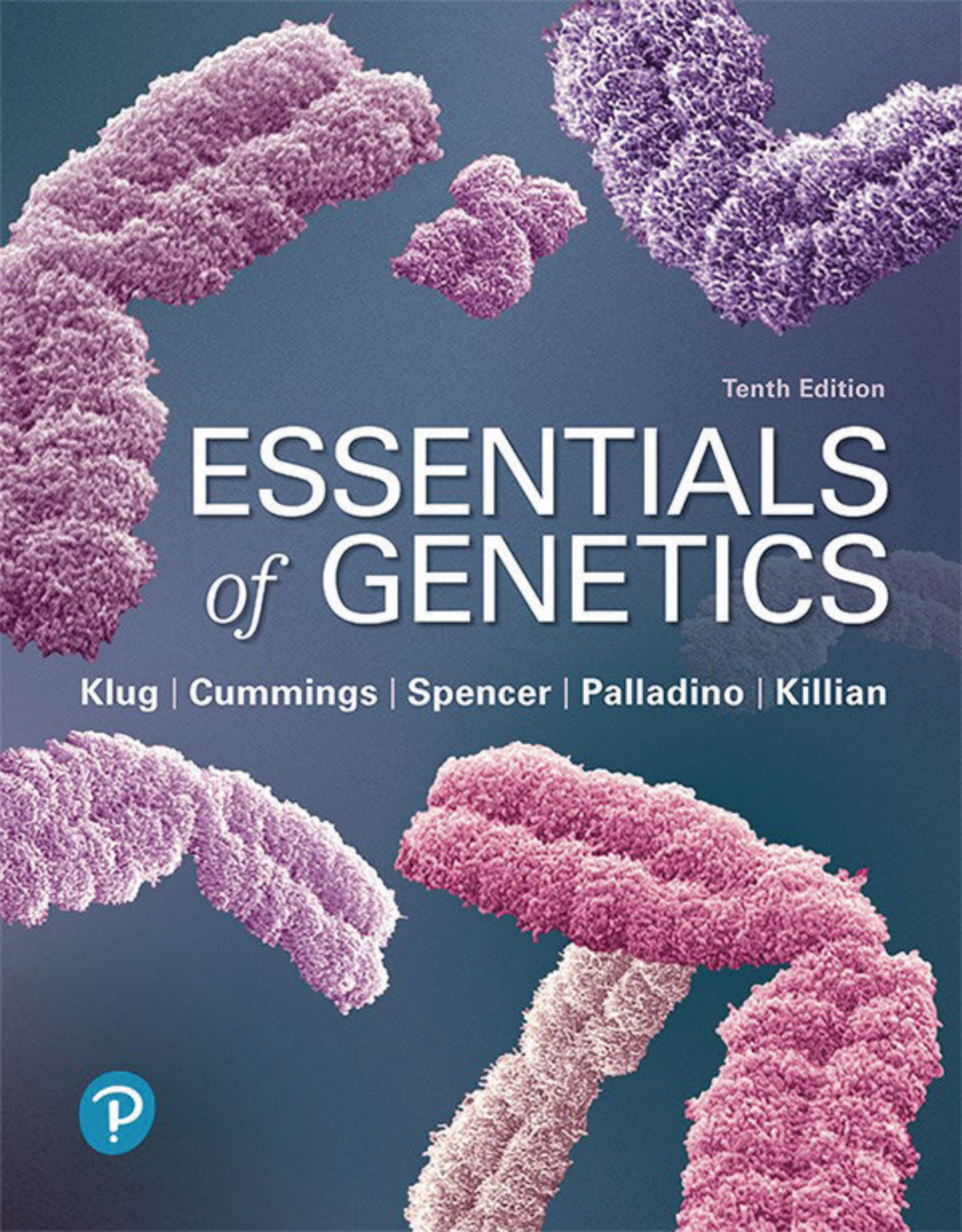
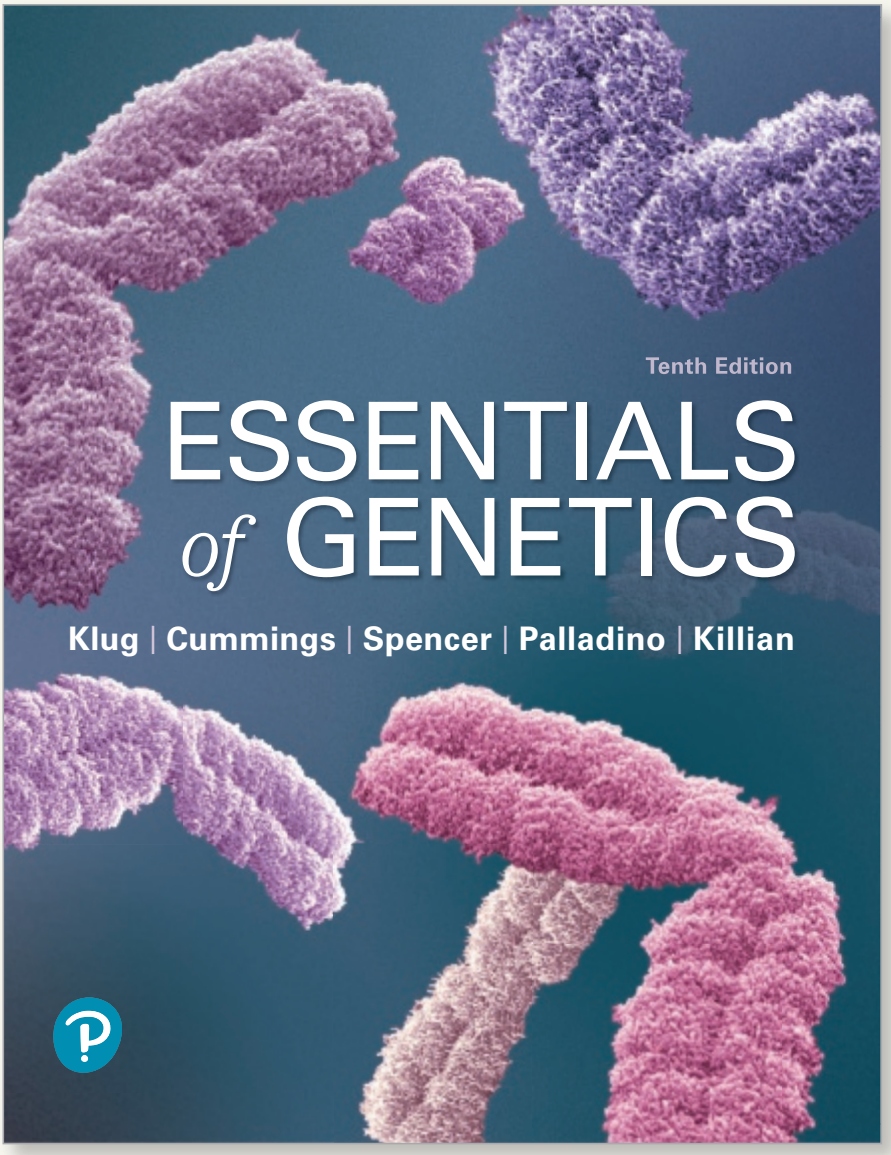

Tenth Edition
ESSENTIALS
of GENETICS
Klug | Cummings | Spencer | Palladino | Killian

# Focus on essential genetic topics and explore the latest breakthroughs

**Known for its focus on conceptual understanding, problem solving, and practical applications, the bestselling *Essentials of Genetics* strengthens problem-solving skills and explores the essential genetics topics that today's students need to understand. The 10th Edition has been extensively updated to provide comprehensive coverage of important, emerging topics such as CRISPR-Cas, epigenetics, and genetic testing. Mastering Genetics includes new tutorials on topics such as CRISPR-Cas and epigenetics, and new, mobile-ready Dynamic Study Modules, which prepare students for class and support the learning of key concepts.**

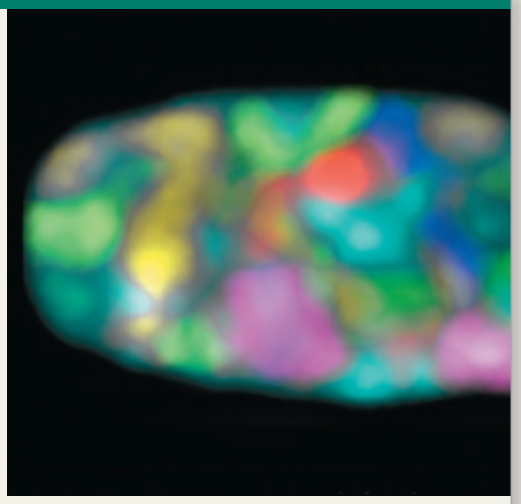



Pearson

# Make genetics relevant . . .

16

## Regulation of Gene Expression in Eukaryotes



Chromosome territories in a human fibroblast cell nucleus. Each chromosome is stained with a different-colored probe.

**CHAPTER CONCEPTS**

- While transcription and translation are tightly coupled in bacteria, in eukaryotes, these processes are spatially and temporally separated, and thus independently regulated.
- Chromatin remodeling, as well as modifications to DNA and histones, play important roles in regulating gene expression in eukaryotes.
- Eukaryotic transcription initiation requires the assembly of transcription regulatory proteins on DNA sites known as promoters, enhancers, and silencers.
- Following transcription, there are several mechanisms that regulate gene expression, referred to as posttranscriptional regulation.
- Alternative splicing allows for a single gene to encode different protein isoforms with different functions.
- RNA-binding proteins regulate mRNA stability, degradation, localization, and translation.
- Noncoding RNAs may regulate gene

Virtually all cells in a multicellular eukaryotic organism contain a complete genome; however, such organisms often possess different cell types with diverse morphologies and functions. This simple observation highlights the importance of the regulation of gene expression in eukaryotes. For example, skin cells and muscle cells differ in appearance and function because they express different genes. Skin cells express keratins, fibrous structural proteins that bestow the skin with protective properties. Muscle cells express high levels of myosin II, a protein that mediates muscle contraction. Skin cells do not express myosin II, and muscle cells do not express keratins.

In addition to gene expression that is cell-type specific, some genes are only expressed under certain conditions or at certain times. For example, when oxygen levels in the blood are low, such as at high altitude or after rigorous exercise, expression of the hormone erythropoietin is upregulated, which leads to an increase in red blood cell production and thus oxygen-carrying capacity.

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**NEW! Regulation of gene expression** has been expanded and is now divided into coverage of bacteria in Chapter 15 and coverage of eukaryotes in Chapter 16.

**Coverage of CRISPR-Cas is expanded and integrated in multiple chapters –** Chapters 1, 15, 17, and Special Topics Chapters ST3 and ST6.

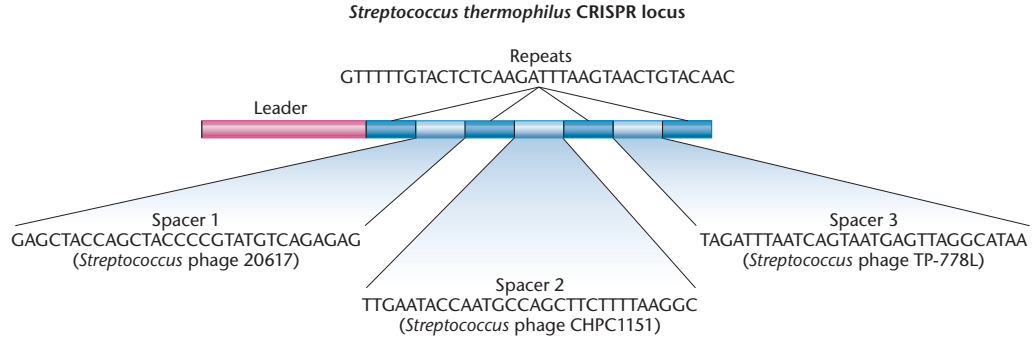


**FIGURE 15.13** A CRISPR locus from the bacterium *Streptococcus thermophilus* (LMG18311). Spacer sequences are derived from portions of bacteriophage genomes and are flanked on either side by a repeat sequence. Only 3 of 33 total spacers in this CRISPR locus are shown.

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# with current high interest topics

SPECIAL TOPICS IN MODERN GENETICS 2

## Genetic Testing

SPECIAL TOPIC X

Earlier in the text (see Chapters 17 and 18), we reviewed essential concepts of recombinant DNA technology and genomic analysis. Because of the Human Genome Project and related advances in genomics, researchers have been making rapid progress in identifying genes involved in both single-gene diseases and complex genetic traits. As a result, **genetic testing**—the ability to analyze DNA, and increasingly RNA, for the purposes of identifying specific genes or sequences associated with different genetic conditions—has advanced very rapidly.

Genetic testing, including genomic analysis by DNA sequencing, is transforming medical diagnostics. Technologies for genetic testing have had major impacts on the diagnosis of disease and are revolutionizing medical treatments based on the development of specific and effective pharmaceuticals. In this Special Topics chapter we provide an overview of applications that are effective for the genetic testing of children and adults and examine historical and modern methods. We consider the impact of different genetic technologies on the diagnosis of human diseases and dystrophy. Other tests have been developed for disorders that may involve multiple genes such as certain types of cancers.

Gene tests are used for prenatal, childhood, and adult prognosis and diagnosis of genetic diseases; to identify carriers; and to identify genetic diseases in embryos created by *in vitro* fertilization, among other applications. For genetic testing of adults, DNA from white blood cells is commonly used. Alternatively, many genetic tests can be carried out on cheek cells, collected by swabbing the inside of the mouth, or on hair cells. Some genetic testing can be carried out on gametes.

