Human Heredity 11e

PRINCIPLES AND ISSUES

Michael R. Cummings

Human Heredity

Principles & Issues

ELEVENTH EDITION

Michael R. Cummings

Illinois Institute of Technology

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***Human Heredity: Principles and Issues*, Eleventh Edition**
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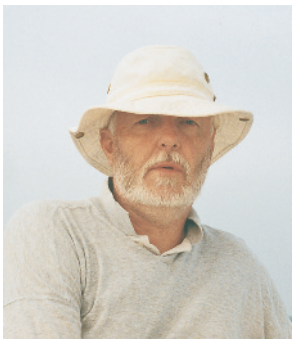
To my daughter, Kerry Eileen, whose *joie de vivre* and passion for life sustain one's faith in the human spirit.

About the Author



MICHAEL R. CUMMINGS received his Ph.D. in Biological Sciences from Northwestern University. His doctoral work, conducted in the laboratory of Dr. R. C. King, centered on ovarian development in *Drosophila melanogaster*. After a year on the faculty at Northwestern, he moved to the University of Illinois at Chicago, where for many years he held teaching and research positions. In 2003, he joined the faculty in the Department of Biology at the Illinois Institute of Technology, and currently holds the title of Research Professor.

At the undergraduate level, he has focused on teaching genetics, human genetics for nonmajors, and general biology to majors and nonmajors. He has received awards given by the university faculty for outstanding teaching, has twice been voted by graduating seniors as the best teacher in their years on campus, and has received several teaching awards from student organizations.

His current research interests involve the organization of DNA sequences in the short-arm and centromere region of human chromosome 21. He is engaged in a collaborative effort to construct a physical map of this region of chromosome 21 for the purpose of exploring molecular mechanisms of chromosome interactions.

In addition to *Human Heredity*, Dr. Cummings is the author and coauthor of a number of other widely used college textbooks, including *Biology: Science and Life*; *Concepts of Genetics*; *Genetics: A Molecular Perspective*; *Essentials of Genetics*; and *Human Genetics and Society*. He has also written articles on aspects of genetics for the *McGraw-Hill Encyclopedia of Science and Technology* and has published a newsletter on advances in human genetics for instructors and students.

He and his wife, Lee Ann, are the parents of two adult children, Brendan and Kerry, and have two grandchildren, Colin and Maggie. He is an avid sailor, enjoys reading and collecting books (biography, history), appreciates music (baroque, opera, and urban electric blues), and is a long-suffering Cubs fan.

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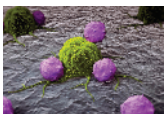

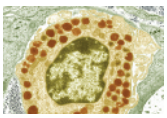

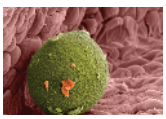

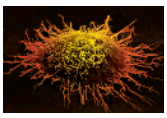

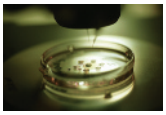

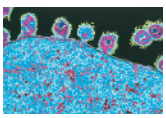

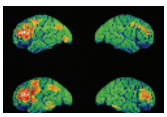

Preface

Genetics is a relatively young science that has made major strides since the beginning of the twentieth century. A closer examination reveals that progress in genetics, like all science, moves forward in fits and starts. At the moment, unexpected discoveries are opening new subdisciplines, re-energizing old ones, and expanding the role of genetics as one of the foundations of biology. For example, epigenetics is providing answers to old questions and is rapidly emerging as an important field linking the environment with the genome and providing insights into the evolution of our species. New approaches in gene therapy offer hope that this field can finally live up to the hopes and expectations that it can be used to treat genetic disorders. Other findings are also rapidly moving from the laboratory to medical practice. These include discoveries about the role of stem cells in the development of cancer and the mobilization of the immune system to fight cancer. The contents of this edition, like the others that have preceded it, have been extensively rewritten and updated to reflect these discoveries, but as with past editions, the underlying rationale and aims have remained constant.

This book is written for a one-term human genetics course for students in humanities, social sciences, business, engineering, and other fields. It assumes that the students who come to this course will have little or no background in biology, chemistry, or mathematics and will have personal, professional, or intellectual reasons for wanting to learn something about human genetics. The book is also intended to serve those who will become *consumers* of genetic-based health care services and those who may become *providers* of health care services.

Because genetic knowledge and technology is rapidly being transferred to many areas of our society, it is imperative that the general public, elected officials, and policy makers outside the scientific community have a working knowledge of genetics to help shape how genetics and its associated technologies will be used in our society. To communicate this knowledge, *Human Heredity* is written to transmit the principles of genetics in a straightforward and accessible way, without unnecessary jargon, detail, or the use of anecdotal stories in place of research-based content. Some descriptive chemistry is used after an appropriate introduction and definition of terms. In the same vein, no advanced math skills are required to calculate elementary probabilities or to calculate genotype and allele frequencies.

Goals of the Text

From its beginnings, this book has held to a few simple goals for teaching students about human genetics. This edition continues that tradition with the following goals:

1. Present the concepts underlying human genetics in clear, concise, jargon-free language to give students a working knowledge of genetics. Each chapter presents a limited number of clearly stated concepts and examples to assist learning a complex topic.
2. Begin each chapter with a relevant example in the form of a case study that nonmajors can understand and which provides examples that students can apply to themselves, their families, and their work environments.

3. Examine the social, cultural, and ethical implications associated with the use of genetic technology.
4. Explain the origin, nature, and amount of genetic diversity present in the human population and how that diversity has been shaped by natural selection.

To achieve these goals, emphasis has been placed on clear writing and the use of accompanying photographs and artwork that teach rather than merely illustrate the ideas under discussion.

Organization

Although it is without formal divisions, the text is organized into four sections: Chapters 1 through 7 cover cell division, transmission of traits from generation to generation, and development. Chapters 8 through 12 emphasize molecular genetics, mutation, and cancer. Chapters 13 through 16 include recombinant DNA technology, genomics, and biotechnology. These chapters cover the basic methods of genetic technology and how they are used in agriculture, medicine, and the biotechnology industry. In addition, these chapters cover genetic screening, genetic testing, and genetic counseling. Chapters 17 through 19 cover specialized topics: the immune system, the genetics of behavior, and population genetics and human evolution.

Instructors teaching genetics to nonmajors come from many different backgrounds and use a wide range of instructional formats, including active learning, peer-to-peer instruction, and adaptive learning. To facilitate this array of approaches, the book is organized to allow both students and instructors to use the material no matter what order of topics is selected. After the first section, the chapters can be used in any order. Within each chapter, outlines and end-of-chapter activities let the instructor and students easily identify and explore central ideas.

What's New in the Eleventh Edition

Each chapter has been updated to reflect the latest advances in genetics. Listed below are some of the most significant revisions in this edition.

