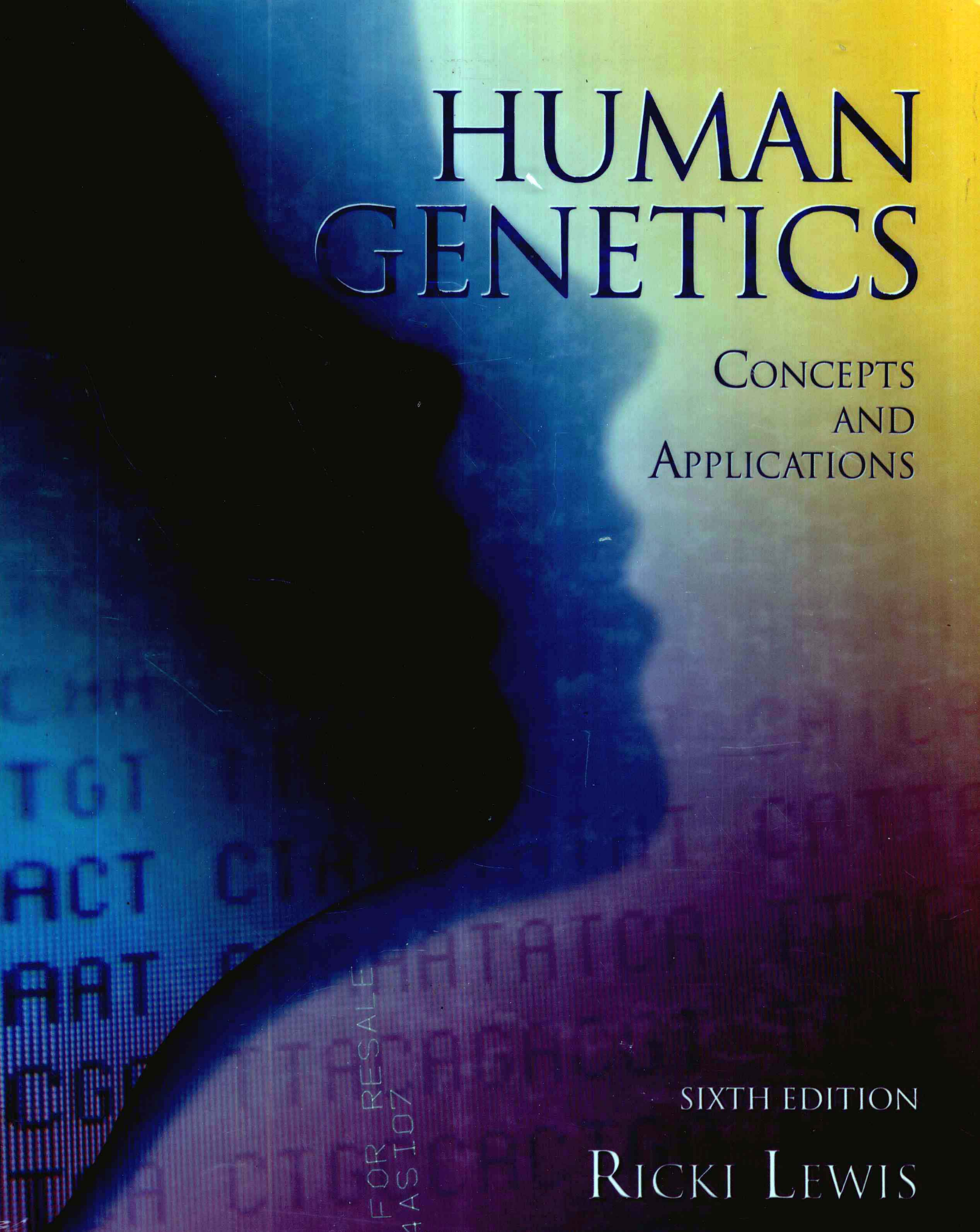

HUMAN GENETICS

CONCEPTS AND APPLICATIONS

SIXTH EDITION

RICKI LEWIS

Human Genetics

Concepts and Applications

Sixth Edition

Ricki Lewis

CareNet Medical Group,
Schenectady, New York

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HUMAN GENETICS: CONCEPTS AND APPLICATIONS, SIXTH EDITION

Published by McGraw-Hill, a business unit of The McGraw-Hill Companies, Inc., 1221 Avenue of the Americas, New York, NY 10020.

2 3 4 5 6 7 8 9 0 VNH/VNH 0 9 8 7 6 5

ISBN 0–07–287735–9 (hardcover)
ISBN 0–07–284605–4 (soft cover)

Publisher: *Martin J. Lange*
Senior sponsoring editor: *Patrick E. Reidy*
Senior developmental editor: *Deborah Allen*
Managing developmental editor: *Patricia Hesse*
Director of development: *Kristine Tibbetts*
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Media technology producer: *Renee Russian*
Senior coordinator of freelance design: *Michelle D. Whitaker*
Cover/interior designer: *John Rokusek*
Cover image composite: Woman's profile: © *Getty Images;* DNA Text Strings: © *Daisuke Morita/Getty Images*
Lead photo research coordinator: *Carrie K. Burger*
Photo research: *Chris Hammond/PhotoFind, LLC*
Supplement producer: *Brenda A. Ernzen*
Compositor: *Precision Graphics*
Typeface: *10/12 Minion*
Printer: *Von Hoffmann Corporation*

The credits section for this book begins on page C-1 and is considered an extension of the copyright page.

Library of Congress Cataloging-in-Publication Data

Lewis, Ricki,
Human genetics : concepts and applications / Ricki Lewis. — 6th ed.
p. cm.
Includes index.
ISBN 0–07–287735–9 (hard copy : alk. paper)
1. Human genetics. I. Title.

QH431.L41855 2005
599.93'5—dc22 2003026153
CIP

www.mhhe.com

About the Author

Photo credit: Barry Palevitz

Ricki Lewis has built a multifaceted career around communicating the excitement of life science, especially genetics and biotechnology. She earned her Ph.D. in genetics in 1980 from Indiana University, working with homeotic mutations in *Drosophila melanogaster.*

Ricki is the original author of *Life,* an introductory biology text; co-author of two human anatomy and physiology textbooks; and author of *Discovery: Windows on the Life Sciences,* an essay collection about research and the nature of scientific investigation. She writes frequently on research and news in genetics, cell biology, biotechnology and other areas for *The Scientist* (www.the-scientist.com). Since 1980, Ricki has published widely, including one of the first stories on DNA fingerprinting in *Discover* magazine. She has taught a variety of life science courses at Miami University, the University at Albany, Empire State College, and community colleges. She brought science experiments to grade school classrooms for three years as part of a traveling science museum, for which she obtained a Howard Hughes Medical Institute grant. Ricki has been a genetic counselor for a large private medical practice in Schenectady, NY, since 1984. She enjoys travel, often to give talks on the human genome, stem cell biology, or how the media reports on science.

Ricki lives in upstate New York with chemist husband Larry, one daughter, and two others away at college, and many cats.

Dedicated to Shirley Epstein Aaronson, who encouraged an inquisitive child to become a scientist.

Preface

Genomics Comes of Age

The transformation of genetics into genomics is finally happening.

