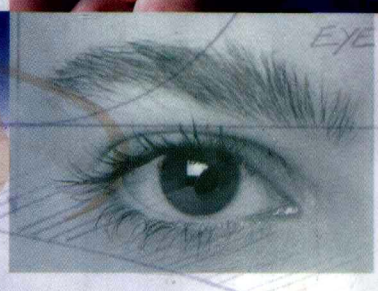
fourth edition

Human GENETICS

Concepts and Applications



Ricki Lewis

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Human GENETICS

Concepts and Applications

Ricki Lewis

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dedicated to
Jesse Gelsinger

About the Author

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 author of *Life,* an introductory biology text; *Human Genetics: Concepts and Applications*; co-author of two human anatomy and physiology textbooks; and author of *Discovery: Explorations in the Life Sciences,* an essay collection about research and the nature of scientific investigation. As a Contributing Editor to *The Scientist,* a newspaper read by scientists worldwide, she writes frequently on the latest research and news in biotechnology. Since 1980, Ricki has published more than 3,000 articles in a variety of magazines, including a cover story on DNA fingerprinting in *Discover* and book reviews for *The New York Times.* Ricki participates in Science Forum, a monthly call-in science program on public radio, and is a frequent invited speaker. She is an adjunct professor at Miami University and the University at Albany, where she has taught a variety of life science courses, and also taught at Empire State College and several 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, where she helps people make decisions about reproductive choices.

Ricki lives in upstate New York with chemist husband Larry, three daughters, four cats, two guinea pigs, a rat, hampster, tortoise, and hedgehog.

Preface

Introduction

Rarely does very much change between the ever-shrinking window of time that separates consecutive editions of a textbook. That certainly isn't true for the fourth edition of *Human Genetics: Concepts and Applications*. The sequencing of the human genome, new with the millennium , is something that Gregor Mendel could not have fathomed, and that Francis Crick once only imagined in the context of unravelling the genetic instructions of a simple bacterium. Yet it has been done.

Whether deciphering the sequence of our genetic blueprints comes to represent a true paradigm shift in the science of genetics remains to be seen. Some have argued that it does not change what has come before but merely continues it, albeit on an enormous, systematic scale. Some have argued that the genome project was not creative or clever, comparing it to climbing Mt. Everest simply because it is there.

Although its impact on science is unclear, human genome information will almost certainly impact health care and, therefore, the average citizen. Once not even included in medical school training, human genetics and genomics are now explaining the underpinnings of many diseases. Medical consumers are asking for information on genetic testing, and the media has so hyped genetic research that some patients are even demanding treatments and procedures that are still many years in the future. Ironically, at the same time that people are looking to gene-based tests and treatments with great hope, rejection of genetically-modified (GM) crops is growing, fueled more by politics and economics than science. The fact that both types of technologies—gene therapy and agricultural biotechnology—use much the same methods of gene transfer and expression, yet evoke such opposite responses, indicates that not everyone is familiar with basic genetic principles. A survey in the United Kingdom, for example, found that people are avoiding "GM foods" because of a fear of consuming DNA!

This book is written for the citizens of the future who will evaluate new medical options and brave new foods, and decide for themselves whether a new technology is valuable, potentially dangerous, unethical, or useless. Being informed in the coming age of genomics requires understanding what genes are, and how they function and interact with each other and environmental stimuli. While Mendel's laws, the DNA double helix, protein synthesis and population dynamics will always form the foundation of the field, the study of human genetics must now embrace much more. Completion of the human genome project has catapulted human genetics to a new level, one that has evolved from the single-gene-at-a-time approach of the last decades of the last century to a more multifactorial view.

Human Genetics: Concepts and Applications, Fourth Edition weaves the thread of genomics throughout the clear and exciting discussion of gene structure and function and biotechnology. Changes to this edition include increased emphasis on clarity and evenness of level, with several new pedagogical features added to ease learning. Updating is everywhere. The book's unique reliance on recounting the experiences of real people remains, bolstered by inclusion of more of my experiences as a genetic counselor.

What's New and Exciting About this Edition

Easier Learning

Particular care has been taken in this revision to provide a clear framework of basic principles. After reading a chapter, students should be able to identify the main concepts and place them into the larger context of genetics. New transitions have been added, chapters are more closely linked, figures are more consistent, and a new host of pedagogical tools have been added to ease learning. These aids include:

- Introductory outlines with summaries of major topics
- Numbered main headings in text, chapter introductions, and chapter summaries
- Brief, straightforward narrative introductions that get to the point fast
- Many new summary tables that encapsulate concepts
- New figures with step-by-step descriptions
- New questions and problems
- Summary of key concepts at the end of each major section
- Websites and OMIM references with each chapter

A Sense of Reality

Human Genetics: Concepts and Applications, Fourth Edition "puts a name on" and personalizes the material. It is real, relevant, and connected to everyday life.

"In Their Own Words" essays are written by individuals who have, or are close to people who have, inherited disease, providing a different view from the researchers who contribute the essays in most textbooks. The essays introduce:

- Don Miller, the first recipient of gene therapy for hemophilia (chapter 1)
- Stefan Schwartz, who has Klinefelter Syndrome (Chapter 11)
- Kathy Naylor, whose little girl died of cri-du-chat syndrome (Chapter 11)
- Blaine Detheridge-Newsom, a teen who has spina bifida (Chapter 14)
- Sandra Thomas, founder of the American Hemochromatosis Society (Chapter 18)

Bioethics: Choices for the Future essays, new to this edition, delve deeper into scientific puzzles and societal responses that may influence our own future.