Chapter 1: A Perspective on Human Genetics

- New chapter opening photo
- New opening case study on translational medicine
- Revised and updated text throughout

Chapter 2: Cells and Cell Division

- Text edited throughout for clarity
- Revised Figure 2.6 The Nucleus
- Revised Figure 2.7 The Cell Cycle

Chapter 3: Transmission of Genes from Generation to Generation

- Revised Section 3-3 Mendel's Experimental Design
- Revised Section 3-4 Crossing Pea Plants

Chapter 4: Pedigree Analysis in Human Genetics

- New chapter opening photo
- Edited and revised Section 4-2 Pedigree Analysis
- Revised Section 4-3 Autosomal Recessive Traits
- Revised Section 4-4 Autosomal Dominant Traits
- Replaced Figure 4.20 OMIM Home Page
- Redrawn Figure 4.23 Common Autosomal Trait

Chapter 5: The Inheritance of Complex Traits

- Revised Section 5-2 Polygenic Traits Are Controlled by Two or More Genes
- Revised Section 5-3 Complex Traits and Variation in Phenotype
- Revised Section 5-9 Skin Color and IQ Are Complex Traits

- Replaced and updated Figure 5.12 Obesity in the United States
- New Figure 5.17 Skin Color and Latitude

Chapter 6: Cytogenetics: Karyotypes and Chromosome Aberrations

- Revised Section 6-2 The Human Chromosome Set
- Section 6-4 Analyzing Karyotypes, new subsection on noninvasive prenatal diagnosis
- Revised Section 6-7 Sex Chromosome Aneuploidy
- New Figure 6.1 Human Chromosome
- New Figure 6.2 Telomeres
- New Figure 6.12 Free Fetal DNA

Chapter 7: Development and Sex Determination

- New chapter opening photo
- Revised Section 7-2 The Human Reproductive System
- Revised Section 7-3 Human Development
- Revised Figure 7.10 Sex Determination
- Revised Figure 7.11 The Segregation of Sex Chromosomes

Chapter 8: The Structure, Replication, and Chromosomal Organization of DNA

- Revised Section 8-3 The Chemistry of DNA
- Revised Section 8-6 DNA Replication

Chapter 9: Gene Expression and Gene Regulation

- Revised Section 9-4 Tracing the Flow of Genetic Information
- Revised Section 9-6 Translation Requires the Interaction of Several Components
- Revised Section 9-9 Several Mechanisms Regulate the Expression of Genes
- New Figure 9.5 mRNA Processing
- New Figure 9.8 Transfer RNA Molecule
- New Figure 9.13 Prion Protein Folding
- Revised Table 9.2 Amino Acids Commonly Found in Proteins

Chapter 10: From Proteins to Phenotypes

- Revised Section 10-4 Phenylketonuria: A Mutation That Affects an Enzyme
- Revised Section 10-8 Pharmacogenetics and Pharmacogenomics

Chapter 11: Genome Alterations: Mutation and Epigenetics

- Reorganized and revised entire chapter
- Revised and expanded Section 11-3 Detecting Mutations and Measuring Mutation Rates
- New Section 11-4 Mutations Can Be Spontaneous or Induced
- Revised Section 11-5 Mutations at the Molecular Level
- Revised Section 11-6 Mutations Can Be Repaired
- Revised Section 11-8 Epigenetic Changes
- New Figure 11.4 Errors in DNA Replication
- New Figure 11.5 Base Pairing in Tautomeric Shifts
- New Figure 11.13 Proofreading in DNA Polymerase
- Revised Figure 11.14 Base-Pair Substitutions
- New Figure 11.15 A DNA Repair System
- New Figure 11.19 Epigenetic Changes to DNA
- New Figure 11.24 The Hypothalamus

Chapter 12: Genes and Cancer

- Revised Section 12-5 Cancer-Causing Mutations
- Revised Section 12-7 Mutant Cancer Alleles
- Revised Section 12-10 Genomics, Epigenetics, and Cancer
- Revised Figure 12.5 The Eukaryotic Cell Cycle
- New Figure 12.6 Normal and Mutant Tumor-Suppressor Genes
- Revised Figure 12.16 Gene Fusion in 9;22 Translocation
- New Figure 12.19 Cigarette Consumption and Lung Cancer
- Updated Table 12.1 Estimated New Cancer Cases
- Updated Table 12.3 Colorectal Cancer in the United States
- New Table 12.7 Cancer-Related Genes Inactivated by Hypermethylation

Chapter 13: An Introduction to Genetic Technology

- Revised Section 13-5 Finding a Specific Gene in a Library
- New Figure 13.12 Extinct Ground Sloth

Chapter 14: Biotechnology and Society

- Revised Section 14-6 DNA Profiles as Tools for Identification
- Revised Table 14.1 Some Products Made by Recombinant DNA Technology

Chapter 15: Genomes and Genomics

- Revised Section 15-6 What Have We Learned So Far About the Human Genome?
- New Section 15-8 The Human Microbiome Is Our Other Genome
- Revised Section 15-9 Proteomics Is an Extension of Genomics
- Revised Figure 15.5 History and Timeline for Genome Projects
- New Figure 15.11 Single Nucleotide Polymorphisms
- New Figure 15.14 Body Sites Sampled for Human Microbiome Project

Chapter 16: Reproductive Technology, Genetic Testing, and Gene Therapy

- Revised Section 16-3 Assisted Reproductive Technologies
- Revised Section 16-5 Genetic Testing and Screening
- Section 16-6 Therapy for Genetic Disorders, new subsection on exon skipping therapy
- New Figure 16.7 Stages in the IVF Procedure
- New Figure 16.8 Injection of Single Sperm into Egg
- Revised Figure 16.16 Gene Therapy
- New Figure 16.17 Exon Skipping
- Revised and updated Figure 16.18 Gene Therapy Clinical Trials 2014
- New Table 16.3 History of Gene Therapy

Chapter 17: Genes and the Immune System

- Revised Section 17-7 Organ Transplants Must Be Immunologically Matched
- Revised Section 17-8 Disorders of the Immune System
- New Figure 17.16 Herrick Twins
- New Figure 17.18 Jim Finn
- New Figure 17.19 Allergic Response
- Revised Table 17.5 Some Autoimmune Diseases

Chapter 18: Genetics of Behavior

- Reorganized and revised
- Revised Section 18-2 Models, Methods, and Phenotypes in Studying Behavior
- New Section 18-3 The Nervous System Is the Focus of Behavior Genetics
- Revised Section 18-4 Single-Gene Mutations Cause Behavioral Disorders
- Revised Section 18-5 Huntington Disease Is a Model for Neurogenerative Disorders
- Revised Section 18-6 Animal Models: The Search for Behavior Genes
- Revised Section 18-7 The Genetics of Complex Behavioral Disorders
- Section 18-8 Genetics and Social Behavior, new subsection on addictive behavior
- New Figure 18.2 The Human Nervous System
- New Figure 18.3a Synapses and Synaptic Transmission
- New Figure 18.11 Genetic Relationship Between Psychiatric Disorders
- New Figure 18.14 Heritability of Addictive Behaviors
- Revised Figure 18.15 Metabolism of Alcohol
- Revised Table 18.2 Selected Neurotransmitters and Some Processes They Affect
- New Table 18.3 Selected Recreational Drugs and the Neurotransmitters They Mimic
- New Table 18.4 Some Behavioral Disorders Associated with Synaptic Defects
- New Table 18.5 Important Risk Factor Genes for Alzheimer Disease
- New Table 18.6 Genes Involved in Nicotine Addiction

