NINTH EDITION

GENETICS

ANALYSIS OF GENES AND GENOMES

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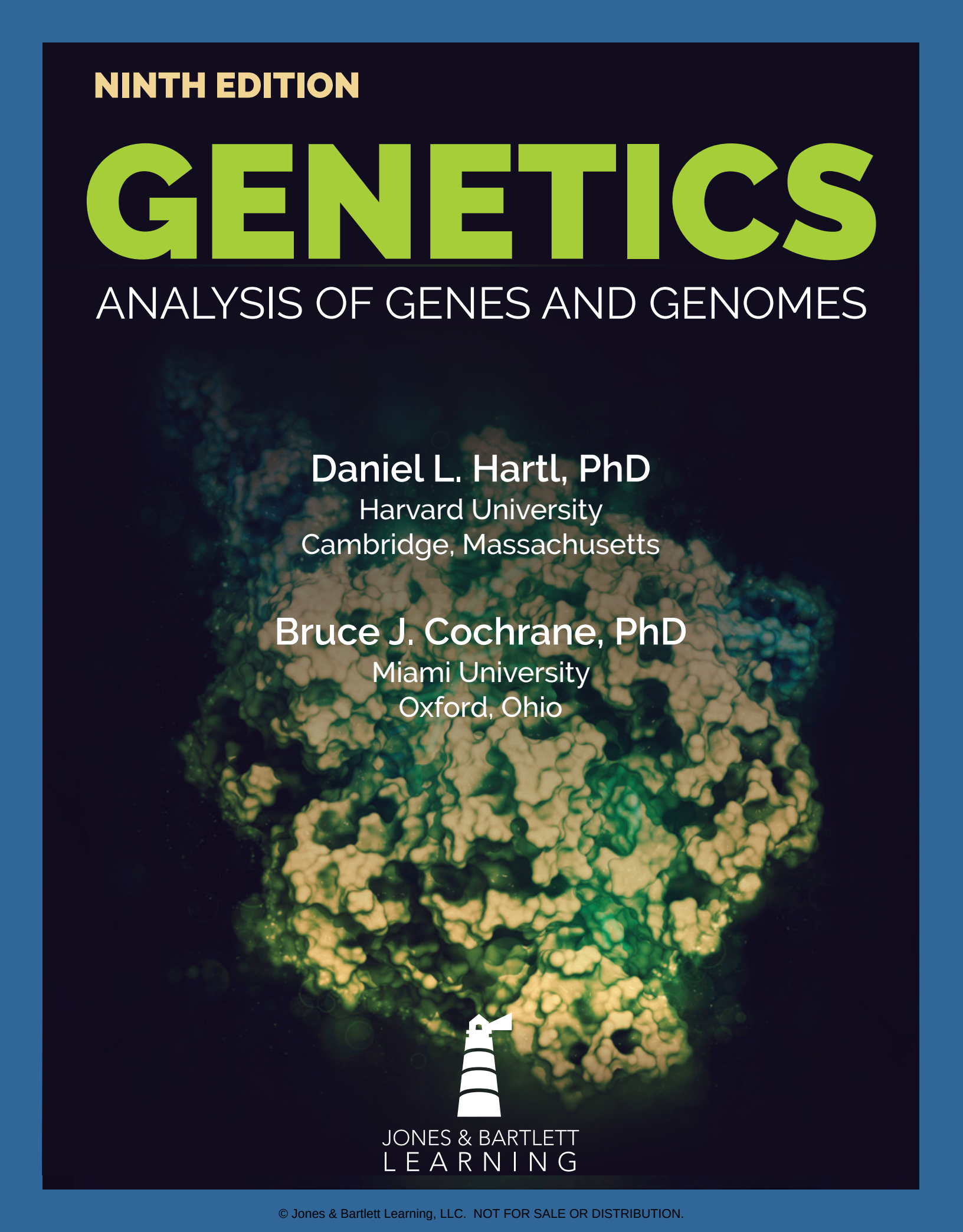

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Preface

Students' curiosity about genetics is refreshed by almost daily reports in the media of new discoveries related to genetic differences in drug responses, genetic risk factors for disease, and genetic evidence for human origins and history. They are also intrigued by ethical controversies related to genetics: Should genetic manipulation be used on patients for the treatment of disease? Should human fetuses be used in research? Should human beings be cloned? What are the biological and ethical implications of gene editing? And there are social controversies: Should there be laws governing genetic privacy? Who should have access to genetic testing records, and for what purpose? What is the proper role of direct-to-consumer genotyping services?

The teacher of genetics, in turn, faces myriad challenges:

- Sustaining students' enthusiasm about this topic
- Motivating their desire to understand the principles of genetics in a comprehensive and rigorous way
- Guiding students in gaining an understanding that genetics is not only a set of principles but also an experimental approach to solving a wide range of biological problems
- Helping students learn to think about genetic problems and about the wider social and ethical issues arising from genetics and genomics

Genetics: Analysis of Genes and Genomes, Ninth Edition, addresses these challenges while emphasizing the beauty, logical clarity, and unity of the subject. Our pedagogical approach is to treat transmission genetics, molecular genetics, and evolutionary genetics as fully integrated subjects. This integration appeals to most modern geneticists, who recognize that the distinctions between the subfields are artificial. The chapters in this text have been arranged into five sections: an overall introduction to genes and genetic analysis, transmission genetics, the organization and replication of DNA, gene expression and regulation, and evolutionary genetics. Recognizing that these topics can be organized in many ways, we have sought to make it possible for individual instructors to customize the order in which they are presented.

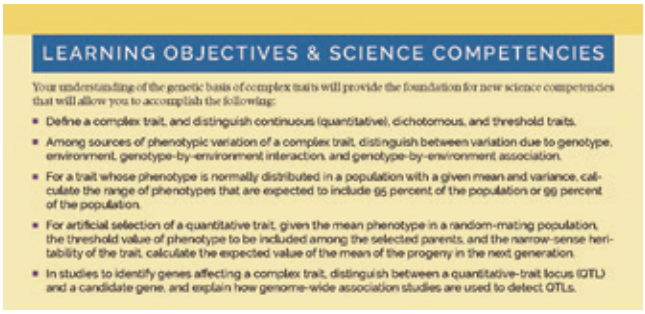
Our aim is to provide a clear, comprehensive, rigorous, and balanced introduction to genetics and genomics at the college level. We believe that a good course should maintain the right balance between two important aspects of genetics: (1) genetics as a body of knowledge pertaining to genetic transmission, function, and mutation; and (2) genetics as an experimental approach, or a kit of "tools," for the study of biological processes such as development or behavior. Any student claiming a knowledge of genetics must achieve the following milestones:

- Understand the basic processes of gene transmission, mutation, expression, and regulation
- Be familiar with the principal experimental methods that geneticists and molecular biologists use in their studies, and recognize the advantages and limitations of these approaches
- Think like a geneticist at the elementary level of being able to formulate genetic hypotheses, work out their consequences, and test the results against observed data
- State genetic principles in his or her own words and recognize the key terms of genetics in context
- Solve problems of several types, including single-concept exercises that require application of definitions or the basic principles of genetics, problems in genetic analysis in which several concepts must be applied in logical order, and problems in quantitative analysis that call for some numerical calculation
- Gain some sense of the social and historical context in which genetics and genomics has developed and is continuing to develop
- Acquire a basic familiarity with the genetic resources and information that are available through the Internet

The Student Experience

We have included many special features to help students achieve these learning goals. The text is clearly and concisely written in a student-friendly and relaxed prose style.

- Each chapter begins with an explicit statement of the **Learning Objectives** and **Science Competencies** that students should aim to achieve. These guideposts are intended to help students identify key concepts and use them at a variety of learning levels, including comprehension, application, analysis, and synthesis. They also serve as powerful study tools when reviewing the material for course and exam preparation.



LEARNING OBJECTIVES & SCIENCE COMPETENCIES

Your understanding of the genetic basis of complex traits will provide the foundation for new science competencies that will allow you to accomplish the following:

- Define a complex trait, and distinguish continuous (quantitative), dichotomous, and threshold traits.
- Among sources of phenotypic variation of a complex trait, distinguish between variation due to genotype, environment, genotype-by-environment interaction, and genotype-by-environment association.
- For a trait whose phenotype is normally distributed in a population with a given mean and variance, calculate the range of phenotypes that are expected to include 95 percent of the population or 99 percent of the population.
- For artificial selection of a quantitative trait, given the mean phenotype in a random-mating population, the threshold value of phenotype to be included among the selected parents, and the narrow-sense heritability of the trait, calculate the expected value of the mean of the progeny in the next generation.
- In studies to identify genes affecting a complex trait, distinguish between a quantitative-trait locus (QTL) and a candidate gene, and explain how genome-wide association studies are used to detect QTLs.