Human Genetics: Concepts and Applications has evolved along with the field it covers. In the decade since the first edition was published, genetics has grown from a focus on the rarest of the rare to a field so familiar that the world watched Saddam Hussein have his DNA sampled shortly after his capture. In the first edition, the human genome project was little more than a footnote and table.

By the fourth edition, genomics had earned its own chapter. By the fifth edition, genomic explanations began to permeate the other chapters, as recognition of many genes increasingly explained the actions of single genes. In this new sixth edition, that trend continues, with genomic information seamlessly integrated with the basic concepts it explains:

- genetic testing of college roommates that has gone from fiction to fact over the editions (chapter 1, "Overview of Genetics")
- scrutinizing the genomes of healthy 100+-year-olds (chapter 3, "Development")
- how the chimp and human genomes differ (chapter 16, "Human Origins and Evolution")
- immunity from the point of view of the pathogen, courtesy of sequenced genomes (chapter 17, "Immunity")
- a new form of leukemia revealed through gene expression DNA microarray analysis (chapter 18, "Cancer")
- accounting for redundant gene function in planning gene therapies (chapter 20, "Gene Therapy and Genetic Counseling").

Audiences Enjoy a Unique Writing Style

From the beginning, the clarity, flavor, and immediacy of *Human Genetics: Concepts and Applications* has been uniquely interesting and accessible to non-scientist readers. Into the book flows my 25 years of experience as a journalist, 20 years as a genetic counselor, and my PhD background in genetics. As a frequent contributor to the magazine *The Scientist* for 15 years, I have had access to scientific meetings and researchers that are simply not available to the average professor-turned-textbook author. I speak regularly to the people in the labs and clinics, to patients, to family members and doctors, and combine their words with my own into articles. From my network of sources, I learn of new research results before they are published, thus avoiding the built-in obsolescence that is the bane of textbooks. *Human Genetics: Concepts and Applications* is and always has been ahead of its time—and that's vital for a scientific field that is racing ahead as fast as genetics/genomics.

My approach is straightforward: present the essential concepts in clear language, then demonstrate them with the very best, sometimes quirky, examples. Tables, illustrations, and pedagogical aids reinforce the main points. Consider chapter 15, "Changing Allele Frequencies," which covers the five ways that genes defy Hardy-Weinberg equilibrium. The cast of characters providing examples includes Genghis Khan, Bulgarian gypsies, a young physician helping Amish children, and the blind Pingelapese of Micronesia. The five mechanisms that form the chapter's core are all wrapped up in figure 15.10, which also summarizes Hardy-Weinberg equilibrium from the previous chapter. A student who masters this illustration will be well prepared for an exam—and more importantly, will understand the intimate relationship between genetics and evolution.

Instructional Art Program Provides Dynamic Examples

The art program is not only spectacular in appearance, but remarkably easy to follow. Often all a reader needs to do is follow the arrows. In this manner, figures 2.19 and 2.20 reduce two complex cellular processes—cell death and signal transduction—to their essentials, fostering instant understanding. Other illustrations provide a size perspective. Figure 9.12, for example, shows how DNA is condensed, and also how it winds into a chromosome, which fits into a nucleus inside a cell. Two photographs bring the illustration to life. Similarly, figure 4.10 depicts Mendel's second law at the level of genes, chromosomes, and peas, all at once—a perspective essential for understanding how gametes connect generations. Figure 14.7 is perhaps the best example of putting molecular information into a familiar context: A man lying in an alley has his DNA analyzed to establish the identities of victim and attacker.

Extraordinary Learning Aids Assist Students

Pedagogical aids ensure that students can identify the basic concepts presented and exemplified within each chapter. Chapters open with an **annotated outline** previewing the chapter contents. At the end of each major section, **key concepts** are summarized to reinforce important core material. **Chapter summaries** review the contents of the chapter, calling attention to important new vocabulary.

Each chapter ends with a great variety of **review questions** to measure content knowledge and **applied questions** to provide practice using that knowledge. Both sets of questions are written to engage students in understanding the mechanisms of

genetics and enable them to master content from a basic to a more advanced level. **Answers** to all questions are provided at the end of the book.

At the end of each chapter, a list of **suggested readings** provides further information and includes the sources used to write the chapter. Instructors can use these references to expand upon specific points, and students can use them to research papers and projects.

New Learning Aids

"Solving a Problem" sections present a step-by-step sample computation that leads to a genetic analysis and conclusion. This approach applies to the obvious—Mendel's laws, X-linked inheritance, and the Hardy-Weinberg equation—but also the not-so-obvious—such as comparing the "indels" (insertions and deletions) that distinguish the human from the chimp genome.

Case studies found after each chapter apply and sometimes extend concepts. These case studies supplement those in the *Case Workbook in Human Genetics* by Ricki Lewis. Relevant cases from the workbook are also listed for each chapter. New case studies include:

- a form of long-QT syndrome that causes excited children to collapse and die (chapter 5, "Extensions and Exceptions to Mendel's Laws")
- the Jukes family and inherited criminality (chapter 16, "Human Origins and Evolution")
- a woman who's ex-partner refuses to let her implant their frozen embryos (chapter 21, "Reproductive Technologies")
- a researcher who patented the use of what others once termed "junk" DNA to diagnose disease and is now charging licensing fees (chapter 22, "The Age of Genomics").

Web activities have been added for each chapter to encourage students to dig deeper. They provide an opportunity to find the newest genetic information and to use some of the latest tools and databases in genetic analysis. An appendix lists the reference information for diseases mentioned in the text to the web resource **Online Mendelian Inheritance in Man.**

What's New in This Edition?

Like a genome, a textbook evolves. This sixth edition has undergone a few insertions, deletions, and rearrangements.

Emphasis on control of gene expression

- Chapter 10 has undergone binary fission: It now focuses on "Gene Action.'
- Chapter 11 presents "Control of Gene Expression." This new chapter explores gene expression through time and tissue; chromatin remodeling via the histone code and RNA interference; and the enigma of a genome that devotes only 1.5 percent of its information to encoding proteins, and the fact that those proteins greatly outnumber the genes that specify them.
- The theme of gene expression continues in a practical sense in chapter 18, "The Genetics of Cancer." Figure 18.2 presents data that have saved lives—DNA microarrays that revealed why some people with a rare form of leukemia do not survive given standard treatments for the more common form; they have a different illness, apparent only at the level of gene expression.

Unparalleled coverage of stem cell biology

- To accompany chapter 2's ("Cells") clear descriptions, four illustrations progress from basic to applied views of stem cells. Unlike most textbook depictions, figures 2.22 and 2.23 show stem cells giving rise to other stem cells, as well as daughter cells that go on to yield differentiated cells. Figure 2.24 takes the reader through the steps of somatic cell nuclear transfer, and figure 2.25 looks at stem cells from adults to heal a young man's heart.
- The stem cell theme continues in figure 11.4, which depicts how differential gene expression guides development of the pancreas into a uniquely dual structure—from a single type of progenitor cell.

Classical genetic observations viewed from a genomic perspective

- Redundancy in gene function sheds new light on chapter 5's "Extensions and Exceptions to Mendel's Laws," a group of important topics ignored in some other books.
- In chapter 7, "Multifactorial Traits," eye color is no longer considered a simple blue or brown, but includes the specks and flecks, shading and intensity that arise from the landscape at the back of the eye, providing great variability. Figure 7.13 summarizes the gene-controlled hormonal interactions that regulate body weight, also a phenotype not as simple as we once thought.

