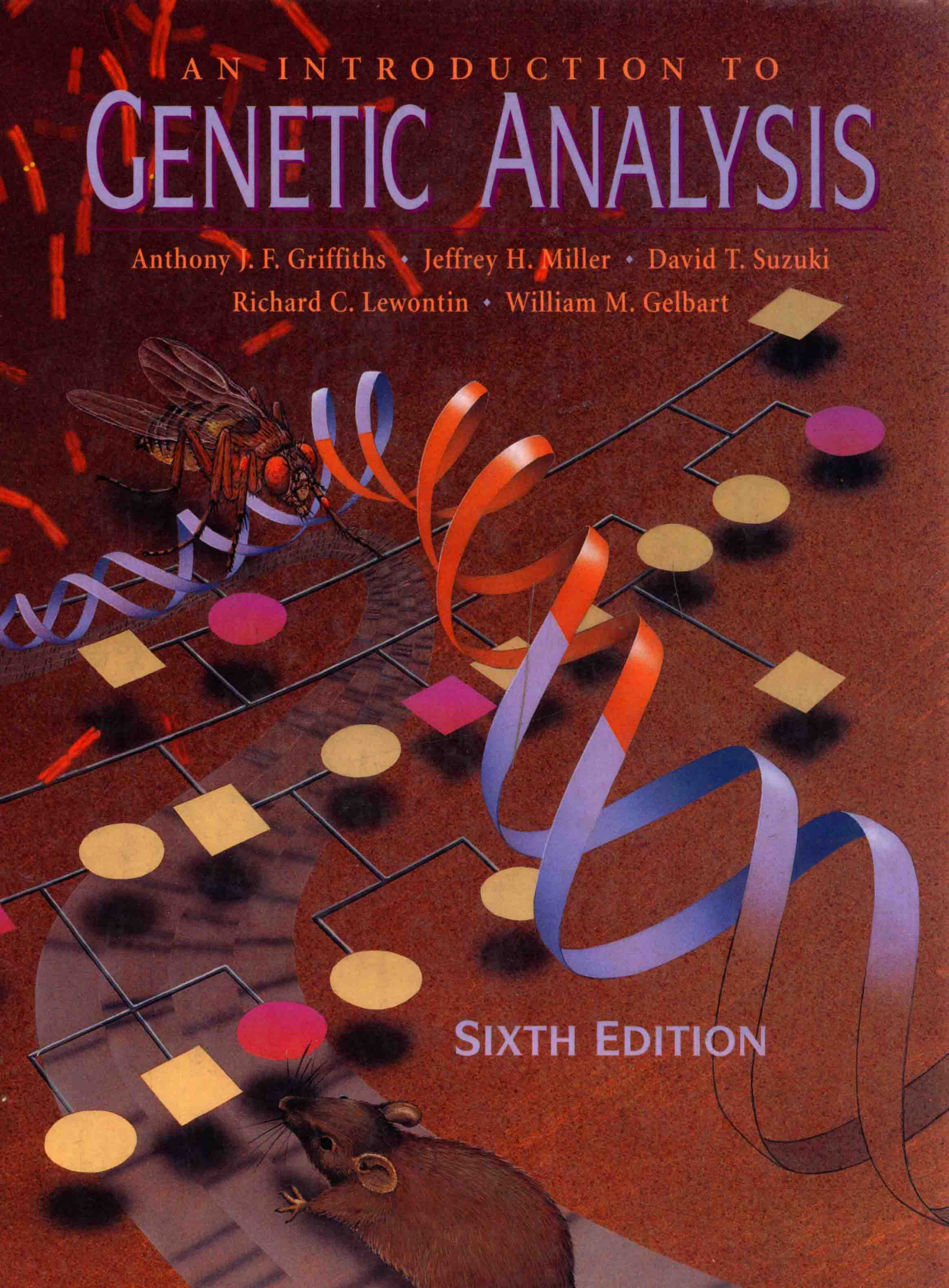
AN INTRODUCTION TO

GENETIC ANALYSIS

Anthony J. F. Griffiths · Jeffrey H. Miller · David T. Suzuki
Richard C. Lewontin · William M. Gelbart



