INTRODUCTION TO GENETIC ANALYSIS

Anthony J. F. Griffiths

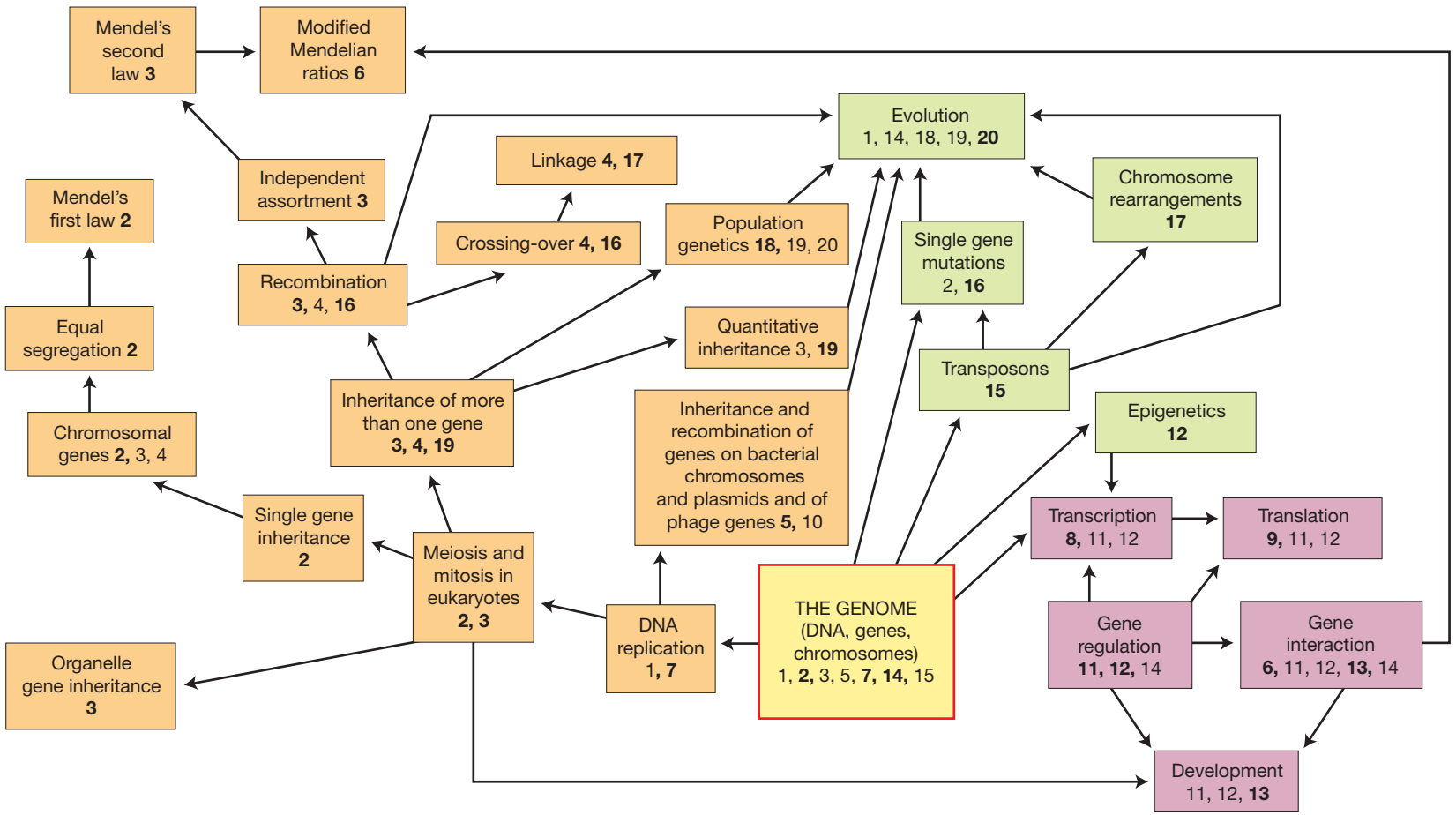
Susan R. Wessler

Sean B. Carroll

John Doebley

ELEVENTH EDITION

A Map of Genetics



The map displays the general divisions of genetics in boxes, with arrows showing the main connections between them covered in this book. Orange, broadly, is inheritance, purple is function, and green is change. Numbers are chapters covering the topic, with main discussions in bold.