Updated examples

- Chapter 15, "Changing Allele Frequencies," discusses the emerging infectious diseases SARS and West Nile virus illness. Discussion of the possible effect of long-ago cannibalism on resistance to prion diseases fleshes out the coverage of balancing selection.
- New topics in Chapter 16, "Human Origins and Evolution," include targeted comparative sequencing to track shared ancestries; the 160,000-year-old *H. sapiens idaltu*, who looked amazingly like us; and a consideration of the many clues pointing to a duplication of the entire human genome.
- Chapter 22, "The Age of Genomics," has translocated material to earlier chapters, and has deleted descriptions of techniques no longer used, yet it preserves the telling of the historic race to sequence the human genome. New topics include "$1000 genome" sequencing technologies; the National Human Genome Research Institute's three-tiered architectural metaphor for the future of genomics; studies that focus on the healthy, rather than people with rare disorders; and a better understanding of the roots of disease. New genetic knowledge is not only providing information for the development of new diagnostic tests and treatments, but is easing identification of non-genetic factors that compromise health.

New "Stories" Integrated into the Narrative

- **Callipyge sheep,** whose giant rears illustrate genomic imprinting (chapter 6, "Matters of Sex")
- **Christina Vena,** a college student with lipodystrophy, cured with leptin shots (chapter 7, "Multifactorial Traits")
- **Let sleeping dogs lie:** how dogs with narcolepsy led to discovery of the gene in humans (chapter 8, "The Genetics of Behavior")
- **Rosalind Franklin's famed "photo 51"** (chapter 9, "DNA Structure and Replication")
- **The "blue people of Troublesome Creek"** (chapter 12, "Gene Mutation").

New Boxes

- The cast of real characters who have shared their experiences in past editions in "In Their Own Words" boxes update their stories, and are joined by some new voices.
- In "The Y Wars" (chapter 6), researcher Jennifer Marshall-Graves laments "The Rise and Fall of the Human Y Chromosome," while David Page describes "Rethinking the Rotting Y Chromosome."
- On a more serious note, parents tell the sad but inspiring tales of their children who have familial dysautonomia (chapter 12) and Li-Fraumeni family cancer syndrome (chapter 18).

New Design, New Tables, and New Figures Throughout

- A bright, modern, bold design sets the stage for the fascinating topic of genetics.
- Tables present the main points to ease studying.
- New figures add historical depth, highlight genomic approaches to traditional ideas, introduce technology, present news, and even offer artists' renditions of genetics.

Teaching and Learning Supplements

McGraw-Hill offers various tools and teaching products to support the sixth edition of *Human Genetics: Concepts and Applications.* Students can order supplemental study materials by contacting their local bookstore. Instructors can obtain teaching aids by calling the Customer Service Department at 800-338-3987, visiting the text website at www.mhhe.com/lewisgenetics6, or contacting your local McGraw-Hill sales representative.

Digital Content Manager

This multimedia collection of visual resources allows instructors to utilize artwork from the text in multiple formats to create customized classroom presentations, visually based tests and quizzes, dynamic course website content, or attractive printed support materials. The digital assets on this cross-platform CD-ROM are grouped by chapter within the following easy-to-use folders:

- **Art Libraries**—All text art in a format compatible with presentation or word processing software.
- **PowerPoint Presentations**—Ready-made presentations cover each chapter of the text.
- **Active Art Library**—Key figures from the text are saved in manipulable layers that can be isolated and customized to meet the needs of the lecture environment. Build images from simple to complex to suit your lecture style.
- **Animations Library**—Numerous full-color animations of key processes are provided. Harness the visual impact of processes in motion by importing these files into classroom presentations or course websites.

Instructor Testing and Resource CD-ROM (ITRCD)

The ITRCD is a cross-platform CD-ROM providing a wealth of resources for the instructor. Supplements featured on this CD-ROM include a computerized test bank utilizing Brownstone Diploma testing software to quickly create customized exams. This user-friendly program allows instructors to search for questions by topic or format, edit existing questions or add new ones, and scramble questions and answer keys for multiple versions of the same test.

Other assets on the ITRCD are grouped within easy-to-use folders. The Instructor's Manual is available on this CD. Word files of the test bank are included for those instructors who prefer to work outside of the test generator software.

Instructor's Manual

The Instructor's Manual, prepared by Cran Lucas of Louisiana State University, is available through the Instructor Resources of the Online Learning Center, (www.mhhe.com/lewisgenetics6). The manual includes chapter outlines and overviews, a chapter-by-chapter resource guide to use of visual supplements, answers to questions in the text, additional questions and answers for each chapter, and Internet resources and activities.

Overhead Transparencies

A set of 100 full-color transparencies showing key illustrations from the text is available for adopters.

For the Student

Genetics: From Genes to Genomes CD-ROM:

This easy-to-use CD covers the most challenging concepts in the course and makes them more understandable through presentation of full-color animations and interactive exercises.

Online Learning Center

Get online at www.mhhe.com/lewisgenetics6. The OLC offers an extensive array of learning and teaching tools. Explore this dynamic site designed to help you get ahead and stay ahead in your study of human genetics. Some of the activities you will find on the website include:

- Self-quizzes to help you master material in each chapter
- Flash cards to ease learning of new vocabulary

- Case studies to practice application of your knowledge of human genetics
- Links to resource articles, popular press coverage, and support groups

Case Workbook in Human Genetics, fourth edition, by Ricki Lewis

This workbook is specifically designed to support the concepts presented in *Human Genetics* through real cases adapted from recent scientific and medical journals, with citations included. The workbook provides practice for constructing and interpreting pedigrees; applying Mendel's laws; reviewing the relationships of DNA, RNA, and proteins; analyzing the effects of mutations; evaluating phenomena that distort Mendelian ratios; designing gene therapies; and applying new genomic approaches to understanding inherited disease. An answer key is available for the instructor.

Acknowledgements

Human Genetics: Concepts and Applications, sixth edition, would not have been possible without the editorial and production dream team: many thanks to Deborah Allen, an extraordinary editor; Toni Michaels, Carrie Burger and Chris Hammond, photo editors; Anne Cody, copyeditor; Rose Koos, project manager, and Michelle Whitaker, designer.

I also thank my wonderful family: Larry, daughters Heather, Sarah, and Carly, and our legions of felines.

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Visual Preview

Instructional Art Program

The art program puts molecular information into a familiar context.