Chapter 19: Population Genetics and Human Evolution

- Revised Section 19-7 The Evolutionary History and Spread of Our Species
- Revised Section 19-8 Genomics and Human Evolution
- New Figure 19.11 Hominin Evolution
- New Figure 19.14 Cave in Denisova, Siberia

Features of the Book

Numbered Chapter Outlines

The beginning of each chapter contains an outline of the primary headings, providing an overview of the main concepts, secondary ideas, and examples. To help students grasp the central points, many of the headings are written as narratives or summaries of the ideas that follow. These outlines also serve as convenient starting points for students to review the material in each chapter. To make the outlines more useful, they have been numbered sequentially and used to organize the summary, the questions, and the problems at the end of each chapter. In this way, students can relate examples and questions to specific topics in the chapter more easily and clearly.

First Section Case Studies

The first section of each chapter contains a case study that is directly related to the main ideas of the chapter, often drawn from real life. Topics include the use of DNA fingerprinting in court cases, the cloning of milk cows, the use of exome sequencing to diagnose a genetic disorder, and the development of *in vitro* fertilization (IVF) and the birth of Louise Brown—the first IVF baby. These case studies are designed to promote student interest in the topics covered in the chapter and to demonstrate that laboratory research often has a direct impact on everyday life. These case studies are linked to another case presented in the ***Genetics in Practice*** section at the end of the chapter.

The Genetic Revolution

The Genetic Revolution is a feature that emphasizes the past, present, and future impact of genetic technology on our daily lives, from genetic testing at birth to the future of cancer therapy. Accompanying questions are designed to be used for classroom discussion, research topics, and student presentations.

Exploring Genetics

Exploring Genetics feature boxes present ideas and applications that are related to and extend the central concepts in a chapter. Some of these examine controversies that arise as genetic knowledge is transferred into technology and services. Accompanying questions are designed to be used for classroom discussion, research topics, and student presentations.

Marginal Glossary

A glossary in the page margins gives students immediate access to definitions of terms as they are introduced in the text. This format also allows definitions to be identified when students are studying or preparing for examinations. The definitions have been gathered into an alphabetical glossary at the back of the book. Because an understanding of the concepts of genetics depends on understanding the relevant terms, more than 350 terms are included in the glossary.

End-of-Chapter Features

Genetics in Practice: Relevant Case Studies

A case study is included at the end of each chapter, illustrating the impact of genetics in our society. These contain scenarios and examples of genetic issues related to health, reproduction, personal decision making, public health, and ethics. Many of the case studies and the accompanying questions can be used for classroom and other activities.

Summary

Each chapter ends with a summary that restates the major ideas covered in the chapter. The beginning outline and ending summary for each chapter use the same content and

order to emphasize major concepts and their applications. Each point of the summary outline is followed by a brief restatement of the chapter material covered under the same heading. This helps students recall the concepts, topics, and examples presented in the chapter. It is hoped that this organization will minimize the chance that they will attempt to learn by rote memorization.

Questions and Problems

The summary's focus on the chapter's main points is continued in the ***Questions and Problems*** at the end of each chapter. The questions and problems are presented under the headings from the chapter outline. This allows students to relate the problems and questions to specific topics presented in the chapter, focus on concepts they find difficult, and work the problems that illustrate those topics. The questions and problems are designed to test students' knowledge of the facts and their ability to reason from the facts to conclusions. To this end, they use an objective question format and a problem-solving format. Because some quantitative skills are necessary in human genetics, almost all chapters include some problems that require students to organize the concepts in the chapter and use those concepts in reasoning to a conclusion. Answers to selected problems are provided in an appendix. Answers to all questions and problems are available in the Instructor's Manual on the password-protected Instructor Companion Site.

Pedagogical Features

Genomic Databases as Resources

To make students aware of the array of genomic resources available to them, genetic disorders mentioned in the book are referenced by their indexing numbers from the comprehensive catalog available online as *Online Mendelian Inheritance in Man* (*OMIM*). OMIM (updated daily) contains text, pictures, and videos, along with literature references. Through Entrez, OMIM is cross-linked to databases containing DNA sequences, protein sequences, chromosome maps, and other resources. Students and an informed public need to be aware of the existence and relevance of such databases, and to be up to date, textbooks must incorporate these resources.

Students can use OMIM to obtain detailed information about a genetic disorder, its mode of inheritance, its phenotype and clinical symptoms, mapping information, biochemical properties, the molecular nature of the disorder, and a bibliography of relevant papers. In the classroom, OMIM and its links are valuable resources for student projects and presentations.

Online Learning and Teaching Solutions

The online learning and teaching solutions that accompany this edition are designed to aid student learning as well as to assist the instructor in preparing lectures and examinations and in keeping abreast of the latest developments in the field. Instructor materials are available to qualified adopters. Please consult your local Cengage learning consultant for details. You may also visit the Brooks/Cole biology site at ***www.cengage.com/biology*** to see samples of these materials, request a desk copy, locate your learning consultant, or purchase a copy online.

MindTap for Biology

MindTap is a fully online, highly customizable learning experience built upon Cengage Learning content. MindTap combines student learning tools—readings, multimedia, activities, and assessments—into a singular Learning Path that guides students through their course. Instructors personalize the experience by customizing authoritative Cengage Learning content and learning tools, including the ability to add their own content in the Learning Path via apps that integrate into the MindTap framework seamlessly with Learning Management Systems. New to this edition! Chapter opening videos, assignable homework, and a digital Study Guide.

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- Cross-compatible capability. Import and export content into other systems.

Instructor Companion Site

Everything you need for your course in one place! This collection of book-specific lecture and class tools is available online via ***www.cengage.com/login***. Access and download PowerPoint presentations, images, instructor's manual, videos, and more.

Cooperative Learning: Making Connections in General Biology, Second Edition

A collection of separate, ready-to-use, short cooperative activities that have broad application for first-year biology courses. They fit perfectly with any style of instruction, whether in large lecture halls or flipped classrooms. The activities are designed to address a range of learning objectives, such as reinforcing basic concepts, making connections between various chapters and topics, data analysis and graphing, developing problem solving skills, and mastering terminology. Since each activity is designed to stand alone, this collection can be used in a variety of courses and with any text. Authored by Mimi Bres and Arnold Weisshaar.

A Problem-Based Guide to Basic Genetics

Provides students with a thorough and systematic approach to solving transmission genetics problems, along with numerous solved problems and practice problems. Written and illustrated by Donald Cronkite of Hope College.