"Genetic testing, including genomic analysis by DNA sequencing, is transforming medical diagnostics. Technologies for genetic testing have had major

What does it mean when a genetic test is performed for *prognostic* purposes, and how does this differ from a *diagnostic* test? A prognostic test predicts a person's likelihood of developing a particular genetic disorder. A diagnostic test for a genetic condition

**NEW! Special Topics chapter on Genetic Testing** guides students through the many contexts in which genetic testing is becoming prominent and explores many questions and ethical concerns related to its use.

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SPECIAL TOPICS IN MODERN GENETICS 4

## Advances in Neurogenetics: The Study of Huntington Disease

SPECIAL TOPIC 4

As the result of groundbreaking advances in molecular genetics and genomics made since the 1970s, new fields in genetics and related disciplines have emerged. One new field is **neurogenetics**—the study of the genetic basis of normal and abnormal functioning of the nervous system, with emphasis on brain functions. Research in this field includes the genes associated with neurodegenerative disorders, with the ultimate goal of developing effective therapies to combat these devastating conditions. Of the many such diseases, including Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis (ALS), **Huntington disease (HD)** stands out as a model for the genetic investigation of neurodegenerative disorders. Not only is it monogenic and 100 percent penetrant, but nearly all analytical approaches in molecular genetics have been successfully applied to the study of HD, validating its significance as a model for these diseases.

HD is an autosomal dominant disorder characterized by adult onset of defined and progressive behavioral changes, including uncontrolled movements (chorea), cognitive decline, and psychiatric disturbances, with death occurring within 10 to 15 years after symptoms appear. HD was one of the first examples of complete dominance in human inheritance, with no differences in phenotypes between homozygotes and heterozygotes. In the vast majority of cases, symptoms do not develop until about age 45. Overall, HD currently affects about 25,000 to 30,000 people in North America.

The disease is named after George Huntington, a nineteenth-century physician. He was not the first to describe the disorder, know about the molecular and cellular mechanisms associated with the disorder, particularly those discovered during the study of transgenic model systems. Finally, we will consider how this information is being used to develop a range of therapies.

"Driving with my father through a wooded road leading from Easthampton to Amagansett, we suddenly came upon two women, mother and daughter, both bowing, twisting, grimacing. I stared in wonderment, almost in fear. What could it mean?"

### ST 4.1 The Search for the Huntington Gene

Mapping the gene for Huntington disease was one of the first attempts to employ a method from a landmark 1980 paper by Botstein, White, and Davis in which the authors proposed that DNA sequence variations in humans could be detected as differences in the length of DNA fragments produced by cutting DNA with restriction enzymes. These differences, known as restriction fragment length polymorphisms (RFLPs), could be visualized using Southern blots (see Chapter 18 for a discussion of RFLPs, and Chapter 17 for a discussion of Southern blots). The authors estimated that a collection of about 150 RFLPs distributed across the genome could be used with pedigrees to detect linkage anywhere in the genome between an RFLP marker and a disease gene of interest. In practical terms, this meant that it would be possible to map a disease gene with no information about the gene, its gene product, or its function—an approach referred to as reverse genetics.

**NEW! Special Topics chapter on Advances in Neurogenetics: The Study of Huntington Disease,** explores how genetic analysis has informed scientists about the disease's causes, symptoms, and future treatment. All Special Topics chapters include a series of questions that help students review key ideas or facilitate personal contemplations and group discussions, and are assignable in Mastering Genetics.

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# Explore the latest ethical considerations

GENETICS, ETHICS, AND SOCIETY

## Down Syndrome and Prenatal Testing—The New Eugenics?

Down syndrome is the most common chromosomal abnormality seen in newborn babies. Prenatal diagnostic tests for Down syndrome have been available for decades, especially to older pregnant women who have an increased risk of bearing a child with Down syndrome. Scientists estimate that there is an abortion rate of about 30 percent for fetuses that test positive for Down syndrome in the United States, and rates of up to 85 percent in other parts of the world, such as Taiwan and France.

Some people agree that it is morally acceptable to prevent the birth of a genetically abnormal fetus. However, others argue that prenatal genetic testing, with the goal of eliminating congenital disorders, is unethical. In addition, some argue that prenatal genetic testing followed by selective abortion is eugenic. How does eugenics apply, if at all, to screening for Down syndrome and other human genetic disorders

The term *eugenics* was first defined by Francis Galton in 1883 as "the science which deals with all influences that improve the inborn qualities of a race; also with those that develop them to the utmost advantage." Galton believed that human traits such as intelligence and personality were hereditary and that humans could selectively mate with each other to create gifted groups of people—analogous to the creation of purebred dogs with specific traits. Galton did not propose coercion but thought that people would voluntarily select mates in order to enhance particular genetic outcomes for their offspring.

In the early to mid-twentieth century, countries throughout the world adopted eugenic policies with the aim of enhancing desirable human traits (positive eugenics) and eliminating undesirable ones (negative eugenics). Many countries, including Britain, Canada, and the United States, enacted compulsory sterilization programs for the "feebleminded," mentally ill, and criminals. The eugenic policies of Nazi Germany were particularly infamous, resulting in forced human genetic experimentation and the slaughter of tens of thousands of people with disabilities. The eugenics movement was discredited after World War II, and the evils perpetuated in its name have tainted the term *eugenics* ever since.

Given the history of the eugenics movement, is it fair to use the term *eugenics* when we speak about genetic testing for Down syndrome and other genetic disorders? Some people argue that it is not eugenic to select for healthy children because there is no coercion, the state is not involved, and the goal is the elimination of suffering. Others point out that such voluntary actions still constitute eugenics, since they involve a form of bioengineering for "better" human beings.

Now that we are entering an era of unprecedented knowledge about our genomes and our predisposition to genetic disorders, we must make decisions about whether our attempts to control or improve human genomes are ethical and what limits we should place on these efforts. The story of the eugenics movement provides us with a powerful cautionary tale about the potential misuses of genetic information.

**Your Turn**

Take time, individually or in groups, to consider the following questions. Investigate the references and links to help you discuss some of the ethical issues surrounding genetic testing and eugenics.

1. Do you think that modern prenatal and preimplantation genetic testing followed by selective abortion is eugenic? Why or why not?

*For background on these questions, see* McCabe, L., and McCabe, E. (2011). Down syndrome: Coercion and eugenics. *Genet. Med.* 13:708–710. *Another useful discussion can be found in* Wilkinson, S., (2015). Prenatal screening, reproductive choice, and public health. *Bioethics* 29:26–35.

2. If genetic technologies were more advanced than today, and you could choose the traits of your children, would you take advantage of that option? Which traits would you choose—height, weight, intellectual abilities, athleticism, artistic talents? If so, would this be eugenic? Would it be ethical?

*To read about similar questions answered by groups of Swiss law and medical students, read* Elger, B., and Harding, T., (2003). Huntington's disease: Do future physicians and lawyers think eugenically? *Clin. Genet.* 64:327–338.

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**Genetics, Ethics, and Society essays** provide synopses of ethical issues related to current findings in genetics that impact directly on society today. They include a section called *Your Turn*, which directs students to related resources of short readings and websites to support deeper investigation and discussion of the main topic of each essay.

**Case Studies at the end of each chapter** have been updated with new topics. Students can read and answer questions about a short scenario related to one of the chapter topics. Each Case Study links the coverage of formal genetic knowledge to everyday societal issues, and they include ethical considerations.

**CASE STUDY** To test or not to test

Thomas discovered a devastating piece of family history when he learned that his brother had been diagnosed with Huntington disease (HD) at age 49. This dominantly inherited autosomal condition usually begins around age 45 with progressive dementia, muscular rigidity, and seizures and ultimately leads to death when affected individuals are in their early 60s. There currently is no effective treatment or cure for this genetic disorder. Thomas, now 38, wonders what the chances are that he also has inherited the mutant allele for HD, leading him to discuss with his wife whether they should seek genetic counseling and whether he should undergo genetic testing. They have two teenage children, a boy and a girl.

1. If they seek genetic counseling, what issues would likely be discussed? Which of these pose grave ethical dilemmas?
2. If you were in Thomas's position, would you want to be tested and possibly learn that you were almost certain to develop the disorder sometime in the next 5–10 years?
3. If Thomas tests positive for the HD allele, should his children be told about the situation, and if so, at what age? Who should make the decision about having the son and daughter tested?

Fulda, K., and Lykens, K. (2006). Ethical issues in predictive genetic testing: A public health perspective. *J. Med. Ethics* 32:143–147.

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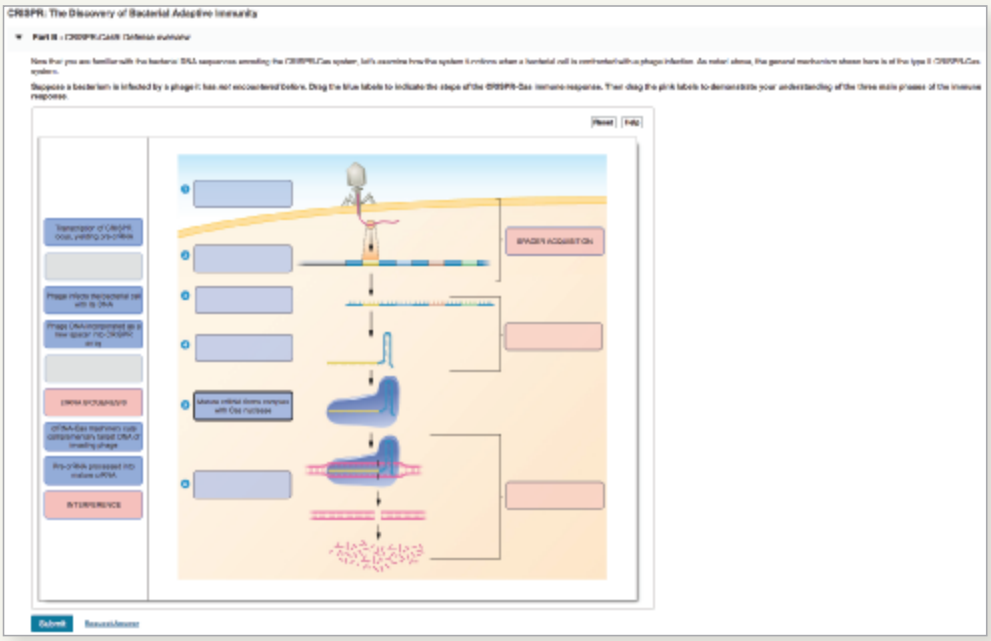
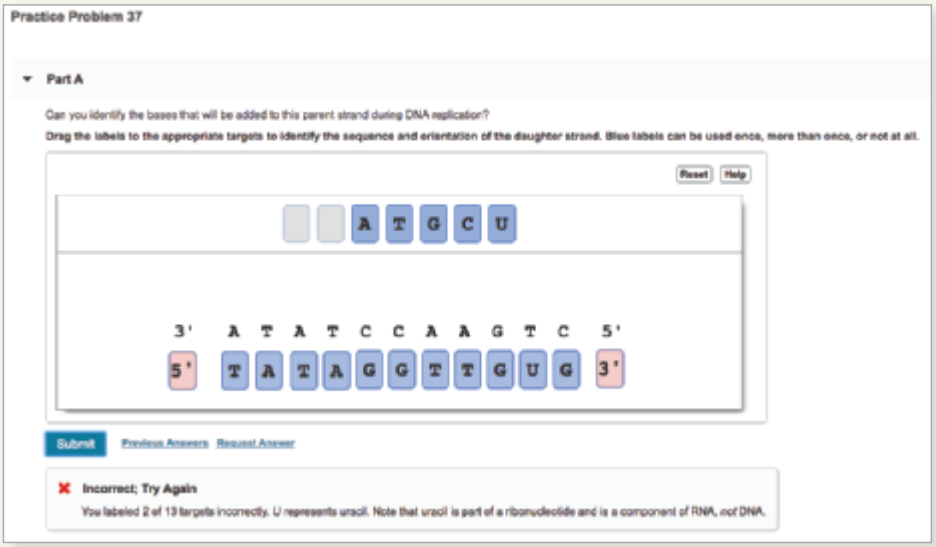
# Learn genetics concepts and problem solving in Mastering Genetics




**NEW! Tutorials** have been added to the library on topics like CRISPR-Cas and epigenetics, to help students master important and challenging concepts.