- Spectacular in appearance
- Easy to follow
- Complex processes focus on essentials

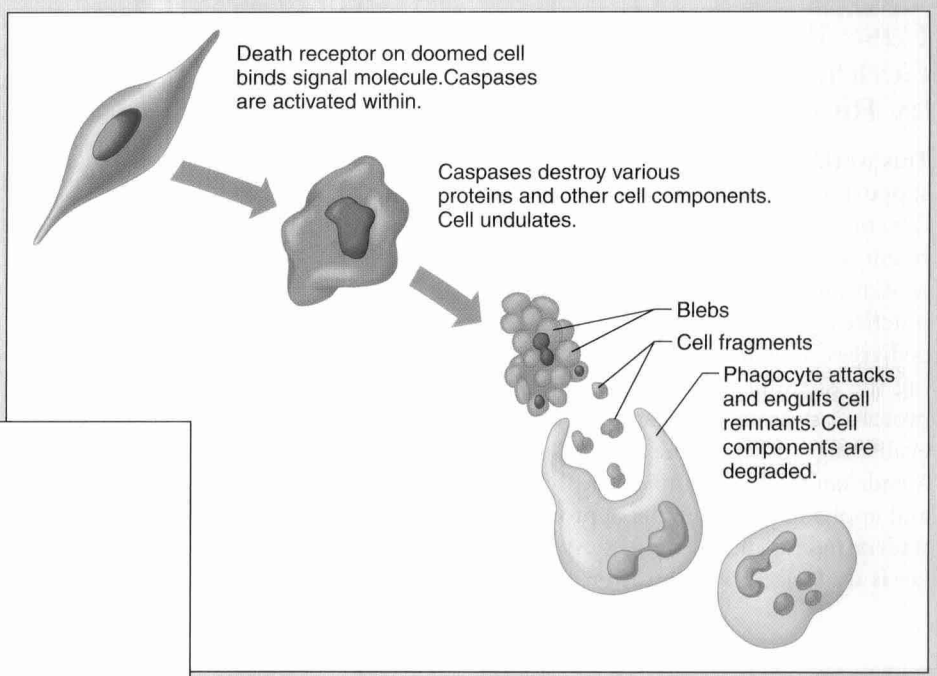


Figure 2.19

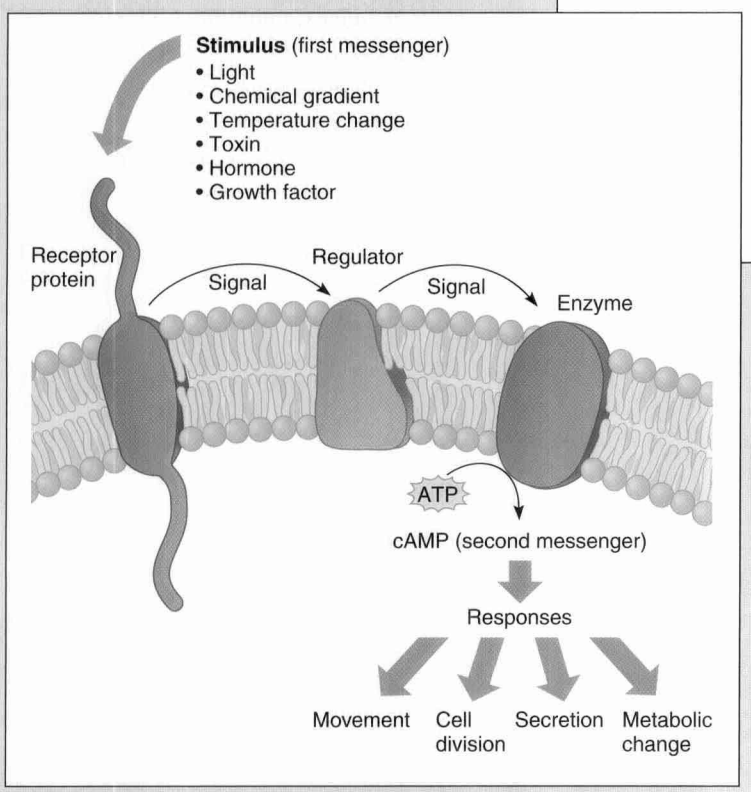


Figure 2.20

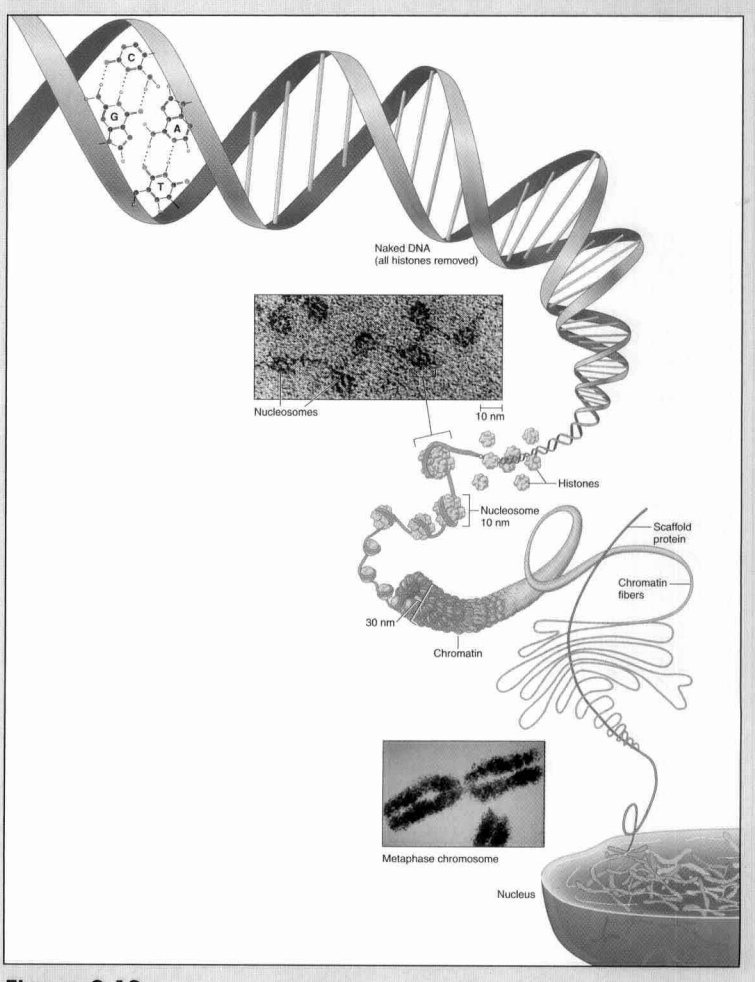


Figure 9.12

Photographs bring illustrations to life

Macro and micro views

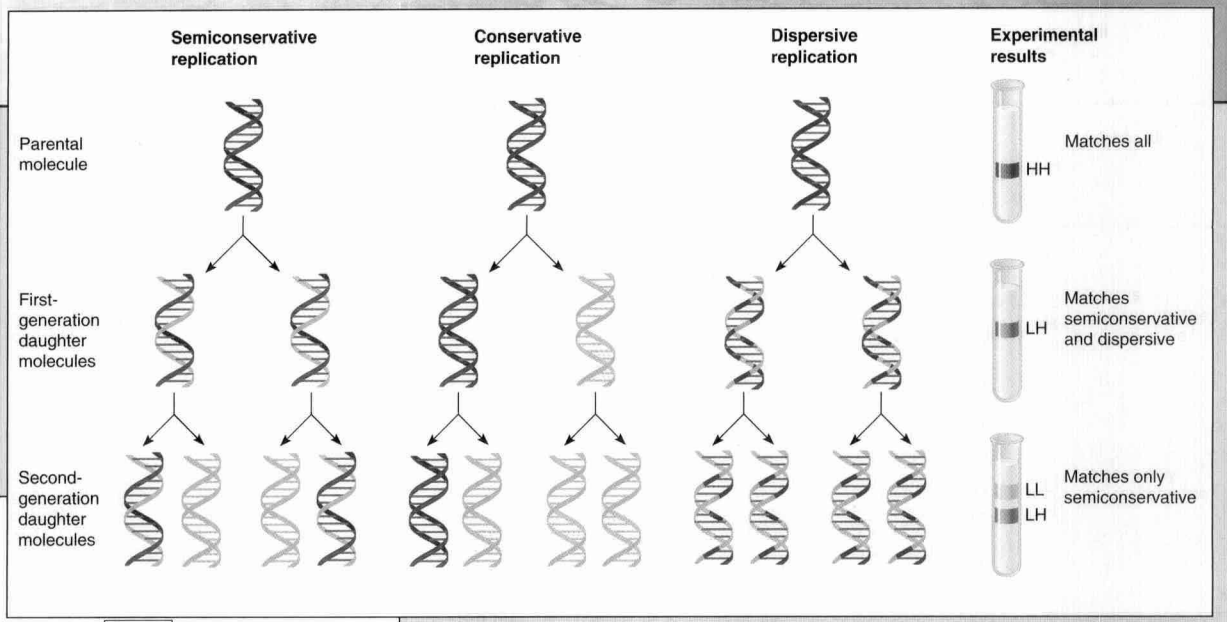


Figure 9.13

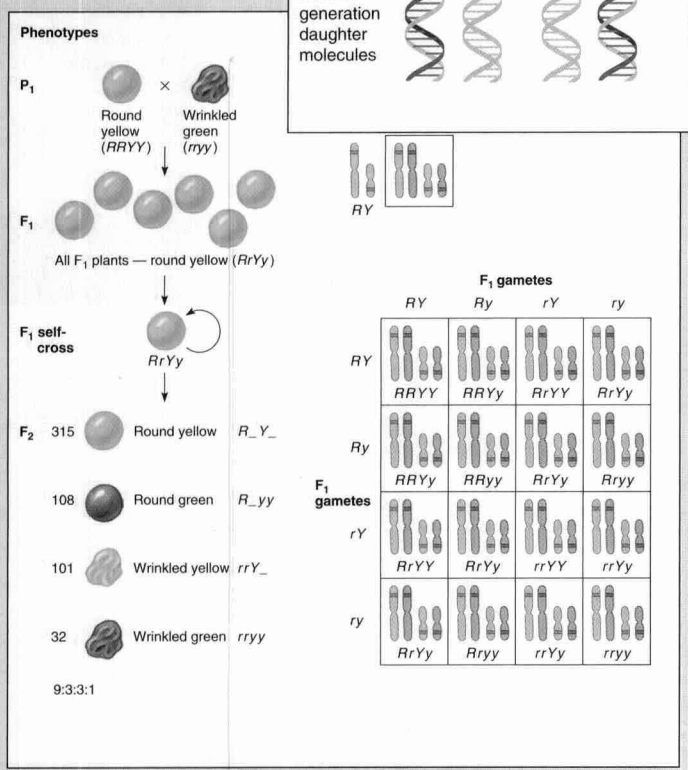


Figure 4.10

Molecular information appears in a familiar context

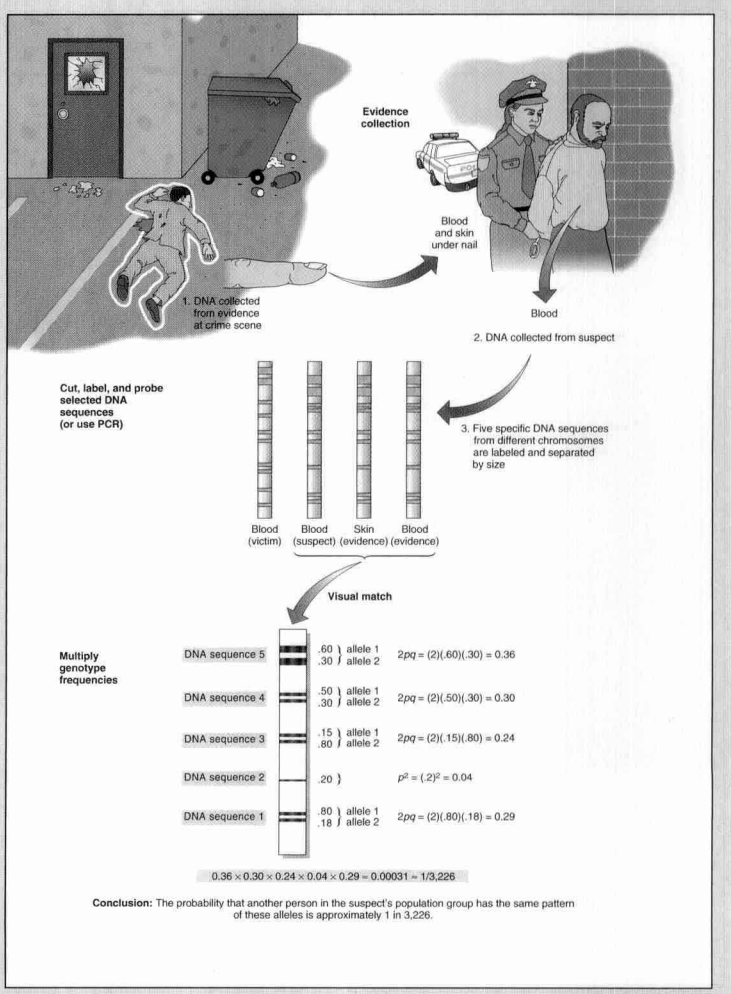


Figure 14.7

Extraordinary Learning Aids

Pedagogical aids ensure that students can identify the basic concepts presented and exemplified within each chapter.

- **Annotated outline** previews the chapter contents.
- **Key concepts** are summarized to reinforce important core material.
- **Chapter summaries** review the contents of the chapter, calling attention to important new vocabulary.
- **Review questions** measure content knowledge.
- **Applied questions** guide students in solving challenges that genetic information presents.
- **Answers** to all questions are at the end of the book.