Virtual Biology Laboratories: Genetics and Genetics 2 (Pedigree Analysis) Modules

These "virtual" online experiments expose students to the tools used in modern biology, support and illustrate lecture material, and allow students to "do" science by performing experiments, acquiring data, and using the data to explain biological phenomena.

Gene Discovery Lab

This is a CD-ROM lab manual that provides a virtual laboratory experience for the student in doing experiments in molecular biology. It includes experiments that use nine of the most common molecular techniques in biology, an overview of scientific method and experimental techniques, and Web links to provide access to data and other resources.

Acknowledgments

Over the course of eleven editions, many reviewers have given their time to improve the pedagogy, presentation of concepts, and ways of inspiring students. From edition to edition, a number of reviewers went to extraordinary lengths to keep my ideas and writing on the straight and narrow path and to make suggestions that have greatly improved the book. George Hudock of Indiana University, H. Eldon Sutton of the University of Texas, and Werner Heim of Colorado College generously gave me access to their collective wisdom, and helped me learn and relearn many of the nuances involved in writing about genetics. I am most grateful for their efforts.

In the last edition, Daniel Friderici of Michigan State University examined the text, figures, and problems from a student's point of view, and helped me present each chapter's important concepts in a straightforward and engaging way. In addition, I greatly appreciate his many suggestions on how to improve the end-of-chapter questions, problems, and how to frame the answers so that the questions become effective teaching tools. I am also very grateful to Patricia Matthews of Grand Valley State University who spent many hours scrutinizing the text, helping me clarify and streamline my writing, pointing out inconsistencies in word use, and improving the flow of ideas throughout the text.

To all the reviewers who helped in the preparation of this and previous editions, I offer my thanks and gratitude for their efforts.

Ted W. Fleming, *Bradley University*
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Pamela L. Hanratty, *Indiana University*
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Brenda Knotts, *Eastern Illinois University*
Clint Magill, *Texas A&M University*
Robert L. Snyder, *State University of New York, Potsdam*
Jan Trybula, *State University of New York, Potsdam*
Jo Ann Wilson, *Florida Gulf Coast University*
Elizabeth T. Wood, *University of Arizona*
Denise Woodward, *Pennsylvania State University*

At Cengage Learning, it was once again a pleasure to work with Peggy Williams, Senior Product Manager. Her vision about how to increase the pedagogical value of texts and her extensive knowledge of the market have strengthened and enhanced the book. Hal Humphrey was the content project manager who pulled together all the resources and people needed to put this edition together. The content developer, Suzannah Alexander, oversaw the preparation of this edition. Her attention to detail and gentle nudging kept the project on schedule.

Lauren Oliveira , Casey Lozier, and Kellie Petruzzelli coordinated the digital package for the book. Photo research was handled by Priya Subbrayal at PreMedia Global, whose hard work provided many excellent choices for photos.

Lynn Lustberg at MPS Limited eased the book through all the twists and turns involved in production.

Contacting the Author

I welcome questions and comments from faculty and students about the book or about questions and issues related to human genetics. Please contact me at: cummings.chicago@gmail.com.