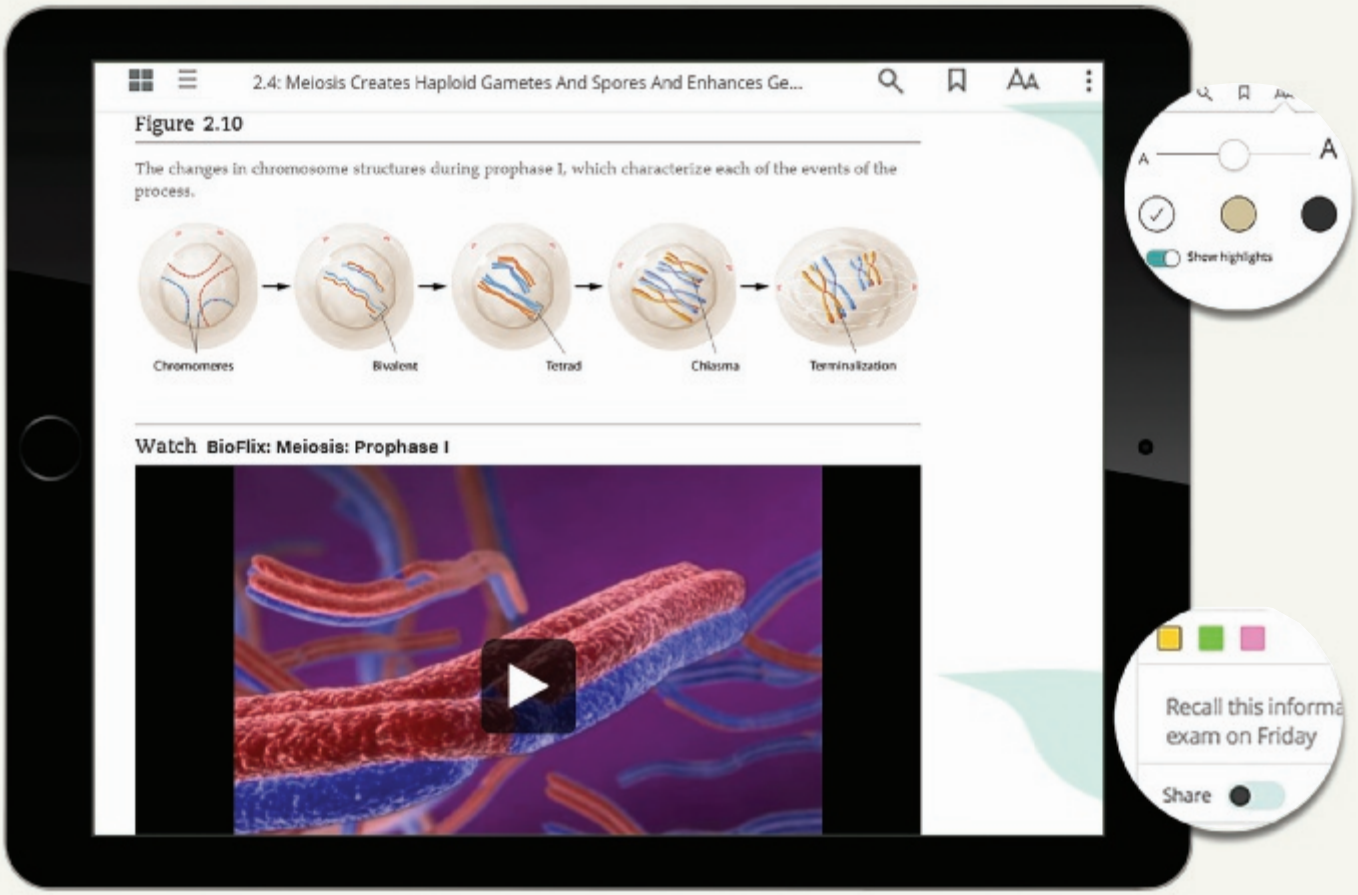
**A library of over 100 Practice Problems** offers more opportunities to assign high quality problems for student homework or practice. These questions appear only in Mastering Genetics and include targeted wrong-answer feedback to help students learn from their mistakes. They are similar to end-of-chapter questions in terms of topic coverage and difficulty.



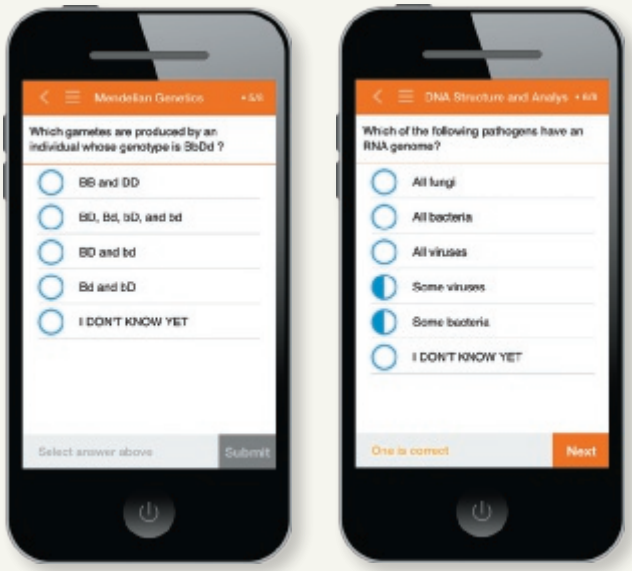
# Give students anytime, anywhere access with Pearson eText

**Pearson eText** is a simple-to-use, mobile-optimized, personalized reading experience available within Mastering. It allows students to easily highlight, take notes, and review key vocabulary all in one place—even when offline. Seamlessly integrated videos and other rich media engage students and give them access to the help they need, when they need it. Pearson eText is available within Mastering when packaged with a new book; students can also purchase Mastering with Pearson eText online.

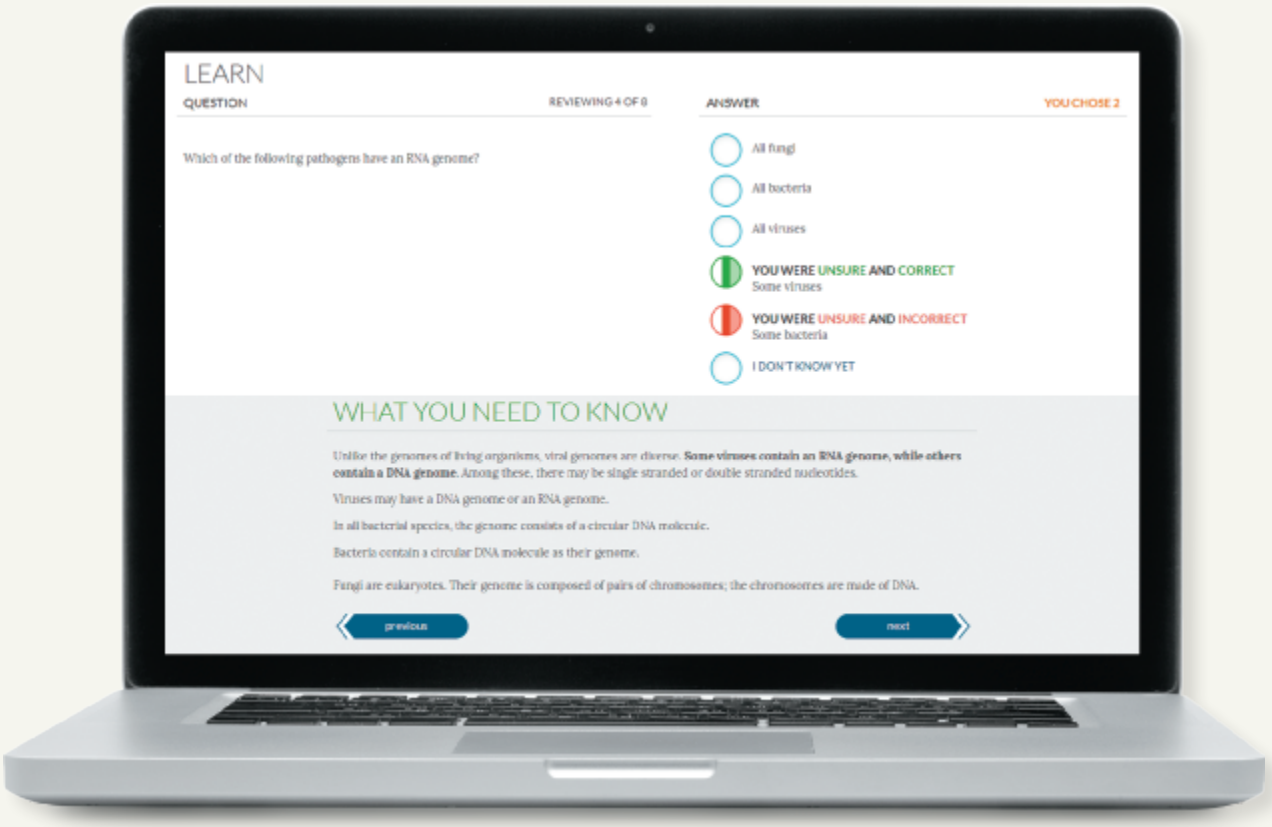
**NEW! Pearson eText** increases student engagement with embedded animations and videos. In addition, interactive Now Solve This problems help students build knowledge and develop problem-solving skills while learning chapter content.



# Improve learning with Dynamic Study Modules

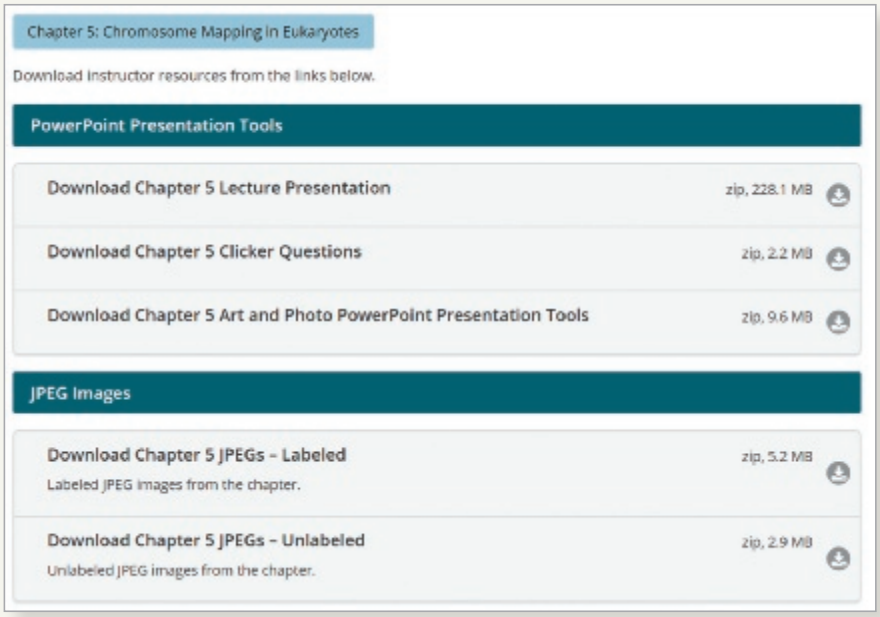



**Dynamic Study Modules in Mastering Genetics** help students study effectively—and at their own pace—by keeping them motivated and engaged. The assignable modules rely on the latest research in cognitive science, using methods—such as adaptivity, gamification, and intermittent rewards—to stimulate learning and improve retention of key concepts.

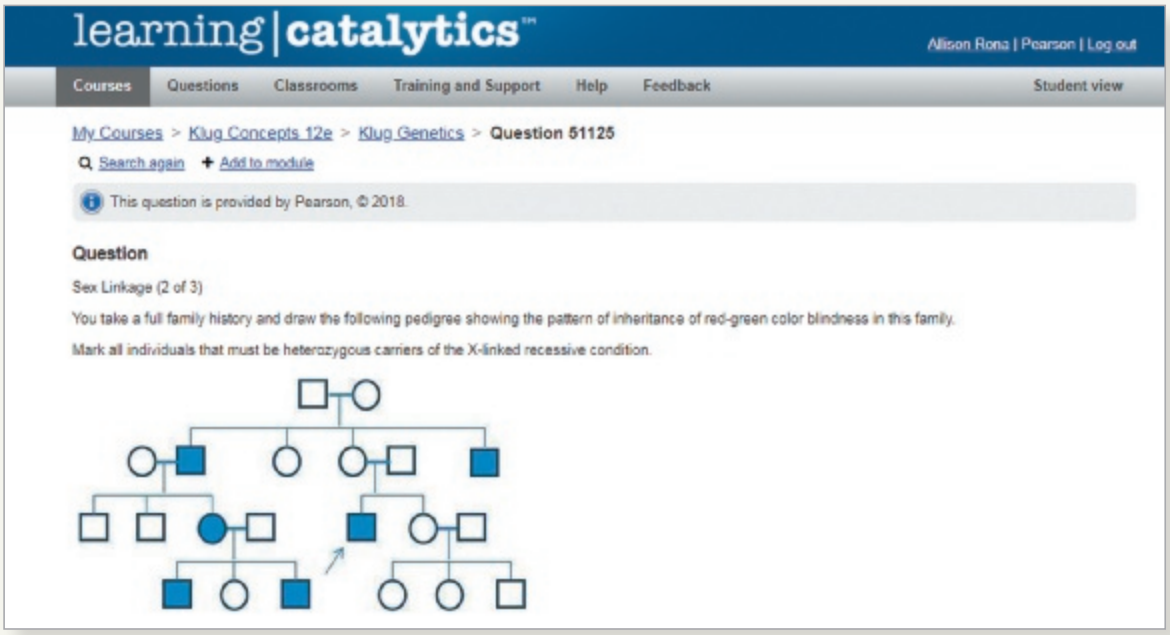



Each module poses a series of questions about a course topic. These question sets adapt to each student's performance and offer personalized, targeted feedback to help them master key concepts. With **Dynamic Study Modules,** students build the confidence they need to deepen their understanding, participate meaningfully, and perform better—in and out of class.