ROOTS OF DISCOVERY

This Land Is Your Land

The Huntington's Disease Collaborative Research Group (1993)

Comprising 58 authors among 9 institutions

A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes

Modern genetic research is sometimes carried out by large collaborative groups in a number of research institutions scattered across several countries. This approach is exemplified by the search for the gene responsible for Huntington disease. The search was highly publicized because of the severity of the disease, the late age of onset, and the dominant inheritance. Famed folk singer Woody Guthrie, who wrote "This Land Is Your Land" and other well-known tunes, died of the disease in 1967. When the gene was identified, it turned out to encode a protein (now called huntingtin) of unknown function that is expressed in many cell types throughout the body and not, as expected, exclusively in nervous tissue. Within the coding sequence of this gene is a trinucleotide repeat (5′-CAG-3′) that is repeated in tandem a number of times according to the general formula (5′-CAG-3′)n. Among normal alleles, the number n of repeats ranges from 11 to 34, with an average of 18; among mutant alleles, the number of repeats ranges from 40 to 86. This tandem repeat is genetically unstable in that it can, by some unknown mechanism, increase in copy number ("expand"). In two cases in which a new mutant allele was analyzed, one had increased in repeat number from 36 to 44 and the other from 33 to 49. This mutational mechanism is quite common in some human genetic diseases. The excerpt cites several other examples. The authors also emphasize that their discovery raises important ethical issues, including those related to genetic testing, confidentiality, and informed consent.

The genetic defect causing HD was assigned to chromosome 4 in one of the first successful linkage analyses using DNA markers in humans. Since that time, we have pursued an approach to isolating and characterizing the HD gene based on progressively refining its localization. . . .

"We consider it of the utmost importance that the current internationally accepted guidelines and counseling protocols for testing people at risk continue to be observed, and that samples from unaffected relatives should not be tested inadvertently or without full consent."

[We have found that a] 500-kb segment is the most likely site of the genetic defect. [The abbreviation "kb" stands for kilobase pairs; 1 kb equals 1000 base pairs.] Within this region, we have identified a large gene, spanning approximately 210 kb, that encodes a previously undescribed protein. The reading frame contains a polymorphic (CAG)n trinucleotide repeat with at least 17 alleles in the normal population, varying from 11 to 34 CAG copies. On HD chromosomes, the length of the trinucleotide repeat is substantially increased. . . . It can be expected that the capacity to monitor directly the size of the trinucleotide repeat in individuals "at risk" for HD will revolutionize testing for the disorder. . . .

The authors then go on to point out the importance of adhering to rigorous ethical standards in testing programs—in particular with respect to testing unaffected relatives of affected individuals without their fully informed consent. In the case of Huntington disease, this is particularly important, since the disease-associated alleles are dominant and do not manifest themselves phenotypically until later in life. Thus, for example, a seemingly healthy young adult could learn as a result of testing that she or he would develop this debilitating and ultimately fatal disease later in life—information that some would rather not know.

Source: MacDonald, ME, Ambrose, CM, Duyao, MP. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell. 72 (1993): 971–983.

- A unique feature of this text is the **Roots of Discovery** boxes. Each chapter contains one or two of these boxes, in which the text material is connected to excerpts from classic papers that report key experiments in genetics or raise important social, ethical, or legal issues in genetics. Each Roots of Discovery feature includes a brief introduction explaining the importance of the experiment and the historical context in which it was carried out, followed by short excerpts from the original literature of genetics, interspersed with commentary connecting the results and conclusions of the paper to the topics covered in the chapter. Many of these boxes offer excerpts from historical papers, such as Mendel's paper, but by no means are they all "old" papers. Indeed, many of these "classic" papers are very recent.

Some of the pieces were published originally in French, others in German. These excerpts appear in English translation. In papers that use outmoded or unfamiliar terminology, or that use archaic gene symbols, we have substituted the modern equivalent because the use of a consistent terminology in the text and in the Roots of Discovery features makes the material more accessible to the student.

- In addition, several chapters contain **Cutting Edge** boxes, which are designed to introduce students to some of the more innovative work being done in the field. Topics such as the bacterial genetics of CRISPR–Cas9, genome-wide association studies based on personal genomics, and the potential of gene drive are designed to help students appreciate the advances being made at the forefront of genetics. While the Roots of Discovery boxes are designed to highlight the experimental foundations of genetics, the Cutting Edge boxes are intended to give students a taste of where it is going. Each of these features focuses on recent work that has the potential to be transformative in the future or that has introduced new methods of analysis that can be applied to questions in genetics and genomics. Each also includes references to the original work that can be incorporated into class activities and assignments. We hope that the Cutting Edge feature will prove both useful and stimulating, and that the format we have used can be applied to other new advances as they occur.

THE CUTTING EDGE: High-Throughput SNP Genotyping

Naturally occurring enzymes are often used for critical steps in molecular genetic analysis. Using restriction enzymes and DNA polymerase for DNA marker analysis and PCR are two examples, and the tremendous diversity of species (especially microbial) on Earth continues to be a source of new tools.

SNP detection is a good example. The basic SNP chip approach, as shown in Figure 2.27, depends on the availability of sufficient genomic DNA to be analyzed; it also requires accurate hybridization of genomic DNA fragments to oligonucleotides on the chip. Both of these limitations have been addressed by the latest techniques.

To increase the quantity of genomic DNA, the technique of PCR-free whole-genome amplification has been developed. PCR by itself has two problems. First, it requires thermal cycling for the denaturation, renaturation, and elongation steps. Second, the *Taq* polymerase (the one most commonly used in PCR) is prone to errors: An incorrect base is inserted every 800 bases or so. To get around these problems, scientists have developed a technique for amplification of whole genomes called **multiple displacement amplification**. As illustrated in **FIGURE A**, random six-base sequences (hexamers) are used as primers. The DNA polymerase comes from the bacteriophage φ29, an enzyme that replicates DNA with high fidelity. Furthermore, when it encounters the 5′ end of a strand that is base-paired to its template, the DNA polymerase displaces that strand; the resulting single strand can then hybridize with another of the hexamer primer sequences present in the reaction, thereby serving as the template for further replication. By this means, total genomic DNA can be amplified from a single cell, and the process occurs without thermal cycling (no denaturation and renaturation is necessary).

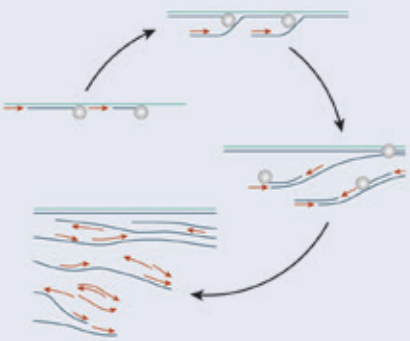


FIGURE A

Once this phase is complete, the amplified DNA is sheared into small fragments, denatured, and hybridized to oligonucleotides (**FIGURE B**). Multiple copies of different oligonucleotides have been attached to microbeads, with their 3′ ends free, and those beads have been embedded in a solid matrix. However, the SNP to be assayed is *not* part of the sequence included in the oligonucleotide; rather, the SNP is the *next* base in the sequence after the oligonucleotide's 3′ end. DNA polymerase is added, along with modified nucleoside triphosphates that can be detected fluorescently, under conditions where one base will be added to the oligonucleotide probe. The identity of that base depends on the SNP allele in the hybridized genomic DNA, and it can be determined by scanning the fluorescence on the chip. In the case illustrated in Figure B the individual being assayed is homozygous for the A allele of SNP 1, heterozygous for the A and G alleles of SNP 2, and homozygous for the G allele of SNP 3.