- **Suggested readings** are useful in learning more about a particular topic.

CHAPTER 1

Overview of Genetics

CHAPTER CONTENTS

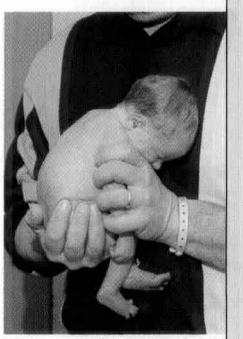
1.1 Genetic Testing
Testing for inherited diseases and susceptibilities will become standard practice, making health care increasingly individualized. Tests that detect specific variations in genetic material will enable physicians to select treatments that a person can tolerate and that are most likely to be effective.

1.2 The Breadth of Genetics
DNA sequences that constitute genes carry information that tells cells how to manufacture specific proteins. A gene's effects are evident at the cell, tissue, organ, and organ system levels. Traits with large inherited components can be traced and predicted in families. Genetic change at the population level underlies evolution. Comparing genomes reveals that humans have much in common with other species.

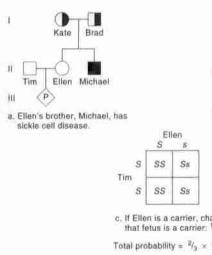
1.3 Genes Do Not Usually Function Alone
In the twentieth century, genetics dealt almost entirely with single-gene traits and disorders. Today it is becoming clear that multiple genes and the environment mold most traits.