SIXTH EDITION

An Introduction to Genetic Analysis

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W. H. FREEMAN AND COMPANY
NEW YORK

The Cover

Two important genetic principles are depicted on the cover. First, most important cellular functions evolved many hundreds of millions of years ago. Second, the protein products of master control genes regulate the developmental fate of cells and tissues. A human disease called *Aniridia*—no iris in the eye—is represented in the pedigree. The bright spots on the human chromosomes indicate the location of the *Aniridia* gene. The DNA sequence of *Aniridia* reveals that it codes for a protein extremely similar to the protein of the *eyeless* gene in the fruit fly, *Drosophila*. Normally, the *eyeless* gene is expressed only in the tissue that will become the eye. If instead the *eyeless* gene is expressed in other tissues, those now develop into ectopic eyes, establishing the role of *eyeless* as a master control gene. If the human *Aniridia* gene is expressed in different tissues in *Drosophila,* then it also forces those other tissues to develop into eye. Thus, all available evidence points to the strong evolutionary conservation of these genes and the developmental pathways they control.

Library of Congress Cataloging-in-Publication Data

An introduction to genetic analysis/Anthony J. F. Griffiths . . . [et al.].—6th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-7167-2604-1 (hard cover)
1. Genetics. 2. Molecular genetics. I. Griffiths, Anthony J. F.
QH430.I62 1996
575.1—dc20 95-44631
CIP

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Printed in the United States of America.

Second printing 1996, RRD

An Introduction To Genetic Analysis

TRADITIONAL STRENGTHS OF *AN INTRODUCTION TO GENETIC ANALYSIS*

Genetics has become an indispensable component of almost all research in modern biology and medicine. This position of prominence has been achieved through the powerful merger of classical and molecular approaches. Each analytical approach has its unique strengths: classical genetics is unparalleled in its ability to explore uncharted biological terrain; molecular genetics is equally unparalleled in its ability to unravel cellular mechanisms. It would be unthinkable to teach one without the other, and each is given due prominence in this book. Armed with both approaches, students are able to form an integrated view of genetic principles.

A Balanced Approach

The partnership of classical and molecular genetics has always presented a teaching dilemma: which of the two partners should the student be introduced to first, the classical or the molecular? We believe that students begin much as biologists did at the turn of the century, asking general questions about the laws governing heredity. Therefore the first half of the book introduces the intellectual framework of classical eukaryotic genetics in more or less historical sequence. Although molecular information is provided where appropriate, it is not emphasized in this half. Having acquired the classical framework, the student then proceeds to the second half of the book, which hangs molecular genetics onto this framework. The coverage of genetic mutation is a case in point. In Chapter 7 the student is treated to the classical principles of gene mutation, while Chapter 19 expands this knowledge to include molecular aspects. Because the progression from general to specific is a natural one, this approach makes sense not only in research but also in teaching about research.

Figure 4-19

Focus on Genetic Analysis

True to its title, the theme of this book is genetic analysis. This theme emphasizes our belief that the best way to understand genetics is by learning how genetic inference is made. On almost every page we recreate the landmark experiments in genetics and have the students analyze the data and draw conclusions as if they had done the research themselves. This proactive process teaches students how to think like scientists. The modes of inference and the techniques of analysis are the keys to future exploration.

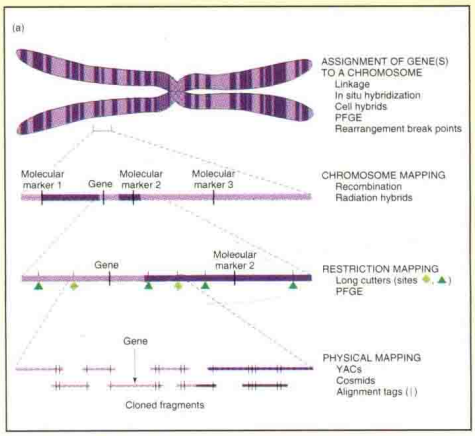

Figure 17-1

Similarly, quantitative analysis is central to the book because many of the new ideas in genetics, from the original conception of the gene to modern techniques such as RFLP mapping, are based on quantitative analysis. The problems at the ends of the chapters provide students with the opportunity to test their understanding in quantitative analyses that effectively simulate the act of doing genetics.

