have a modular construction that has allowed rapid evolution of complexity. Finally, our focus in this book is on human genetics and the application of genetic discoveries to human problems.

Figure 1.1 The biological information in DNA generates an enormous diversity of living organisms.


(a) Bacteria


(b) Clown fish


(c) Lion


(d) Oak tree


(e) Poppies


(f) Hummingbird


(g) Red-eyed tree frog


(h) Humans

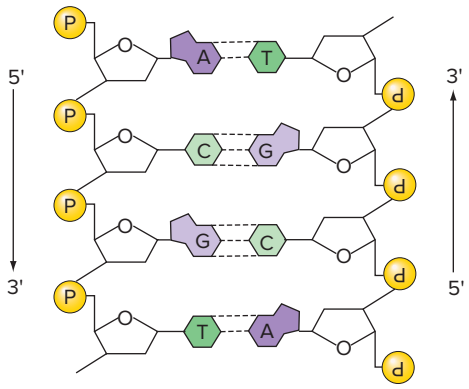
1.1 DNA: Life's Fundamental Information Molecule

learning objectives

1. Relate the structure of DNA to its function.
2. Differentiate between a chromosome, DNA, a gene, a base pair, and a protein.

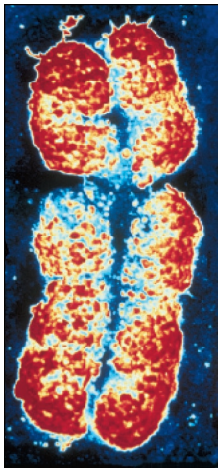
The process of **evolution**—the change in traits of groups of organisms over time—has taken close to 4 billion years to generate the amazing mechanisms for storing, replicating, expressing, and diversifying biological information seen in organisms now inhabiting the earth. The linear **DNA** molecule stores biological information in units known as **nucleotides.** Within each DNA molecule, the sequence of the four letters of the DNA alphabet—G, C, A, and T—specify which proteins an organism will make as well as when and where protein synthesis will occur. The letters refer to the **bases**—guanine, cytosine, adenine, and thymine—that are components of the nucleotide building blocks of DNA. The DNA molecule itself is a double strand of nucleotides carrying complementary G–C or A–T base pairs (**Fig. 1.2**). These **complementary base pairs** bind together through hydrogen bonds. The molecular **complementarity** of double-stranded DNA is its most important property and the key to understanding how DNA functions.

Figure 1.2 Complementary base pairs are a key feature of the DNA molecule. A single strand of DNA is composed of nucleotide subunits each consisting of a deoxyribose sugar (*white pentagons*), a phosphate (*yellow circles*), and one of four nitrogenous bases—adenine, thymine, cytosine, or guanine (designated as *lavender* or *green* A*s*, *T*s, *C*s, or *G*s). Hydrogen bonds (*dotted lines*) enable A to associate tightly with T, and C to associate tightly with G. Thus the two strands are complementary to each other. The arrows labeled 5′ to 3′ show that the strands have opposite orientations.



Although the DNA molecule is three-dimensional, most of its information is one-dimensional and digital. The information is one-dimensional because it is encoded as a specific sequence of letters along the length of the molecule. It is digital because each unit of information—one of the four letters of the DNA alphabet—is discrete. Because genetic information is digital, it can be stored as readily in a computer memory as in a DNA molecule. Indeed, the

Figure 1.3 A human chromosome. Each chromosome contains hundreds to thousands of genes.



combined power of DNA sequencers, computers, and DNA synthesizers makes it possible to store, interpret, replicate, and transmit genetic information electronically from one place to another anywhere on the planet.

The DNA regions that encode proteins are called **genes.** Just as the limited number of letters in a written alphabet places no restrictions on the stories one can tell, so too the limited number of letters in the genetic code alphabet places no restrictions on the kinds of proteins and thus the kinds of organisms genetic information can define.

Within the cells of an organism, DNA molecules carrying the genes are assembled into **chromosomes:** organized structures containing DNA and proteins that package and manage the storage, duplication, expression, and evolution of DNA (**Fig. 1.3**). The DNA within the entire collection of chromosomes in each cell of an organism is its **genome.** Human cells, for example, contain 24 distinct kinds of chromosomes carrying approximately 3×10^9 base pairs and roughly 27,000 genes. The amount of information that can be encoded in this size genome is equivalent to 6 million pages of text containing 250 words per page, with each letter corresponding to one *base pair*.