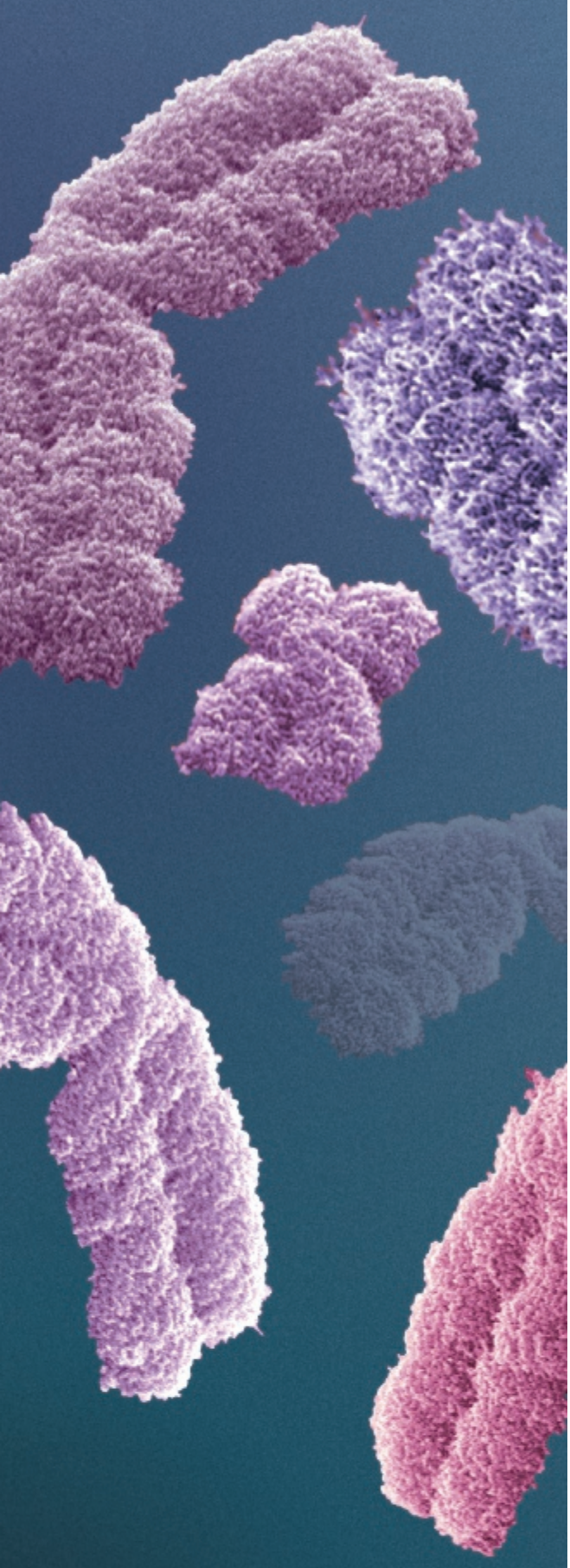
# Instructor support you can rely on




***Essentials of Genetics*** includes a full suite of instructor support materials in the Instructor Resources area in Mastering Genetics. Resources include lecture presentations, clicker questions, and art and photos in PowerPoint®; labeled and unlabeled JPEGs of images from the text; and a test bank.




**Instructors also have access to Learning Catalytics.** With Learning Catalytics, you'll hear from every student when it matters most. You can pose a variety of questions in class that help students recall ideas, apply concepts, and develop critical-thinking skills. Your students respond using their own smartphones, tablets, or laptops. You can monitor responses with real-time analytics and find out what your students do—and don't—understand. Then, you can adjust your teaching accordingly and even facilitate peer-to-peer learning, helping students stay motivated and engaged. Write your own questions, pull from a shared library of community-generated questions, or use Pearson's content clusters, which pose 2-5 questions about a single data set or scenario.



# ESSENTIALS *of* GENETICS

Tenth Edition


William S. Klug
The College of New Jersey

Michael R. Cummings
Illinois Institute of Technology

Charlotte A. Spencer
University of Alberta

Michael A. Palladino
Monmouth University

Darrell J. Killian
Colorado College



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# About the Authors

**William S. Klug** is an Emeritus Professor of Biology at The College of New Jersey (formerly Trenton State College) in Ewing, New Jersey, where he served as Chair of the Biology Department for 17 years. He received his B.A. degree in Biology from Wabash College in Crawfordsville, Indiana, and his Ph.D. from Northwestern University in Evanston, Illinois. Prior to coming to The College of New Jersey, he was on the faculty of Wabash College, where he first taught genetics, as well as general biology and electron microscopy. His research interests have involved ultrastructural and molecular genetic studies of development, utilizing oogenesis in *Drosophila* as a model system. He has taught the genetics course as well as the senior capstone seminar course in Human and Molecular Genetics to undergraduate biology majors for over four decades. He was the recipient in 2001 of the first annual teaching award given at The College of New Jersey, granted to the faculty member who "most challenges students to achieve high standards." He also received the 2004 Outstanding Professor Award from Sigma Pi International, and in the same year, he was nominated as the Educator of the Year, an award given by the Research and Development Council of New Jersey. When not revising one of his textbooks, immersed in the literature of genetics, or trying to avoid double bogies, Dr. Klug can sometimes be found paddling in the Gulf of Mexico or in Maine's Penobscot Bay.

**Michael R. Cummings** is a Research Professor in the Department of Biological, Chemical, and Physical Sciences at Illinois Institute of Technology, Chicago, Illinois. For more than 25 years, he was a faculty member in the Department of Biological Sciences and in the Department of Molecular Genetics at the University of Illinois at Chicago. He has also served on the faculties of Northwestern University and Florida State University. He received his B.A. from St. Mary's College in Winona, Minnesota, and his M.S. and Ph.D. from Northwestern University in Evanston, Illinois. In addition to this text, he has written textbooks in human genetics and general biology. His research interests center on the molecular organization and physical mapping of the heterochromatic regions of human acrocentric chromosomes. At the undergraduate level, he teaches courses in molecular genetics, human genetics, and general biology, and has received numerous awards for teaching excellence given by university faculty, student organizations, and graduating seniors. When not teaching or writing, Dr. Cummings can often be found far offshore fishing for the one that got away.

**Charlotte A. Spencer** is a retired Associate Professor from the Department of Oncology at the University of Alberta in Edmonton, Alberta, Canada. She has also served as a faculty member in the Department of Biochemistry at the University of Alberta. She received her B.Sc. in Microbiology from the University of British Columbia and her Ph.D. in Genetics from the University of Alberta, followed by postdoctoral training at the Fred Hutchinson Cancer Research Center in Seattle, Washington. Her research interests involve the regulation of RNA polymerase II transcription in cancer cells, cells infected with DNA viruses, and cells traversing the mitotic phase of the cell cycle. She has taught undergraduate and graduate courses in biochemistry, genetics, molecular biology, and oncology. She has also written booklets in the Prentice Hall Exploring Biology series. When not writing and editing contributions to genetics textbooks, Dr. Spencer works on her hazelnut farm and enjoys the peace and quiet of a remote Island off the west coast of British Columbia.

**Michael A. Palladino** is Vice Provost for Graduate Studies, former Dean of the School of Science, and Professor of Biology at Monmouth University in West Long Branch, New Jersey. He received his B.S. degree in Biology from The College of New Jersey and his Ph.D. in Anatomy and Cell Biology from the University of Virginia. For more than 15 years he directed a laboratory of undergraduate student researchers supported by external funding from the National Institutes of Health, biopharma companies, and other agencies. He and his undergraduates studied molecular mechanisms involved in innate immunity of mammalian male reproductive organs and genes involved in oxygen homeostasis and ischemic injury of the testis. He has taught a wide range of courses including genetics, biotechnology, endocrinology, and cell and molecular biology. He has received several awards for research and teaching, including the 2009 Young Andrologist Award of the American Society of Andrology, the 2005 Distinguished Teacher Award from Monmouth University,

and the 2005 Caring Heart Award from the New Jersey Association for Biomedical Research. He is co-author of the undergraduate textbook *Introduction to Biotechnology*. He was Series Editor for the Benjamin Cummings *Special Topics in Biology* booklet series, and author of the first booklet in the series, *Understanding the Human Genome Project*. When away from the university or authoring textbooks, Dr. Palladino can often be found watching or playing soccer or attempting to catch most any species of fish in freshwater or saltwater.

**Darrell J. Killian** is an Associate Professor in the Department of Molecular Biology at Colorado College in Colorado Springs, Colorado. He received his B.A. degree in Molecular Biology and Biochemistry from Wesleyan University in Middletown, Connecticut, prior to working as a Research Technician in Molecular Genetics at Rockefeller University in New York, New York. He earned his Ph.D. in Developmental Genetics from New York University in New York, New York, and received his postdoctoral training at the University of Colorado–Boulder in the Department of Molecular, Cellular, and Developmental Biology. Prior to joining Colorado College, he was an Assistant Professor of Biology at the College of New Jersey in Ewing, New Jersey. His research focuses on the genetic regulation of animal development, and he has received funding from the National Institutes of Health and the National Science Foundation. Currently, he and his undergraduate research assistants are investigating the molecular genetic regulation of nervous system development using *C. elegans* and *Drosophila* as model systems. He teaches undergraduate courses in genetics, molecular and cellular biology, stem cell biology, and developmental neurobiology. When away from the classroom and research lab, Dr. Killian can often be found on two wheels exploring trails in the Pike and San Isabel National Forests.

## Dedication

We dedicate this edition to our long-time colleague and friend Harry Nickla, who sadly passed away in 2017. With decades of experience teaching Genetics to students at Creighton University, Harry's contribution to our texts included authorship of the Student Handbook and Solutions Manual and the test bank, as well as devising many of the data-based problems found near the end of each chapter. He was also a source of advice during the planning session for each new edition. We always appreciated his professional insights, friendship, and conviviality. We were lucky to have him as part of our team, and we miss him greatly.

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# Preface

*Essentials of Genetics* is written for courses requiring a text that is briefer and less detailed than its more comprehensive companion, *Concepts of Genetics*. While coverage is thorough and modern, *Essentials* is written to be more accessible to biology majors, as well as to students majoring in a number of other disciplines, including agriculture, animal husbandry, chemistry, nursing, engineering, forestry, psychology, and wildlife management. Because *Essentials of Genetics* is shorter than many other texts, it is also more manageable in one-quarter and trimester courses.

## Goals

In this edition of *Essentials of Genetics*, the two most important goals have been to introduce pedagogic innovations that enhance learning and to provide carefully updated, highly accessible coverage of genetic topics of both historical and modern significance. As new tools and findings of genetics research continue to emerge rapidly and grow in importance in the study of all subdisciplines of biology, instructors face tough choices about what content is truly essential as they introduce the discipline to novice students. We have thoughtfully revised each chapter in light of this challenge, by selectively scaling back the detail or scope of coverage in the more traditional chapters in order to provide expanded coverage and broader context for the more modern, cutting-edge topics. Our aim is to continue to provide efficient coverage of the fundamental concepts in transmission and molecular genetics that lay the groundwork for more in-depth coverage of emerging topics of growing importance—in particular, the many aspects of the genomic revolution that is already relevant to our day-to-day lives.

While we have adjusted this edition to keep pace with changing content and teaching practices, we remain dedicated to the core principles that underlie this book. Specifically, we seek to

- Emphasize concepts rather than excessive detail.
- Write clearly and directly to students in order to provide understandable explanations of complex analytical topics.
- Emphasize problem solving, thereby guiding students to think analytically and to apply and extend their knowledge of genetics.
- Provide the most modern and up-to-date coverage of this exciting field.
- Propagate the rich history of genetics that so beautifully elucidates how information is acquired as the discipline develops and grows.
- Create inviting, engaging, and pedagogically useful figures enhanced by meaningful photographs to support student understanding.
- Provide outstanding interactive media support to guide students in understanding important concepts through animations, tutorial exercises, and assessment tools.

The above goals serve as the cornerstone of *Essentials of Genetics*. This pedagogic foundation allows the book to accommodate courses with many different approaches and lecture formats. While the book presents a coherent table of contents that represents one approach to offering a course in genetics, chapters are nevertheless written to be independent of one another, allowing instructors to utilize them in various sequences.

## New to This Edition

In addition to updating information with new findings in all chapters throughout the text, four chapters are new to this edition.

- **Two new chapters expand the coverage of the regulation of gene expression** The topic of genetic regulation was previously covered in a single chapter, but has now been split into two new chapters. The first (Chapter 15) involves regulation in bacteria, while the second (Chapter 16) focuses on eukaryotes. The bacterial coverage represents the pioneering work in this field and then concludes with an introduction to CRISPR-Cas. The eukaryotic coverage focuses on the regulation of gene expression first at the level of transcription, and then post-transcriptionally, where the expanded coverage focuses on mechanisms that regulate RNA. Research into posttranscriptional regulation in the past 15 years has highlighted the importance of topics such as alternative splicing, mRNA stability and decay, and regulatory noncoding RNAs. Collectively, the addition of these two new chapters provides students and instructors with a thorough, up-to-date presentation of these important aspects of genetics.
- **Two new Special Topics in Modern Genetics chapters** Special Topics chapters are focused and flexible, providing abbreviated, cohesive coverage of important topics in genetics. There are seven Special Topics chapters in this edition, two of which are new. Special Topics Chapter 2—*Genetic Testing* explores how genetic testing is becoming prominent in many contexts and how its use raises many questions and ethical concerns. Special Topics Chapter 4—*Advances in Neurogenetics: The Study of Huntington Disease* illustrates the many advances that have been made in the study of Huntington disease, a

monogenic human disorder that has been subjected to analysis using multiple approaches involving molecular genetics. As such, the chapter exemplifies the growing body of information that has accrued regarding the causes, symptoms, and future treatment of this disorder.