- Considering Cloning (Chapter 3)
- Beryllium Sensitivity Screening (Chapter 14)
- Pig Parts (Chapter 15)
- The Ethics of a Recombinant Drug: EPO (Chapter 17)
- Gene Therapy Fatalities (Chapter 18)
- The Butterfly that Roared (Chapter 19)
- Technology Too Soon? The Case of ICSI (Chapter 20)

Coverage of **Genetic Counseling,** a special combination of scientific, medical, and psychological skills to educate and comfort people facing the possibility of inherited illness, appears throughout this edition.

- *BRCA1—A Genetic Counseling Nightmare* and Table 16.5 *Reasons Why Genetic Counseling for Familial Breast Cancer is Complex* (other books get it wrong!)
- Down Syndrome recurrence risks based on age and family history (Chapter 11)
- *Scenes from a Sickle Cell Disease Clinic* (Chapter 18)
- Discussion of how genetic counseling relates to other health care professions
- *Genetic Counseling Quandaries and Challenges* based on actual cases (Chapter 18)
- New Chapters 1 and 21 cover genetic counseling as part of 21st century genetic medicine

Not Just Up-to-Date—Ahead

Previous editions of *Human Genetics: Concepts and Applications* covered genetic markers, antisense technology, gene targeting, and human embryonic stem cells before they became headlines. This new edition continues that up-to-the-minute coverage with updates of current technologies and introduction of new ones, such as vegetable vaccines (Chapter 15), semen pharming (Chapter 17), chimeraplasty (Chapter 18), rhizosecretion and bioremediation (Chapter 19), and pharmacogenomics and DNA microarrays (Chapter 21). Yet at the same time, the book traces discoveries and developments that led to today's and tomorrow's technologies. **Technology Timelines** chronicle the gestation and birth of transplantation (Chapter 15), patenting life (Chapter 17), assisted reproductive technologies (Chapter 20) and the human genome project (Chapter 21).

Significant Changes in Content

Major goals of this revision are to engage the student with relevant coverage and to update the instructor with the latest developments in the field, but the main thrust of this revision is to ensure that the **fundamental concepts** of genetics are clearly presented to students. Significant content changes that address this goal include:

- A new section on calculating risk (Chapter 1)
- Added coverage of the cell membrane (Chapter 2)
- More material on the cell cycle, apoptosis and stem cells (Chapter 2)
- A new section on multiple births (Chapter 3)
- A clear explanation of the meaning of dominance and recessiveness (Chapter 4)
- Real examples of "linkage mapping" (Chapter 5)
- Clearer coverage of genomic imprinting (Chapter 6)
- More structured discussions of polygenic and multifactorial traits (Chapter 7)
- Expanded coverage of DNA repair disorders (Chapter 8)

- Simplified discussion of gene expression (Chapter 9)
- New sections on globin disorders and prion disorders (Chapter 10)
- Story of the development of prenatal testing (Chapter 11)
- Clear step-by-step discussion of Hardy-Weinberg mathematics (Chapter 12)
- Augmented discussion of balanced polymorphisms (Chapter 13)
- Balanced discussion of mitochondrial Eve and the multiregional hypothesis (Chapter 14)
- Coverage of innate immunity and new vaccines (Chapter 15)
- New section on the epidemiology of cancer (Chapter 16)
- Expanded discussion of how to make recombinant DNA (Chapter 17)
- New coverage of genetic counseling (Chapter 18)
- Discussion of controversy over genetically modified foods (Chapter 19)
- New discussion of the ethics of reproductive technology (Chapter 20)
- New chapter on functional genomics—beyond the Human Genome Project (Chapter 21)

Supplements

As a full service publisher of quality educational products, McGraw-Hill does much more than just sell textbooks to your students. We create and publish an extensive array of print, video, and digital supplements to support instruction on your campus. Orders of new (versus used) textbooks help us to defray the cost of developing such supplements, which is substantial. Please consult your local McGraw-Hill representative to learn about the availability of the supplements that accompany *Human Genetics: Concepts and Applications.*

For the Student

Case Study Workbook in Human Genetics, Second Edition by Ricki Lewis. 0-07-232530-5
This workbook is specifically designed to support the concepts presented in *Human Genetics* through new real cases adapted from recent scientific and medical journals, with citations included. It 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 manual** is available for the instructor.

Genetics: From Genes to Genomes CD ROM
This CD covers the most challenging concepts in the course and makes them more understandable through presentation of full-color narrated animations and interactive exercises. Icons in the text indicate related topics on the CD.

For the Instructor

Instructor's Manual and Test Item File
prepared by Jack Fabian, Keene State College

In addition to chapter outlines, answers to in-text questions, and additional questions with answers that have supported previous editions, Jack Fabian has added a number of new features to this edition. These include:

- An overview section that summarizes the material in each chapter
- A list of transparencies, Web resources, and CD presentations that support each chapter
- Ideas for classroom instruction
- A list of Internet resources and activities

Moreover, multiple choice questions and answers that instructors may use for testing are provided for each chapter. The test item file is also available in **computerized form** compatible with either Windows or Macintosh.

Transparencies
A set of transparencies showing key illustrations from the text is available for adopters. Additional images are available for download on the book's website.