1.4 Geneticists Use Statistics to Represent Risks
Risk is an estimate of the likelihood that a particular individual will have a particular trait. It may be absolute for an individual, or relative based on comparison to other people.

1.5 Applications of Genetics
Genetics impacts our lives in diverse ways. Genetic tests can establish identities and diagnose disease. Genetic manipulations can provide new agricultural variants.



The genome fucked into each of this newborn's cells will influence much of the new individual's future—but the environment has a powerful effect too.



a. Ellen's brother, Michael, has sickle cell disease.

b. Probability that Ellen is a carrier: $^2/_3$

c. If Ellen is a carrier, chance that fetus is a carrier: $^1/_2$

Total probability = $^2/_3 \times {}^1/_2 = {}^1/_3$

Figure 4.18 Making predictions. Ellen's brother, Michael, has sickle cell disease, as depicted in the pedigree **(a)**. Ellen wonders what the chance is that her fetus has inherited the sickle cell allele from her. First, she must calculate the chance that she is a carrier. The Punnett square in **(b)** shows that this risk is 2 in 3. (She must be genotype *SS* or *Ss*, but cannot be *ss* because she does not have the disease.) The risk that the fetus is a carrier, assuming that the father is not a carrier, is half Ellen's risk of being a carrier, or 1 in 3 **(c)**.

surrogate mothers and artificial insemination by donor (chapter 21). Moreover, many people cannot trace their families back more than three or four generations, so they lack sufficient evidence to reveal a mode of inheritance. Still, the pedigree is perhaps the most classic genetic tool, and it remains a powerful way to see, at a
passes from generation t
as Gregor Mendel did wit

Key Con

Pedigrees are charts
family relationships a
transmission of inherit
represent males, and
horizontal lines link tw
lines show generation
horizontal lines depic
for heterozygotes are
and symbols for indiv
express the trait unde
completely shaded.
reveal mode of inher
with Punnett squares
that apply Mendel's
predict the recurren
inherited disorders o

Summary

4.1 Following the Inheritance of One Gene—Segregation

1. Gregor Mendel described the two basic laws of inheritance using pea plant crosses. The laws, which derive from the actions of chromosomes during meiosis, apply to all diploid organisms.
2. Mendel used a statistical approach to investigate why some traits seem to disappear in the hybrid generation. The **law of segregation** states that alleles of a gene are distributed into separate gametes during meiosis. Mendel demonstrated this using seven traits in pea plants.
3. A diploid individual with two identical alleles of a gene is **homozygous.** A **heterozygote** has two different alleles of a gene. A gene may have many alleles.
4. A **dominant** allele masks the expression of a **recessive** allele. An individual may be homozygous dominant, homozygous recessive, or heterozygous.
5. Mendel repeatedly found that when he crossed two true-breeding types, then bred the resulting hybrids to each other, the two variants of the trait appeared in a 3:1 phenotypic ratio. Crossing these progeny further revealed a genotypic ratio of 1:2:1.
6. A **Punnett square** is a chart used to follow the transmission of alleles. It is based on probability.

4.2 Single-Gene Inheritance in Humans

7. Traits or disorders caused by single genes are called Mendelian or unifactorial traits.
8. **Modes of inheritance** enable geneticists to predict phenotypes. In **autosomal dominant** inheritance, males and females may be affected, and the trait does not skip generations. Inheritance of an **autosomal recessive** trait may affect either males or females and may skip generations. Autosomal recessive conditions are more likely to occur in famil
consanguinity. Recess
be more severe and ca
earlier than dominant
9. Genetic problems can
alleles as gametes form
in a new individual.
10. Dominance and recess
alleles affect the abund
the gene's protein prod

**4.3 Following the Inh
Two Genes—Inde
Assortment**

11. Mendel's second law, t
independent assortm
transmission of two or
different chromosome
random assortment of
paternally derived chr
meiosis results in gam
different combination

Chapter 4 Mendelian Inhe

12. The chance that two independent genetic events will both occur is equal to the product of the probabilities that each event will occur on its own. This principle, called the product rule, is useful in calculating the risk that certain individuals will inherit a particular genotype and in following the inheritance of two genes on different chromosomes.

4.4 Pedigree Analysis

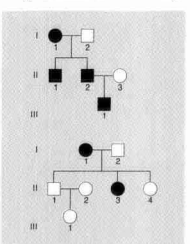
13. A **pedigree** is a chart that depicts family relationships and patterns of inheritance for particular traits. A pedigree can be inconclusive.

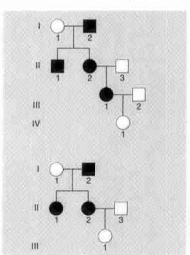
Review Questions

1. How does meiosis explain Mendel's laws of segregation and independent assortment?
2. How was Mendel able to derive the two laws of inheritance without knowing about chromosomes?
3. Distinguish between
   a. autosomal recessive and autosomal dominant inheritance.
   b. Mendel's first and second laws.
   c. a homozygote and a heterozygote.
   d. a monohybrid and a dihybrid cross.
   e. a Punnett square and a pedigree.
4. Why would Mendel's results for the dihybrid cross have been different if the genes for the traits he followed were located near each other on the same chromosome?
5. Why are extremely rare autosomal recessive disorders more likely to appear in families in which blood relatives have children together?
6. How does the pedigree of the ancient Egyptian royal family in figure 4.14a differ from a pedigree a genetic counselor might use today?
7. People who have Huntington disease inherit one mutant and one normal allele. How would a person who is homozygous dominant for the condition arise?
8. What is the probability that two individuals with an autosomal recessive trait, such as albinism, will have a child with the same genotype and phenotype as they do?

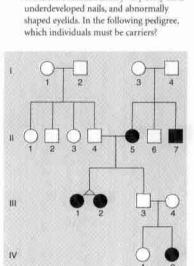
Applied Questions

1. Achondroplasia is a common form of hereditary dwarfism that causes very short limbs, stubby hands, and an enlarged forehead. Below are four pedigrees depicting families with this specific type of dwarfism. What is the most likely mode of inheritance? Cite a reason for your answer.





2. Draw a pedigree to depict the following family:
   One couple has a son and a daughter with normal skin pigmentation. Another couple has one son and two daughters with normal skin pigmentation. The daughter from the first couple has three children with the son of the second couple. Their son and one daughter have albinism; their other daughter has normal skin pigmentation.
3. Chands syndrome is an autosomal recessive condition characterized by very curly hair, underdeveloped nails, and abnormally shaped eyelids. In the following pedigree, which individuals must be carriers?



4. Caleb has a double row of eyelashes, which he inherited from his mother as a dominant trait. His maternal grandfather is the only other relative to have the trait. Veronica, a woman with normal eyelashes, falls madly in love with Caleb, and they marry. Their

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New Learning Aids

"Solving a Problem" sections appear throughout the book where students are faced with learning how to perform a genetic analysis. Each new section presents a step-by-step sample computation.

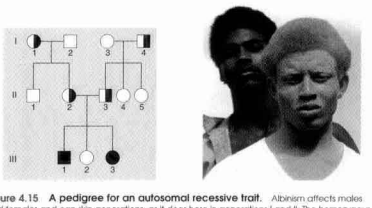


Figure 4.15 A pedigree for an autosomal recessive trait. Albinism affects males and females and can skip generations, as it does here in generations I and II. The homozygous recessive individual lacks an enzyme needed to produce melanin, which colors the eyes, skin, and hair.

carriers. One partner from each pair of grandparents must also be a carrier, which can sometimes be determined using a carrier test, inferred from family history, or deduced from a map of DNA sequence of the affected chromosome.