To appreciate the long journey from a finite amount of genetic information easily storable on a computer disk to the production of a human being, we next must examine proteins, the primary molecules that determine how complex systems of cells, tissues, and organisms function.

essential concepts

- *DNA*, a double-stranded macromolecule composed of four nucleotides, is the repository of genetic information.
- DNA is organized into *chromosomes* (of 24 different types in humans) that collectively constitute an organism's *genome*.
- The human genome contains about 27,000 genes, most of which encode *proteins*.

1.2 Proteins: The Functional Molecules of Life Processes

learning objectives

1. Compare the chemical structures of DNA and proteins.
2. Differentiate between the functions of DNA and the functions of proteins.

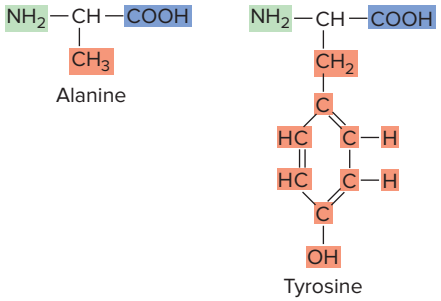
Although no single characteristic distinguishes living organisms from inanimate matter, you would have little trouble deciding which entities in a group of objects are alive. Over time, these living organisms, governed by the laws of physics and chemistry as well as a genetic program, would be able to reproduce themselves. Most of the organisms would also have an elaborate and complicated structure that would change over time—sometimes drastically, as when an insect larva metamorphoses into an adult. Yet another characteristic of life is the ability to move. Animals swim, fly, walk, or run, while plants grow toward or away from light. Still another characteristic is the capacity to adapt selectively to the environment. Finally, a key characteristic of living organisms is the ability to use sources of energy and matter to grow—that is, the ability to convert foreign material into their own body parts. The chemical and physical reactions that carry out these conversions are known as *metabolism.*

Most properties of living organisms arise ultimately from the class of molecules known as **proteins**—large polymers composed of hundreds to thousands of **amino acid** subunits strung together in long chains. Each chain folds into a specific three-dimensional conformation dictated by the sequence of its amino acids (**Fig. 1.4**). Most proteins are composed of 20 different amino acids. The information in the DNA of genes dictates, via a *genetic code,* the order of amino acids in a protein molecule.

You can think of proteins as constructed from a set of 20 different kinds of snap beads distinguished by color and shape. If you were to arrange the beads in any order, make strings of a thousand beads each, and then fold or twist the chains into shapes dictated by the order of their beads, you would be able to make a nearly infinite number of different three-dimensional shapes. The astonishing diversity of three-dimensional protein structures generates the extraordinary diversity of protein functions that is the basis

Figure 1.4 Proteins are polymers of amino acids that fold in three dimensions. **(a)** Structural formulas for two amino acids: alanine and tyrosine. All amino acids have a basic amino group (—NH_2; *green*) at one end and an acidic carboxyl group (—COOH; *blue*) at the other. The specific side chain (*red*) determines the amino acid's chemical properties. **(b)** The amino acid sequences of two different human proteins: the ß chain of hemoglobin (*green*), and the enzyme lactate dehydrogenase (*purple*). **(c)** The different amino acid sequences of these proteins dictate different three-dimensional shapes. The specific sequence of amino acids in a chain determines the precise three-dimensional shape of the protein.

(a)



(b)

Hemoglobin β chain

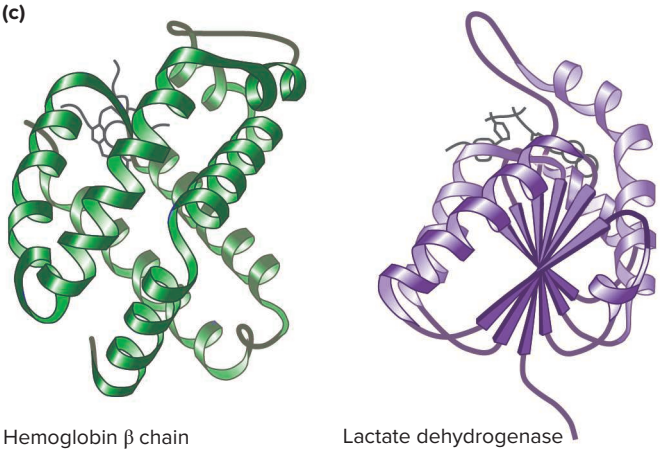
MVHLTPEEKSAVTALWGKVNVDEVGEALGRLLVVYPWTQRLFESFGDLFTPDAVMGNPKVKAHG
KKVLGAFSDGPAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAA
YQKVVAGVANALAHKYH