Michael R. Cummings

Human Heredity

1 A Perspective on Human Genetics

CHAPTER OUTLINE

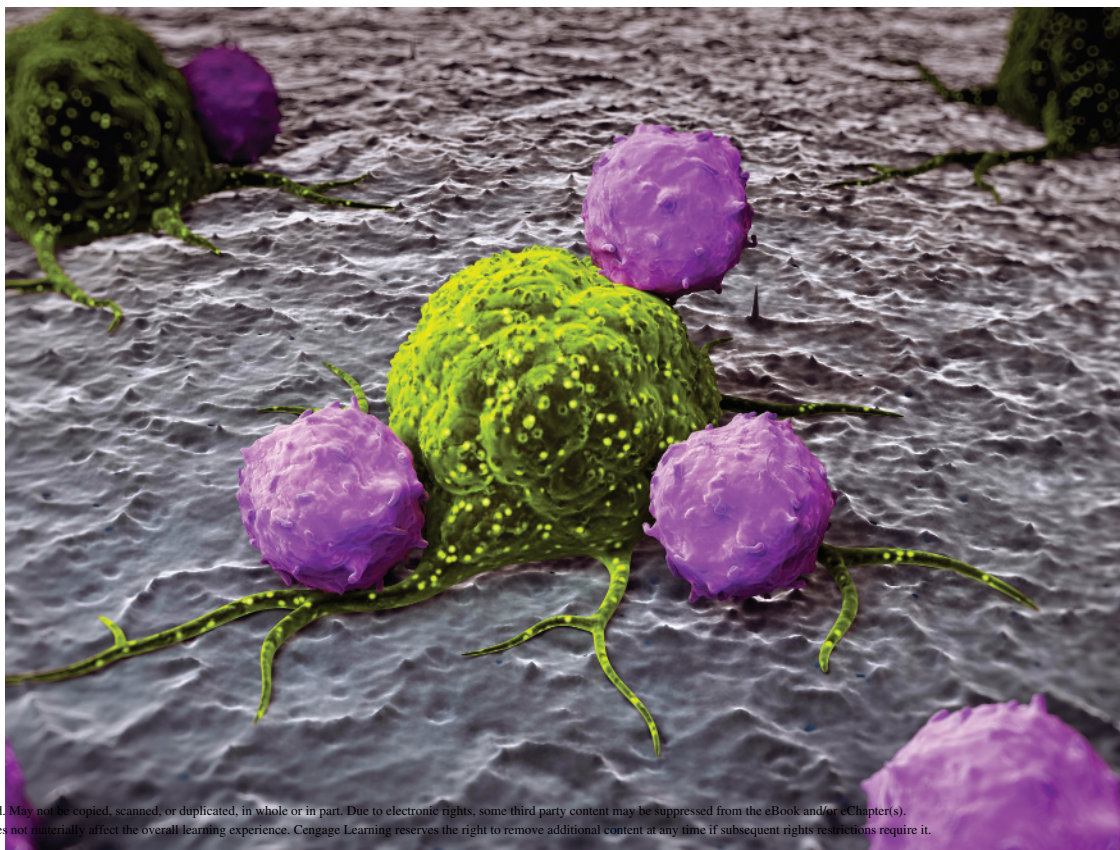
1-1 Genetics and Translational Medicine

CASE STUDY

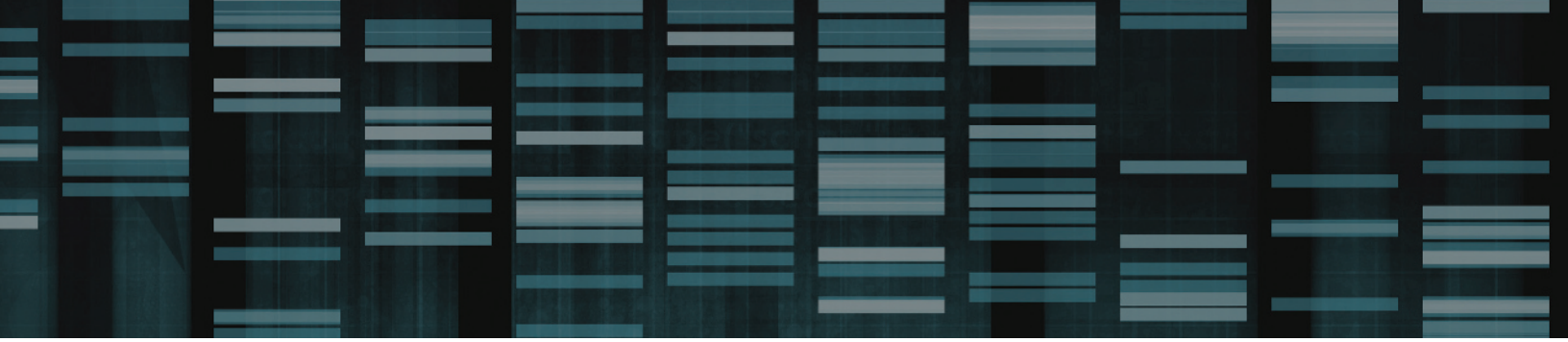
Cancer is a feared and devastating disease that will affect one in three Americans in their lifetime. Although the number of cancer deaths has declined in recent decades, one in four deaths in the United States is still caused by cancer. Because age is the greatest risk factor for cancer, more than 75% of new cancer cases occur in those who are 55 and older. This segment of the population is increasing in size, and, as a result, cancer may soon become the leading cause of death in the United States.

However, results from the Human Genome Project and the development of new technologies have revolutionized the detection, diagnosis, and treatment of cancer, offering optimism that the impact of cancer as a public health problem can be reduced. Researchers and clinicians are now working together to rapidly move new genetic discoveries from the laboratory to the hospital bedside, a process called **translational medicine**. The diagnosis and treatment of cancer is a high priority for many of those working in translational medicine.

Translational medicine The union of research and medicine that seeks to quickly translate research findings into methods for the diagnosis and treatment of diseases.



Cells of the immune system (purple) attacking a cancer cell (green).



One of the most promising new methods involves stimulating the immune system to identify, attack, and kill cancer cells. This method, called **immunotherapy**, is one example of how basic research on the immune system developed into one of the newest and most promising tools in cancer treatment.

Immunotherapy A method for treating disease by stimulating or enhancing an immune response.

The immune system is a collection of organs, cells, and molecules produced by these cells that help protect the body against infection by viruses, bacteria, and other disease-causing agents. The immune system works by attacking anything recognized as foreign, usually by first detecting molecules on the surface of invading viruses and cells and then mobilizing to attack and inactivate or kill the invader. Cancer cells often carry surface molecules that are not recognized by the immune system. Sometimes the immune system recognizes the cancer cells as foreign but does not respond strongly enough to kill all the malignant cells. Some cancers evade the immune system by producing molecules that repress the immune response.

Scientists at the University of Pennsylvania worked to reprogram immune cells so they would recognize, attack, and kill cancerous cells. Their target was abnormal immune system cells that cause leukemia. Basic research had discovered that normal white blood cells (called B cells) and cancerous B cells that cause leukemia carry a unique surface protein called CD-19. If immune cells could be reprogrammed to attack and kill all cells carrying this protein, the treatment might bring about remission. To do this, the scientists removed immune cells from a 64-year-old man with an advanced form of leukemia called CLL. In the laboratory, the immune cells were genetically reprogrammed by inserting a gene that encodes a surface protein that binds to the CD-19 protein and triggers the death of CLL cells. The immune cells also received instructions to produce chemical signals that would trigger multiplication of other immune cells to focus on total destruction of the leukemia cells.

After modification, the immune cells were returned to the affected man's body in the hope that they would identify and kill all the cancerous cells. For the first 2 weeks after treatment, there were no changes in the number of cancer cells, although blood tests showed a large increase in the number of genetically modified immune cells. However, on day 14, the patient developed chills, nausea, and fever and tumor cells began to die in large numbers. By 28 days after treatment, there were no signs of leukemia. This therapy was extended to two other patients with advanced forms of CLL. One patient experienced complete remission; the other had temporary remission, followed by a relapse and death. In spite of the small number of patients treated and one death, the results were considered a success. The only other available treatment was a bone marrow transplant, a procedure that has a 20% risk of death and only a 50% chance of success for the survivors.

This work spurred efforts by other research teams to develop similar methods to kill leukemia cells, and the field of immunotherapy was born. In 2013, the University of Pennsylvania team reported that 15 of 32 individuals with CLL responded to immunotherapy, with 7 showing complete remission. Treatment of individuals with a form of leukemia called ALL showed 86% remission in children and 100% remission at 6 months after treatment in adults. These encouraging results led a leading scientific journal to select cancer immunotherapy as the scientific breakthrough of the year for

2013. The University of Pennsylvania has entered into an agreement with a large pharmaceutical company to further develop and market immunotherapy.

Immunotherapy doesn't help everyone with cancer, and more research is needed to understand why. But the survival of so many individuals with advanced disease gives new hope that linking genetic research with clinical medicine will dramatically change the way cancer is treated.

1-2 Genetics Is the Key to Biology

Genetics The scientific study of heredity.

Trait Any observable property of an organism.

As the first step in studying human genetics, we should ask, what *is* genetics? As a working definition, we can say that **genetics** is the scientific study of heredity. Like all definitions, this leaves a lot unsaid. To be more specific, what geneticists do is study how **traits** (such as eye color and hair color) and diseases (such as cystic fibrosis and sickle cell anemia) are passed from generation to generation. They also study the molecules that make up genes and gene products as well as the way in which genes are turned on and off. Some geneticists study why variants of some genes occur more frequently in one population than in others. Other geneticists work in industry to develop products for agricultural and pharmaceutical firms. This work is part of the biotechnology industry, which is now a multi-billion-dollar component of the U.S. economy.

In a sense, genetics is the key to all of biology; genes control what cells look like and what they do as well as how babies develop and how we reproduce. An understanding of what genes are, how they are passed from generation to generation, and how they work is essential to our understanding of all life on Earth, including our species, *Homo sapiens*.

In the chapters that follow, we will ask and answer many questions about genetics: How are genes passed from parents to their children? What are genes made of? Where are they located? How do they encode products called proteins, and how do proteins create the differences among individuals that we can see and study? Because this book is about human genetics, we will use human genetic disorders as examples of inherited traits (see Exploring Genetics: Genetic Disorders in Culture and Art). We will also examine how genetic knowledge and genetic technology interact with and shape many of our social, political, legal, and ethical institutions and policies.