- **Expanded coverage of CRISPR-Cas** Since the previous edition was published, techniques for genome editing have vastly improved due to CRISPR-Cas technology. Thus, we have integrated information about CRISPR-Cas in several different locations within the text. The impact of genome editing with CRISPR-Cas is briefly introduced in Chapter 1. Then, in Chapter 15, students learn how CRISPR-Cas was originally discovered as a bacterial system that regulates the gene expression of bacterial viruses (bacteriophages), providing an immunity against infection. The mechanism and applications to biotechnology are subsequently covered in Chapter 17. Finally, the use of CRISPR-Cas genome editing for gene therapy and the production of genetically modified foods is discussed in Special Topics Chapter 3—*Gene Therapy* and Special Topics Chapter 6—*Genetically Modified Foods*.
- **Increased emphasis on ethics** We recognize in this edition the importance of providing an increased emphasis on ethical considerations that genetics is bringing into everyday life. Regarding this point, we have converted the essay feature previously called *Genetics, Technology, and Society* to one with added emphasis on ethics and renamed it *Genetics, Ethics, and Society*. Approximately half the chapters have new or revised essays. In each case, a synopsis is presented of an ethical issue related to a current finding in genetics that impacts directly on society today. The feature then includes a section called *Your Turn*, which directs students to related resources of short readings and Web sites to support deeper investigation and discussion of the main topic of each essay. In addition, another feature called *Case Study*, which appears near the end of all chapters, has been recast with an increased focus on ethics. Both of these features increase the opportunities for active and cooperative learning as well.

## New and Updated Coverage

Below is a chapter-by-chapter list of the most significant new and updated coverage present in this edition.

**Ch. 1: Introduction to Genetics** • New chapter introduction vignette emphasizing the significance of the discovery of CRISPR-Cas9, a powerful genome-editing system.

**Ch. 2: Mitosis and Meiosis** • New information on microtubules and microfilaments • Revised Figure 2.9 on Meiotic Prophase I • New Exploring Genomics (EG) entry: PubMed: Exploring and Retrieving Biomedical Literature • New Case Study (CS): Timing Is Everything

**Ch. 3: Mendelian Genetics** • New Table 3.2 on Dominant and Recessive Human Traits • New Now Solve This (NST) 3.5 on pedigree analysis

**Ch. 4: Modification of Mendelian Ratios** • New information in the "Mitochondria, Human Health, and Aging" section • New information on the *MERFF* mutation • New Genetics, Ethics, and Society (GES) entry: Mitochondrial Replacement and Three-Parent Babies

**Ch. 5: Sex Determination and Sex Chromosomes** • New information on Klinefelter syndrome • New GES: A Question of Gender: Sex Selection in Humans

**Ch. 6: Chromosome Mutations: Variation in Number and Arrangement** • Updated information on copy number variation • New GES: Down Syndrome and Prenatal Testing—The New Eugenics? • A new end of chapter problem involving mapping analysis in *Drosophila*.

**Ch. 8: Genetic Analysis and Mapping in Bacteria and Bacteriophages** • New GES: Multidrug-Resistant Bacteria: Fighting with Phage

**Ch. 10: DNA Replication and Recombination** • New details about DNA unwinding during replication • New section entitled "Telomeres in Disease, Aging, and Cancer" • Two new end of chapter problems involving telomeres and telomerase

**Ch. 12: The Genetic Code and Transcription** • Revised coverage of transcription and RNA processing in eukaryotes • New information on termination of transcription in bacteria • New section entitled "Why Do Introns Exist?" • New GES: Treating Duchene Muscular Dystrophy

**Ch. 13: Translation and Proteins** • Revised coverage of ribosome and tRNA structure • Revised coverage of translation in bacteria • Expanded coverage of translation in eukaryotes including new information on closed-loop translation, illustrated in a new figure (Fig. 13.10)

**Ch. 14: Gene Mutation, DNA Repair, and Transposition** • Reorganization of the section on mutation classification, including new table summaries • New and expanded coverage of human germ-line and somatic mutation rates • New, reorganized, and revised coverage of transposable elements, focusing on the major characteristics of retrotransposons and DNA transposons, as well as on how transposons create mutations • Three new figures and one new table

**Ch. 15: Regulation of Gene Expression in Bacteria** • New chapter that focuses specifically on gene regulation in bacteria • Expanded coverage on the roles of RNA in bacterial gene regulation • New coverage of CRISPR-Cas-mediated regulation of invading viral DNA sequences

**Ch. 16: Regulation of Gene Expression in Eukaryotes** • New chapter that focuses specifically on gene regulation in eukaryotes • Revised and expanded coverage of alternative splicing, including a new figure, and its relevance to human disease • Expanded coverage on RNA stability and RNA decay including a new figure (Fig. 16.11) • Updated information on noncoding RNAs that regulate gene expression • Enriched coverage of ubiquitin-mediated protein degradation, including a new figure (Fig. 16.14)

**Ch. 17: Recombinant DNA Technology** • Updated content on modern sequencing technologies including a new figure (Fig. 17.12) on third-generation sequencing (single-strand DNA sequencing) • New section, "Genome Editing with CRISPR-Cas," describes this system as a genome editing tool and includes a new figure (Fig. 17.16)

**Ch. 18: Genomics, Bioinformatics, and Proteomics** • A new section, "DNA Sequence Analysis Relies on Bioinformatics Applications and Genome Databases," integrating applications of bioinformatics, genome databases, and functional genomics for analyzing and understanding gene function by sequence analysis • Reorganized and revised content on the Human Genome Project, including a new end of chapter problem citing the PANTHER database as part of the Human Genome Project • Updated content on personal genome projects • New content on diploid genomes, mosaicism, and reference genomes and the pangenome to emphasize human genetic variations, including a new figure (Fig. 18.8) • Incorporated coverage of the Human Microbiome Project into a new section, "Metagenomics," and expanded content to include a new Figure (Fig. 18.9) displaying microbiome results of patients with different human disease conditions • A new section titled "RNA Sequencing" • A new section, "Synthetic Genomes and the Emergence of Synthetic Biology," including a new figure (Fig. 18.13) • New GES: Privacy and Anonymity in the Era of Genomic Big Data • Several new and revised end of chapter problems

**Ch. 19: The Genetics of Cancer** • Extended coverage of environmental agents that contribute to human cancers, including more information about both natural and human-made carcinogens • New subsection entitled "Tobacco Smoke and Cancer" explaining how a well-studied carcinogen induces a wide range of genetic effects that may lead to mutations and cancer

**Ch. 20: Quantitative Genetics and Multifactorial Traits** • Revised coverage of Expression QTLs (eQTLs) in the regulation of gene expression • New GES: Rice, Genes, and the Second Green Revolution • New CS: A Chance Discovery

**Ch. 21: Population and Evolutionary Genetics** • New figure (Fig. 21.7) on the relationship between genotype and allele frequency • Important modifications to Figures 21.8 and 21.9 illustrating allele selection • New figure (Fig. 21.13) on the impact of selection types on the phenotypic mean and variance • Revised text and figure (Fig. 21.24) on molecular clocks • Updated information about the origins of the human genome • New figure (Fig. 21.26) on hominin contributions to the genome of modern humans

**Special Topic 1: Epigenetics** • Revised, updated, and expanded coverage of epigenetic topics, including histone modifications, noncoding RNAs, assisted reproductive technologies, and the heritability of stress-induced behaviors • Updated coverage of epigenetics and cancer • New section on "Epigenetics and Monoallelic Gene Expression" • New figures on DNA methylation, chemical modification of histones, genomic imprinting, random autosomal monoallelic gene expression, imprinting in germ cells, and maternal behavior and stress responses in rat pups

**Special Topic 2: Genetic Testing** • New Special Topics chapter emphasizing modern approaches to genetic testing including prenatal genetic testing, noninvasive procedures for testing fetal DNA, testing using allele-specific oligonucleotides, microarrays, and genetic analysis by DNA and RNA sequencing • Includes coverage of the recommended uniform screening panel, undiagnosed diseases network, and genetic analysis for pathogen identification during infectious disease outbreaks • Section on genome-wide association studies incorporates approaches for genomic analysis of disease conditions at the population level • A range of ethical, social, and legal considerations are discussed

**Special Topic 3: Gene Therapy** • Updated information on gene therapy trials that are under way • An expanded section "Genome Editing" highlighting the application of the CRISPR-Cas system and describing some of the most promising trials under way in humans and animals • New ethical considerations of CRISPR-Cas and germ-line and embryo editing • New section, "RNA-Based Therapeutics," that includes coverage of antisense RNA; RNA interference; and updated trials for RNA-based therapeutics, including Spinraza as an antisense RNA modifying splicing for the treatment of spinal muscular atrophy • Updated content on roles of stem cells in gene therapy • New content on combining genome editing with immunotherapy

**Special Topic 4: Advances in Neurogenetics: The Study of Huntington Disease** • New Special Topics chapter that surveys the study of Huntington Disease (HD) from 1970 to the present • Coverage includes the genetic basis and progression of HD, the mapping and isolation of the gene responsible for the disorder, and information on the mutant gene product • Discussions

include information on the molecular and cellular alterations caused by the mutant protein, the use of transgenic animal models of HD, and the molecular and cellular approaches to therapy

**Special Topic 5: DNA Forensics** • New section entitled "DNA Phenotyping," describing a controversial forensic method, including descriptions of how law-enforcement agencies currently use this new technology

**Special Topic 6: Genetically Modified Foods** • New section, entitled "Gene Editing and GM Foods," describing how scientists are using the new techniques of gene editing (including ZFN, TALENS, and CRISPR-Cas) to create GM food plants and animals, and how these methods are changing the way in which GM foods are being regulated • A new box, "The New CRISPR Mushroom," describing the development and regulatory approval of the first CRISPR-created GM food to be cleared for human consumption

**Special Topic 7: Genomics and Precision Medicine** • New section, entitled "Precision Oncology," describing two targeted cancer immunotherapies: adoptive cell transfer and engineered T-cell therapy • Updated section, "Pharmacogenomics," including a discussion of new trends in preemptive gene screening for pharmacogenomic variants • New box, "Preemptive Pharmacogenomic Screening: The pGEN-4Kids Program," discussing preemptive gene screening that integrates DNA analysis into patient electronic health records

## Emphasis on Concepts

*Essentials of Genetics* focuses on conceptual issues in genetics and uses problem solving to develop a deep understanding of them. We consider a concept to be a cognitive unit of meaning that encompasses a related set of scientifically derived findings and ideas. As such, a concept provides broad mental imagery, which we believe is a very effective way to teach science, in this case, genetics. Details that might be memorized, but soon forgotten, are instead subsumed within a conceptual framework that is more easily retained. Such a framework may be expanded in content as new information is acquired and may interface with other concepts, providing a useful mechanism to integrate and better understand related processes and ideas. An extensive set of concepts may be devised and conveyed to eventually encompass and represent an entire discipline—and this is our goal in this genetics textbook.

To aid students in identifying the conceptual aspects of a major topic, each chapter begins with a section called ***Chapter Concepts***, which identifies the most important ideas about to be presented. Then, throughout each chapter, ***Essential Points*** are provided that establish the key issues that have been discussed. And in the ***How Do We Know?*** question that starts each chapter's problem set, students are asked to identify the experimental basis of important genetic findings presented in the chapter. As an extension of the learning approach in biology called "Science as a Way of Knowing," this feature enhances students' understanding of many key concepts covered in each chapter. Finally, the second entry in each chapter's problem set is labeled as a **Concepts Question**, which asks the student to review and comment on specific aspects of the Chapter Concepts found at the beginning of each chapter.

Collectively, these features help to ensure that students easily become aware of and understand the major conceptual issues as they confront the extensive vocabulary and the many important details of genetics. Carefully designed figures also support this approach throughout the book.

## Emphasis on Problem Solving

Helping students develop effective problem-solving skills is one of the greatest challenges of a genetics course. The feature called ***Now Solve This***, integrated throughout each chapter, asks students to link conceptual understanding in a more immediate way to problem solving. Each entry provides a problem for the student to solve that is closely related to the current text discussion. A pedagogic hint is then provided to aid in arriving at the correct solution. All chapters conclude with ***Insights and Solutions***, a popular and highly useful section that provides sample problems and solutions that demonstrate approaches useful in genetic analysis. These help students develop analytical thinking and experimental reasoning skills. Digesting the information in *Insights and Solutions* primes students as they move on to the lengthier ***Problems and Discussion Questions*** section that concludes each chapter. Here, we present questions that review topics in the chapter and problems that ask students to think in an analytical and applied way about genetic concepts. The addition of Mastering Genetics extends our focus on problem solving online, and it allows students to get help and guidance while practicing how to solve problems.

## Continuing Features

The Tenth Edition has maintained several popular features that are pedagogically useful for students as they study genetics. Together, these create a platform that seeks to challenge students to think more deeply about, and thus understand more comprehensively, the information he or she has just finished studying.