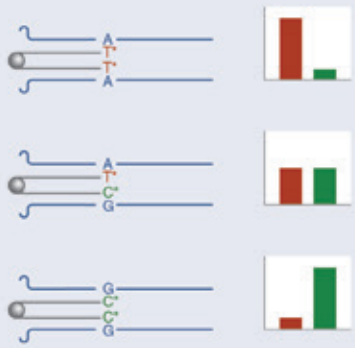
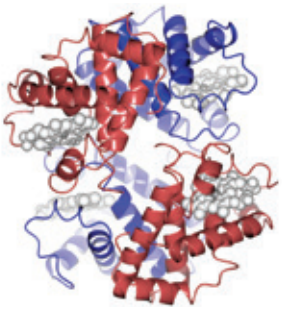
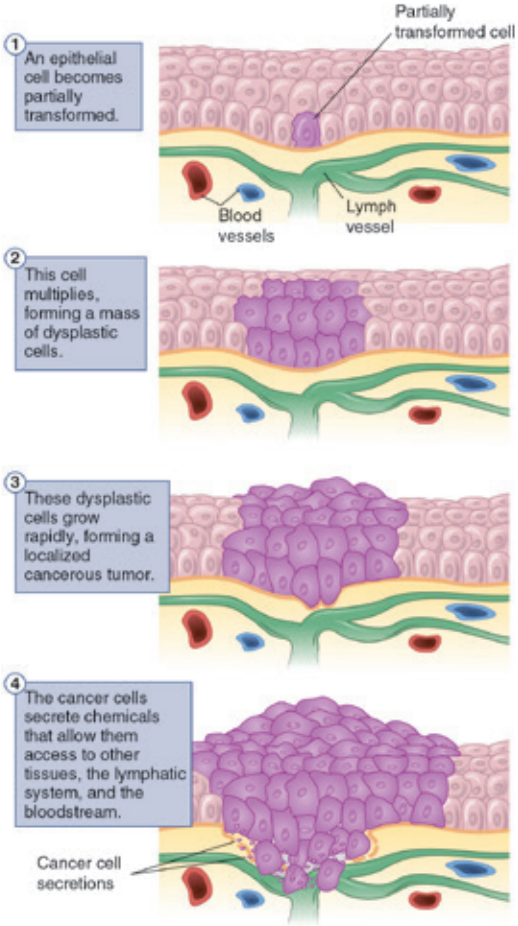


FIGURE B

These kinds of cutting-edge methods make SNP genotyping fast and efficient with even only a very small amount of starting material (such as the saliva samples used by the personal genomics company 23andMe), and they can generate enormous amounts of data. In fact, as many as 48 samples can be genotyped for 300,000 or more SNPs in as little as three days. These methods do require some sophisticated instrumentation (much of it can be done robotically), but they remain fundamentally grounded in the biological processes of base pairing and DNA replication.

- The **art program** is spectacular and a learning aid in itself. Every chapter is richly illustrated with beautiful graphics in which color is used functionally to enhance the value of each illustration as a learning aid. The illustrations are also heavily annotated with explanatory boxes explaining in a step-by-step fashion what is happening at each level of the illustration. These labels make the art inviting as well as informative. They also allow the illustrations to stand relatively independently of the text, enabling students to review material without rereading the whole chapter. The art program is used not only for its visual appeal but also to increase the pedagogical value of the text.





- Characteristic colors and shapes have been used consistently throughout the text to indicate different types of molecules—DNA, mRNA, tRNA, and so forth. For example, DNA is illustrated in any one of a number of ways, depending on the level of resolution necessary for the illustration, and each time a particular level of resolution is depicted, the DNA is shown in the same way. A great deal of potential confusion is avoided by ensuring that DNA, RNA, and proteins are represented in the same manner in every chapter.
- Numerous full-color photographs feature molecular models in three dimensions; these give a strong visual reinforcement of the concept of macromolecules as physical entities with defined three-dimensional shapes and charge distributions that serve as the basis of interaction with other macromolecules.
- The page design is clean, crisp, and uncluttered. As a result, the text is pleasant to look at and easy to read.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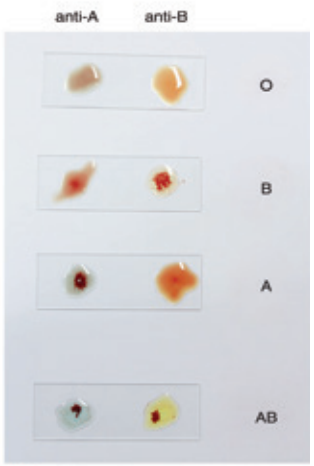
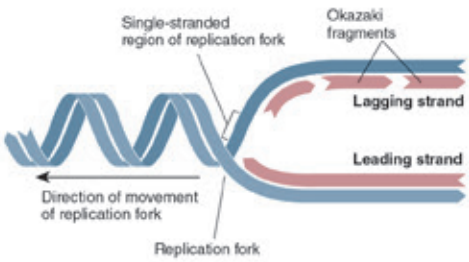




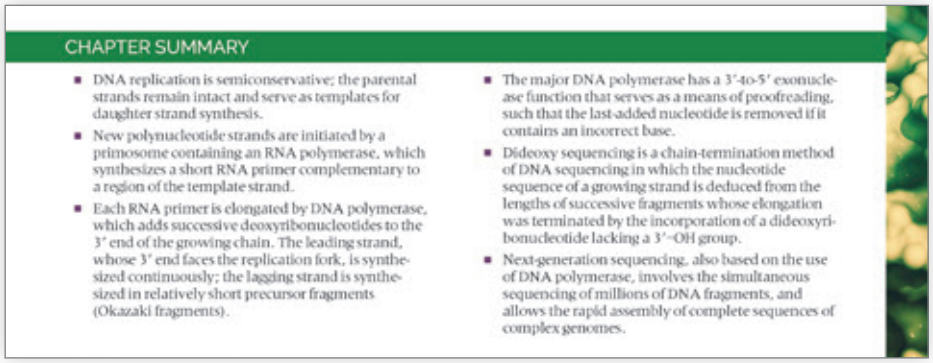
SUMMING UP

- The nematode *C. elegans* is a model of animal development in which cell lineages can be accurately traced.
- Genetic analysis of nematode development involves mutations that alter specific patterns of cell division and differentiation.
- Apoptosis plays an important role in the developmental process.
- Genetic analysis of development makes use of both gain-of-function and loss-of-function mutations.
- These mutations, and epistatic interactions among them, are valuable tools in elucidating switch-regulation pathways in development.
- Vulval development provides an example of how these genetic approaches have been used in nematodes.

SUMMING UP

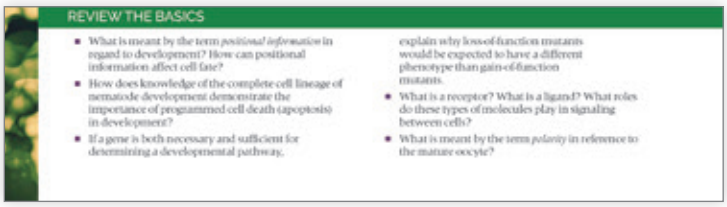
- The Meselson–Stahl experiment demonstrated that DNA replication is semiconservative.
- Circular DNA molecules such as the *E. coli* genome are replicated bidirectionally, forming theta structures as replication intermediates.
- In either F factor or Hfr conjugation, as well as in phage replication, rolling circle replication results in the production of tandem linear repeats of the original circular molecule.

- To help students focus on the key details of this challenging subject, each numbered section concludes with a **Summing Up** feature that highlights the most important concepts. Then, at the end of each chapter, a **Chapter Summary** in bulleted list form collects key learning points for students.
- Each chapter concludes with approximately 50 problems for solution, graded in difficulty, for the students to test their understanding. The problems are of several different types.



CHAPTER SUMMARY

- DNA replication is semiconservative; the parental strands remain intact and serve as templates for daughter strand synthesis.
- New polynucleotide strands are initiated by a primosome containing an RNA polymerase, which synthesizes a short RNA primer complementary to a region of the template strand.
- Each RNA primer is elongated by DNA polymerase, which adds successive deoxyribonucleotides to the 3′ end of the growing chain. The leading strand, whose 3′ end faces the replication fork, is synthesized continuously; the lagging strand is synthesized in relatively short precursor fragments (Okazaki fragments).
- The major DNA polymerase has a 3′-to-5′ exonuclease function that serves as a means of proofreading, such that the last-added nucleotide is removed if it contains an incorrect base.
- Dideoxy sequencing is a chain-termination method of DNA sequencing in which the nucleotide sequence of a growing strand is deduced from the lengths of successive fragments whose elongation was terminated by the incorporation of a dideoxyribonucleotide lacking a 3′–OH group.
- Next-generation sequencing, also based on the use of DNA polymerase, involves the simultaneous sequencing of millions of DNA fragments, and allows the rapid assembly of complete sequences of complex genomes.