Website
Get Online! Visit us at www.mhhe.com/lewisgenetics
Explore this dynamic website that provides additional resources for both student and instructor including:

- Images and tables from the text available for downloading
- Case histories and opinion articles for discussion
- Online quizzes to support study
- Resource articles and popular press coverage
- Support groups and information sites for genetic diseases
- Internet links to related Websites

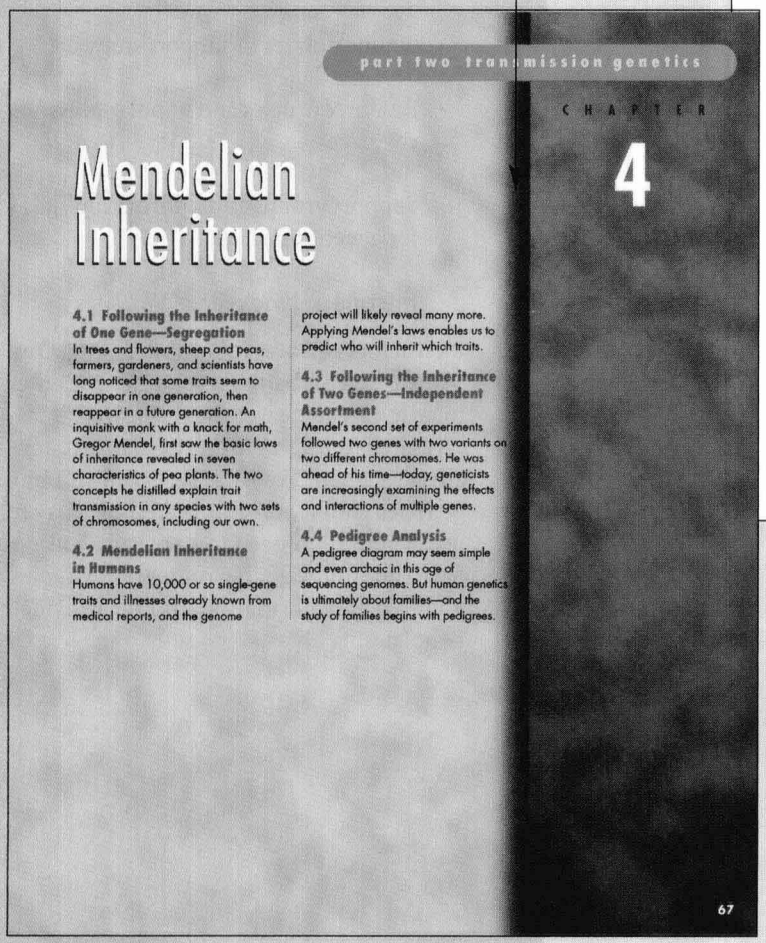
Instructors will also find a link to **PageOut: The Course website Development Center** to create a course website. Its powerful features help create a customized, professionally designed Website for your human genetics course, yet it is incredibly easy to use. There is no need to know any coding. Save time and valuable resources by typing your course information into the provided templates.

Visual Preview

The next few pages show you the tools found throughout the text to provide a clear framework for learning the fundamental concepts of human genetics.

Chapter Opener

An outline of major topics accompanied by an introductory narrative prepares you for what you will learn in this chapter.



part two transmission genetics

CHAPTER 4

Mendelian Inheritance

4.1 Following the Inheritance of One Gene—Segregation
In trees and flowers, sheep and peas, farmers, gardeners, and scientists have long noticed that some traits seem to disappear in one generation, then reappear in a future generation. An inquisitive monk with a knack for math, Gregor Mendel, first saw the basic laws of inheritance revealed in seven characteristics of pea plants. The two concepts he distilled explain trait transmission in any species with two sets of chromosomes, including our own.

4.2 Mendelian Inheritance in Humans
Humans have 10,000 or so single-gene traits and illnesses already known from medical reports, and the genome project will likely reveal many more. Applying Mendel's laws enables us to predict who will inherit which traits.

4.3 Following the Inheritance of Two Genes—Independent Assortment
Mendel's second set of experiments followed two genes with two variants on two different chromosomes. He was ahead of his time—today, geneticists are increasingly examining the effects and interactions of multiple genes.

4.4 Pedigree Analysis
A pedigree diagram may seem simple and even archaic in this age of sequencing genomes. But human genetics is ultimately about families—and the study of families begins with pedigrees.

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Technology TIMELINE

Patenting Life and Genes

1790 U.S. patent act is enacted. An invention must be new, useful, and not obvious to earn a patent.

1873 Louis Pasteur is awarded first patent on a life form for yeast used in industrial processes.

1930 New plant variants can be patented.

1980 First patent is awarded on a genetically engineered organism, a bacterium given four plasmids (DNA rings) that enable it to metabolize components of crude oil. The plasmids are naturally occurring, but do not all occur naturally in the manipulated bacteria.

1988 First patent is awarded for a transgenic organism, a mouse that manufactures human protein in its milk. Harvard University granted patent for "OncoMouse" transgenic for cancer.

1992 Biotechnology company is awarded a broad patent covering all forms of transgenic cotton. Groups concerned that this will limit the rights of subsistence farmers contest the patent several times.

1996–1999 Companies patent partial gene sequences and certain disease-causing genes as the basis for developing specific medical tests.

2000 With gene and genome discoveries pouring into the Patent and Trademark Office, requirements for showing utility of a DNA sequence are made more stringent.

tially focused on direct gene products such as peptides and proteins with therapeutic actions, such as insulin, growth hormone, and clotting factors. However, the technology can target other biochemicals by affecting the genes that encode enzymes required to synthesize other substances, such as carbohydrates and lipids.