- **Exploring Genomics** Appearing in numerous chapters, this feature illustrates the pervasiveness of genomics in the current study of genetics. Each entry asks students to access one or more genomics-related Web sites that collectively are among the best publicly available resources and databases. Students work through interactive exercises that ensure their familiarity with the type of

genomic or proteomic information available. Exercises instruct students on how to explore specific topics and how to access significant data. Questions guide student exploration and challenge them to further explore the sites on their own. Importantly, *Exploring Genomics* integrates genomics information throughout the text, as this emerging field is linked to chapter content. This feature provides the basis for individual or group assignments in or out of the classroom.

- **Case Studies** This feature, with an increased emphasis on ethical considerations, appears at the end of each chapter and provides the basis for enhanced classroom interactions. In each entry, a short scenario related to one of the chapter topics is presented, followed by several questions. These ask students to apply their newly acquired knowledge to real-life issues that may be explored in small-group discussions or serve as individual assignments.

## For the Instructor

### Mastering Genetics
### http://www.masteringgenetics.com

Mastering Genetics engages and motivates students to learn and allows you to easily assign automatically graded activities. Tutorials provide students with personalized coaching and feedback. Using the gradebook, you can quickly monitor and display student results. Mastering Genetics easily captures data to demonstrate assessment outcomes. Resources include:

- In-depth tutorials that coach students with hints and feedback specific to their misconceptions.
- A new, robust library of **Practice Problems** offers more opportunities to assign challenging problems for student homework or practice. These questions include targeted wrong answer feedback to help students learn from their mistakes. They appear only in Mastering Genetics, and solutions are not included in the Student Solutions Manual.
- An item library of assignable questions including end of chapter problems, test bank questions, and reading quizzes. You can use publisher-created prebuilt assignments to get started quickly. Each question can be easily edited to match the precise language you use.
- A gradebook that provides you with quick results and easy-to-interpret insights into student performance.

### Instructor Resources

The Instructor Resources, available for download in the Instructor area of Mastering Genetics, offer adopters of the text convenient access to a comprehensive and innovative set of lecture presentation and teaching tools. Developed to meet the needs of veteran and newer instructors alike, these resources include:

- The JPEG files of all text line drawings with labels individually enhanced for optimal projection results (as well as unlabeled versions) and all text tables.
- Most of the text photos, including all photos with pedagogical significance, as JPEG files.
- The JPEG files of line drawings, photos, and tables preloaded into comprehensive PowerPoint presentations for each chapter.
- A second set of PowerPoint presentations consisting of a thorough lecture outline for each chapter augmented by key text illustrations.
- An impressive series of concise instructor animations adding depth and visual clarity to the most important topics and dynamic processes described in the text.
- The instructor animations preloaded into PowerPoint presentation files for each chapter.
- PowerPoint presentations containing a comprehensive set of in-class Classroom Response System (CRS) questions for each chapter.
- In Word files, a complete set of the assessment materials and study questions and answers from the test bank, the text's in-chapter text questions, and the student media practice questions.

### TestGen EQ Computerized Testing Software

***(ISBN: 0135272823 / 9780135272824)***

Test questions are available as part of the TestGen EQ Testing Software, a text-specific testing program that is networkable for administering tests. It also allows instructors to view and edit questions, export the questions as tests, and print them out in a variety of formats.

## For the Student

### Student Handbook and Solutions Manual

Authored by Michelle Gaudette, Tufts University, and Harry Nickla ***(ISBN: 0132300728 / 9780135300428)***

This valuable handbook provides a detailed step-by-step solution or lengthy discussion for every problem in the text. The handbook also features additional study aids, including extra study problems, chapter outlines, vocabulary exercises, and an overview of how to study genetics.

### Mastering Genetics
### http://www.masteringgenetics.com

Used by over a million science students, the Mastering platform is the most effective and widely used online tutorial, homework, and assessment system for the sciences. Perform better on exams with Mastering Genetics. As an instructor-assigned homework system, Mastering Genetics is designed to provide students with a variety of assessments to help them understand key topics and concepts and to build problem-solving skills. Mastering Genetics tutorials guide

students through the toughest topics in genetics with self-paced tutorials that provide individualized coaching with hints and feedback specific to a student's individual misconceptions. Students can also explore Mastering Genetics' Study Area, which includes animations, the eText, *Exploring Genomics* exercises, and other study aids. The interactive eText 2.0 allows students to access their text on mobile devices, highlight text, add study notes, review instructor's notes, and search throughout the text, 24/7.

## Acknowledgments

### Contributors

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# 1

# Introduction to Genetics

Newer model organisms in genetics include the roundworm, *Caenorhabditis elegans*; the zebrafish, *Danio rerio*; and the mustard plant, *Arabidopsis thaliana*.

## CHAPTER CONCEPTS

- Genetics in the twenty-first century is built on a rich tradition of discovery and experimentation stretching from the ancient world through the nineteenth century to the present day.
- Transmission genetics is the general process by which traits controlled by genes are transmitted through gametes from generation to generation.
- Mutant strains can be used in genetic crosses to map the location and distance between genes on chromosomes.
- The Watson–Crick model of DNA structure explains how genetic information is stored and expressed. This discovery is the foundation of molecular genetics.
- Recombinant DNA technology revolutionized genetics, was the foundation for the Human Genome Project, and has generated new fields that combine genetics with information technology.
- Biotechnology provides genetically modified organisms and their products that are used across a wide range of fields including agriculture, medicine, and industry.
- Model organisms used in genetics research are now utilized in combination with recombinant DNA technology and genomics to study human diseases.
- Genetic technology is developing faster than the policies, laws, and conventions that govern its use.

One of the small pleasures of writing a genetics textbook is being able to occasionally introduce in the very first paragraph of the initial chapter a truly significant breakthrough in the discipline that has started to have a major, diverse impact on human lives. In this edition, we are fortunate to be able to discuss the discovery of **CRISPR-Cas,** a molecular mechanism found in bacteria that has the potential to revolutionize our ability to rewrite the DNA sequence of genes from any organism. As such, it represents the ultimate tool in genetic technology, whereby the genome of organisms, including humans, may be precisely edited. Such gene modification represents the ultimate application of the many advances in biotechnology made in the last 35 years, including the sequencing of the human genome.

Although gene editing was first made possible with other methods, the CRISPR-Cas system is now the method of choice for gene modification because it is more accurate, more efficient, more versatile, and easier to use. CRISPR-Cas was initially discovered as a "seek and destroy" mechanism that bacteria use to fight off viral infection. CRISPR (clustered regularly interspersed short palindromic repeats) refers to part of the bacterial genome that produces RNA molecules, and Cas (CRISPR-associated) refers to a nuclease, or DNA-cutting enzyme. The CRISPR RNA binds to a matching sequence in the viral DNA (seek) and recruits the Cas nuclease to cut it (destroy). Researchers have harnessed this technology by synthesizing CRISPR RNAs that direct Cas nucleases to any chosen DNA sequence. In laboratory experiments, CRISPR-Cas has already been used to repair mutations in cells derived from individuals with genetic disorders, such as cystic fibrosis, Huntington disease,

sickle-cell disease, and muscular dystrophy. In the United States a clinical trial using CRISPR-Cas for genome editing in cancer therapy is recruiting participants, while proposals for treating a genetic form of blindness and genetic blood disorders are in preparation. In China, at least 86 patients have already started receiving treatments in CRISPR-Cas clinical trials for cancer.

The application of this remarkable system goes far beyond developing treatments for human genetic disorders. In organisms of all kinds, wherever genetic modification may benefit human existence and our planet, the use of CRISPR-Cas will find many targets. For example, one research group edited a gene in mosquitoes, which prevents them from carrying the parasite that causes malaria in humans. Other researchers have edited the genome of algae to double their output for biofuel production. The method has also been used to create disease-resistant strains of wheat and rice.

The power of this system, like any major technological advance, has already raised ethical concerns. For example, genetic modification of human embryos would change the genetic information carried by future generations. These modifications may have unintended and significant negative consequences for our species. In 2017, an international panel of experts discussed the science, ethics, and governance of human genome editing. The panel recommended caution, but not a ban, stating that human embryo modification should "only be permitted for compelling reasons and under strict oversight."

CRISPR-Cas may turn out to be one of the most exciting genetic advances in decades. We will return later in the text to discuss its discovery in bacteria (Chapter 15), its development as a gene-editing tool (Chapter 17), its potential for gene therapy (Special Topic Chapter 3 Gene Therapy), and its uses in genetically edited foods (Special Topic Chapter 6 Genetically Modified Foods).

For now, we hope that this short introduction has stimulated your curiosity, interest, and enthusiasm for the study of genetics. The remainder of this chapter provides an overview of many important concepts of genetics and a survey of the major turning points in the history of the discipline.

## 1.1 Genetics Has an Interesting Early History

While as early as 350 B.C., Aristotle proposed that active "humors" served as bearers of hereditary traits, it was not until the 1600s that initial strides were made to understand the biological basis of life. In that century, the physician and anatomist William Harvey proposed the theory of **epigenesis,** which states that an organism develops from the fertilized egg by a succession of developmental events that eventually transform the egg into an adult. The theory of epigenesis directly conflicted with the theory of **preformationism,** which stated that the fertilized egg contains a complete miniature adult, called a **homunculus** (**Figure 1.1**). Around 1830, Matthias Schleiden and Theodor Schwann proposed the **cell theory,** stating that all organisms are composed of basic structural units called cells, which are derived from preexisting cells. The idea of **spontaneous generation,** the creation of living organisms from nonliving components, was disproved by Louis Pasteur later in the century, and living organisms were then considered to be derived from preexisting organisms and to consist of cells.

In the mid-1800s the work of Charles Darwin and Gregor Mendel set the stage for the rapid development of genetics in the twentieth and twenty-first centuries.

### Darwin and Mendel

In 1859, Darwin published *On the Origin of Species*, describing his ideas about evolution. Darwin's geological, geographical, and biological observations convinced him that existing species arose by descent with modification from ancestral species. Greatly influenced by his voyage on the HMS *Beagle* (1831–1836), Darwin's thinking led him to formulate the theory of **natural selection,** which presented an explanation of the mechanism of evolutionary change. Formulated and proposed independently by Alfred Russel Wallace, natural selection is based on the observation

**FIGURE 1.1** Depiction of the *homunculus*, a sperm containing a miniature adult, perfect in proportion and fully formed.

that populations tend to produce more offspring than the environment can support, leading to a struggle for survival among individuals. Those individuals with heritable traits that allow them to adapt to their environment are better able to survive and reproduce than those with less adaptive traits. Over time, advantageous variations, even very slight ones, will accumulate. If a population carrying these inherited variations becomes reproductively isolated, a new species may result.

Darwin, however, lacked an understanding of the genetic basis of variation and inheritance, a gap that left his theory open to reasonable criticism well into the twentieth century. Shortly after Darwin published his book, Gregor Johann Mendel published a paper in 1866 showing how traits were passed from generation to generation in pea plants and offered a general model of how traits are inherited. His research was little known until it was partially duplicated and brought to light by Carl Correns, Hugo de Vries, and Erich Tschermak around 1900.

By the early part of the twentieth century, it became clear that heredity and development were dependent on genetic information residing in genes contained in chromosomes, which were then contributed to each individual by gametes—the so-called *chromosome theory of inheritance*. The gap in Darwin's theory was closed, and Mendel's research now serves as the foundation of genetics.

## 1.2 Genetics Progressed from Mendel to DNA in Less Than a Century

Because genetic processes are fundamental to life itself, the science of genetics unifies biology and serves as its core. The starting point for this branch of science was a monastery garden in central Europe in the late 1850s.

### Mendel's Work on Transmission of Traits

Gregor Mendel, an Augustinian monk, conducted a decade-long series of experiments using pea plants. He applied quantitative data analysis to his results and showed that traits are passed from parents to offspring in predictable ways. He further concluded that each trait in pea plants is controlled by a pair of factors (which we now call genes) and that members of a gene pair separate from each other during gamete formation (the formation of egg cells and sperm). Mendel's findings explained the transmission of traits in pea plants and all other higher organisms. His work forms the foundation for **genetics,** the branch of biology concerned with the study of heredity and variation. Mendelian genetics will be discussed later in the text (see Chapters 3 and 4).

### The Chromosome Theory of Inheritance: Uniting Mendel and Meiosis

Mendel did his experiments before the structure and role of chromosomes were known. About 20 years after his work was published, advances in microscopy allowed researchers to identify chromosomes and establish that, in most eukaryotes, members of each species have a characteristic number of chromosomes called the **diploid number (2*n*)** in most of their cells. For example, humans have a diploid number of 46 (**Figure 1.2**). Chromosomes in diploid cells exist in pairs, called **homologous chromosomes.**

Researchers in the last decades of the nineteenth century also described chromosome behavior during two forms of cell division, **mitosis** and **meiosis.** In mitosis, chromosomes are copied and distributed so that each daughter cell receives a diploid set of chromosomes identical to those in the parental cell. Meiosis is associated with gamete formation. Cells produced by meiosis receive only one chromosome from each chromosome pair, and the resulting number of chromosomes is called the **haploid number (*n*).** This reduction in chromosome number is essential if the offspring arising from the fusion of egg and sperm are to maintain the constant number of chromosomes characteristic of their parents and other members of their species.