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Tools for Analyzing Genetics

Strengths of the previous editions have been retained and reinforced.

KEY CONCEPTS

- Recombinant DNA is made by splicing a foreign DNA fragment into a small replicating molecule (such as a plasmid), which will then amplify the fragment along with itself resulting in a molecular "clone" of the inserted DNA fragment.
- A collection of DNA clones that together encompass the entire genome is called a *genomic library*.
- An indivual DNA clone in a library can be detected by using a specific probe for the DNA or its protein product, or by its ability to transform a null mutant.
- Restriction enzymes cut DNA at specific target sites, resulting in defined fragments with sticky ends suitable for cloning.
- Different-sized DNA fragments produced by restriction enzyme digestion can be fractionated because they migrate to different positions on an electrophoretic gel.

The **Key Concepts** at the chapter openings give an overview of the main principles to be covered in the chapter, stated in simple prose without genetic terminology. These provide a strong pedagogic direction for the reader.

Boxed **Messages** throughout the chapters provide convenient milestones at which the reader can pause and contemplate the material just presented.

Message

At mitosis, nondisjunction, chromosome loss, crossing-over and haploidization all cause a heterozygous pair of alleles to segregate in somatic tissue, resulting in a mosaic expressing the phenotypes of both alleles.

SUMMARY

Genomics is the branch of genetics that deals with the systematic molecular characterization of whole genomes. Some of the methods used are traditional genetic mapping procedures, but in addition specialized techniques have been developed for manipulating the large amounts of DNA in a genome. Genomic analysis is important for two reasons: first, it represents a way of obtaining an overview of the genetic architecture of an organism, and second, it forms a set of basic information that can be

Chapter **Summaries** provide a short distillation of the chapter material and an immediate reinforcement of the concepts. All these items are useful in text review, especially for exam study.

Another end-of-chapter feature is the problems requiring **Concept Maps.** Concept maps grew out of the constructivist movement in education, which asserts that student learning is most effective when new information is brought into direct conflict with previous understanding. The concept map provides a powerful method for visualizing and resolving such conflicts and also aids concept integration.

Concept Map

Draw a concept map interrelating as many of the following terms as possible. Note that the terms are listed in no particular order.

recombinant DNA/probe/in situ hybridization/genetherapy/RFLP/transgenic/mapping/ in vitro mutagenesis/genetic screening

CHAPTER INTEGRATION PROBLEM

Some recessive mutations in maize affect the color, texture, or shape of the kernel. To discuss these mutations in general, we'll use *m* to represent the recessive allele. These mutations can be detected in a straightforward manner by crossing an m^+m^+male with an *mm* female. Any new mutations are found by visually scanning many seeds, in other words, millions of kernels on thousands of corncobs. Finding a seed with the recessive phenotype shows that the gene mutated in the male. When maize geneticists sow seeds with the mutant phenotype and self the resulting plants, they find one or the other of two kinds of results:

If the mutation was spontaneous, the progeny from the selfing are generally all mutant.

If the mutation followed treatment of the pollen with a mutagen, the progeny from the selfing are generally 3/4 wild type and 1/4 mutant.

Provide an explanation for these two different outcomes.

Solution

As usual, if we restate the results in a slightly different way, it gives us a clue as to what is going on. The difference between outcomes seems to reflect some difference between spontaneous and induced mutation. From a spontaneous mutation, we obtain an individual that seems to be of genotype *mm* because it breeds true for the mutant phenotype. From an induced mutation, we obtain an individual that seems from the 3:1 phenotypic ratio

The **Chapter Integration Problems** are solved problems that emphasize concept integration both within and between chapters. These chapter integration problems help to show how one set of learned skills builds on and interacts with previous ones. They also enable students to develop a holistic perspective as they begin to organize diverse concepts into a coherent body of knowledge.

The problems at the end of each chapter are prefaced by **Solved Problems** that illustrate the ways that geneticists apply principles to experimental data. Research in science education has shown that this application of principles is a process that professionals find second nature, whereas students find it a major stumbling block. The Solved Problems demonstrate this process and prepare the students for solving problems on their own.