Constructing Recombinant DNA Molecules

Manufacturing recombinant DNA molecules requires several components:

- enzymes that cut the donor and recipient DNA (**restriction enzymes**)
- DNA circles to carry the donor DNA (**cloning vectors**)
- recipient cells (bacteria or cultured cells)

After inserting the donor DNA into the vectors, the procedure requires several steps:

- selecting cells that harbor DNA circles that, in turn, harbor foreign genes
- selecting those recombinant cells that contain the specific gene of interest
- stimulating expression of the foreign gene, so that its protein product can be collected

The natural function of restriction enzymes is to protect bacteria by cutting and thereby inactivating the DNA of infecting viruses. Protective methyl (CH_3) groups shield the bacterium's own DNA from its restriction enzymes. Bacteria have hundreds of types of restriction enzymes. Each cuts DNA at a particular 4-, 5-, or 6-base sequence. These targets are symmetrical in a particular way—the recognized sequence reads the same, from the 5' to 3' direction, on both strands of the DNA. For example, the restriction enzyme EcoR1, shown in figure 17.2, cuts at the sequence GAATTC. The complementary sequence on the other strand is CTTAAG, which, read backwards, is GAATTC. (You can try this with other sequences to see that it rarely works this way!) This type of symmetry is called a palindrome in the English language, referring to a sequence of letters that reads the same in both directions, such as "Madam, I'm Adam." However, palindromic sequences in DNA reflect the sequences on two strands.

The cutting action of a restriction enzyme on double-stranded DNA creates single-stranded extensions of DNA called "sticky ends," so-named because they are complementary to each other and attract each other. The reason restriction enzymes work as molecular scissors in creating recombinant DNA molecules is that they cut at the same sequence in any DNA source. In other words, the same sticky ends result from the same restriction enzyme, whether the DNA is from a mockingbird or a maple. Any pieces of DNA bearing complementary sticky ends can join.

Another natural "tool" used in recombinant DNA technology is a cloning vector. This structure, usually made of DNA, carries DNA from the cells of one species into the cells of another. The term *cloning* refers to the action of making many copies of a selected DNA sequence. (The use of the word in molecular biology predated its use as applied to farm animals by many years.)

A vector can be any piece of DNA that an organism's DNA can attach to for transfer into the cell of another organism. A commonly used type of vector is a **plasmid,** a small circle of double-stranded DNA found in some bacteria, yeasts, plant cells, and other types of organisms (figure 17.3).

Viruses that infect bacteria, called bacteriophages, provide another type of vector. Bacteriophages are manipulated so that they transport genetic material but do not cause disease. Disabled retroviruses (viruses that use RNA as their genetic material) are used as vectors too, as are artificially constructed chromosomes from bacteria and yeast. A researcher chooses a cloning vector according to its capacity—that is, the desired gene must be short enough to insert into the vector. Gene size is typically measured in **kilobases** (kb), which are thousands of bases. Table 17.1 lists the capacities of a few types of cloning vectors.

The process of creating a recombinant DNA molecule begins when a restriction enzyme cuts DNA isolated from a donor cell (figure 17.4). An enzyme is used that cuts DNA at sequences known to bracket the gene of interest. The enzyme leaves single-stranded ends dangling from the cut DNA, each bearing a characteristic base

Chapter Seventeen Genetic Engineering 327

In-Chapter Study Aids

In addition to numerous table and figures, you will find **Key Terms** printed in bold type and included in a glossary at the end of the text.
Technology Timelines that trace the developments and discoveries leading to today's technologies.
CD Icons that identify topics supported by the accompanying CD Rom.

brain. People whose prion protein genes are homozygous at position 129, therefore, are at higher risk to develop the associated illness. Further studies on the gene revealed that a mutation at a different site raises the risk even higher. Comparing the prion proteins of healthy individuals to those who inherited a prion disorder showed that normally prion protein folds so that amino acid 129 is near amino acid 178, which is aspartic acid. People who inherit prion diseases are not only homozygous for the gene at position 129, they also display another mutation that changes amino acid 178 to asparagine. Interestingly, people with two valines at 129 develop a condition called fatal familial insomnia, whereas those with two methionines develop a form of Creutzfeldt-Jakob syndrome.

Although we still have much to learn about the genetic underpinnings of the strange prion disorders, researchers are already applying the little that is known. For example, sheep and cows, which are prone, respectively, to the prion disorders scrapie and bovine spongiform encephalopathy (BSE, or "mad cow disease"), are being genetically engineered to have valine and methionine at position 129 and aspartic acid at position 178, the genotype that seems to prevent prion disorders.

KEY CONCEPTS

Whether a mutation alters the phenotype, and how it does so, depends upon where in the protein the change occurs. Mutations in the globin genes are well-studied and diverse; they may cause anemia or cyanosis or they may be silent. Hemoglobin M affects the state of the bound iron. Mutations in two parts of the prion protein gene predispose an individual to developing a prion disorder.

10.5 Factors that Lessen the Effects of Mutation

Mutation is a natural consequence of DNA's ability to change, an ability that has been and continues to be essential for evolution. However, many factors prevent mutations from affecting the phenotype.

The genetic code seems at first glance to have too much information—61 codons specify only 20 amino acids. This redundancy of the genetic code, which is called **degeneracy**, lowers the likelihood of mutation. Degenerate codons ensure that many alterations in the third codon position are "silent." For example, a change from RNA codon CAA to CAG does not alter the designated amino acid, glutamine, so a protein containing the change would not be altered.

The genetic code has other nuances that seem to protect against drastically altered proteins. Mutations in the second codon position, for example, sometimes replace one amino acid with another that has a similar conformation. Often, this does not disrupt the protein's form too drastically. For example, a GCC mutated to GGC replaces alanine with glycine; both are very small amino acids.