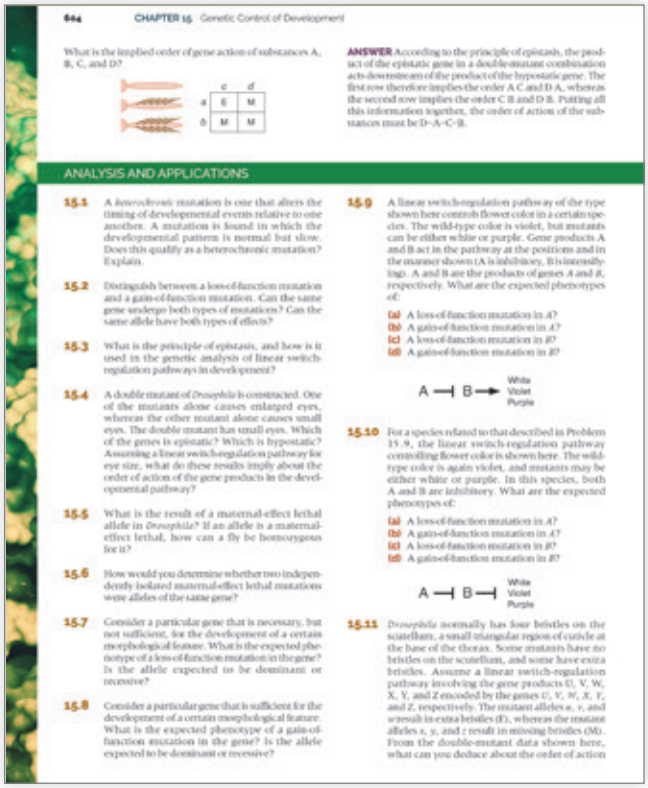


REVIEW THE BASICS

- What is meant by the term *positional information* in regard to development? How can positional information affect cell fate?
- How does knowledge of the complete cell lineage of nematode development demonstrate the importance of programmed cell death (apoptosis) in development?
- If a gene is both necessary and sufficient for determining a developmental pathway, explain why loss-of-function mutants would be expected to have a different phenotype than gain-of-function mutants.
- What is a receptor? What is a ligand? What roles do these types of molecules play in signaling between cells?
- What is meant by the term *polarity* in reference to the mature oocyte?

- **Review the Basics** questions review the major concepts by presenting questions for discussion. These questions ask for genetic principles to be restated in the student's own words; some are matters of definition or call for the application of elementary principles.

- The **Guide to Problem Solving** demonstrates typical problems that apply the principles. The problems are worked in full, showing the concepts needed to solve the problem and the reasoning behind the answer. This feature serves as a review of the important concepts used in working problems. It also highlights some of the most common mistakes made by beginning students and gives pointers on how the student can avoid falling into these conceptual traps.
- A large number of **Analysis and Applications** problems are provided (with answers to even-numbered problems at the end of the text). In these more traditional types of genetic problems, several concepts must be applied in logical order and some numerical calculation may be required. The level of mathematics is that of arithmetic and elementary probability as it pertains to genetics. None of the problems uses mathematics beyond elementary algebra.



604 CHAPTER 15 Genetic Control of Development

What is the implied order of gene action of substances A, B, C, and D?

ANSWER According to the principle of epistasis, the product of the epistatic gene in a double-mutant combination acts downstream of the product of the hypostatic gene. The first row therefore implies the order A-C and D-A, whereas the second row implies the order C-B and D-B. Putting all this information together, the order of action of the substances must be D–A–C–B.

ANALYSIS AND APPLICATIONS

15.1 A *heterochronic* mutation is one that alters the timing of developmental events relative to one another. A mutation is found in which the developmental pattern is normal but slow. Does this qualify as a heterochronic mutation? Explain.

15.2 Distinguish between a loss-of-function mutation and a gain-of-function mutation. Can the same gene undergo both types of mutations? Can the same allele have both types of effects?

15.3 What is the principle of epistasis, and how is it used in the genetic analysis of linear switch-regulation pathways in development?

15.4 A double mutant of *Drosophila* is constructed. One of the mutants alone causes enlarged eyes, whereas the other mutant alone causes small eyes. The double mutant has small eyes. Which of the genes is epistatic? Which is hypostatic? Assuming a linear switch-regulation pathway for eye size, what do these results imply about the order of action of the gene products in the developmental pathway?

15.5 What is the result of a maternal-effect lethal allele in *Drosophila*? If an allele is a maternal-effect lethal, how can a fly be homozygous for it?

15.6 How would you determine whether two independently isolated maternal-effect lethal mutations were alleles of the same gene?

15.7 Consider a particular gene that is necessary, but not sufficient, for the development of a certain morphological feature. What is the expected phenotype of a loss-of-function mutation in the gene? Is the allele expected to be dominant or recessive?

15.8 Consider a particular gene that is sufficient for the development of a certain morphological feature. What is the expected phenotype of a gain-of-function mutation in the gene? Is the allele expected to be dominant or recessive?

15.9 A linear switch-regulation pathway of the type shown here controls flower color in a certain species. The wild-type color is violet, but mutants can be either white or purple. Gene products A and B act in the pathway at the positions and in the manner shown (A is inhibitory, B is intensifying). A and B are the products of genes *A* and *B*, respectively. What are the expected phenotypes of:

(a) A loss-of-function mutation in *A*?
(b) A gain-of-function mutation in *A*?
(c) A loss-of-function mutation in *B*?
(d) A gain-of-function mutation in *B*?

A ⊣ B → White / Violet / Purple

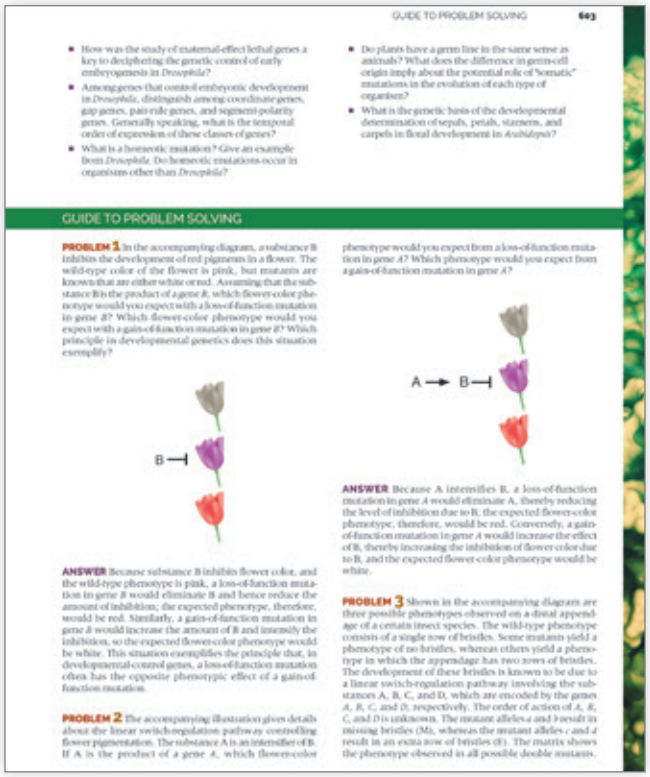
15.10 For a species related to that described in Problem 15.9, the linear switch-regulation pathway controlling flower color is shown here. The wild-type color is again violet, and mutants may be either white or purple. In this species, both A and B are inhibitory. What are the expected phenotypes of:

(a) A loss-of-function mutation in *A*?
(b) A gain-of-function mutation in *A*?
(c) A loss-of-function mutation in *B*?
(d) A gain-of-function mutation in *B*?

A ⊣ B ⊣ White / Violet / Purple

15.11 *Drosophila* normally has four bristles on the scutellum, a small triangular region of cuticle at the base of the thorax. Some mutants have no bristles on the scutellum, and some have extra bristles. Assume a linear switch-regulation pathway involving the gene products U, V, W, X, Y, and Z encoded by the genes *U*, *V*, *W*, *X*, *Y*, and *Z*, respectively. The mutant alleles *u*, *v*, and *w* result in extra bristles (E), whereas the mutant alleles *x*, *y*, and *z* result in missing bristles (M). From the double-mutant data shown here, what can you deduce about the order of action

- **Challenge Problems** are similar to the Analysis and Applications problems but are more challenging, often because they require a more extensive analysis of data before the question can be answered.



GUIDE TO PROBLEM SOLVING 603

- How was the study of maternal-effect lethal genes a key to deciphering the genetic control of early embryogenesis in *Drosophila*?
- Among genes that control embryonic development in *Drosophila*, distinguish among coordinate genes, gap genes, pair-rule genes, and segment-polarity genes. Generally speaking, what is the temporal order of expression of these classes of genes?
- What is a homeotic mutation? Give an example from *Drosophila*. Do homeotic mutations occur in organisms other than *Drosophila*?
- Do plants have a germ line in the same sense as animals? What does the difference in germ-cell origin imply about the potential role of "somatic" mutations in the evolution of each type of organism?
- What is the genetic basis of the developmental determination of sepals, petals, stamens, and carpels in floral development in *Arabidopsis*?

GUIDE TO PROBLEM SOLVING

PROBLEM 1 In the accompanying diagram, a substance B inhibits the development of red pigments in a flower. The wild-type color of the flower is pink, but mutants are known that are either white or red. Assuming that the substance B is the product of a gene *B*, which flower-color phenotype would you expect with a loss-of-function mutation in gene *B*? Which flower-color phenotype would you expect with a gain-of-function mutation in gene *B*? Which principle in developmental genetics does this situation exemplify?