INTRODUCTION TO

GENETIC ANALYSIS

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Contents in Brief

Preface xiii

1 The Genetics Revolution 1

PART I TRANSMISSION GENETICS

2 Single-Gene Inheritance 31

3 Independent Assortment of Genes 87

4 Mapping Eukaryote Chromosomes by Recombination 127

5 The Genetics of Bacteria and Their Viruses 173

6 Gene Interaction 215

PART II FROM DNA TO PHENOTYPE

7 DNA: Structure and Replication 259

8 RNA: Transcription and Processing 291

9 Proteins and Their Synthesis 319

10 Gene Isolation and Manipulation 351

11 Regulation of Gene Expression in Bacteria and Their Viruses 397

12 Regulation of Gene Expression in Eukaryotes 431

13 The Genetic Control of Development 469

14 Genomes and Genomics 507

PART III MUTATION, VARIATION, AND EVOLUTION

15 The Dynamic Genome: Transposable Elements 547

16 Mutation, Repair, and Recombination 581

17 Large-Scale Chromosomal Changes 617

18 Population Genetics 665

19 The Inheritance of Complex Traits 715

20 Evolution of Genes and Traits 761

A Brief Guide to Model Organisms 759

Appendix A: Genetic Nomenclature 775

Appendix B: Bioinformatics Resources for Genetics and Genomics 776

Glossary 779

Answers to Selected Problems 797

Index 809

Contents

Preface xiii

1 The Genetics Revolution 1

1.1 The Birth of Genetics 2

Gregor Mendel—A monk in the garden 3

Mendel rediscovered 5

The central dogma of molecular biology 9

1.2 After Cracking the Code 10

Model organisms 10

Tools for genetic analysis 12

1.3 Genetics Today 14

From classical genetics to medical genomics 14

Investigating mutation and disease risk 17

When rice gets its feet a little too wet 20

Recent evolution in humans 23

PART I TRANSMISSION GENETICS

2 Single-Gene Inheritance 31

2.1 Single-Gene Inheritance Patterns 34

Mendel's pioneering experiments 34

Mendel's law of equal segregation 36

2.2 The Chromosomal Basis of Single-Gene Inheritance Patterns 39

Single-gene inheritance in diploids 40

Single-gene inheritance in haploids 44

2.3 The Molecular Basis of Mendelian Inheritance Patterns 45

Structural differences between alleles at the molecular level 45

Molecular aspects of gene transmission 46

Alleles at the molecular level 48

2.4 Some Genes Discovered by Observing Segregation Ratios 50

A gene active in the development of flower color 51

A gene for wing development 51

A gene for hyphal branching 52

Predicting progeny proportions or parental genotypes by applying the principles of single-gene inheritance 53

2.5 Sex-Linked Single-Gene Inheritance Patterns 53

Sex chromosomes 54

Sex-linked patterns of inheritance 54

X-linked inheritance 55

2.6 Human Pedigree Analysis 58
Autosomal recessive disorders 59
Autosomal dominant disorders 61
Autosomal polymorphisms 63
X-linked recessive disorders 65
X-linked dominant disorders 68
Y-linked inheritance 68
Calculating risks in pedigree analysis 69

3 Independent Assortment of Genes 87
3.1 Mendel's Law of Independent Assortment 89
3.2 Working with Independent Assortment 93
Predicting progeny ratios 93
Using the chi-square test on monohybrid and dihybrid ratios 96
Synthesizing pure lines 98
Hybrid vigor 99
3.3 The Chromosomal Basis of Independent Assortment 101
Independent assortment in diploid organisms 101
Independent assortment in haploid organisms 103
Independent assortment of combinations of autosomal and X-linked genes 104
Recombination 104
3.4 Polygenic Inheritance 108
3.5 Organelle Genes: Inheritance Independent of the Nucleus 110
Patterns of inheritance in organelles 111
Cytoplasmic segregation 113
Cytoplasmic mutations in humans 115
mtDNA in evolutionary studies 116

4 Mapping Eukaryote Chromosomes by Recombination 127
4.1 Diagnostics of Linkage 129
Using recombinant frequency to recognize linkage 129
How crossovers produce recombinants for linked genes 132
Linkage symbolism and terminology 132
Evidence that crossing over is a breakage-and-rejoining process 133
Evidence that crossing over takes place at the four-chromatid stage 133
Multiple crossovers can include more than two chromatids 134
4.2 Mapping by Recombinant Frequency 135
Map units 136
Three-point testcross 139
Deducing gene order by inspection 141
Interference 141
Using ratios as diagnostics 142
4.3 Mapping with Molecular Markers 144
Single nucleotide polymorphisms 144
Simple sequence length polymorphisms 145
Detecting simple sequence length polymorphisms 146
Recombination analysis using molecular markers 146
4.4 Centromere Mapping with Linear Tetrads 148
4.5 Using the Chi-Square Test to Infer Linkage 150
4.6 Accounting for Unseen Multiple Crossovers 151
A mapping function 151
The Perkins formula 152
4.7 Using Recombination-Based Maps in Conjunction with Physical Maps 154
4.8 The Molecular Mechanism of Crossing Over 155