In a **conditional mutation**, the phenotype is affected only under certain conditions and this can be protective, because an individual can learn to avoid the exposures that trigger symptoms. This is the case for a common variant of the X-linked gene that encodes glucose 6-phosphate dehydrogenase (G6PD), an enzyme that immature red blood cells use to extract energy from glucose.

One hundred million people worldwide have G6PD deficiency. The phenotype is severe—life-threatening hemolytic anemia, in which red blood cells burst. Fortunately, anemia develops only under rather unusual conditions—when one is eating fava beans, inhaling pollen in Baghdad, or taking an antimalarial drug.

In the fifth century B.C., the Greek mathematician Pythagorus wouldn't allow his followers to consume broad beans—he had discovered that it would make some of them ill. During the second world war, several soldiers taking the antimalarial drug primaquine developed hemolytic anemia. A study began shortly after the war to investigate the effects of the drug on volunteers at the Stateville Penitentiary in Joliet, Illinois, and researchers soon identified abnormal G6PD in people who developed anemia when they took the drug.

What do fava beans, antimalarial drugs, and dozens of other triggering substances have in common? They "stress" red blood cells by exposing them to oxidants, chemicals that strip electrons from other compounds. Without the G6PD enzyme, the stress causes the red blood cells to burst.

The mutations discussed in this chapter occur in single genes. Genetic change can occur at the chromosomal level, too, often affecting many genes. Chromosomal abnormalities are the subject of the next chapter.

KEY CONCEPTS

Genetic code degeneracy ensures that some third-codon-position mutations do not alter the specified amino acid. Changes in the second codon position often replace an amino acid with a structurally similar one. Conditional mutations are expressed only in certain environments.

summary

10.1 Mutations Can Alter Proteins—Three Examples

1. A **mutation** is a change in a gene's nucleotide base sequence that may or may not cause a **mutant** phenotype.
2. A **germline mutation** originates in meiosis and affects all cells of an individual. A **somatic mutation** originates in mitosis and affects a subset of cells.
3. A mutation causes illness by disrupting the function or amount of a protein. In sickle cell disease, beta globin is misshapen; in beta thalassemia, it is absent or reduced. Mutations readily disrupt the highly symmetrical gene encoding collagen. One form of Alzheimer disease is caused by mutation in a receptor protein.

10.2 Causes of Mutation

4. A **spontaneous mutation** arises due to chemical phenomena or to an error in DNA replication. A particular spontaneous mutation rate is characteristic of certain genes, and may be related to how repeated or symmetrical sequences are.
5. **Mutagens** are chemicals or forms of radiation that can induce mutation by deleting, substituting, or adding bases. An organism may be exposed to a mutagen intentionally, accidentally, or naturally.

10.3 Types of Mutations

6. A **point mutation** alters a single DNA base. It may be a **transition** (purine to purine or pyrimidine to pyrimidine) or a **transversion** (purine to pyrimidine or vice versa). A **missense mutation** substitutes one amino acid for another, while a **nonsense mutation** substitutes a "stop" codon for a codon that specifies an amino acid, shortening the protein product.
7. Adding or deleting genetic material may upset the reading frame or otherwise alter protein function.
8. A **pseudogene** has a sequence similar to a functional gene, but is not translated.
9. **Transposons** are genes that move among the chromosomes. They may disrupt the functions of other genes when they jump into them.
10. Expanding triplet repeat mutations add stretches of the same amino acid to a protein, usually one that functions in the brain. This type of mutation may add a function, often leading to a neurodegenerative disease when the number of repeats exceeds a threshhold level.

10.4 The Importance of a Mutation's Position in the Gene

11. Several types of mutations can affect a gene.
12. Mutations in the globin genes may affect the ability of the blood to transport oxygen, or have no effect.
13. Susceptibility to prion disorders requires one to inherit two mutations that affect different parts of the protein that interact as the amino acid chain folds.

10.5 Factors that Lessen the Effects of Mutation

14. The genetic code decreases the chance of mutation due to **degeneracy** in the third position. Similarity in the structure of the amino acids specified by codons with the same base in the second position also helps prevent mutation.
15. **Conditional mutations** are expressed only in response to certain environmental triggers.

review questions

1. Distinguish between a germinal and a somatic mutation. Which is likely to be more severe? Which is more likely to be transmitted to offspring?
2. Why is the collagen gene particularly prone to mutation?
3. Describe how a spontaneous mutation can arise.
4. What is the physical basis of a mutational hot spot?
5. What are three different types of mutations known to cause Gaucher disease?
6. Cite three ways in which the genetic code protects against mutation.
7. List four ways that DNA can mutate without affecting the phenotype.
8. What is a conditional mutation?
9. List two types of mutations that can disrupt the reading frame.
10. Why can a mutation that retains an intron's sequence and a triplet repeat mutation have a similar effect on a gene's product?
11. Cite two ways that a jumping gene can disrupt gene function.
12. Cite two reasons it takes many years to detect induction of recessive mutations in a human population.
13. What is a physical, molecular explanation for anticipation, the worsening of an inherited illness over successive generations?
14. Compare and contrast the ways that short repeats within a gene, long triplet repeats within a gene, and repeated genes can cause disease.
15. A confusing aspect of medical genetics is that in some genes, any mutation produces a variant of the same disorder, such as cystic fibrosis or Gaucher disease. For other genes, however, different mutations are associated with different diseases. Give an example from the chapter in which mutations in the same gene yield distinct medical conditions.