B ⊣

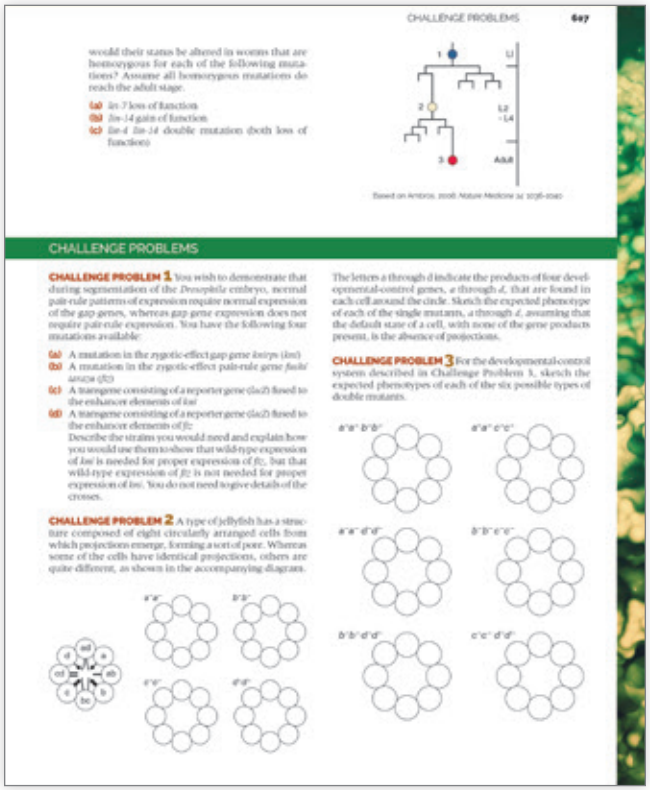
ANSWER Because substance B inhibits flower color, and the wild-type phenotype is pink, a loss-of-function mutation in gene *B* would eliminate B and hence reduce the amount of inhibition; the expected phenotype, therefore, would be red. Similarly, a gain-of-function mutation in gene *B* would increase the amount of B and intensify the inhibition, so the expected flower-color phenotype would be white. This situation exemplifies the principle that, in developmental-control genes, a loss-of-function mutation often has the opposite phenotypic effect of a gain-of-function mutation.

PROBLEM 2 The accompanying illustration gives details about the linear switch-regulation pathway controlling flower pigmentation. The substance A is an intensifier of B. If A is the product of a gene *A*, which flower-color phenotype would you expect from a loss-of-function mutation in gene *A*? Which phenotype would you expect from a gain-of-function mutation in gene *A*?

A → B ⊣

ANSWER Because A intensifies B, a loss-of-function mutation in gene *A* would eliminate A, thereby reducing the level of inhibition due to B; the expected flower-color phenotype, therefore, would be red. Conversely, a gain-of-function mutation in gene *A* would increase the effect of B, thereby increasing the inhibition of flower color due to B, and the expected flower-color phenotype would be white.

PROBLEM 3 Shown in the accompanying diagram are three possible phenotypes observed on a distal appendage of a certain insect species. The wild-type phenotype consists of a single row of bristles. Some mutants yield a phenotype of no bristles, whereas others yield a phenotype in which the appendage has two rows of bristles. The development of these bristles is known to be due to a linear switch-regulation pathway involving the substances A, B, C, and D, which are encoded by the genes *A*, *B*, *C*, and *D*, respectively. The order of action of *A*, *B*, *C*, and *D* is unknown. The mutant alleles *a* and *b* result in missing bristles (M), whereas the mutant alleles *c* and *d* result in an extra row of bristles (E). The matrix shows the phenotype observed in all possible double mutants.



CHALLENGE PROBLEMS 607

would their status be altered in worms that are homozygous for each of the following mutations? Assume all homozygous mutations do reach the adult stage.

(a) *lin-3* loss of function
(b) *lin-14* gain of function
(c) *lin-4 lin-14* double mutation (both loss of function)

Based on Ambros, 2008, *Nature Medicine* 14: 1036–1040

CHALLENGE PROBLEMS

CHALLENGE PROBLEM 1 You wish to demonstrate that during segmentation of the *Drosophila* embryo, normal pair-rule patterns of expression require normal expression of the gap genes, whereas gap gene expression does not require pair-rule expression. You have the following four mutations available:

(a) A mutation in the zygotic-effect gap gene *knirps* (*kni*)
(b) A mutation in the zygotic-effect pair-rule gene *fushi tarazu* (*ftz*)
(c) A transgene consisting of a reporter gene (*lacZ*) fused to the enhancer elements of *kni*
(d) A transgene consisting of a reporter gene (*lacZ*) fused to the enhancer elements of *ftz*

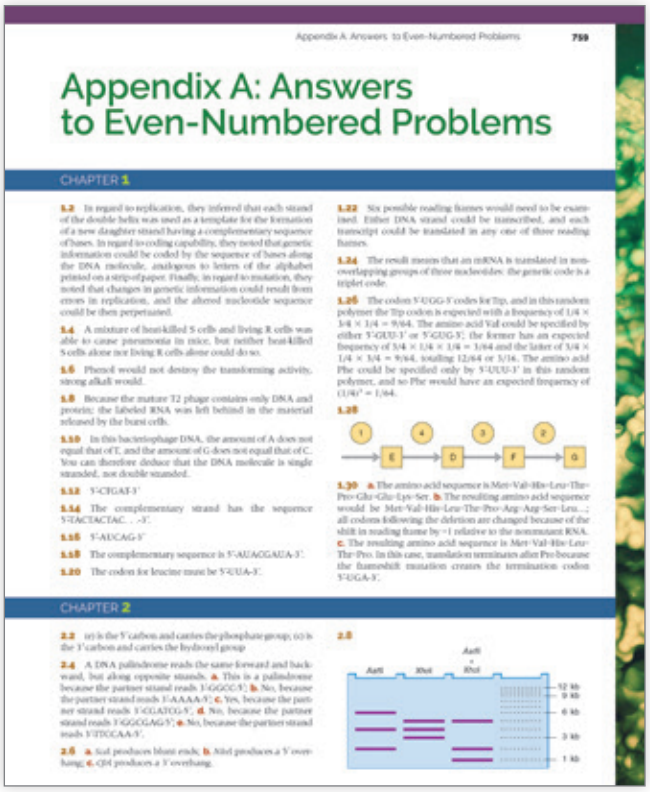
Describe the strains you would need and explain how you would use them to show that wild-type expression of *kni* is needed for proper expression of *ftz*, but that wild-type expression of *ftz* is not needed for proper expression of *kni*. You do not need to give details of the crosses.

CHALLENGE PROBLEM 2 A type of jellyfish has a structure composed of eight circularly arranged cells from which projections emerge, forming a sort of pore. Whereas some of the cells have identical projections, others are quite different, as shown in the accompanying diagram.

The letters a through d indicate the products of four developmental-control genes, *a* through *d*, that are found in each cell around the circle. Sketch the expected phenotype of each of the single mutants, *a* through *d*, assuming that the default state of a cell, with none of the gene products present, is the absence of projections.

CHALLENGE PROBLEM 3 For the developmental-control system described in Challenge Problem 3, sketch the expected phenotypes of each of the six possible types of double mutants.

- At the end of the text are **Answers to Even-Numbered Problems**, in which the logic of each answer is explained in full. The answers are complete, explaining the logical foundation of the solution and laying out the methods used. We find that many of our students, like students everywhere, often sneak a look at the answer before attempting to solve a problem. This is a pity. Working backward from the answer should be a last resort, because problems are valuable opportunities to learn. Problems that the student cannot solve are usually more important than the ones that the student can solve, because the sticklers usually identify trouble spots, areas of confusion, or gaps in understanding. Therefore, we urge our students to try to answer each question before looking at the answer. The answers to the odd-numbered questions are provided to the instructor as part of the Teaching Tools package so they could be assigned for a grade.
- At the end of the text, we include a short list of **Word Roots** that are used in many of the technical terms of genetics. The Word Roots are intended to help students interpret and remember the meaning of key terms, and master the essential terminology of genetics and genomics.