An autosomal dominant trait does not skip generations and can affect both sexes. A typical pedigree for an autosomal dominant trait has some squares and circles filled in to indicate affected individuals in each generation (**figure 4.16**).

A pedigree may be inconclusive, which means that either autosomal recessive or autosomal dominant inheritance can explain the pattern of filled-in symbols. **Figure 4.17** shows one such pedigree, for a type of hair loss called alopecia. According to the pedigree, this trait can be passed in an autosomal dominant mode because it affects both males and females and is present in every generation. However, the pedigree can also depict autosomal recessive inheritance if the individuals represented by unfilled symbols are carriers. Inconclusive pedigrees tend to arise when families are small and the trait is not severe enough to impair fertility.

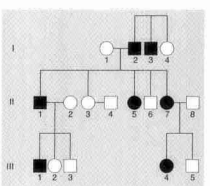


Figure 4.16 A pedigree for an autosomal dominant trait. Autosomal dominant traits do not skip generations. This trait is brachydactyly, or short fingers.

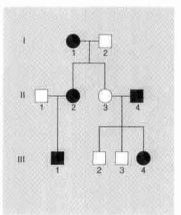


Figure 4.17 An inconclusive pedigree. This pedigree could account for an autosomal dominant trait or an autosomal recessive trait that does not prevent affected individuals from having children. (Unfilled symbols could represent carriers.)

Solving a Problem: Conditional Probability

Often genetic counselors are asked to predict the probability that a condition will occur in a particular individual, such as an offspring. Mendel's laws, pedigrees, and Punnett squares provide clues, as do logic and common sense. Consider the family depicted in **figure 4.18.**

Michael Stewart has sickle cell disease, which is inherited as an autosomal recessive condition. This means that his unaffected parents, Kate and Brad, must each be heterozygotes (carriers). Michael's sister, Ellen, also healthy, is expecting her first child. Ellen's husband, Tim, has no family history of sickle cell disease. Ellen wants to know the risk that her child will inherit the mutant allele from her and be a carrier.

Ellen's request really contains two questions. First, what is the risk that she herself is a carrier? Because Ellen is the product of a monohybrid cross, and we know that she is not homozygous recessive, she has a 2 in 3 chance of being a carrier, as the Punnett square indicates. If Ellen is a carrier, what is the chance that she will pass the mutant allele to an offspring? It is 1 in 2, because she has two copies of the gene, and according to Mendel's first law, only one goes into each gamete.

To calculate the overall risk to Ellen's child, we can apply the product rule and multiply the probability that Ellen is a carrier by the chance that, if she is, she will pass the mutant allele on. This result, following two events, is a conditional probability, because the likelihood of the second event—the child being a carrier—depends upon the first event—that Ellen is a carrier. If we assume Tim is not a carrier, Ellen's chance of giving birth to a child who carries the mutant allele is therefore 2/3 times 1/2, which equals 2/6, or 1/3. Ellen thus has a theoretical 1 in 3 chance of giving birth to a child who is a carrier for sickle cell disease.

Pedigrees can be difficult to construct and interpret for several reasons. People sometimes hesitate to supply information because they are embarrassed by symptoms affecting behavior or mental stability. Family relationships can be complicated by adoption, children born out of wedlock, serial relationships, blended families, and assisted reproductive technologies such as

Applied Questions

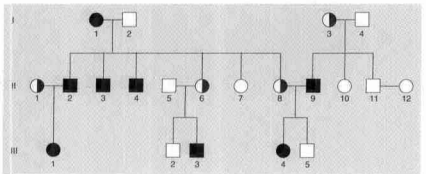
1. In Hunter syndrome, lack of the enzyme iduronate sulfate sulfatase leads to buildup of carbohydrates called mucopolysaccharides. In severe cases, this may swell the liver, spleen, and heart. In mild cases, deafness may be the only symptom. A child with this syndrome is deaf and has unusual facial features. Hunter syndrome is X-linked recessive. Intellect is usually unimpaired and life span can be normal. Suppose a man who has mild Hunter syndrome has a child with a carrier.
   a. What is the probability that a male child would inherit Hunter syndrome?
   b. What is the chance that a female child would inherit Hunter syndrome?
   c. What is the chance that a girl would be a carrier?
   d. How might a carrier of this condition experience symptoms?
2. Coffin-Lowry syndrome causes short, tapered fingers; abnormal finger and toe bones; puffy hands; soft, elastic skin; curved fingernails; facial anomalies; and sometimes hearing loss and heart problems. Evidence suggests that the syndrome is X-linked recessive, but girls are affected to a much lesser degree than boys. Suggest two explanations for why girls tend to have milder cases.
3. Amelogenesis imperfecta is an X-linked dominant condition that affects tooth enamel. Affected males have extremely thin enamel layers all over each tooth. Female carriers have grooved teeth from the uneven deposition of enamel. Explain the difference in phenotype between the sexes.
4. A prenatal test finds that cells of a fetus have two Barr bodies. What sex is the fetus?
5. Huntington disease (see Bioethics: Choices for the Future, Chapter 4) begins earlier and symptoms progress faster if the affected person inherits the disorder from his or her father. Explain this observation.

Web Activities

6. Identify an X-linked disorder at http://www.ncbi.nlm.nih.gov/disease/chr21-Y.html, then find it in OMIM and describe it.
7. From the Imprinted Gene Catalogue at http://cancer.otago.ac.nz/IGC/web/homc.html, click on "search by species name" and then click on "complete list." Find two disorders that involve imprinting, one transmitted from the mother and one from the father, and use OMIM to describe them.

Case Studies

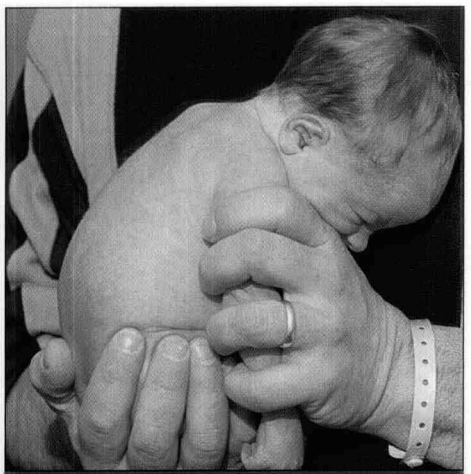
8. Reginald has mild hemophilia A that he can control by taking a clotting factor. He marries Lydia, whom he met at the hospital where he and Lydia's brother, Marvin, receive their treatment. Lydia and Marvin's mother and father, Emma and Clyde, do not have hemophilia. What is the probability that Reginald and Lydia's son will inherit hemophilia A?
9. Harold works in a fish market, but the odor does not bother him because he has anosmia, an X-linked recessive lack of sense of smell. Harold's wife, Shirley, has a normal sense of smell. Harold's sister, Maude, also has a normal sense of smell, as does her husband, Phil, and daughter, Marsha, but their identical twin boys, Alvin and Simon, cannot detect odors. Harold and Maude's parents, Edgar and Florence, can smell normally. Draw a pedigree for this family, indicating people who must be carriers of the anosmia gene.
10. Metacarpal 4–5 fusion is an X-linked recessive condition in which certain finger bones are fused. It occurs in many members of the Flabudgett family, depicted in the pedigree to the left:
    a. Why are three females affected, considering that this is an X-linked condition?
    b. What is the risk that individual III-1 will have an affected son?
    c. What is the risk that individual III-5 will have an affected son?