Lactate dehydrogenase

MATIKSELIKNFAEEEAIHHNKISIVGTGSVGVACAISILLKGLSDELVLVDVDEGKLKGETMDL
QHGSPFMKMPNIVSSKDYLVTANSNLVIITAGARQKKGETRLDLVQRNVSIFKLMIPNITQYSPH
CKLLIVTNPVDILTYVAWKLSGFPKNRVIGSGCNLDSARFRYFIGQRLGIHSESCHGLILGEHGD
SSVPVWSGVNIAGVPLKDLNPDIGTDKDPEQWENVHKKVISSGYEMVKMKGYTSWGISLSVADLT
ESILKNLRRVHPVSTLSKGLYGINEDIFLSVPCILGENGITDLIKVKLTLEEEACLQKSAETLWEIQKELKL

A = Ala	= alanine	G = Gly	= glycine	M = Met	= methionine	S = Ser	= serine
C = Cys	= cysteine	H = His	= histidine	N = Asn	= asparagine	T = Thr	= threonine
D = Asp	= aspartic acid	I = Ile	= isoleucine	P = Pro	= proline	V = Val	= valine
E = Glu	= glutamic acid	K = Lys	= lysine	Q = Gln	= glutamine	W = Trp	= tryptophan
F = Phe	= phenylalanine	L = Leu	= leucine	R = Arg	= arginine	Y = Tyr	= tyrosine

(c)



Hemoglobin β chain — Lactate dehydrogenase

of each organism's complex and adaptive behavior (Fig. 1.4b and c). The structure and shape of the hemoglobin protein, for example, allow it to transport oxygen in the bloodstream and release it to the tissues. In contrast, lactate dehydrogenase is an enzyme that converts lactate to pyruvate, an important step in producing cellular energy. Most of the properties associated with life emerge from the constellation of protein molecules that an organism synthesizes according to instructions contained in its DNA.

essential concepts

- *Proteins* are responsible for most biological functions of cells and organisms.
- A protein is a macromolecule consisting of *amino acids* linked in a linear sequence.
- The sequences of amino acids in proteins are encoded by *genes* within the DNA.

1.3 Molecular Similarities of All Life-Forms

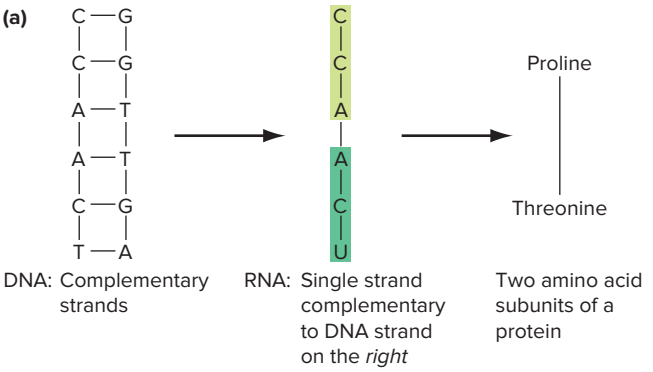
learning objective

1. Summarize the molecular evidence for the common origin of living organisms.

The evolution of biological information is a fascinating story spanning the 4 billion years of earth's history. Many biologists think that **RNA** was the first information-processing molecule to appear. Very similar to DNA, RNA molecules are also composed of four subunits: the bases G, C, A, and U (for uracil, which replaces the T of DNA). Like DNA, RNA has the capacity to store, replicate, and express information; like proteins, RNA can fold in three dimensions to produce molecules capable of catalyzing the chemistry of life. In fact, you will learn that the ultimate function of some genes is to encode RNA molecules instead of proteins. RNA molecules, however, are intrinsically unstable. Thus, it is probable that the more stable DNA took over the linear information storage and replication functions of RNA, while proteins, with their far greater capacity for diversity, preempted in large part the functions derived from RNA's three-dimensional folding. With this division of labor, RNA became primarily an intermediary in converting the information in DNA into the sequence of amino acids in protein (**Fig. 1.5a**). The separation that placed information storage in DNA and biological function mainly in proteins was so successful that all known organisms alive today descend from the first organisms that happened upon this molecular specialization.