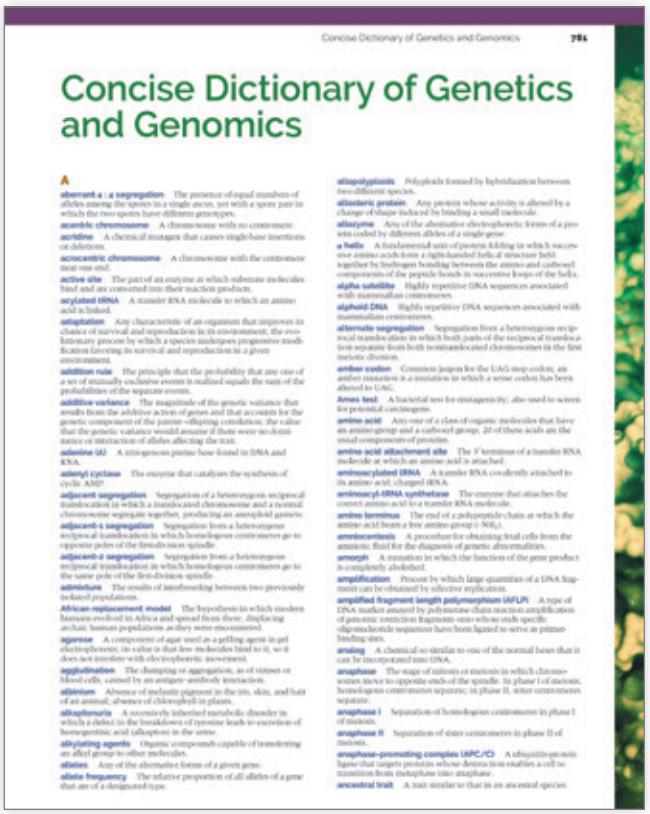

Appendix A: Answers to Even-Numbered Problems

CHAPTER 1

CHAPTER 2


Word Roots: Prefixes, Suffixes, and Combining Forms

- The **Concise Dictionary of Genetics** found at the end of the text enables students to check their understanding of the key words or look up any technical terms they may have forgotten. It includes not only the key words but also genetic terms that students are likely to encounter in exploring the Internet or in their further reading.


Concise Dictionary of Genetics and Genomics

What's New in the Ninth Edition?

This edition has been completely revised and updated. Each chapter has been thoroughly reworked, and the organization of topics, as reflected in the order of chapters, has been revised. To a great extent, this reorganization was driven by developments in the field—especially the explosion of data being generated by high-throughput DNA sequencing, particularly in humans. These advances have revolutionized the study of genetic variation in populations and brought genome-wide association studies (GWAS) and related methods to the forefront. The subject of GWAS is introduced in the context of gene mapping (Chapter 5) and expanded upon with respect to the genetics of complex traits (now Chapter 7). Other applications of high-throughput approaches to genetics include greatly expanded coverage of RNA-seq (Chapter 14), cancer genomics (Chapter 16), and ancient DNA analysis (Chapter 19).

Roots of Discovery boxes (formerly Connections boxes) have been rewritten, in most cases reducing the extent of direct quotes from the original papers and providing readers with focused connections to the major points of the topic being covered. All Roots of Discovery boxes contain complete citations of the papers profiled, including URLs, so that they can easily be explored in more depth, either by the interested student or as part of an instructor-designed activity. Cutting Edge boxes, a new feature, also provide connections to the literature to facilitate further exploration.

Chapter Organization

To help students keep track of the main issues and avoid being distracted by details, each chapter opens with an Outline that shows the road map of the territory ahead. This is followed by a list of Learning Objectives and Science Competencies identifying the most important concepts and principles. An opening paragraph gives an overview of the chapter, illustrates the subject with some specific examples, and shows how the material is connected to genetics as a whole. The text makes liberal use of numbered and bulleted lists to help students organize their learning, as well as summary statements set off in special type to emphasize important principles. Each numbered section concludes with a bulleted list entitled "Summing Up," which highlights the major points covered in the section and will help the student review and master the material covered. Each chapter ends with a Chapter Summary, questions for discussion called Review the Basics, a Guide to Problem Solving, problems for solution in a section called Analysis and Applications, and Challenge Problems.

Contents and Organization

Today, most students learn about DNA in grade school or high school; in our teaching, we have found it artificial to pretend that DNA does not exist until the middle of the term. Thus, an important feature is the presence of two introductory chapters providing a broad overview of DNA, genes, and genomes—what they are, how they function, how they change by mutation, and how they evolve through time. The introductory chapters serve to connect the more advanced concepts that students are about to learn with what they already know. They also serve to provide each student with a solid framework for integrating the material that comes later. An important role they play is to provide a sufficient grounding in the molecular basis of genetics—DNA structure and replication, as well as the central dogma of molecular biology—so that molecular concepts can be integrated into chapters covering "classical" topics such as Mendelian genetics and gene mapping.

Throughout each chapter, there is a balance between observation and theory, between principle and concrete example, and between challenge and motivation. Molecular, classical, and evolutionary genetics are integrated throughout the text. Frequent references are made to human genetics. The text is also liberally populated with applications to other animals and plants, including the key model organisms used in genetics and genomics.

Next, we describe some of the highlights of the five major sections of the text.

Defining and Working with Genes

- *Genes, Genomes, and Genetic Analysis* (Chapter 1) is an overview of genetics designed to bring students with disparate backgrounds to a common level of understanding. This chapter enables classical, molecular, and evolutionary genetics to be integrated in the rest of the text. Included in this chapter are the basic concepts of molecular genetics: DNA structure, replication, expression, and mutation. A feature of this chapter is a detailed exploration of the work of Beadle and Tatum that led to the one-gene-one-enzyme hypothesis and

the use of complementation analysis as a tool for genetic inference

- *DNA Structure and Genetic Variation* (Chapter 2) emphasizes that the primary tools of the modern geneticist are methods for the experimental manipulation of DNA. It includes a more detailed look at DNA structure, and it introduces the principal methods of DNA manipulation, including restriction enzymes, electrophoresis, DNA hybridization, Southern blotting, and the polymerase chain reaction (PCR). We also introduce single-nucleotide polymorphisms (SNPs) and copy-number polymorphisms (CNPs) and discuss how these types of genetic markers can be assayed on a genome-wide scale using oligonucleotide microarrays (DNA chips). The use of simple-sequence repeat variation for genotyping is given expanded coverage.

Transmission Genetics

- *Mendelian Genetics: The Principle of Segregation and Assortment* (Chapter 3) introduces the fundamental Mendelian concepts of random segregation and independent assortment, not only as they can be inferred from crosses involving experimental organisms like peas and flies, but also by analysis of human pedigrees. The role of probability in genetic analysis is also introduced. A unique feature of this chapter is the integration of molecular genetics with Mendel's experiments. We describe the molecular basis of the wrinkled mutation and show how a modern geneticist would carry out Mendel's study, examining the molecular phenotypes on the one hand and the morphological phenotypes on the other hand. This pedagogy provides a solid basis for understanding not only Mendel's experiments as he actually performed and interpreted them, but also the use of modern molecular approaches in genetic analysis. Molecular markers are also integrated into human genetic analysis.
- *The Chromosomal Basis of Inheritance* (Chapter 4) covers the cell cycle, mitosis and meiosis, and hypothesis testing in genetics. The approach to the chi-squared test has been revised by introducing random variables and their distributions, first with respect to the binomial distribution and then with respect to the chi-squared distribution. Computer-simulated distributions are used to illustrate the logic of significance testing, after which the mechanics of actually performing a chi-squared test are described.
- *Genetic Linkage and Chromosome Mapping* (Chapter 5) covers linkage analysis and gene mapping. The classical approach, involving test crosses in experimental organisms, has been retained, as has streamlined coverage of tetrad analysis in fungi. New to the ninth edition is a section on genetic mapping in humans, which includes expanded coverage of lod score analysis of pedigrees, as well as an entirely new section on gene localization by association analysis.
- *Human Karyotypes and Chromosome Behavior* (Chapter 6) covers the principles of chromosome mechanics with special reference to human chromosome number and structure and the types of aberrations that are found in human chromosomes. The genetic implications of chromosome abnormalities—duplications, deficiencies, inversions, and translocations—are also discussed. The evolutionary significance of gene duplication is introduced, and the genetic consequences of translocation heterozygosity (pseudolinkage) is described.
- *The Genetic Basis of Complex Traits* (Chapter 7) covers quantitative genetics. It is a revision of Chapter 18 from the previous edition. We chose to introduce this material earlier because of the growing importance of genome-wide association studies in both agriculture and medicine. Crohn's disease is used as a model for doing so, and both the strengths and weaknesses of GWAS as a tool are highlighted. Coverage of heritability has been revised, and a new section on misconceptions about it has been added.
- *Genetics of Bacteria and Their Viruses* (Chapter 8) extends the use of genetic analysis to bacteria (mainly *Escherichia coli*) and viruses, and serves as a transition into the more molecular subjects covered in subsequent chapters. The section on plasmids has been revised to focus more specifically on the F plasmid; more detailed coverage of bacterial plasmids in general has been moved to the *Molecular Organization of Chromosomes and Genomes* chapter. Some of the classical experiments and methods, such as replica plating and the "U-tube" experiment, are highlighted. The description of the origin of the term "cistron" and the *cis-trans* test has been expanded, and CRISPR–Cas9 as a bacterial system is introduced in a Cutting Edge box.