SOLVED PROBLEMS

1. About 70 percent of all white North Americans can taste the chemical phenylthiocarbamide, and the remainder cannot. The ability to taste is determined by the dominant allele *T*, and the inability to taste is determined by the recessive allele *t*. If the population is assumed to be in Hardy-Weinberg equilibrium, what are the genotypic and allelic frequencies in this population?

Solution

Since 70 percent are tasters (*TT*), 30 percent must be nontasters (*tt*). This homozygous recessive frequency is equal to q^2, so to obtain q, we simply take the square root of 30:

$$q = \sqrt{0.30} = 0.55$$

Since $p + q = 1$, we can write

$$p = 1 - q = 1 - 0.55 = 0.45$$

Now we can calculate

$$p2 = (0.45)2 = 0.20\ (TT)$$

$$2pq = 0 \times 0.45 \times 0.55 = 0.50\ (Tt)$$

$$q2 = 0.3\ (tt)$$

2. In a large natural population of *Mimulus guttatus* one leaf was sampled from each of a large number of plants

The **Problems** themselves continue to be one of the strengths of the book. The problems are generally arranged to start from the simple and proceed to the more difficult. Particularly challenging problems are marked with an asterisk. All problems have been classroom tested. Answers to selected problems are found at the back of the book, and the full set of solutions is in the *Student Companion,* prepared by Diane Lavett (Emory University).

PROBLEMS

5. Some genes can be mutated to become oncogenes by increasing the copy number of the gene. This, for example, is true of the *c-myc* transcription factor. On the other hand, oncogenic mutations of *ras* are always point mutations that alter the protein structure of *ras*. Rationalize these observations in terms of the roles of normal and oncogenic versions of *ras* and *c-myc*.

NEW FEATURES OF THE SIXTH EDITION

Revised and Updated

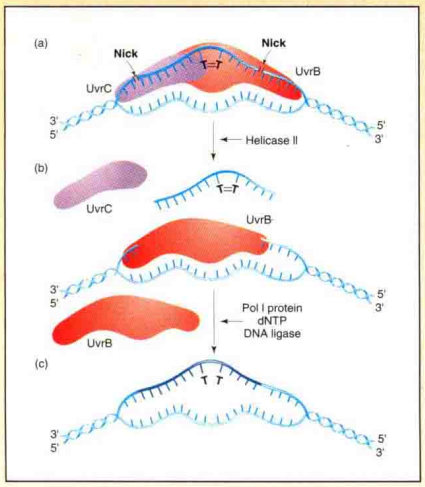


Figure 19-32

All chapters have been revised and updated. Text has been clarified, and new diagrams and photographs have been used throughout. Most of the major revision has been in the chapters that focus on molecular genetic technology (Chapters 14–17) and on the fast-moving field of developmental genetics (Chapters 23–25).

Much of **Chapter 14** (Recombinant DNA Technology) has been rewritten and reorganized. The first part of the chapter focuses on the reasons why geneticists clone DNA and proceeds to a step-by step elucidation of the general methods used. The chapter ends with a description of some other useful techniques in molecular analysis: DNA sequencing (with a new section on automated sequencing), DNA electrophoresis (including Southern and Northern analysis and restriction mapping), and the polymerase chain reaction. Other new topics include pUC plasmids, cloning by functional complementation, positional cloning, cloning by tagging, design of oligonucleotide probes based on amino acid sequence, and ORF analysis. The creation and utilization of DNA libraries has been expanded.