Items about some aspect of human genetics appear in the media on a daily basis. These stories may report the discovery of a gene responsible for a genetic disorder, a controversy about genetic testing, or a debate on the wisdom of genetically modifying our children. In many cases, as we will see, technology is far ahead of public policy and laws. To make informed decisions about genetics and biotechnology in your personal and professional life, you will need to have a foundation based on a knowledge of genetics. In the rest of this chapter, we will preview some of the concepts of human genetics that are covered in more detail later in the book and introduce some of the social issues and controversies generated by genetic research. Many of these concepts and issues are explored in more detail in the chapters that follow.

1-3 What Are Genes and How Do They Work?

Gene The fundamental unit of heredity and the basic structural and functional unit of genetics.

DNA A helical molecule consisting of two strands of nucleotides that is the primary carrier of genetic information.

Simply put, a **gene** is the basic structural and functional unit of genetics. In molecular terms, a gene is a string of chemical subunits (nucleotides) in a **DNA** molecule (**Figure 1.1**). (DNA is shorthand for deoxyribonucleic acid.) There are four different nucleotides in DNA, each composed of a sugar, a base, and a phosphate group. The nucleotides are abbreviated as single letters:

- A for adenine
- T for thymine
- G for guanine
- C for cytosine

EXPLORING GENETICS

Genetic Disorders in Culture and Art

It is difficult to pinpoint the time in history when the inheritance of specific traits in humans was first recognized. Descriptions of people with heritable disorders appear in myths and legends of many cultures. In some of these cultures, assigned social roles—from prophets and priests to kings and queens—were hereditary. The belief that certain traits were heritable helped shape the development of many social customs.

Steve Cole/Getty Images

In some societies, the birth of a deformed child was regarded as a sign of impending war or famine. Clay tablets excavated from Babylonian ruins record more than 60 types of birth defects, along with the dire consequences thought to accompany such births. Later societies, from Roman to those of eighteenth-century Europe, regarded malformed individuals (such as dwarfs) as curiosities rather than figures of impending doom; they were highly prized by royalty as courtiers and entertainers.

Over the millennia, artists have portrayed both famous and anonymous individuals with genetic disorders in paintings, sculptures, and other forms of the visual arts. These portrayals are detailed, highly accurate, and easily recognizable today. In fact, across time, culture, and artistic medium, affected individuals in these portraits often resemble each other more closely than they do their siblings, peers, or relatives. In some cases, the representations allow a disorder to be diagnosed at a distance of several thousand years.

Throughout the book, you will find fine-art representations of individuals with genetic disorders. These portraits represent a long-standing link between science and the arts in many cultures. They are not intended as a gallery of freaks or monsters but as a reminder that being human encompasses a wide range of conditions. A more thorough discussion of genetic disorders in art is in *Genetics and Malformations in Art* by J. Kunze and I. Nippert, published by Grosse Verläg, Berlin, 1986.

Questions

1. Ancient societies used knowledge that traits are heritable in domesticating animals and developing agricultural crops. What might account for the failure to recognize that the same processes operate in humans?
2. Why do unrelated children with a disorder such as Down syndrome resemble each other more closely than they do their siblings?

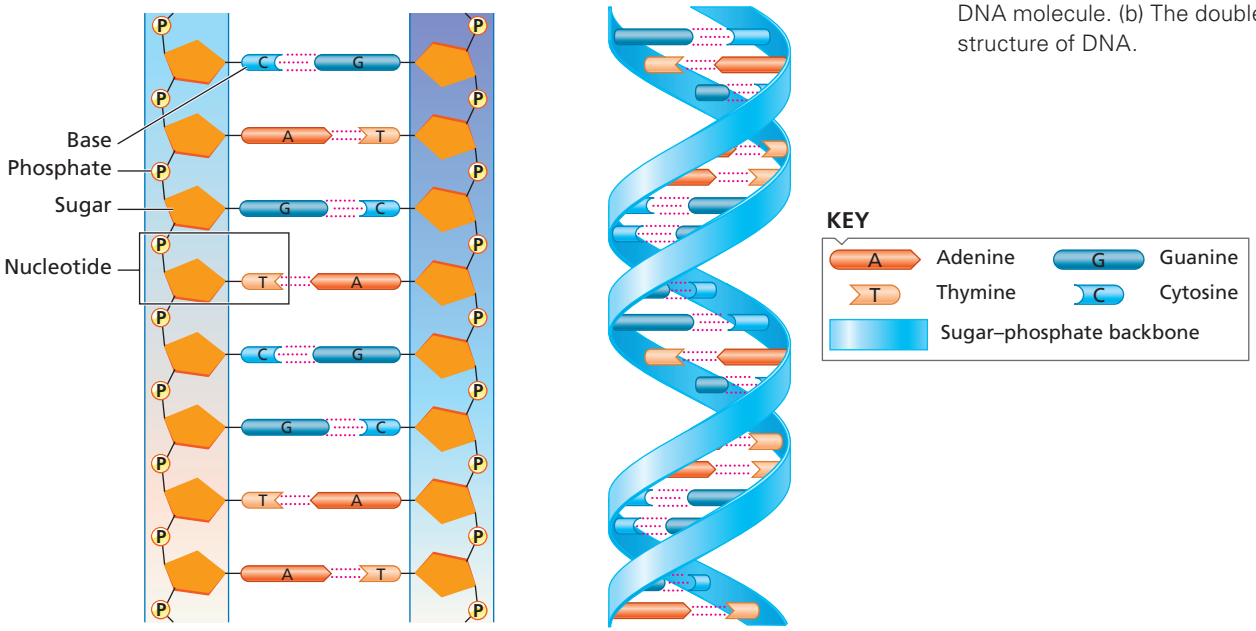
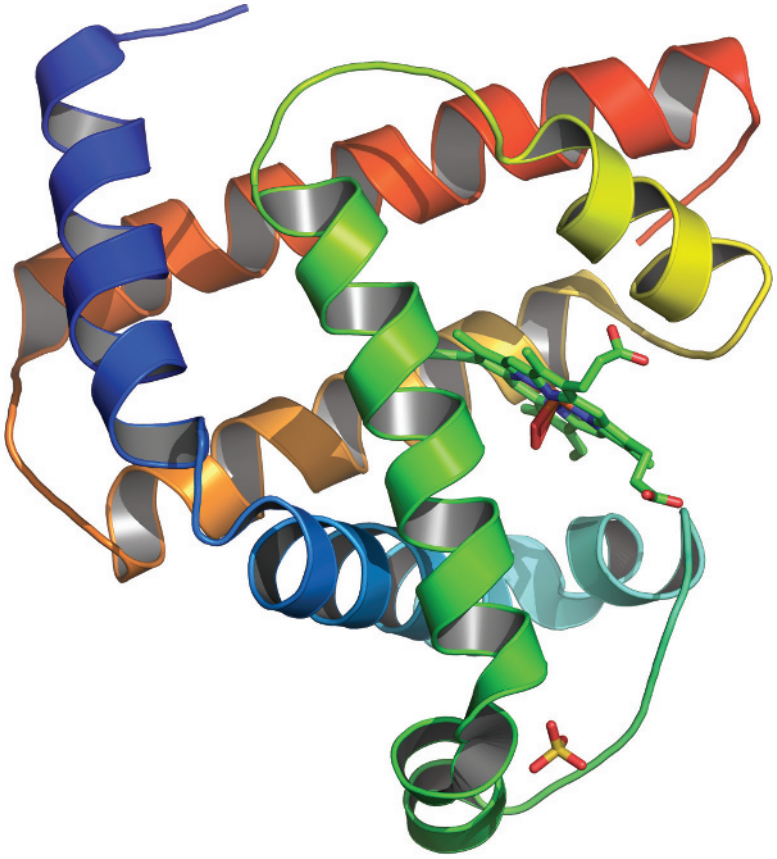


FIGURE 1.1 (a) Genes are composed of a sequence of nucleotides in a DNA molecule. (b) The double helix structure of DNA.