The evidence for the common origin of all living forms is present in their DNA sequences. All living organisms use essentially the same **genetic code** in which various triplet groupings of the four letters of the DNA and RNA alphabets encode the 20 letters of the amino acid alphabet (**Fig. 1.5b**).

Figure 1.5 RNA is an intermediary in the conversion of DNA information into protein via the genetic code. (a) The linear bases of DNA are copied through molecular complementarity into the linear bases of RNA. The bases of RNA are read three at a time (that is, as triplets) to encode the amino acid subunits of proteins. **(b)** The genetic code dictionary specifies the relationship between RNA triplets and the amino acid subunits of proteins.



(b)

First letter	Second letter: U	Second letter: C	Second letter: A	Second letter: G	Third letter
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

Figure 1.6 Comparisons of gene products in different species provide evidence for the relatedness of living organisms. This chart shows the amino acid sequence for equivalent portions of the cytochrome c protein in six species: *Saccharomyces cerevisiae* (yeast), *Arabidopsis thaliana* (a weedlike flowering plant), *Caenorhabditis elegans* (a nematode), *Drosophila melanogaster* (the fruit fly), *Mus musculus* (the house mouse), and *Homo sapiens* (humans). Consult Fig. 1.4b for the key to amino acid names.

* Indicates identical and . indicates similar

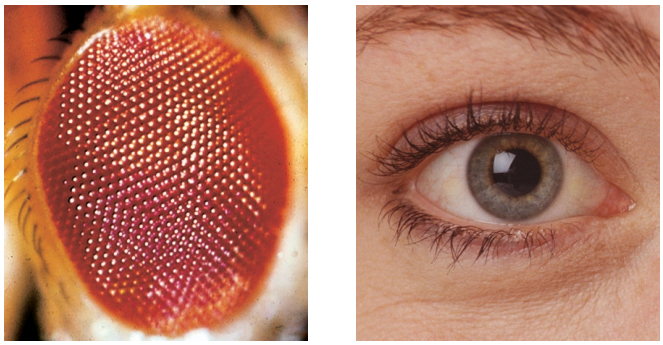
The relatedness of all living organisms is also evident from comparisons of genes with similar functions in very different organisms. A striking similarity exists between the genes for many corresponding proteins in bacteria, yeast, plants, worms, flies, mice, and humans. For example, most of the amino acids in the cytochrome c proteins of diverse species are identical to each other (**Fig. 1.6**), indicating that these proteins all derived from a common ancestral protein. It is also important to note that some amino acids in these various cytochrome c proteins are different. The reason is that different **mutations,** that is, changes in nucleotide pairs, can occur when genes are passed from one generation of an organism to the next. The accumulation of these mutations in genomes is the main driving force of evolution.

Despite the occurrence of mutations that alter DNA and thus protein sequences, it is often possible to place a gene from one organism into the genome of a very different organism and see it function normally in the new environment. Human genes that help regulate cell division, for example, can replace related genes in yeast and enable the yeast cells to function normally.

One of the most striking examples of relatedness at this level of biological information was uncovered in studies of eye development. Both insects and vertebrates (including humans) have eyes, but they are of very different types (**Fig. 1.7**). Biologists had long assumed that the evolution of eyes occurred independently, and in many evolution textbooks, eyes were used as an example of *convergent evolution,* in which structurally unrelated but functionally analogous organs emerge in different species as a result of natural selection. Studies of a gene called *Pax6* have turned this view upside down.

Mutations in the *Pax6* gene lead to a failure of eye development in both people and mice, and molecular studies have suggested that *Pax6* might play a central role in the initiation of eye development in all vertebrates. Remarkably, when the human *Pax6* gene is expressed in cells along the surface of the fruit fly body, it induces numerous little eyes to develop there. It turns out that fruit flies also have a gene specifying

Figure 1.7 The eyes of insects and humans have a common ancestor. (a) A fly eye and **(b)** a human eye.



(a) (b)

a protein whose amino acid sequence is distantly but clearly related to that of the protein specified by human *Pax6*; and furthermore, certain mutations in the fly gene result in animals lacking eyes. Taken together, these results demonstrate that during 600 million years of *divergent evolution,* an ancestral gene that served as the main control switch for initiating eye development accumulated different mutations in the lineages leading to people and fruit flies, but the gene still serves the same function in both species.