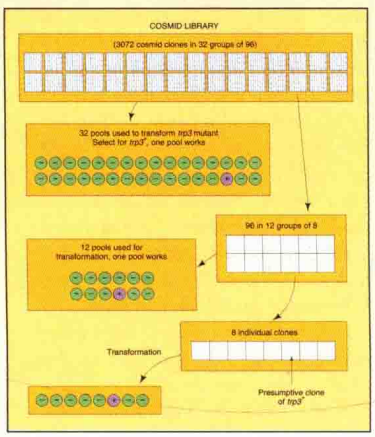


Figure 14-15

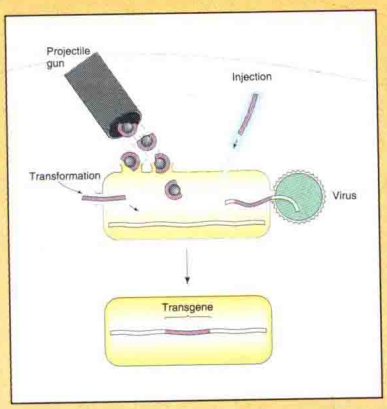


Figure 15-14

Chapter 15 (Applications of Recombinant DNA Technology) has also been extensively revised. Broadly, the new emphasis is on what geneticists can do with cloned genes once they have them. There is new emphasis and explanation of the techniques of reverse genetics, including in vitro mutagenesis, gene disruption, and gene replacement. There is a new section on human gene therapy.

In Chapter 16 (The Structure and Function of Eukaryotic Chromosomes) the description of repetitive DNA has been revised to bring the terminology into line with that used in Chapter 17, for example, minisatellite and microsatellite DNA.

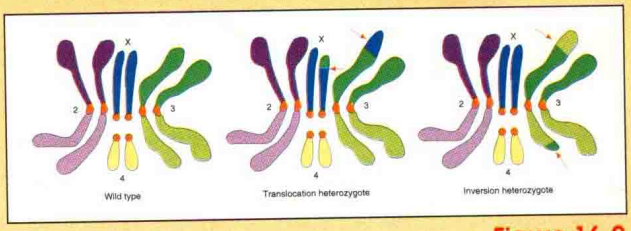


Figure 16-2

Chapter 17 is a new chapter on the topic of Genomics, reflecting current research interest in this area and the interest of the public in the human genome project. The chapter brings together the traditional techniques for genome analysis, such as recombination mapping and somatic cell hybridization, and new approaches designed specifically to manipulate the large amounts of DNA found in eukaryotic chromosomes. New sections deal with fluorescence in situ hybridization, pulsed field gel electrophoresis, mapping by restriction fragment length polymorphisms (RFLPs), mapping by simple sequence length polymorphisms (SSLPs), sperm genotyping, randomly amplified polymorphic DNAs (RAPDs), irradiation and fusion gene transfer (IFGT), contigs, fluorescence-activated sequence-tagged sites, chromosome sorting (FACS), candidate gene approach, and physical mapping of the human Y chromosome.

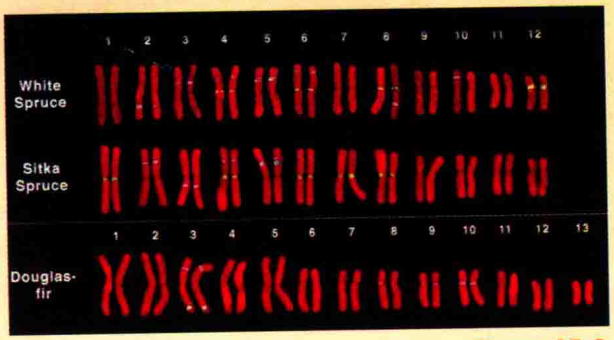


Figure 17-2

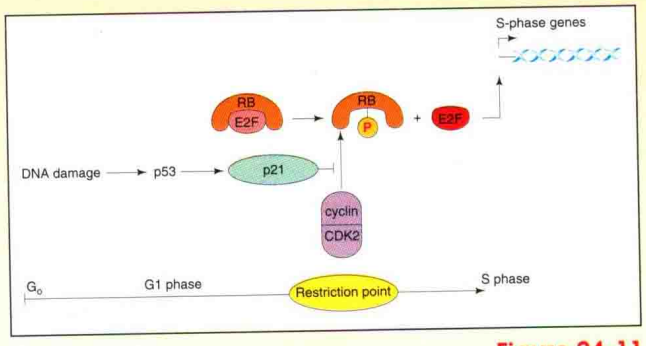


Figure 24-11

Chapters 23–25 are a major revision of Chapters 22–23 in the Fifth Edition to reflect recent advances in the dynamic and changing landscape of developmental genetics. New sections have been added to each of the chapters, and other material has been eliminated to streamline them. Each chapter focuses on a clear theme in developmental genetics. **Chapter 23** discusses how protein activities in a cell are regulated during development and builds on the individual regulatory events to introduce the student to the concept of developmental pathways. New to Chapter 23 is a discussion of epigenetic phenomena, including paramutation in plants and parental imprinting in mammals. In recent years, the dividing line between cell and developmental biology has been blurred. **Chapter 24**