(a) Genes are sequences of nucleotides in DNA

(b) DNA molecule showing arrangement of polynucleotide strands



Carl Fürstenberg

FIGURE 1.2 The three-dimensional structure of a protein.

Combinations of these four nucleotides in the form of genes store all the genetic information carried by an individual. The nucleotide sequence encoded in a gene defines the chemical subunits (amino acids) that make up gene products (proteins). When a gene is activated, its stored information is decoded and used to make a polypeptide, which folds into a three-dimensional shape and becomes a functional protein (**Figure 1.2**). The action of proteins produces characteristics we can see (such as eye color or hair color) or measure (blood proteins or height). Understanding how different proteins are produced and how they work in the cell are important parts of genetics. We will cover these topics in Chapters 9 and 10.

We can also define genes by their properties. Genes are copied (replicated), they undergo change (mutate), they are expressed (they can be switched on or off), and they can move from one chromosome to another (recombine). In later chapters, we will explore these properties and see how alterations in these processes result in genetic disease.

National Library of Medicine

FIGURE 1.3 Gregor Mendel, the Augustinian monk whose work on pea plants provided the foundation for genetics as a scientific discipline.

1-4 How Are Genes Transmitted from Parents to Offspring?

Thanks to the work of Gregor Mendel (**Figure 1.3**), a European monk who lived in the nineteenth century, we know how genes are passed from parents to offspring in plants and animals, including humans. When Mendel began his experiments, many people thought that traits carried by parents were blended together in their offspring. According to this idea, crossing a plant with red flowers and one with white flowers should produce plants with pink flowers (the pink color is a blend of red and white). Mendel's experiments on pea plants showed that genes are passed intact from generation to generation and that traits are not blended. As we will see, however, things are

not always simple. There are cases in which crossing plants with red flowers and plants with white flowers *does* produce plants with pink flowers. We will discuss these cases in Chapter 3 and show that crosses between plants with red flowers and plants with white flowers that produce plants with pink flowers do not contradict the principles of inheritance discovered by Mendel.

Working at a monastery in what is now the Czech Republic, Mendel conducted research on the inheritance of traits in pea plants for more than a decade. He chose parental plants that each had a different distinguishing characteristic, called a trait. For example, Mendel bred tall pea plants with short pea plants. Plant height is the trait in this case and has two variations: tall and short. He also bred plants carrying green seeds with plants having yellow seeds. In this work, seed color is the trait; green and yellow are the variations of the trait he studied. In these breeding experiments, he wanted to see how traits such as height and seed color were passed from generation to generation.

Mendel kept careful records of the number and type of traits present in each generation. He also recorded the number of individual plants that carried each trait. He discovered patterns in the way traits were passed from parent to offspring through several generations. Based on those patterns, Mendel concluded that traits such as plant height and seed color are passed from generation to generation by "factors" that are transmitted from parent to offspring. What he called "factors" we now call genes.

Mendel reasoned that each parent carries two genes (a gene pair) for a specific trait (flower color, plant height, etc.) but that each parent contributes only one of those genes to its offspring; otherwise, the number of genes for a trait would double in each generation and soon reach astronomical numbers.

Mendel proposed that the two copies of a gene separate from each other during the formation of egg and sperm. As a result, only one copy of each gene is present in a sperm or an egg. When an egg and a sperm fuse at fertilization, the genes from the mother and father become members of a new gene pair in the offspring. In the mid-twentieth century, researchers discovered that genes are made of DNA and that this molecule is part of cellular structures known as chromosomes. Chromosomes (**Figure 1.4**) are found in the nucleus

Andrew Syred/Science Source

FIGURE 1.4 Replicated human chromosomes as seen by scanning electron microscopy.

Transmission genetics The branch of genetics concerned with the mechanisms by which genes are transferred from parent to offspring.

Pedigree analysis The construction of family trees and their use to follow the transmission of genetic traits in families. It is the basic method of studying the inheritance of traits in humans.

Cytogenetics The branch of genetics that studies the organization and arrangement of genes and chromosomes by using the techniques of microscopy.

Karyotype A complete set of chromosomes from a cell that has been photographed during cell division and arranged in a standard sequence.

Molecular genetics The study of genetic events at the biochemical level.

Recombinant DNA technology A series of techniques in which DNA fragments from an organism are linked to self-replicating vectors to create recombinant DNA molecules, which are replicated or cloned in a host cell.

Clones Genetically identical molecules, cells, or organisms, all derived from a single ancestor.

of human cells and other higher organisms. As we will see in Chapter 2, the separation of genes during the formation of the sperm and egg and the reunion of genes at fertilization is explained by the behavior of chromosomes in a form of cell division called meiosis.

When Mendel published his work on the inheritance of traits in pea plants (discussed in Chapter 3), there was no well-accepted idea of how traits were transmitted from parents to offspring; his evidence changed that situation. To many, Mendel was the first geneticist and the founder of genetics, a field that has expanded in numerous directions in the last 125 years. If you want to read more about the beginnings of genetics, the story of Mendel's work is told in an engaging book entitled *The Monk in the Garden: The Lost and Found Genius of Gregor Mendel, the Father of Genetics* by Robin M. Henig.

1-5 How Do Scientists Study Genes?

Ideas that form the foundation of genetics were discovered by studying many different organisms, including bacteria, yeast, and insects, as well as plants and animals, including humans. Because genetic mechanisms (and often genes) are the same across species, discoveries made in one organism (such as yeast) can be applied to other species, including humans. This close genetic relationship allows researchers to study human genetic disorders using experimental organisms, including insects, yeast, and mice. Although geneticists study many different species, they use a relatively small set of investigative methods, some of which are outlined in the following section.

Some basic methods in genetics.