Case studies found after each chapter apply, and sometimes extend, concepts. These case studies supplement those in the *Case Workbook in Human Genetics* by Ricki Lewis.

Web activities encourage students to find information about human genetics that particularly interests them. They also provide an opportunity to find the latest genetic information and to use some of the latest tools and databases in genetic analysis. An appendix lists the reference information for diseases mentioned in the text to the web resource, **Online Mendelian Inheritance in Man.**

Brief Contents



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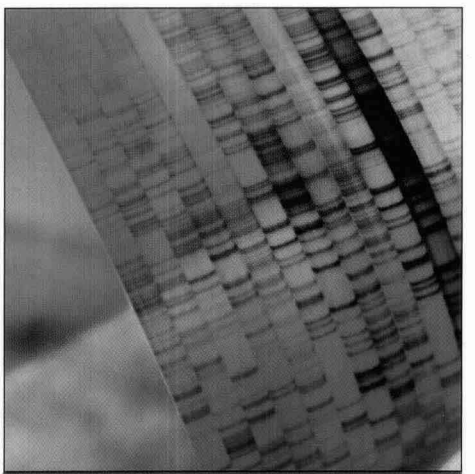

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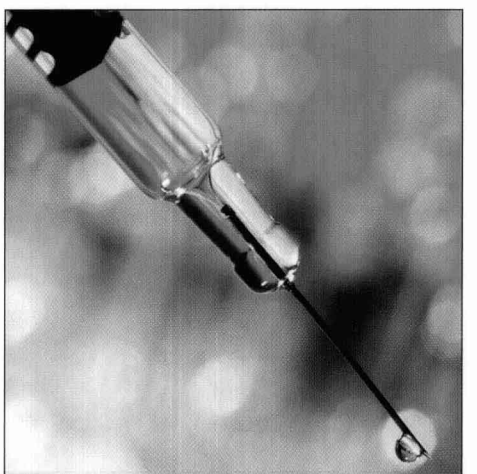

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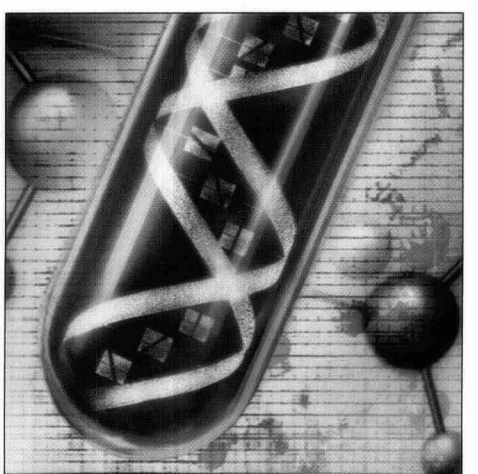

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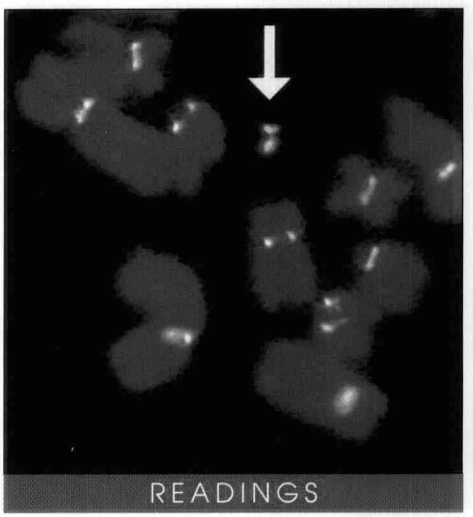
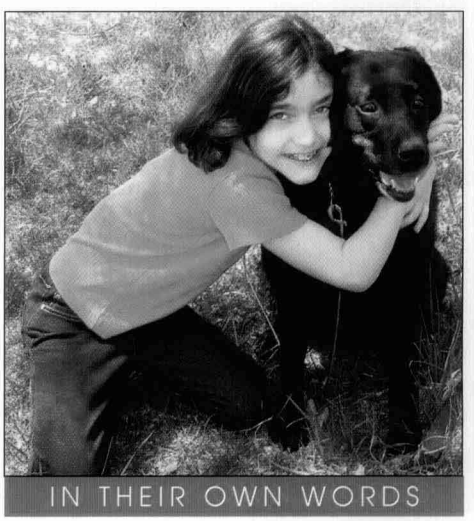
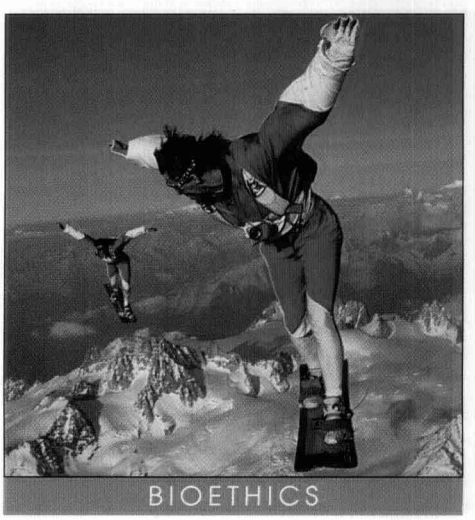
Readings

In Their Own Words

Bioethics: Choices for the Future

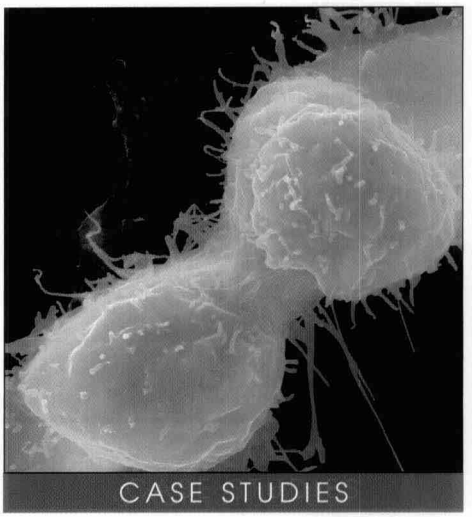




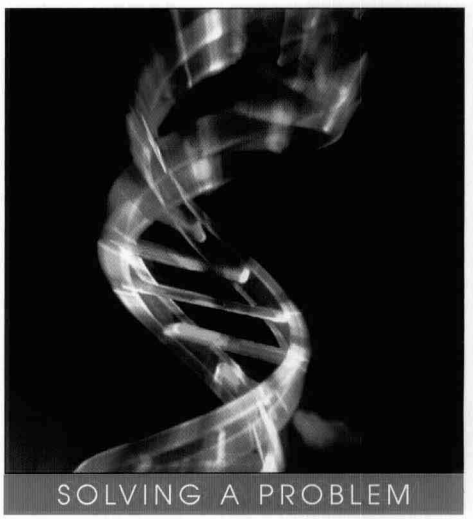


Clinical Coverage

Case Studies



Solving a Problem



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