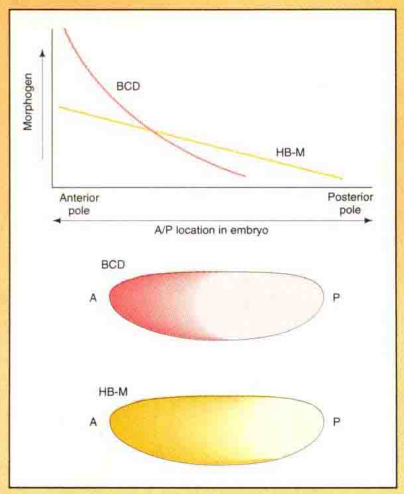


Figure 25-10

addresses this by discussing several areas of cell biology that impact on developmental genetics. New topics include the cytoskeleton and cell shape, the cell cycle, and intercellular communication. The chapter culminates with a discussion of the genetics of cancer, bringing together many of the principles discussed in Chapters 23 and 24. Finally, Chapter 25 focuses on the formation of complex biological patterns. It uses the most exquisite case of early *Drosophila* development to exemplify how geneticists are attacking this major problem in developmental biology. Considerable emphasis is placed on how spatial information is incorporated and read out in the developing oocyte and the early embryo and how the principles of cell biology are exploited to pattern the egg. The chapter ends with a consideration of mammalian developmental genetics and the emerging theme that the mechanisms of pattern formation are ancient and highly conserved among animals.

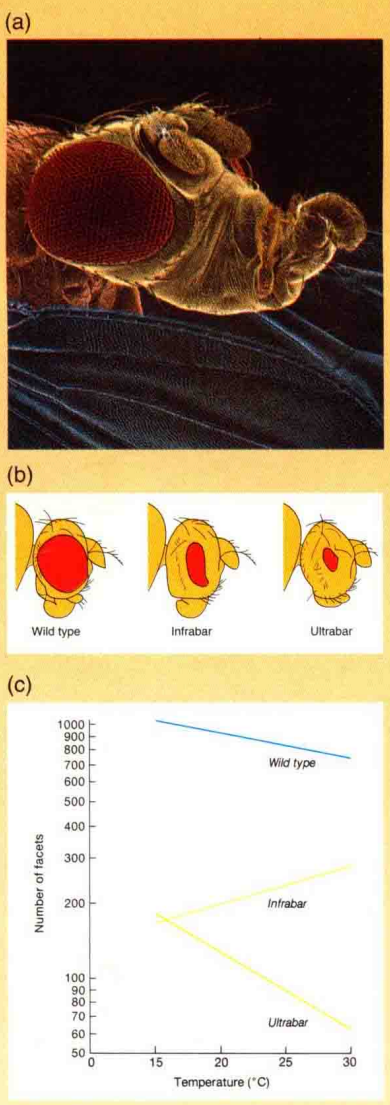


Figure 1-17

Chapter 26, Population Genetics, now precedes the chapter on Quantitative Genetics (Chapter 27), reversing the order in previous editions. Many of the users of the book found that it is a great deal easier to understand quantitative genetics if students first have a grounding in the principles of population genetics, and it is indeed the case that the modern treatment of quantitative genetics grew out of population genetic theory. We have also added a section on the mapping of quantitative trait loci (QTLs) by the new methods of molecular genetics, a subject of considerable interest at present in both human genetics and agriculture.