Organization and Replication of Chromosomes and DNA

- *Molecular Organization of Chromosomes and Genomes* (Chapter 9) continues the transition into the molecular basis of inheritance, covering the organization of DNA in the genomes of both prokaryotes and eukaryotes. It now includes an introduction to mobile DNA in both types of

organisms. The section on *Cot* kinetics has been shortened, recognizing that while historically and conceptually important, this methodology is no longer in active use. The description of chromosome condensation has been updated, and its connection to mitosis (and meiosis) has been made more explicit.

- *DNA Replication and Sequencing* (Chapter 10) covers the mechanics of DNA replication and methods of sequencing as the starting point for an in-depth discussion of the molecular basis of genetics. The mechanisms of DNA replication are described first for prokaryotes and then for eukaryotes. Coverage of Sanger sequencing is followed by a description of sequencing-by-synthesis, using the Illumina platform as a model.
- *Mutation, Repair, and Recombination* (Chapter 11) covers mutation, DNA repair, and recombination. In previous editions, mutation was presented in a later chapter, but by having it immediately follow coverage of DNA replication, we hope to emphasize the importance of all of these processes in both the maintenance of genetic continuity and the generation of new variation. Coverage of the classical Luria–Delbruck experiment, showing that mutation is random with respect to adaptation, has been added. Coverage of mechanisms of recombination has been incorporated in this chapter, emphasizing the similarity between these mechanisms and post-replication repair mechanisms.

Gene Expression

- *Molecular Biology of Gene Expression* (Chapter 12) covers the processes of transcription, translation, and RNA processing. Transcription mechanisms in prokaryotes and eukaryotes are more clearly differentiated; the concept of consensus sequences is introduced more comprehensively, along with visualizations of them as "sequence logos."
- *Molecular Mechanisms of Gene Regulation* (Chapter 13) covers the regulation of gene expression. Mechanisms in prokaryotes and eukaryotes have been separated, so that they can be better compared and contrasted. The section on the role played by noncoding RNAs in regulation has been expanded, highlighting their roles in processes such as X-chromosome inactivation, alternative mRNA splicing, and translational regulation.
- *Manipulating Genes and Genomes* (Chapter 14) covers experimental methods of gene manipulation, beginning with the classical methods of gene cloning and proceeding forward to genomic analysis, transcriptomics, and gene editing with CRISPR–Cas9. Included are the use of restriction enzymes and vectors in recombinant DNA, cloning strategies, site-directed mutagenesis, the production of genetically defined transgenic animals and plants, and applications of genetic engineering. Coverage of whole-exome sequencing has been expanded, and a new section on functional genomics has been added. This material includes expanded coverage of RNA-seq and a description of quantitative PCR for transcript quantification. A subsection on use of RNAi for gene expression knockdown has been added, as has a major section on gene editing with CRISPR–Cas9. Associated with the latter is a Cutting Edge box on the use of these methods in a mouse model of muscular dystrophy.
- *Genetic Control of Development* (Chapter 15) focuses on genetic analysis of development in nematodes (*Caenorhabditis elegans*) and *Drosophila* and includes a thorough examination of the genetic basis of floral development in *Arabidopsis thaliana*. A new section on the role of regulatory RNAs in the control of development has been added, including examples from nematodes, flies, and mammalian *Hox* genes.
- *Molecular Genetics of the Cell Cycle and Cancer* (Chapter 16) investigates cancer from the standpoint of the genetic control of cell division, with emphasis on the checkpoints that, in normal cells, result either in inhibition of cell division or in programmed cell death (apoptosis). Cancer results from a series of successive mutations, usually in somatic cells that overcome the normal checkpoints that control cellular proliferation. A new section on cancer genomics has been added, using pancreatic cancer as a model for characterization of the mutational and transcriptisomal changes that are associated with tumor progression.

Variation

- *Mitochondrial DNA and Extranuclear Inheritance* (Chapter 17) covers non-nuclear genetics, including genetic defects in human mitochondrial DNA. A new section has been added that describes the transmission of *Wolbachia* in arthropods.
- *Genes in Populations* (Chapter 18) covers population genetics (material on molecular evolution has been moved to the *Molecular and Human Evolutionary Genetics* chapter). The section on DNA fingerprinting has been updated to illustrate use of short tandem repeats as markers. A new subsection on linkage disequilibrium has been added, along with "heat map" illustrations of disequilibrium derived from genomic data. In

the discussion of evolutionary processes, the order of topics has been rearranged so that genetic drift—a random process found in all finite populations—is addressed prior to examining the deterministic process of natural selection. A new section on molecular signals of selection has been added, incorporating material on lactase persistence in humans. A Cutting Edge box describes the principles of "gene drive" based on CRISPR–Cas9 and explains how it might be used to control mosquito vectors of malaria.

- *Molecular and Human Evolutionary Genetics* (Chapter 19) covers both molecular and human evolution, since most of the advances in the latter have resulted from developments in the former. Other changes in this chapter include an expanded section on ancient DNA analysis and the use of *Alu1* insertion sites to resolve hominid phylogeny. Coverage of diversity in the genus *Homo* has been revised to include new findings about *H. denisova* and *H. floresiensis*. The section on genetic variation in *H. sapiens* has been revised to incorporate data from the 1000 Genomes Project (as opposed to HapMap in previous editions) and to include the use of genetic assignment methods ("STRUCTURE") for characterization of modern human variation. A new Cutting Edge box focuses on use of ancient DNA genotyping to characterize the peopling of Western Europe.

Flexibility

There is no requirement to start at the beginning of this text and proceed straight to the end. In fact, doing so in a typical one-semester course borders on the impossible. In this ninth edition, each chapter has been designed to be a self-contained unit that stands on its own. This feature gives instructors the option of using whatever order suits them, and of skipping particular chapters that do not fit with their course design. We have integrated molecular and classical principles throughout the text, so you can begin a course with almost any of the chapters. Most instructors will prefer to start with the overview in the *Genes, Genomes, and Genetic Analysis* chapter because it brings every student to the same basic level of understanding. The *DNA Structure and Genetic Variation* chapter introduces the basic experimental manipulations used in modern genetics and serves to integrate molecular and classical genetics in the discussion of Mendel in the *Transmission Genetics: The Principle of Segregation* chapter. Some other approaches that instructors might use to structure the beginning of their course are outlined here.

Approach	Chapters to begin with
Mendel-early format	*Genes, Genomes, and Genetic Analysis*
	Transmission Genetics: The Principle of Segregation
	DNA Structure and Genetic Variation
Chromosome-early format	*Genes, Genomes, and Genetic Analysis*
	Chromosomes and Sex-Chromosome Inheritance
	DNA Structure and Genetic Variation
	Transmission Genetics: The Principle of Segregation
	Genetic Linkage and Chromosome Mapping
Genomes-first format	*Genes, Genomes, and Genetic Analysis*
	DNA Structure and Genetic Variation
	Chromosomes and Sex-Chromosome Inheritance

The writing and illustration program were designed to accommodate a variety of formats, and we encourage teachers to take advantage of this flexibility to meet their own unique needs.

Teaching Tools

Jones & Bartlett Learning offers a suite of traditional and interactive multimedia supplements to assist instructors and aid students in mastering genetics. Additional information and review copies of any of the following items are available through your Jones & Bartlett Learning sales representative.

- The **PowerPoint Image Bank** is an easy-to-use multimedia tool that provides all of the illustrations and photos from the text (to which Jones & Bartlett Learning holds the rights to reproduce electronically) for use in classroom presentation. You can select images you need or easily generate your own slide shows, or you can print the files for transparency creation. Many images have already been inserted into the PowerPoint Lecture Outline presentations for ease of use.

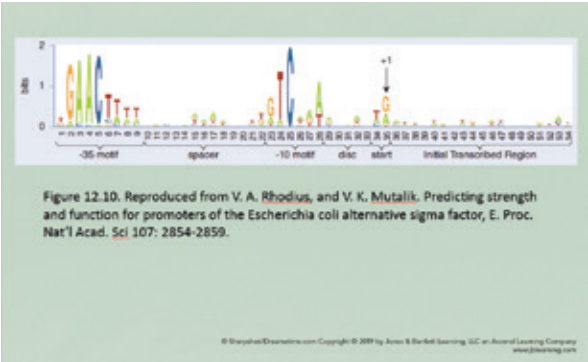


Figure 12.10. Reproduced from V. A. Rhodius, and V. K. Mutalik. Predicting strength and function for promoters of the Escherichia coli alternative sigma factor, E. Proc. Nat'l Acad. Sci 107: 2854-2859.