applied questions

1. A condition called "congenital insensitivity to pain with anhidrosis" causes loss of the ability to feel pain, inability to sweat, fever, mental retardation, and self-mutilation. The genetic cause is a mutation that replaces a glycine with an arginine. List every way this change can occur.
2. Retinitis pigmentosa causes night blindness and loss of peripheral vision before age 20. A form of X-linked retinitis pigmentosa is caused by a frameshift mutation that deletes 199 amino acids. How can a simple mutation have such a drastic effect?
3. One form of Ehlers-Danlos syndrome (not the "stretchy skin" type described in the chapter) can be caused by a mutation that changes a C to a T. This change results in the formation of a "stop" codon and premature termination of procollagen. Consult the genetic code table and suggest a way that this can happen.
4. Townes-Brocks syndrome causes several unrelated problems, including extra thumbs, a closed anus, hearing loss, and malformed ears. The causative mutation occurs in a transcription factor. How can a mutation in one gene cause such varied symptoms?
5. Susceptibility to developing prion diseases entails a mutation from aspartic acid to asparagine. What nucleotide base changes make this happen?
6. Two teenage boys meet at a clinic set up to treat muscular dystrophy. The boy who is more severely affected has a two-base insertion at the start of his dystrophin gene. The other boy has the same two-base insertion but also has a third base inserted a few bases away. Explain why the second boy's illness is milder.
7. About 10 percent of cases of amyotrophic lateral sclerosis (also known as ALS and Lou Gehrig disease) are inherited. This disorder causes loss of neurological function over a five-year period. Two missense mutations cause ALS. One alters the amino acid asparagine (*asn*) to lysine (*lys*). The other changes an isoleucine (*ile*) to a threonine (*thr*). List the codons involved and describe how single base mutations alter the amino acids they specify.
8. In one family, Tay-Sachs disease stems from a four-base insertion, which changes an amino-acid-encoding codon into a "stop" codon. What type of mutation is this?
9. Epidermolytic hyperkeratosis is an autosomal dominant condition that produces scaly skin. It can be caused by a missense mutation that substitutes a histidine (*his*) amino acid for an arginine (*arg*). Write the mRNA codons that could account for this change.
10. Fanconi anemia is an autosomal recessive condition that causes bone marrow abnormalities and an increased risk of certain cancers. It is caused by a transversion mutation that substitutes a valine (*val*) for an aspartic acid (*asp*) in the amino acid sequence. Which mRNA codons are involved?
11. Aniridia is an autosomal dominant eye condition in which the iris is absent. In one family, an eleven-base insertion in the gene causes a very short protein to form. What kind of mutation must the insertion cause?

suggested readings

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on the Web

www.chdct.org Coalition for Heritable Disorders of Connective Tissue

www.thalassemia.org Cooley's Anemia Foundation

www.ednf.org Ehlers-Danlos National Foundation

www.fraxa.org FRAXA Research Foundation Inc. (Fragile X)

www3.ncbi.nlm.nih.gov/omim/searchomim.html Mendelian Inheritance in Man

alkaptonuria 203500
alpha thalassemia 141800
Alzheimer disease 104300, 104310, 104311, 600759
Becker muscular dystrophy 310200
beta thalassemia 141900
Duchenne muscular dystrophy 310200
Ehlers-Danlos syndrome 130050
familial hypercholesterolemia 143890
fragile X syndrome 309550
G6PD deficiency 305900
hemoglobin M 250800
myotonic dystrophy 160900
prion protein 176640
sickle cell disease 603903

www.mdausa.org/ Muscular Dystrophy Association

Focus on Concepts

Numbered Headings identify each major topic and are directly related to the chapter introduction and the chapter summary.
Key Concepts are summarized at the end of each major section.

End-of-Chapter Study Aids

Chapter Summary is presented in list format, organized by major topic.
Review Questions reinforce major concepts.
Applied Questions ask you to solve real-life problems.
Suggested Readings cites the articles that were the sources of chapter information.
on the Web lists links that immerse you in the modern world of human genetics without ever leaving your computer. Includes **OMIM** references.

This text is unparalleled in its practicality and sense of reality. You will read true stories based on the author's own experience as a scientist, genetic counselor and journalist. She regularly interviews not only leading researchers, but also people who suffer from genetic disorders.

In Their Own Words

Personal interviews with real people provide a different view from the standard textbook descriptions, or essays written by researchers.

In Their Own Words

A Personal Look at Klinefelter Syndrome

I was diagnosed with Klinefelter syndrome (KS) a little more than a year ago, at age twenty-five, in February 1996. Being diagnosed has been . . . a big sigh of relief after a life of frustrations. Throughout my early childhood, teens, and even somewhat now, I was very shy, reserved, and had trouble making friends. I would fly into rages for no apparent reason. My parents knew when I was very young that there was something about me that wasn't right.

I saw many psychologists, psychiatrists, therapists, and doctors, and their only diagnosis was "learning disabilities." In the seventh grade, I was told by a psychologist that I was stupid and lazy, and I would never amount to anything. After barely graduating high school, I started out at a local community college. I received an associate degree in business administration, and never once sought special help. I transferred to a small liberal arts college to finish up my bachelor of science degree, and spent an extra year to complete a second degree. Then I started a job as a software engineer for an Internet-based company. I have been using computers for seventeen years and have learned everything I needed to know on my own.