New Problems

We have added more than 100 new problems, including many problems involving molecular analysis. In addition, most chapters have a new exercise in problem solving called "Unpacking the Problem." This exercise was devised to illustrate the idea that a genetics problem represents only the tip of a vast iceberg of knowledge (we originally considered calling them "iceberg problems"). It is only when the structure of the underlying levels of knowledge is understood that the problem can be solved constructively. The unpacking exercises access this underlying knowledge without actually solving the problem. Some of the component questions in an unpacking exercise might sound trivial, but often they address the kind of fundamental levels of misunderstanding that prevent students from successfully solving problems.

Unpacking the Problem

8. John and Martha are contemplating having children, but John's brother has galactosemia (an autosomal recessive disease), and Martha's great-grandmother also had galactosemia. Martha has a sister who has three children, none of whom has galactosemia. What is the probability that John and Martha's first child will have galactosemia?

In some chapters we expand one specific problem with a list of exercises that help mentally process the principles and other knowledge surrounding the subject area of the problem. You can make up similar exercises yourself for other problems.

Before attempting a solution, consider some expansion questions such as the following, which are meant only as examples:

a. Can the problem be restated as a pedigree? If so, write one.

b. Can parts of the problem be restated using Punnett squares?

c. Can parts of the problem be restated using branch diagrams?

d. In the pedigree, identify a mating

Course Syllabi

For a two-semester course, the entire text provides an appropriate course structure and syllabus that reflects the range of modern genetics. A syllabus for a one-semester course can be designed around selected chapters. For students familiar with DNA structure and function from introductory biology or cell biology courses, a possible selection of chapters for a one-semester course is Chapters 2, 3, 4, 5, 7, 9, 10, 12, 14, 16, 23, and 25. A one-semester course in molecular genetics could be based on Chapters 10 through 25.

Supplements

A number of useful supplements benefit students and instructors using the textbook. The *Student Companion and Complete Solutions*, by Diane K. Lavett of Emory University, offers worked-out answers to all the problems in the textbook. Dr. Lavett has revised and expanded the section in each chapter devoted to the text's concept maps as a means of helping students build problem-solving skills. Questions and answers about the maps are intended to test student understanding of the connections among the key ideas being taught. Concept maps can also be used by instructors to structure the presentation of chapters.

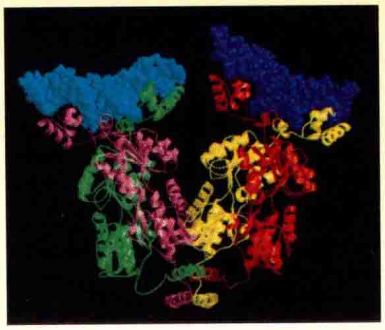
Figure 1-5

A full-color *overhead transparency set* of about 130 key illustrations from the textbook is available free of charge to qualified adopters. Instructors will find all the approximately 1100 numbered figures and tables in the book, along with their legends, in the *An Introduction to Genetic Analysis CD-ROM*. The images can be viewed on a computer and can be displayed with a projection unit during a lecture. The CD contains special software that allows users to select a sequence of images in advance. The CD also gives the option of showing figures with or without their labels, or with labels that the user has created. The CD is also free to qualified adopters. For more information, instructors should contact their local Freeman representative.

Acknowledgments

Thanks are due to the following people at W. H. Freeman and Company for their considerable support throughout the preparation of this edition: Mary Shuford, Director of Development; Randi Rossignol, Senior Developmental Editor; Philip McCaffrey, Managing Editor; Penny Hull, Project Editor; Vicki Tomaselli, Designer; Denise Wiles and Susan Wein, Illustration Coordinators; Travis Amos, Senior Photo Editor; Larry Marcus, Assistant Photo Editor; Ellen Cash, Production Manager; and Julia DeRosa, Production Coordinator. We also thank the copy editor, William O'Neal; the layout artist, Leon Bolognese; the indexer, Susan Thomas; and the proofreader, Lynn Contrucci.

Tony Griffiths thanks Barbara Moon for showing him the power of concept maps and generally converting him to constructivism. He also thanks Jolie Mayer-Smith for the idea behind the problem-unpacking exercises. Dick Lewontin thanks Rachel Nasca for her work in preparing the manuscript, and Jeffrey Miller and Bill Gelbart thank



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CHAPTER

1

Genetics and the Organism

KEY CONCEPTS

- Genetics unifies the biological sciences.
- Genetics is of direct relevance to human affairs.
- Genetics may be defined as the study of genes.
- Genetic variation contributes to variation in nature.
- As an organism develops, its unique set of genes interacts with its unique environment in determining its characteristics.