The most basic approach studies the pattern of inheritance as traits are passed from generation to generation; this is called **transmission genetics** (see Chapters 3 and 4). Using experimental organisms, geneticists study how traits such as height, eye color, flower color, and so on, are passed from parents to offspring. These experimental results are analyzed to establish how a trait is inherited. As we discussed in an earlier section, Gregor Mendel did the first significant work in transmission genetics using pea plants as his experimental organism. His methods form the foundation of transmission genetics—methods that are still used today.

To study the inheritance of traits in humans, a more indirect method called **pedigree analysis** is used. Pedigree analysis begins by reconstructing the pattern of inheritance associated with a trait as it passes through several generations. These results are used to determine how a trait is inherited and to establish the risk of having affected children (**Figure 1.5**). Pedigrees are constructed from information obtained from interviews, medical files, letters, diaries, photographs, and family records.

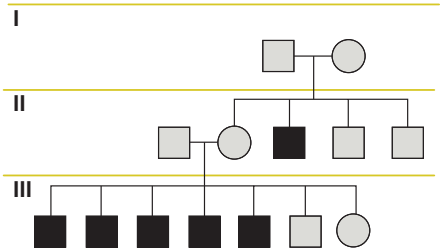


FIGURE 1.5 A pedigree represents the inheritance of a trait through several generations of a family. In this pedigree, males are symbolized by squares, females by circles. Darker symbols indicate those expressing the trait being studied; lighter symbols indicate unaffected individuals.

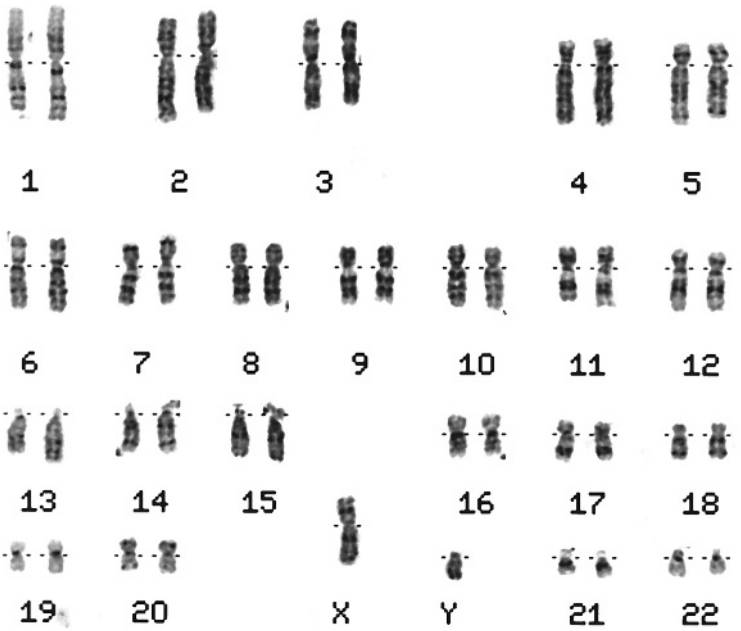
Cytogenetics is a branch of genetics that studies chromosome number and structure (discussed in Chapter 6). At the beginning of the twentieth century, observations on chromosome behavior were used to propose (correctly) that genes are located on chromosomes. Cytogenetics is one of the most important investigative approaches in human genetics and is used, among other things, to map genes and study chromosome structure and abnormalities in chromosome number and organization. In clinical settings, cytogeneticists prepare **karyotypes** (**Figure 1.6**), standardized arrangements of chromosomes that are used to diagnose or rule out certain genetic disorders. In a karyotype, chromosomes are arranged by size, shape, and other characteristics that we will describe in Chapter 6.

A third approach, **molecular genetics**, has had the greatest impact on human genetics over the last several decades. Molecular genetics uses **recombinant DNA technology** to identify, isolate, and produce millions of copies of genes (**clones**) that can be studied in the laboratory. These methods have greatly advanced our knowledge of how genes are organized and how they work at the molecular level. This technology is

used for prenatal diagnosis of genetic disorders and in **gene therapy** to transfer human genes as a treatment for genetic disorders. Cloned genes also can be transferred between individuals and between species to produce transgenic organisms. Transgenic organisms (also called genetically modified organisms—GMOs) are used in laboratory research, agriculture, and the pharmaceutical industry.

Recombinant DNA technology was used in the Human Genome Project to sequence the human **genome**, the complete set of genetic information we all carry, and has generated a new field of genetics called **genomics**. Scientists working in genomics use information from genome projects to study the origin, function, and evolution of genes and their interactions. New genomics technology is now being used to identify the genetic components of complex diseases such as diabetes, obesity, cardiovascular disease, and neurological disorders (including Alzheimer and Parkinson's) and is revolutionizing the study of human genetics.

The development and use of recombinant DNA technology has generated debate about the social, legal, and ethical aspects of genetics, including the genetic modification of plants and animals, the use of genetic testing for diagnosis and employment, and the modification of humans by gene therapy.



Courtesy of Iffi Ahmed

FIGURE 1.6 A karyotype arranges the chromosomes in a standard format so that they can be analyzed for abnormalities. This karyotype is that of a normal male.

A fourth approach studies the distribution of genes in populations. Population geneticists are interested in the forces that change the frequency of genes in a population over many generations and the way those changes are involved in evolution. **Population genetics** defines how much genetic variation exists in populations and how forces such as migration, population size, and natural selection change this variation. The coupling of population genetics with genomic technology has helped us understand the evolutionary history of our species and the migrations that distributed humans across Earth. This technology has been used to develop methods of DNA fingerprinting and DNA identification, techniques widely used in paternity testing and forensics.

Gene therapy Procedure in which normal genes are transplanted into humans carrying defective copies as a means of treating genetic diseases.

Genome The set of DNA sequences carried by an individual.

Genomics The study of the organization, function, and evolution of genomes.

Population genetics The branch of genetics that studies inherited variation in populations of individuals and the forces that alter gene frequency.

Genetics is used in basic and applied research.

Genetics is a discipline that crosses and recrosses the line between basic research and applied research, often blurring distinctions between the two. In general, scientists do basic research in laboratory and field settings to understand how something works or why it works the way it does. In basic research, there is no immediate goal of solving a practical problem or making a commercial product; knowledge itself is the goal. In turn, the results of basic research generate new ideas and more basic research. In this way, we gain detailed information about the structure and function of cells, why animals behave in certain ways, and how plants turn carbon dioxide into sugar. Among other things, basic research in genetics has provided us with details about genes, how they work, and, more importantly, what happens when they don't work properly.

Applied research is usually done to solve a practical problem or turn a discovery into a commercial service or product. Applied research uses basic methods such as transmission genetics to study the way in which a trait is inherited, and it also uses biotechnology to make products such as transgenic organisms, medicines, and nutritionally enhanced foods. In agriculture, applied genetic research has increased crop yields, lowered the fat content of pork, and created new forms of corn and soybeans that are resistant to herbicides and pests. In medicine, new diagnostic tests, the synthesis of customized proteins for treating disease, and the production of vaccines are just a few examples of applied genetic research.