To find out my KS diagnosis, I had gone to my general physician for a physical. He noticed that my testes were smaller than they should be and sent me for blood work. The karyotype showed Klinefelter syndrome, 47, XXY. After seeing the symptoms of KS and what effects they might have, I found it described me perfectly. But, after getting over the initial shock and dealing with the denial, depression, and anger, I decided that there could be things much worse in life. I decided to take a positive approach.

There are several types of treatments for KS. I give myself a testosterone injection in the thigh once every two weeks. My learning and thought processes have become stronger, and I am much more outgoing and have become more of a leader. Granted, not all of this is due to the increased testosterone level, some of it is from a new confidence level and from maturing.

I feel that parents who are finding out prior to the birth of their son (that he will have Klinefelter syndrome) or parents of affected infants or young children are very lucky. There is so much they can do to help their child have a great life. I have had most all of the symptoms at some time in my life, and I've gotten through and done well.

Stefan Schwarz
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(Stefan Schwarz runs a Boston-area support group for KS.)

Today, we know that 96 percent of XYY males are apparently normal. The only symptoms attributable to the extra chromosome may be great height, acne, and perhaps speech and reading problems. An explanation of the continued prevalence of XYY among mental-penal institution populations may be more psychological than biological. Large body size may lead teachers, employers, parents, and others to expect more of these people, and a few of them may deal with this stress by becoming aggressive.

Geneticists have never observed a sex chromosome constitution of one Y and no X. Since the Y chromosome carries little genetic material, and the gene-packed X chromosome would not be present, the absence of so many genes makes development beyond a few cell divisions in a Y embryo impossible.

KEY CONCEPTS

Polyploids have extra sets of chromosomes, while aneuploids have an extra or missing chromosome. Nondisjunction during meiosis causes aneuploidy. Trisomics are more likely to survive than monosomics, and sex chromosome aneuploidy is less severe than autosomal aneuploidy. Mitotic nondisjunction produces chromosomal mosaics.

Down syndrome (trisomy 21) is the most common autosomal aneuploid, followed by trisomies 18 and 13. Sex chromosome aneuploids include Turner syndrome (X), triplo-X females, Klinefelter syndrome (XXY), and XYY syndrome males.

11.4 Abnormal Chromosome Structure

Chromosome aberrations can involve parts of chromosomes. Many of these types of mutations arise from the rearrangement of chromosomes that occurs when they break and rejoin abnormally. When these events occur between homologs, the result is deletion or duplication of genetic material. Breakage and reunion between chromosomes that are not homologs results in an exchange of genetic material called a **translocation**. Structural defects include missing, extra, or inverted genetic material within a chromosome or exchanged chromosomal parts (figure 11.12).

Bioethics: Choices for the Future

From Iceland to *GATTACA*

This chapter has briefly introduced some of the ways that genetic research is beginning to impact our everyday lives. That effect is certain to continue. How will societies embrace and integrate the coming avalanche of genetic information? Bioethicists are already pondering how we will deal with so much information about ourselves, looking to mistakes of the past to help us wisely confront the future.

Negative forecasts of governments using genetic information to control and oppress citizens are the stuff of science fiction. The film *GATTACA*, for example, depicts a government that knows the genome sequence of every individual. A cell from a stray eyelash gives away the main character's true identity. But even science fiction can give us cause for thought. Many geneticists are concerned that a *GATTACA*-like situation is arising in Iceland. A company has government permission to collect existing health and genealogy records, to be supplemented eventually with DNA data, to establish a nationwide health sector database. The government has made vague promises of free medical care in the future if the information leads to the development of new treatments. Participation is presumed—a citizen must file a special form to opt out of the database. In most nations, such consent must be informed and voluntary.

Will a society where the government records each citizen's genome sequence become a temptation in Iceland—and elsewhere—once the human genome project is complete and the technology is available to rapidly sequence genomes? What can we do to prevent a *GATTACA*, or even establishment of a genetic database of citizens who are not entirely informed or willing to participate? Bioethicists are struggling with these questions now. Some suggestions to assure fair use of genetic information include:

- Protecting the privacy of individuals by legally restricting access to genome information.
- Preserving choice in seeking genetic tests.
- Tailoring tests to those genes most relevant to an individual.
- Refusing to screen for trivial traits, as when parents want to select a child destined to have blue eyes and black hair.
- Educating the public so that people can make knowledgeable decisions concerning genetic information, including decisions about evaluating the risks and benefits of genetic tests, judging the accuracy of forensic data, or eating genetically modified foods.

If these goals can be reached, the human genome project and the genomics era that will follow will reveal the workings of the human body at the molecular level and add an unprecedented precision and personalization to health care. This new millennium is perhaps the most exciting time ever to be studying human genetics. The field will directly affect many of us.

Bioethics: Choices for the Future

Discussions of difficult issues illuminate the complexities of applying genetic principles to everyday life.