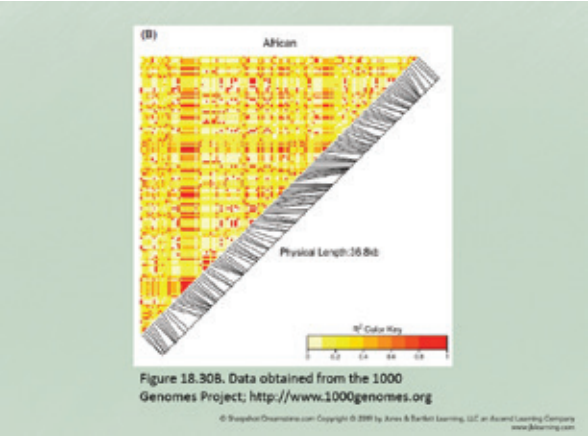


Figure 18.30B. Data obtained from the 1000 Genomes Project; http://www.1000genomes.org

- A PowerPoint presentation containing the detailed outline for each chapter of *Genetics: Analysis of Genes and Genomes, Ninth Edition*, is included. This presentation, which is designed to mirror the text, is constructed flexibly to meet your lecture's organization. The outline is open, allowing you to provide the elements you deem necessary, whether it be new text or more images from the Image Bank.

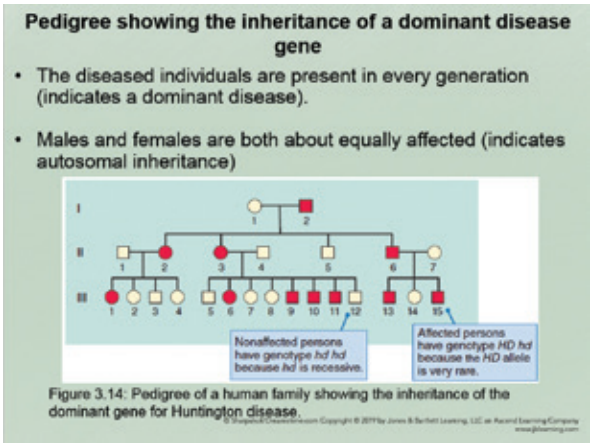


Figure 3.14: Pedigree of a human family showing the inheritance of the dominant gene for Huntington disease.

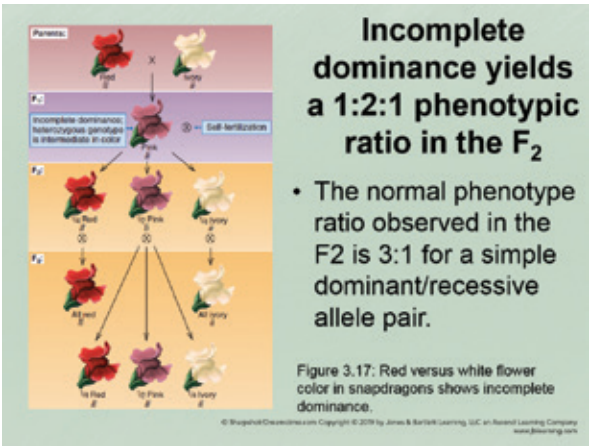


Figure 3.17: Red versus white flower color in snapdragons shows incomplete dominance.

- A **Test Bank** containing more than 1,000 questions and complete answers is available. The questions are a mix of factual, descriptive, and quantitative types. A typical chapter contains multiple choice, fill-in-the-blank, and short-answer questions. The Test Bank is provided as Microsoft Word documents.

- The **Instructor's Manual** includes Chapter Summaries, Teaching Tips, References, Suggested Activities, and more.

CHAPTER 5
INSTRUCTOR'S MANUAL

Genetics: Analysis of Genes and Genomes, Ninth Edition
Daniel L. Hartl and Bruce J. Cochrane

Genetic Linkage and Chromosome Mapping

Chapter Summary

Nonallelic genes located in the same chromosome tend to remain together in meiosis rather than to undergo independent assortment. This phenomenon is called linkage. The indication of linkage is a significant deviation from the 1 : 1 : 1 : 1 ratio of phenotypes in the progeny of a cross of the form *Aa bb* × *aa bb*. When alleles of two linked genes segregate, more than 50% of the gametes produced have parental combinations of the segregating alleles, and fewer than 50% have nonparental (recombinant) combinations of the alleles. The recombination of linked genes results from crossing-over, a process in which nonsister chromatids of the homologous chromosomes exchange corresponding segments in the first meiotic prophase.

The frequency of recombination between different genes can be used to determine the relative order and locations of the genes in chromosomes. This type of analysis is called genetic mapping. The distance between adjacent genes in such a map (a genetic or linkage map) is defined to be proportional to the frequency of recombination between them; the unit of map distance (the map unit or centimorgan (cM)) is defined as 1% recombination. One map unit corresponds to a physical length of the chromosome in which a crossover event takes place, on the average, once in every 50 meiotic divisions. For short distances, map units are additive. (For example, for three genes with order *a b c*, if the map distances *a* to *b* and *b* to *c* are 2 and 3 map units, respectively, then the map distance *a* to *c* is 2 + 3 = 5 map units.) The recombination frequency underestimates actual genetic distance if the region between the genes being considered is too great. This discrepancy results from multiple crossover events, which yield either no recombinants or the same number produced by a single event. For example, two crossovers in the region between two genes may yield no recombinants, and three crossover events may yield recombinants of the same type as that from a single crossover.

When many genes are mapped in a particular species, they form linkage groups equal in number to the haploid chromosome number of the species. The maximum frequency of recombination between any two genes in a cross is 50%; this happens when the genes are in nonhomologous chromosomes and assort independently or when the genes are sufficiently far apart in the same chromosome that at least one crossover is formed between them in every meiosis. The map distance between two genes may be considerably greater than 50 centimorgans, because the map distance is equal to half of the average number of crossovers per chromosome times 100. A mapping function is the mathematical relation between the genetic map distance across an interval and the observed percent recombination in the interval.

In many organisms, including human beings, model experimental organisms, and agricultural animals and plants, the genetic map includes hundreds or thousands of genetic markers distributed more or less uniformly throughout the euchromatin. Some of the most useful genetic markers are DNA polymorphisms (changes in nucleotide sequence present in wild-type organisms that are not associated with any phenotypic abnormalities) because of their high level of

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Genetics: Analysis of Genes and Genomes, Ninth Edition
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chromosome can be mapped. Linkage analysis in unordered tetrads is based on the frequencies of parental-ditype (PD), nonparental-ditype (NPD), and tetratype (TT) tetrads. The observation of NPD < PD is a sensitive indicator of linkage.

Teaching Tips

This chapter combines the classical approaches to mapping via recombination analysis with an introduction to modern genome-wide association studies for localization of genes that contribute to complex traits. The latter is a topic that will be addressed again in Chapter 7; in this chapter it is introduced as a concept in human genetic mapping, but issues such as the heritability of complex traits are not addressed.

It is thus possible to use the material in this chapter in different ways. For a classical approach to recombination, sections 5.1 to 5.4 can be covered in depth, including two-point and three-point test cross analysis, mechanisms of crossing over with respect to chromatids, and analysis of recombination in ordered and unordered tetrads. For a more human-focused approach, these sections can be covered more briefly, and section five can be the focus. Section six, on special features of recombination, can or cannot be included, regardless of overall approach.

References

In a classical approach, Morgan and Cattell (1912) describes the original experiments in *Drosophila* with respect to linkage of X chromosome genes, and Perkins (1953) does similarly for tetrad analysis. Lewis and Knight (2012) introduces the principles of *GWAS*, and WTTC (2007) is a paradigm of a large scale *GWAS* of multiple traits.

Key Words

ascospore
ascus
attached-X chromosome
centimorgan
chromatid interference
chromosome interference
chromosome map
cis configuration
coefficient of coincidence
compound-X chromosome
coupling configuration
euchromatin
false discovery rate
first-division segregation
frequency of recombination
genetic association
genetic map
genome-wide association study (GWAS
heterochromatin
likelihood ratio
linkage
linkage group
linkage map
lod score
map distance
map unit
mapping function
nonparental-ditype (NPD) tetrad
parental type
parental-ditype (PD) tetrad
random-spore analysis
recombinant
recombination
repulsion configuration
second-division segregation
somatic mosaics
syntenic genes
tetratype (TT) tetrad
three-point cross
trans configuration

Suggested Activities

The first 23 Analysis and Application Problems involve the basic concepts of recommination mapping. Problem 25 is a straightforward application of the principles of tetrad analysis. Many of the remaining problems address the detection of linkage in pedigrees, so would be appropriate for assignment in a more human-oriented approach.

With respect to GWAS's, one intriguing source of original research is the list of publications to which the personal genomics company 23andMe has contributed, available at https://www.23andme.com/publications/for-scientists/. A possible project for students, either individually or in groups, would be to select a particular case-control GWAS of interest and, at this point, get some basic information, such as

a. What were the study populations – how many and how were the recruited?
b. How many SNPs were assayed and what was the false discovery rate cutoff?
c. How many significant associations were identified, and on what chromosomes?
d. What if any candidate genes were suggested based on the results of the study?

This project could then be returned to in the context of chapter 7, when the key issue of heritability is covered.

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