The usefulness of the relatedness and unity at all levels of biological information cannot be overstated. It means that in many cases, the experimental manipulation of organisms known as *model organisms* can shed light on gene functions in humans. If genes similar to human genes function in simple model organisms such as fruit flies or bacteria, scientists can determine gene function and regulation in these experimentally manipulable organisms and bring these insights to an understanding of the human organism.

essential concepts

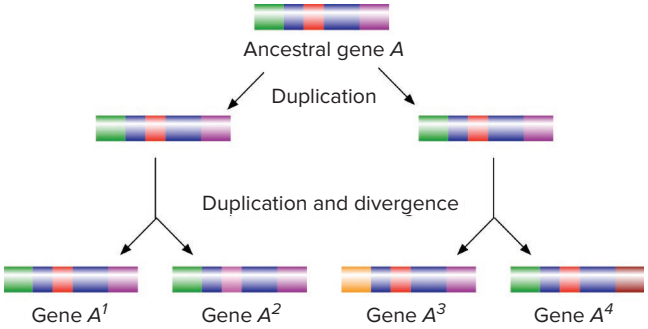
- Living organisms exhibit marked similarities at the molecular level in the ways they use DNA and RNA to make proteins.
- Certain genes have persisted throughout the evolution of widely divergent species.

1.4 The Modular Construction of Genomes

learning objectives

1. Describe mechanisms by which new genes could arise.
2. Explain how regulation of gene expression can alter gene function.

Figure 1.8 How genes arise by duplication and divergence. Ancestral gene *A* contains exons (*green, red,* and *purple*) separated by introns in *blue*. Gene *A* is duplicated to create two copies that are originally identical, but mutations in either or both (*other colors*) cause the copies to diverge. Additional rounds of duplication and divergence create a family of related genes.

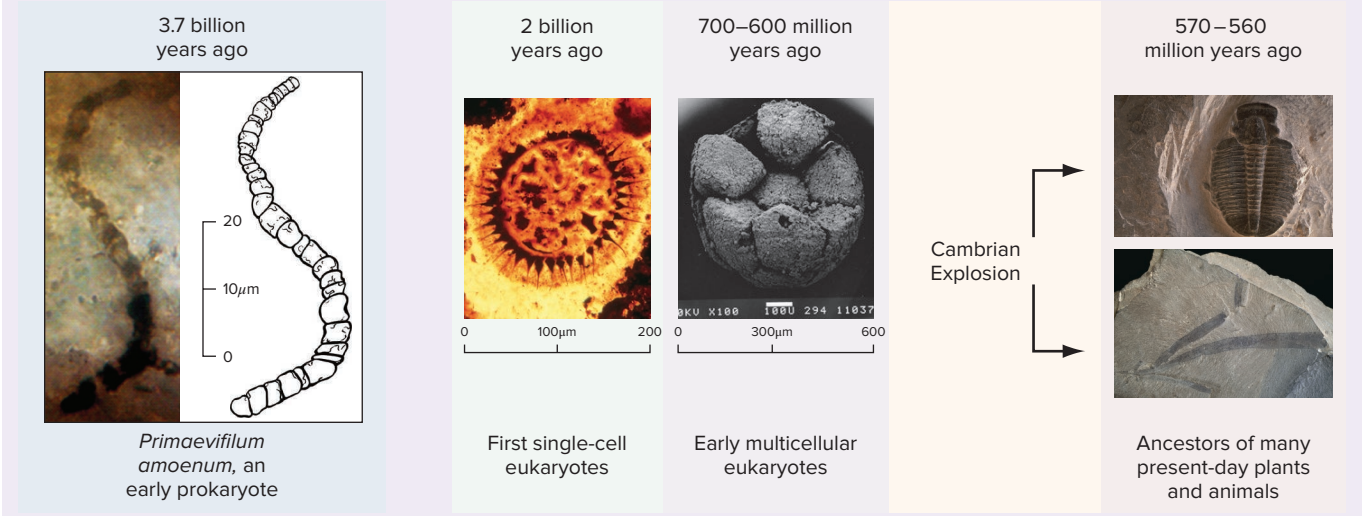


We have seen that roughly 27,000 genes direct human growth and development. How did such complexity arise? Recent technical advances have enabled researchers to complete structural analyses of the entire genome of many organisms. The information obtained reveals that **gene families** have arisen by duplication of a primordial gene; after duplication, mutations may cause the two copies to diverge from each other (**Fig. 1.8**). In both humans and chimpanzees, for example, four different genes produce different rhodopsin proteins that are expressed in photoreceptors of distinct retinal cells. Each of these proteins functions in a slightly different way so that four kinds of retinal cells respond to light of different wavelengths and intensities, resulting in color vision. The four rhodopsin genes arose from a single primordial gene by several duplications followed by slight divergences in structure.