Early in the twentieth century, Walter Sutton and Theodor Boveri independently noted that the behavior of chromosomes during meiosis is identical to the behavior of genes

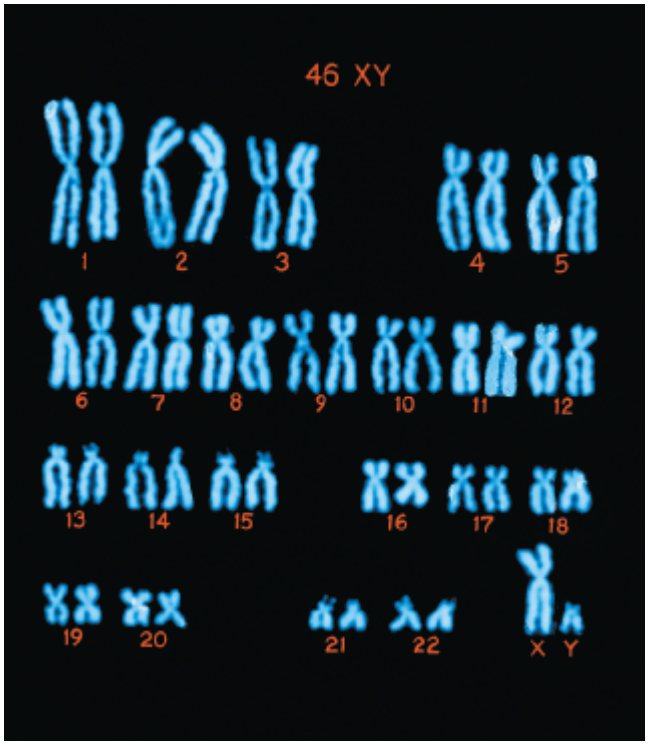



**FIGURE 1.2** A colorized image of a replicated set of human male chromosomes. Arranged in this way, the set is called a karyotype.

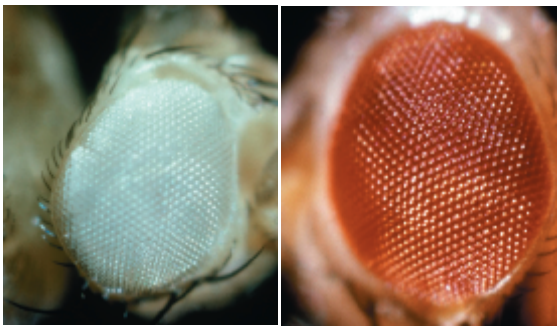


**FIGURE 1.3** The white-eyed mutation in *D. melanogaster* (top) and the normal red eye color (bottom).

during gamete formation described by Mendel. For example, genes and chromosomes exist in pairs, and members of a gene pair and members of a chromosome pair separate from each other during gamete formation. Based on these and other parallels, Sutton and Boveri each proposed that genes are carried on chromosomes. They independently formulated the **chromosomal theory of inheritance,** which states that inherited traits are controlled by genes residing on chromosomes faithfully transmitted through gametes, maintaining genetic continuity from generation to generation.

**ESSENTIAL POINT**

The chromosome theory of inheritance explains how genetic information is transmitted from generation to generation. ■

### Genetic Variation

About the same time that the chromosome theory of inheritance was proposed, scientists began studying the inheritance of traits in the fruit fly, *Drosophila melanogaster*. Early in this work, a white-eyed fly (**Figure 1.3**) was discovered among normal (wild-type) red-eyed flies. This variation was produced by a **mutation** in one of the genes controlling eye color. Mutations are defined as any heritable change in the DNA sequence and are the source of all genetic variation.

The white-eye variant discovered in *Drosophila* is an **allele** of a gene controlling eye color. Alleles are defined as alternative forms of a gene. Different alleles may produce differences in the observable features, or **phenotype,** of an organism. The set of alleles for a given trait carried by an organism is called the **genotype.** Using mutant genes as markers, geneticists can map the location of genes on chromosomes (Figure 1.5).

### The Search for the Chemical Nature of Genes: DNA or Protein?

Work on white-eyed *Drosophila* showed that the mutant trait could be traced to a single chromosome, confirming the idea that genes are carried on chromosomes. Once this relationship was established, investigators turned their attention to identifying which chemical component of chromosomes carries genetic information. By the 1920s, scientists knew that proteins and DNA were the major chemical components of chromosomes. There are a large number of different proteins, present in both the nucleus and cytoplasm, and many researchers thought proteins carried genetic information.

In 1944, Oswald Avery, Colin MacLeod, and Maclyn McCarty, researchers at the Rockefeller Institute in New York, published experiments showing that DNA was the carrier of genetic information in bacteria. This evidence, though clear-cut, failed to convince many influential scientists. Additional evidence for the role of DNA as a carrier of genetic information came from Alfred Hershey and Martha Chase who worked with viruses. This evidence that DNA carries genetic information, along with other research over the next few years, provided solid proof that DNA, not protein, is the genetic material, setting the stage for work to establish the structure of DNA.

## 1.3 Discovery of the Double Helix Launched the Era of Molecular Genetics

Once it was accepted that DNA carries genetic information, efforts were focused on deciphering the structure of the DNA molecule and the mechanisms by which information stored in it produce a phenotype.

### The Structure of DNA and RNA

One of the great discoveries of the twentieth century was made in 1953 by James Watson and Francis Crick, who described the structure of DNA. DNA is a long, ladder-like macromolecule that twists to form a double helix (**Figure 1.4**). Each linear strand of the helix is made up of subunits called **nucleotides.** In DNA, there are four different nucleotides, each of which contains a nitrogenous base, abbreviated A (adenine), G (guanine), T (thymine),

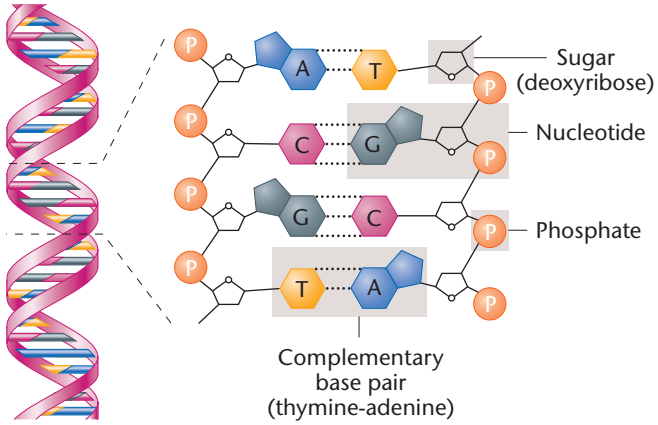



**FIGURE 1.4** The structure of DNA showing the arrangement of the double helix (on the left) and the chemical components making up each strand (on the right). The dotted lines on the right represent weak chemical bonds, called hydrogen bonds, which hold together the two strands of the DNA helix.

or C (cytosine). These four bases, in various sequence combinations, ultimately encode genetic information. The two strands of DNA are exact complements of one another, so that the rungs of the ladder in the double helix always consist of A=T and G=C base pairs. Along with Maurice Wilkins, Watson and Crick were awarded a Nobel Prize in 1962 for their work on the structure of DNA. We will discuss the structure of DNA later in the text (see Chapter 9).

Another nucleic acid, RNA, is chemically similar to DNA but contains a different sugar (ribose rather than deoxyribose) in its nucleotides and contains the nitrogenous base uracil in place of thymine. RNA, however, is generally a single-stranded molecule.

## Gene Expression: From DNA to Phenotype

The genetic information encoded in the order of nucleotides in DNA is expressed in a series of steps that results in the formation of a functional gene product. In the majority of cases, this product is a protein. In eukaryotic cells, the process leading to protein production begins in the nucleus with **transcription,** in which the nucleotide sequence in one strand of DNA is used to construct a complementary RNA sequence (top part of **Figure 1.5**). Once an RNA molecule is produced, it moves to the cytoplasm, where the RNA—called **messenger RNA,** or **mRNA** for short—binds to a **ribosome.** The synthesis of proteins under the direction of mRNA is called **translation** (center part of Figure 1.5). The information encoded in mRNA (called the **genetic code**) consists of a linear series of nucleotide triplets. Each triplet, called a **codon,** is complementary to the information stored in DNA and specifies the insertion of a specific amino acid into a protein. Proteins (lower part of Figure 1.5) are polymers made up of amino acid monomers. There are 20 different amino acids commonly found in proteins.

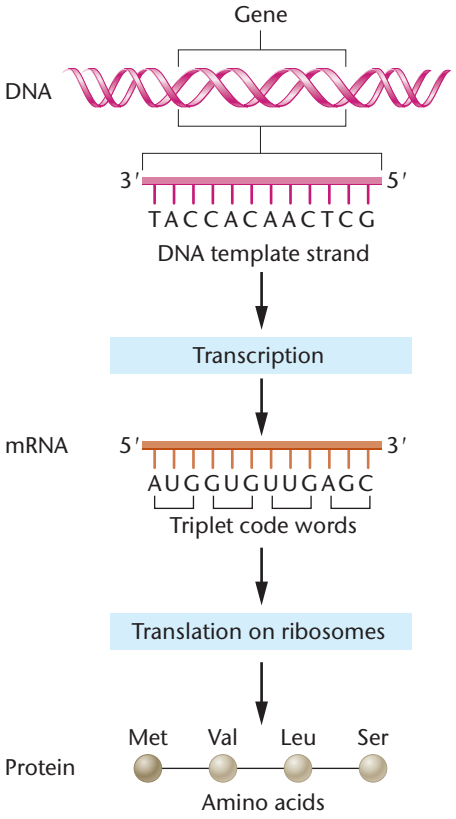



**FIGURE 1.5** Gene expression consists of transcription of DNA into mRNA (top) and the translation (center) of mRNA (with the help of a ribosome) into a protein (bottom).

Protein assembly is accomplished with the aid of adapter molecules called **transfer RNA (tRNA).** Within the ribosome, tRNAs recognize the information encoded in the mRNA codons and carry the proper amino acids for construction of the protein during translation.

We now know that gene expression can be more complex than outlined here. Some of these complexities will be discussed later in the text (see Chapters 15 and 16).

## Proteins and Biological Function

In most cases, proteins are the end products of gene expression. The diversity of proteins and the biological functions they perform—the diversity of life itself—arises from the fact that proteins are made from combinations of 20 different amino acids. Consider that a protein chain containing 100 amino acids can have at each position any one of 20 amino acids; the number of possible different 100-amino-acid proteins, each with a unique sequence, is therefore equal to

$$20^{100}$$

Obviously, proteins are molecules with the potential for enormous structural diversity and serve as a mainstay of biological systems.

**Enzymes** form the largest category of proteins. These molecules serve as biological catalysts, lowering the energy

of activation in reactions and allowing cellular metabolism to proceed at body temperature.

Proteins other than enzymes are critical components of cells and organisms. These include hemoglobin, the oxygen-binding molecule in red blood cells; insulin, a pancreatic hormone; collagen, a connective tissue molecule; and actin and myosin, the contractile muscle proteins. A protein's shape and chemical behavior are determined by its linear sequence of amino acids, which in turn is dictated by the stored information in the DNA of a gene that is transferred to RNA, which then directs the protein's synthesis.

## Linking Genotype to Phenotype: Sickle-Cell Anemia

Once a protein is made, its biochemical or structural properties play a role in producing a phenotype. When mutation alters a gene, it may modify or even eliminate the encoded protein's usual function and cause an altered phenotype. To trace this chain of events, we will examine sickle-cell anemia, a human genetic disorder.

Sickle-cell anemia is caused by a mutant form of hemoglobin, the protein that transports oxygen from the lungs to cells in the body. Hemoglobin is a composite molecule made up of two different proteins, $\alpha$-globin and $\beta$-globin, each encoded by a different gene. In sickle-cell anemia, a mutation in the gene encoding $\beta$-globin causes an amino acid substitution in 1 of the 146 amino acids in the protein. **Figure 1.6** shows the DNA sequence, the corresponding mRNA codons, and the amino acids occupying positions 4–7 for the normal and mutant forms of $\beta$-globin. Notice that the mutation in sickle-cell anemia consists of a change in one DNA nucleotide, which leads to a change in codon 6 in mRNA from GAG to GUG, which in turn changes amino acid number 6 in $\beta$-globin from glutamic acid to valine. The other 145 amino acids in the protein are not changed by this mutation.

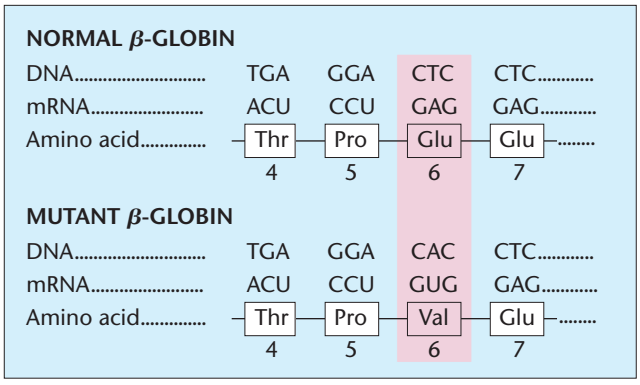



**FIGURE 1.6** A single-nucleotide change in the DNA encoding $\beta$-globin (CTC → CAC) leads to an altered mRNA codon (GAG → GUG) and the insertion of a different amino acid (Glu → Val), producing the altered version of the $\beta$-globin protein that is responsible for sickle-cell anemia.