Genetic variation in the color of corn kernels. Each kernel represents a separate individual with a distinct genetic makeup. The photograph symbolizes the history of humanity's interest in heredity. Humans were breeding corn thousands of years before the rise of the modern discipline of genetics. Extending this heritage, corn today is one of the main research organisms in classical and molecular genetics. (William Sheridan, University of North Dakota; photo by Travis Amos.)

Why study genetics? There are two basic reasons. First, genetics has come to occupy a pivotal position in the entire subject of biology; for any serious student of plant, animal, or microbial life, an understanding of genetics is thus essential. Second, genetics, like no other scientific discipline, has become central to numerous aspects of human affairs. It touches our humanity in many different ways. Indeed, genetic issues seem to surface daily in our lives, and no thinking person can afford to be ignorant of its discoveries. In this chapter we take an overview of the science of genetics, showing how it has come to occupy its crucial position. In addition we provide a perspective from which to view the subsequent chapters.

First we need to define what genetics is. Some define it as the study of heredity, but hereditary phenomena have been interesting to humans since before the dawn of civilization. Long before biology or genetics existed as the scientific disciplines we know today, ancient peoples were improving plant crops and domesticated animals by selecting desirable individuals for breeding. They also must have puzzled about the inheritance of traits in humans, and asked such questions as "Why do children resemble their parents?" and "How can various diseases run in families?" But these people could not be called geneticists. Genetics as a set of principles and analytical procedures did not begin until the 1860s when an Augustinian monk named Gregor Mendel (Figure 1-1) performed a set of experiments that pointed to the existence of biological elements called **genes.** The word *genetics* comes from "genes," and genes provide the focus for the subject. Whether geneticists study at the molecular, cellular, organismal, family, population, or evolutionary level, genes are always central in their studies. Simply stated, genetics is the study of genes.

What is a gene? A gene is a section of a threadlike molecule called **deoxyribonucleic acid,** abbreviated **DNA.** DNA, the hereditary material that passes from one generation to the next, dictates the inherent properties of a species. Each cell in an organism has one or two sets of the basic DNA complement, called a **genome.** The genome itself is made up of one or more extremely long molecules of DNA that are called **chromosomes.** The genes are the functional regions of the DNA and are simply active segments ranged along the chromosomes (Figure 1-2). In complex organisms chromosomes generally number in the order of tens, but genes number in the order of tens of thousands. Armed with these definitions of genetics and genes, let us go on to see how understanding these subjects has become so important. We will start with the impact of genetics on our own species.

Figure 1-1 Gregor Mendel. (Moravian Museum, Brno)

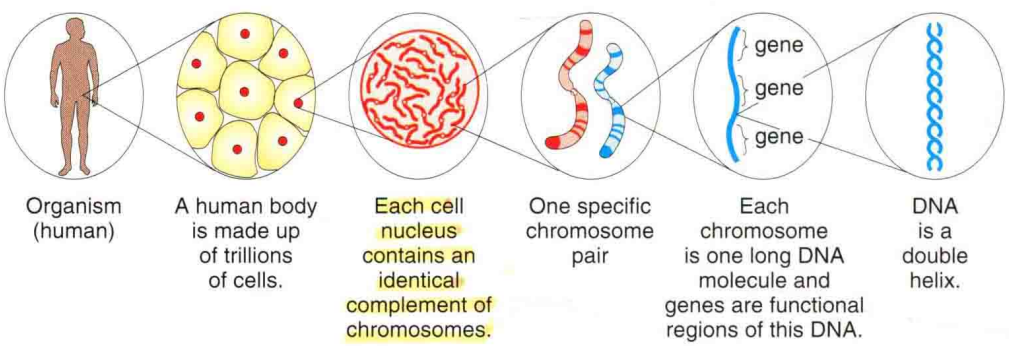

Figure 1-2 Successive enlargements of an organism to focus on the genetic material.

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