Duplication followed by divergence underlies the evolution of new genes with new functions. This principle appears to have been built into the genome structure of all multicellular organisms. The protein-coding region of most genes is subdivided into as many as 10 or more small pieces (called *exons*), separated by DNA that does not code for protein (called *introns*) as shown in Fig. 1.8. This modular construction facilitates the rearrangement of different modules from different genes to create new combinations during evolution. It is likely that this process of modular reassortment facilitated the rapid diversification of living forms about 570 million years ago (see Fig. 1.8).

The tremendous advantage of the duplication and divergence of existing pieces of genetic information is evident in the history of life's evolution (**Table 1.1**). *Prokaryotic* cells such as bacteria, which do not have a membrane-bounded nucleus, evolved about 3.7 billion years ago; *eukaryotic* cells such as algae, which have a membrane-bounded nucleus, emerged around 2 billion years ago; and multicellular eukaryotic organisms appeared 700–600 million years ago. Then, about 570 million years

TABLE 1.1 Fossil Evidence for Some Major Stages in the Evolution of Life



(prokaryote): © J.W. Schopf; (eukaryotes): © Prof. Andrew Knoll; (trilobite): © Brand X Pictures/PunchStock RF; (sponge): © Alan Sirulnikoff/Science Source

ago, within the relatively short evolutionary time of roughly 20–50 million years known as the *Cambrian explosion*, the multicellular life-forms diverged into a bewildering array of organisms, including primitive vertebrates.

Figure 1.9 Two-winged and four-winged flies. Geneticists converted a contemporary normal two-winged fly to a four-winged insect resembling the fly's evolutionary antecedent. They accomplished this by mutating a key element in the fly's regulatory network. Note the club-shaped halteres (*arrows*) behind the wings of the fly at the top.

(both): © Edward Lewis, California Institute of Technology

A fascinating question is: How could the multicellular forms achieve such enormous diversity in only 20–50 million years? The answer lies, in part, in the hierarchic organization of the information encoded in chromosomes. Exons are arranged into genes; genes duplicate and diverge to generate gene families; and gene families sometimes rapidly expand to **gene superfamilies** containing hundreds of related genes. In both mouse and human adults, for example, the immune system is encoded by a gene superfamily composed of hundreds of closely related but slightly divergent genes. With the emergence of each successively larger informational unit, evolution gains the ability to duplicate increasingly complex informational modules through single genetic events.

Probably even more important for the evolution of complexity is the rapid change of regulatory networks that specify how genes behave (that is, when, where, and to what degree they are expressed) during development. For example, the two-winged fly evolved from a four-winged ancestor not because of changes in gene-encoded structural proteins, but rather because of a rewiring of the regulatory network, which converted one pair of wings into two small balancing organs known as *halteres* (**Fig. 1.9**).

essential concepts

- *Gene duplication* followed by the *divergence* of copies is one explanation for how new functions evolve.
- The *reshuffling of exons* in eukaryotes provides another mechanism for the rapid diversification of genomes.
- Changes in DNA that affect *gene regulation*—where, when, and to what degree genes are expressed—also generate evolutionary change.

1.5 Modern Genetic Techniques

learning objectives

1. Explain how advances in technology have accelerated the analysis of genomes.
2. Compare the knowledge obtained from genetic dissection and from genome sequencing.
3. Discuss how genome sequence information can be used to treat or cure diseases.

The complexity of living systems has developed over 4 billion years from the continuous amplification and refinement of genetic information. The simplest bacterial cells contain about 1000 genes that interact in complex networks. Yeast cells, the simplest eukaryotic cells, contain about 5800 genes. Nematodes (roundworms) contain about 20,000 genes, and fruit flies contain roughly 13,000 genes. Humans have approximately 27,000 genes; surprisingly, the flowering plant *Arabidopsis* has as many and the zebrafish *D. rerio* has even more (**Fig. 1.10**). Each of these organisms has provided valuable insights into aspects of biology that are conserved among all organisms as well as other phenomena that are species-specific.