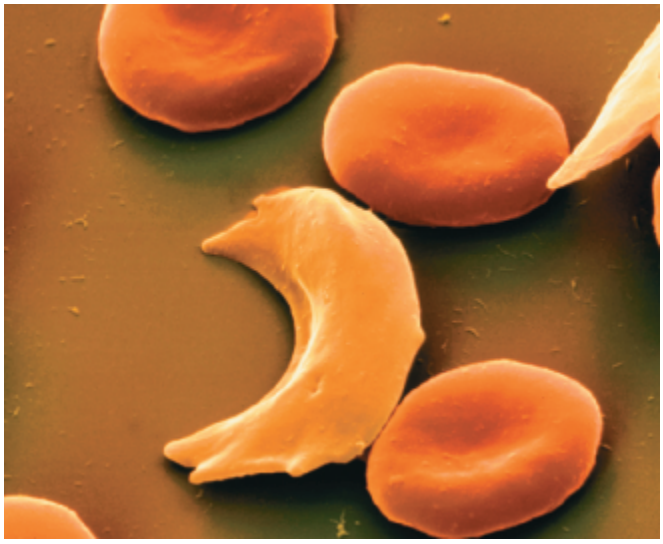


**FIGURE 1.7** Normal red blood cells (round) and sickled red blood cells. The sickled cells block capillaries and small blood vessels.

**ESSENTIAL POINT**

The central dogma of molecular biology -- that DNA is a template for making RNA, which in turn directs the synthesis of proteins -- explains how genes control phenotype. ■

Individuals with two mutant copies of the $\beta$-globin gene have sickle-cell anemia. Their mutant $\beta$-globin proteins cause hemoglobin molecules in red blood cells to polymerize when the blood's oxygen concentration is low, forming long chains of hemoglobin that distort the shape of red blood cells (**Figure 1.7**). Deformed cells are fragile and break easily, reducing the number of circulating red blood cells (anemia is an insufficiency of red blood cells). Sickle-shaped cells block blood flow in capillaries and small blood vessels, causing severe pain and damage to the heart, brain, muscles, and kidneys. All the symptoms of this disorder are caused by a change in a single nucleotide in a gene that changes one amino acid out of 146 in the $\beta$-globin molecule, demonstrating the close relationship between genotype and phenotype.

## 1.4 Development of Recombinant DNA Technology Began the Era of DNA Cloning

The era of recombinant DNA began in the early 1970s, when researchers discovered that **restriction enzymes,** used by bacteria to cut and inactivate the DNA of invading viruses, could be used to cut any organism's DNA at

specific nucleotide sequences, producing a reproducible set of fragments.

Soon after, researchers discovered ways to insert the DNA fragments produced by the action of restriction enzymes into carrier DNA molecules called **vectors** to form recombinant DNA molecules. When transferred into bacterial cells, thousands of copies, or **clones,** of the combined vector and DNA fragments are produced during bacterial reproduction. Large amounts of cloned DNA fragments can be isolated from these bacterial host cells. These DNA fragments can be used to isolate genes, to study their organization and expression, and to study their nucleotide sequence and evolution.

Collections of clones that represent an organism's **genome,** defined as the complete haploid DNA content of a specific organism, are called genomic libraries. Genomic libraries are now available for hundreds of species.

**Recombinant DNA technology** has not only accelerated the pace of research but also given rise to the biotechnology industry, which has grown to become a major contributor to the U.S. economy.

**FIGURE 1.8** Dolly, a Finn Dorset sheep cloned from the genetic material of an adult mammary cell, shown next to her first-born lamb, Bonnie.

## 1.5 The Impact of Biotechnology Is Continually Expanding

The use of recombinant DNA technology and other molecular techniques to make products is called **biotechnology.** In the United States, biotechnology has quietly revolutionized many aspects of everyday life; products made by biotechnology are now found in the supermarket, in health care, in agriculture, and in the court system. A later chapter (see Chapter 18) contains a detailed discussion of biotechnology, but for now, let's look at some everyday examples of biotechnology's impact.

### Plants, Animals, and the Food Supply

The use of recombinant DNA technology to genetically modify crop plants has revolutionized agriculture. Genes for traits including resistance to herbicides, insects, and genes for nutritional enhancement have been introduced into crop plants. The transfer of heritable traits across species using recombinant DNA technology creates **transgenic organisms.** Herbicide-resistant corn and soybeans were first planted in the mid-1990s, and transgenic strains now represent about 88 percent of the U.S. corn crop and 93 percent of the U.S. soybean crop. It is estimated that more than 70 percent of the processed food in the United States contains ingredients from transgenic crops.

We will discuss the most recent findings involving genetically modified organisms later in the text. (Special Topics Chapter 6—Genetically Modified Foods).

New methods of cloning livestock such as sheep and cattle have changed the way we use these animals. In 1996, Dolly the sheep (**Figure 1.8**) was cloned by nuclear transfer, a method in which the nucleus of an adult cell is transferred into an egg that has had its nucleus removed. This makes it possible to produce dozens or hundreds of genetically identical offspring with desirable traits with many applications in agriculture and medicine.

Biotechnology has also changed the way human proteins for medical use are produced. Through use of gene transfer, transgenic animals now synthesize these therapeutic proteins. In 2009, an anticlotting protein derived from the milk of transgenic goats was approved by the U.S. Food and Drug Administration for use in the United States. Other human proteins from transgenic animals are now being used in clinical trials to treat several diseases. The biotechnology revolution will continue to expand as gene editing by CRISPR/Cas and other new methods are used to develop an increasing array of products.

### Biotechnology in Genetics and Medicine

More than 10 million children or adults in the United States suffer from some form of genetic disorder, and every childbearing couple faces an approximately 3 percent risk of having a child with a genetic anomaly. The molecular basis for hundreds of genetic disorders is now known, and most of these genes have been mapped, isolated, and cloned. Biotechnology-derived genetic testing is now available to perform prenatal diagnosis of heritable disorders and to test parents for their status as heterozygous carriers of more than 100 inherited disorders. Newer methods now offer the possibility of scanning an entire genome to establish an

individual's risk of developing a genetic disorder or having an affected child. The use of genetic testing and related technologies raises ethical concerns that have yet to be resolved.

**ESSENTIAL POINT**

Biotechnology has revolutionized agriculture and the pharmaceutical industry, while genetic testing has had a profound impact on the diagnosis of genetic diseases. ■

## 1.6 Genomics, Proteomics, and Bioinformatics Are New and Expanding Fields

The ability to create genomic libraries prompted scientists to consider sequencing all the clones in a library to derive the nucleotide sequence of an organism's genome. This sequence information would be used to identify each gene in the genome and establish its function.

One such project, the Human Genome Project (HGP), began in 1990 as an international effort to sequence the human genome. By 2003, the publicly funded HGP and a private, industry-funded genome project completed sequencing of the gene-containing portion of the genome.

As more genome sequences were acquired, several new biological disciplines arose. One, called **genomics** (the study of genomes), studies the structure, function, and evolution of genes and genomes. A second field, **proteomics,** identifies the set of proteins present in a cell under a given set of conditions, and studies their functions and interactions. To store, retrieve, and analyze the massive amount of data generated by genomics and proteomics, a specialized subfield of information technology called **bioinformatics** was created to develop hardware and software for processing nucleotide and protein data.

Geneticists and other biologists now use information in databases containing nucleic acid sequences, protein sequences, and gene-interaction networks to answer experimental questions in a matter of minutes instead of months and years. A feature called "Exploring Genomics," located at the end of many of the chapters in this textbook, gives you the opportunity to explore these databases for yourself while completing an interactive genetics exercise.

### Modern Approaches to Understanding Gene Function

Historically, an approach referred to as **classical** or **forward genetics** was essential for studying and understanding gene function. In this approach geneticists relied on the use of naturally occurring mutations or intentionally induced mutations (using chemicals, X-rays, or UV light as examples) to cause altered phenotypes in model organisms, and then worked through the labor-intensive and time-consuming process of identifying the genes that caused these new phenotypes. Such characterization often led to the identification of the gene or genes of interest, and once the technology advanced, the gene sequence could be determined.

Classical genetics approaches are still used, but as whole genome sequencing has become routine, molecular approaches to understanding gene function have changed considerably in genetic research. These modern approaches are what we will highlight in this section.

For the past two decades or so, geneticists have relied on the use of molecular techniques incorporating an approach referred to as **reverse genetics.** In reverse genetics, the DNA sequence for a particular gene of interest is known, but the role and function of the gene are typically not well understood. For example, molecular biology techniques such as **gene knockout** render targeted genes nonfunctional in a model organism or in cultured cells, allowing scientists to investigate the fundamental question of "what happens if this gene is disrupted?" After making a knockout organism, scientists look for both apparent phenotype changes, as well as those at the cellular and molecular level. The ultimate goal is to determine the function of the gene being studied.

**ESSENTIAL POINT**

Recombinant DNA technology gave rise to several new fields, including genomics, proteomics, and bioinformatics, which allow scientists to explore the structure and evolution of genomes and the proteins they encode. ■

## 1.7 Genetic Studies Rely on the Use of Model Organisms

After the rediscovery of Mendel's work in 1900, research using a wide range of organisms confirmed that the principles of inheritance he described were of universal significance among plants and animals. Geneticists gradually came to focus attention on a small number of organisms, including the fruit fly (*Drosophila melanogaster*) and the mouse (*Mus musculus*) (**Figure 1.9**). This trend developed for two main reasons: First, it was clear that genetic mechanisms were the same in most organisms, and second, these organisms had characteristics that made them especially suitable for genetic research. They were easy to grow, had relatively short life cycles, produced many offspring, and their genetic analysis was fairly straightforward. Over time, researchers created a large catalog of mutant strains for these species,

(a) (b)

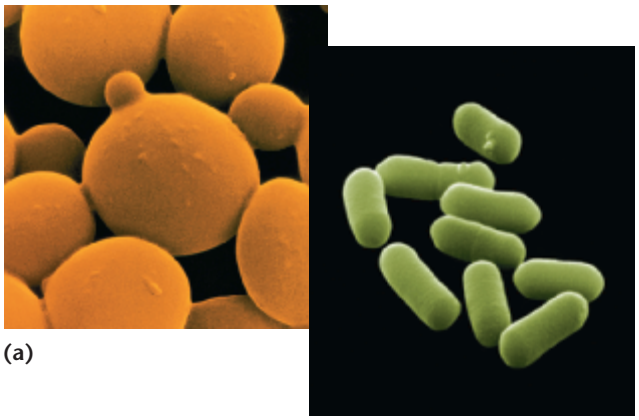
**FIGURE 1.9** The first generation of model organisms in genetic analysis included (a) the mouse, *Mus musculus,* and (b) the fruit fly, *Drosophila melanogaster*.

and the mutations were carefully studied, characterized, and mapped. Because of their well-characterized genetics, these species became **model organisms,** defined as organisms used for the study of basic biological processes. In later chapters, we will see how discoveries in model organisms are shedding light on many aspects of biology, including aging, cancer, and behavior.

## The Modern Set of Genetic Model Organisms

Gradually, geneticists added other species to their collection of model organisms: viruses (such as the T phages and lambda phage) and microorganisms (the bacterium *Escherichia coli* and the yeast *Saccharomyces cerevisiae*) (**Figure 1.10**).

More recently, additional species have been developed as model organisms, three of which are shown in the chapter opening photograph. Each species was chosen to allow study of some aspect of embryonic development. The nematode *Caenorhabditis elegans* was chosen as a model system to study the development and function of the nervous system because its nervous system contains only a few hundred cells and the developmental fate of these and all other cells in the body has been mapped out. *Arabidopsis thaliana*, a small plant with a short life cycle, has become a model organism for the study of many aspects of plant biology. The zebrafish, *Danio rerio*, is used to study vertebrate development: it is small, it reproduces rapidly, and its egg, embryo, and larvae are all transparent.



(a) (b)

**FIGURE 1.10** Microbes that have become model organisms for genetic studies include (a) the yeast *Saccharomyces cerevisiae* and (b) the bacterium *Escherichia coli*.

## Model Organisms and Human Diseases

The development of recombinant DNA technology and the results of genome sequencing have confirmed that all life has a common origin. Because of this, genes with similar functions in different organisms tend to be similar or identical in structure and nucleotide sequence. Much of what scientists learn by studying the genetics of model organisms can therefore be applied to humans as the basis for understanding and treating human diseases. In addition, the ability to create transgenic organisms by transferring genes between species has enabled scientists to develop models of human diseases in organisms ranging from bacteria to fungi, plants, and animals (**Table 1.1**).

The idea of studying a human disease such as colon cancer by using *E. coli* may strike you as strange, but the basic steps of DNA repair (a process that is defective in some forms of colon cancer) are the same in both organisms, and a gene involved in DNA repair (*mutL* in *E. coli* and *MLH1* in humans) is found in both organisms. More importantly, *E. coli* has the advantage of being easier to grow (the cells divide every 20 minutes), and researchers can easily create and study new mutations in the bacterial *mutL* gene in order to figure out how it works. This knowledge may eventually lead to the development of drugs and other therapies to treat colon cancer in humans.

The fruit fly, *Drosophila melanogaster*, is also being used to study a number of human diseases. Mutant genes

**TABLE 1.1 Model Organisms Used to Study Some Human Diseases**

| Organism | Human Diseases |
|---|---|
| *E. coli* | Colon cancer and other cancers |
| *S. cerevisiae* | Cancer, Werner syndrome |
| *D. melanogaster* | Disorders of the nervous system, cancer |
| *C. elegans* | Diabetes |
| *D. rerio* | Cardiovascular disease |
| *M. musculus* | Lesch–Nyhan syndrome, cystic fibrosis, fragile-X syndrome, and many other diseases |