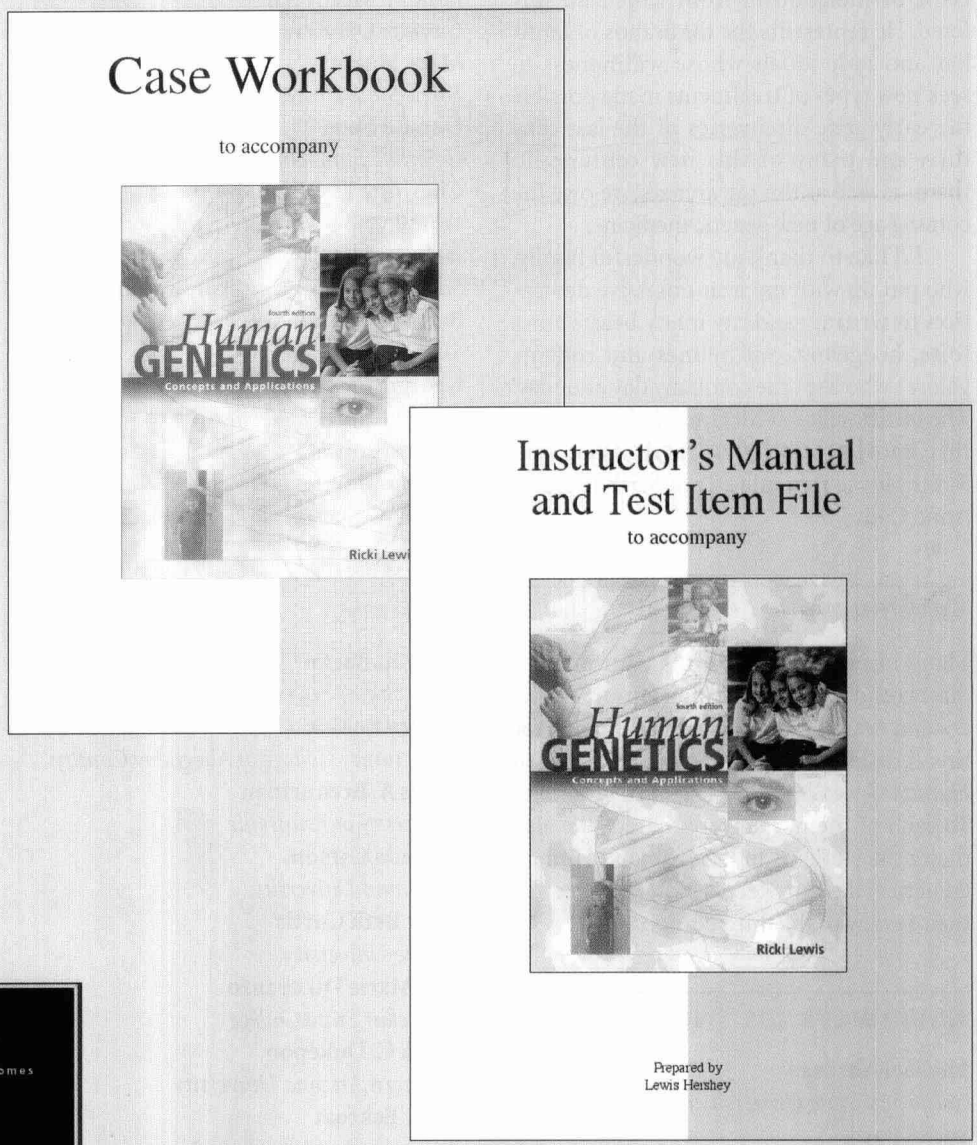
Supplements

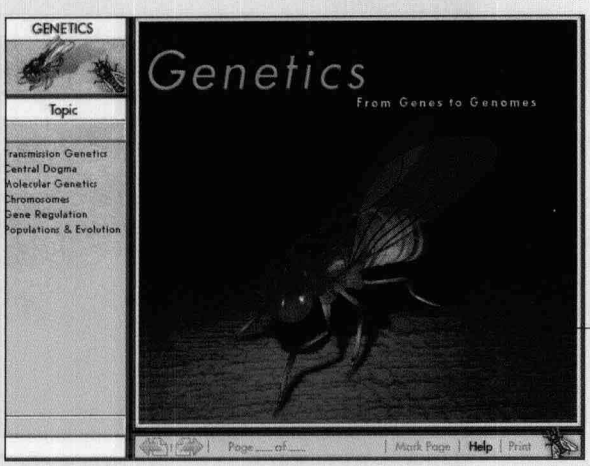
Case Workbook in Human Genetics, Second Edition

Written by Ricki Lewis, the case study approach encourages students to analyze problems in the same way geneticists do. Many new cases support fundamental concepts with real situations adapted from recent journals. An answer manual is available for the instructor.

Instructor's Manual and Test Item File

Revised by Jack Fabian, the Instructor's Manual features a chapter overview, a teaching outline, ideas for classroom discussion, internet resources and activities, correlation notes for multimedia supplements, answers to end-of-chapter questions, additional questions with answers, and multiple choice questions for testing.





Multimedia Support

- **Genetics: From Genes to Genomes CD ROM** reinforces fundamental concepts with animations and interactive exercises. Icons in the text indicate related topics on the CD.
- Lewis *Human Genetics* **website** provides additional resources for both student and instructor. Instructor may also link to the website for McGraw-Hill's *PageOut: The Course Website Development Center.*
- **Computerized Test Item File** compatible with either Windows or Macintosh.
- **Transparency Acetates** of key illustrations from the text.

Acknowledgments

This edition is dedicated to Jesse Gelsinger, the selfless young man who gave his life in a gene therapy experiment, so that babies would no longer have to die of the inborn error of metabolism from which he suffered. He represents the thousands of families and individuals whose willingness to seek new types of treatments made possible the early gene discoveries of the last century, and many of this new century. To them, as well as the researchers, we owe the coming age of new genetic medicine.

I'd like to thank my wonderful family, who put up with my near obsessive dedication to writing, and my many beasts (tortoise, hedgehog, and felines and rodents galore) who kept me company day after day. The terrific team at McGraw-Hill also made this book possible—Deborah Allen, Jim Smith, Joyce Berendes, Toni Michaels, and Anne Cody.

Reviewers

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