Genetic Dissection of Model Organisms Reveals the Working of Biological Processes

Model organisms including bacteria, yeast, nematodes, fruit flies, *Arabidopsis*, zebrafish, and mice are extremely valuable to researchers, who can use these organisms to analyze the complexity of a genome piece by piece. The logic used in *genetic dissection* is quite simple: inactivate a gene in a model organism and observe the consequences. For example, the loss of a gene for visual pigment produces fruit flies with white eyes instead of eyes of the normal red color. One can thus conclude that the protein product of this gene plays a key role in eye pigmentation. From their study of model organisms, geneticists are amassing a detailed picture of the complexity of living systems.

Whole-Genome Sequencing Can Identify Mutant Genes that Cause Disease

A complementary way to study an organism's genetic complexity is to look not just at one gene at a time, but rather at the genome as a whole. The new tools of **genomics,** particularly high-throughput DNA sequencers, have the capacity to analyze all the genes of any living thing. In fact, the complete nucleotide sequences of representative genomes of the model species listed above, as well as of humans, have all been determined.

The first draft of the human genome sequence announced by the Human Genome Project in 2001 cost $3 billion and took over 10 years to produce. Since then, rapid advances in genome sequencing technology have made it possible in 2016 to determine the genome sequence of an individual in just a few days for about $1000. Alongside the advances in DNA sequencing technology have been the development of computer algorithms to analyze the sequence data and the establishment of online databases that catalog the differences in individual genome sequences.

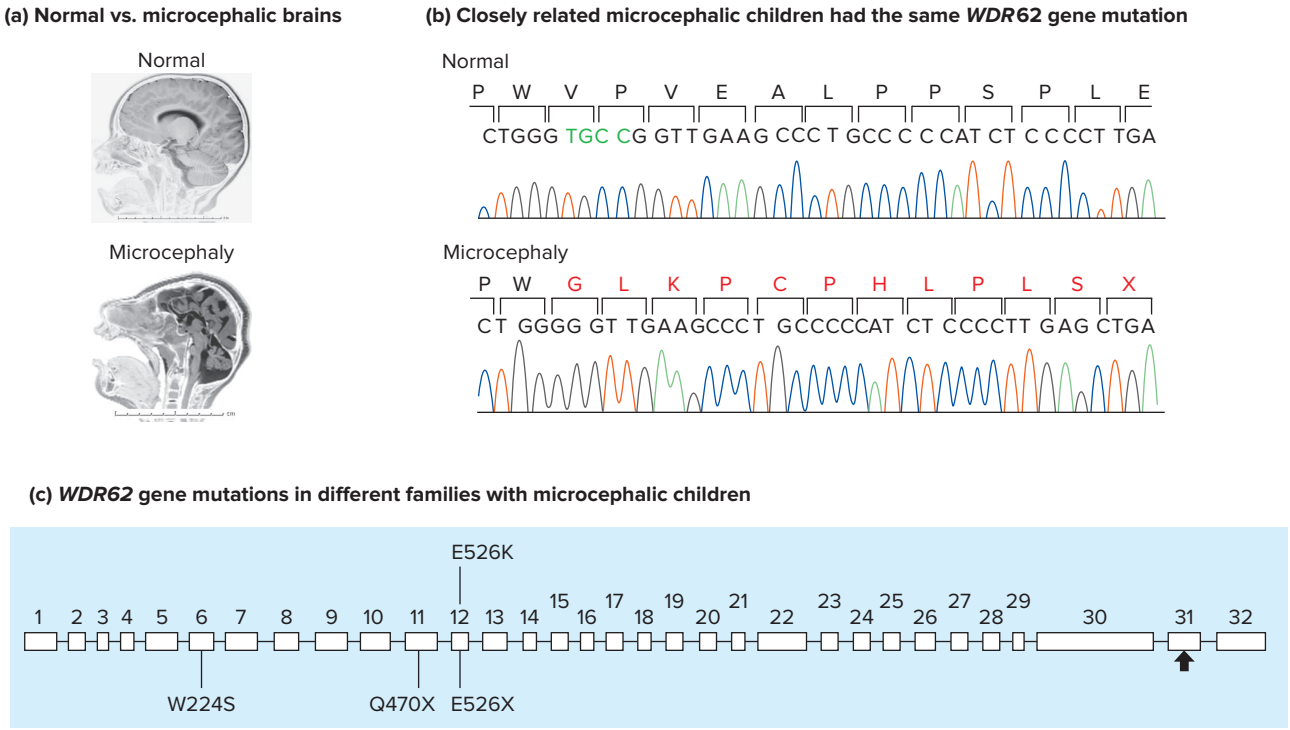
No example better illustrates the power of genome sequencing technology than its use in the identification of gene mutations that cause human genetic diseases. For diseases that result from mutation of a single gene, the gene responsible often may be identified by determining the genome sequence of just a few people or sometimes even that of a single individual.

In the case shown in **Fig. 1.11a,** geneticists analyzed whole genome sequences to find a gene mutation underlying a rare brain malformation disease called *microcephaly.* The

Figure 1.10 Seven model organisms whose genomes were sequenced as part of the Human Genome Project. The chart indicates genome size in millions of base pairs, or megabases (Mb). The bottom row shows the approximate number of genes for each organism. (*E. coli*): © David M. Phillips/Science Source; (*S. cerevisiae*): © CMSP/Getty Images; (*C. elegans*): © Sinclair Stammers/Science Source; (*A. thaliana*): Source: Courtesy USDA/Peggy Greb, photographer; (*D. melanogaster*): © Hemis.fr/SuperStock; (*D. rerio*): © A Hartl/Blickwinkel/agefotostock; (*M. musculus*): © imageBROKER/SuperStock RF

Organism	*E. coli*	*S. cerevisiae*	*C. elegans*	*A. thaliana*	*D. melanogaster*	*D. rerio*	*M. musculus*
Genome size	4.6 Mb	12 Mb	100 Mb	125 Mb	130 Mb	1500 Mb	2700 Mb
Number of protein-coding genes (approximate)	4300	5800	20,000	27,000	13,000	36,000	25,000

Figure 1.11 A causal gene for microcephaly identified by genome sequencing. **(a)** Magnetic resonance images of normal and microcephalic brains. **(b)** Sequence analysis of normal and mutant copies of the *WDR62* gene. The mutation is a deletion of the four nucleotides TGCC (*green*) that causes a major change in the amino acid sequence of the protein product of the gene. The letters above each triplet sequence identify the encoded amino acid. **(c)** Five different mutations in the *WDR62* gene in five different families are shown. Four of the mutations affect the identity of a single amino acid in the protein encoded by the gene. For example, W224S means that the 224th amino acid is normally W (tryptophan) but is changed to S (serine) by the mutation. The *arrow* indicates the position of the TGCC deletion mutation shown in (b).



inheritance pattern observed for microcephaly indicated that it is a so-called *recessive* disease, meaning that diseased people inherit two mutant gene copies, one from each normal parent. The parents have one normal gene copy and one mutant copy, explaining why the parents' brains do not have this malformation. Sequencing and analysis of the genomes of two children with microcephaly from the same family identified a single rare gene mutation present in both siblings—a deletion of four base pairs within a gene called *WDR62* (**Fig. 1.11b**). Each parent was found to have one normal copy of *WDR62* and one copy with the four base pair deletion (Fig. 1.11b). Subsequently, the researchers found that different families with microcephalic children harbored different mutations in the same gene (**Fig. 1.11c**), thus confirming *WDR62* as a causative gene for microcephaly.

Gene Therapy May Help Cure Genetic Diseases

By enabling rapid disease gene discovery, the sequencing of whole genomes is revolutionizing medicine. Knowledge of disease genes can inform parents whether their children might suffer from a severely debilitating disease like microcephaly, allowing the parents to consider ways in which to avoid or to prepare for such an outcome. Moreover, identification of a disease gene provides information about the protein encoded by that gene that can sometimes guide the design of effective therapeutics to treat the disease. This strategy has not yet been useful in the case of microcephaly, but it has already been of tremendous value in developing drugs to combat other genetic diseases, including certain kinds of cancer.

Dramatic progress within the last few years offers hope that medical scientists may eventually be able to treat genetic diseases by modifying the genomes of the *somatic* (body) *cells* affected by the disease syndrome. One method under development is called **gene therapy;** here, scientists introduce normal copies of genes into human cells, where they can be expressed and compensate for their mutant, nonfunctional counterparts in the genome. An alternative, very recent gene therapy approach is *genome editing,* in which researchers change the base-pair sequence of a mutant gene to that of its normal counterpart. Gene therapy and genome editing have been used in model organisms such as mice to restore proper gene function and sometimes reverse the disease process, but the application of these techniques to human conditions is still only in very early stages.