5 The Genetics of Bacteria and Their Viruses 173
5.1 Working with Microorganisms 176
5.2 Bacterial Conjugation 177
Discovery of conjugation 177
Discovery of the fertility factor (F) 178
Hfr strains 179
Mapping of bacterial chromosomes 184
F plasmids that carry genomic fragments 188
R plasmids 188
5.3 Bacterial Transformation 191
The nature of transformation 191
Chromosome mapping using transformation 191
5.4 Bacteriophage Genetics 192
Infection of bacteria by phages 192
Mapping phage chromosomes by using phage crosses 194
5.5 Transduction 196
Discovery of transduction 196
Generalized transduction 197
Specialized transduction 198
Mechanism of specialized transduction 200
5.6 Physical Maps and Linkage Maps Compared 201

6 Gene Interaction 215
6.1 Interactions Between the Alleles of a Single Gene: Variations on Dominance 216
Complete dominance and recessiveness 216
Incomplete dominance 218
Codominance 219
Recessive lethal alleles 220

6.2 Interaction of Genes in Pathways 223
Biosynthetic pathways in *Neurospora* 224
Gene interaction in other types of pathways 226
6.3 Inferring Gene Interactions 227
Sorting mutants using the complementation test 227
Analyzing double mutants of random mutations 231
6.4 Penetrance and Expressivity 239

PART II FROM DNA TO PHENOTYPE

7 Structure and Replication 259
7.1 DNA: The Genetic Material 260
Discovery of transformation 261
Hershey–Chase experiment 263
7.2 DNA Structure 264
DNA structure before Watson and Crick 264
The double helix 267
7.3 Semiconservative Replication 270
Meselson–Stahl experiment 271
The replication fork 272
DNA polymerases 273
7.4 Overview of DNA Replication 274
7.5 The Replisome: A Remarkable Replication Machine 277
Unwinding the double helix 279
Assembling the replisome: replication initiation 280
7.6 Replication in Eukaryotic Organisms 280
Eukaryotic origins of replication 280
DNA replication and the yeast cell cycle 281
Replication origins in higher eukaryotes 282
7.7 Telomeres and Telomerase: Replication Termination 283

8 RNA: Transcription and Processing 291
8.1 RNA 293
Early experiments suggest an RNA intermediate 293
Properties of RNA 294
Classes of RNA 294
8.2 Transcription 296
Overview: DNA as transcription template 296
Stages of transcription 298
8.3 Transcription in Eukaryotes 301
Transcription initiation in eukaryotes 303
Elongation, termination, and pre-mRNA processing in eukaryotes 304
8.4 Intron Removal and Exon Splicing 307
Small nuclear RNAs (snRNAs): the mechanism of exon splicing 307
Self-splicing introns and the RNA world 308
8.5 Small Functional RNAs That Regulate and Protect the Eukaryotic Genome 310
miRNAs are important regulators of gene expression 310
siRNAs ensure genome stability 311
Similar mechanisms generate siRNA and miRNA 314

9 Proteins and Their Synthesis 319
9.1 Protein Structure 322
9.2 The Genetic Code 324
Overlapping versus nonoverlapping codes 325
Number of letters in the codon 325
Use of suppressors to demonstrate a triplet code 325
Degeneracy of the genetic code 327
Cracking the code 328
Stop codons 329
9.3 tRNA: The Adapter 329
Codon translation by tRNA 331
Degeneracy revisited 331
9.4 Ribosomes 332
Ribosome features 333
Translation initiation, elongation, and termination 335
Nonsense suppressor mutations 338
9.5 The Proteome 339
Alternative splicing generates protein isoforms 339
Posttranslational events 340

10 Gene Isolation and Manipulation 351
10.1 Overview: Isolating and Amplifying Specific DNA Fragments 353
10.2 Generating Recombinant DNA Molecules 354
Genomic DNA can be cut up before cloning 355
The polymerase chain reaction amplifies selected regions of DNA in vitro 356
DNA copies of mRNA can be synthesized 358
Attaching donor and vector DNA 358
Amplification of donor DNA inside a bacterial cell 362
Making genomic and cDNA libraries 366
10.3 Using Molecular Probes to Find and Analyze a Specific Clone of Interest 367
Finding specific clones by using probes 367
Finding specific clones by functional complementation 369
Southern- and Northern-blot analysis of DNA 371
10.4 Determining the Base Sequence of a DNA Segment 374

10.5 Aligning Genetic and Physical Maps to Isolate Specific Genes 377
Using positional cloning to identify a human-disease gene 378
Using fine mapping to identify genes 379
10.6 Genetic Engineering 382
Genetic engineering in *Saccharomyces cerevisiae* 383
Genetic engineering in plants 383
Genetic engineering in animals 386

11 Regulation of Gene Expression in Bacteria and Their Viruses 397
11.1 Gene Regulation 399
The basics of prokaryotic transcriptional regulation: genetic switches 400
A first look at the *lac* regulatory circuit 401
11.2 Discovery of the *lac* System: Negative Control 404
Genes controlled together 405
Genetic evidence for the operator and repressor 405
Genetic evidence for allostery 407
Genetic analysis of the *lac* promoter 408
Molecular characterization of the Lac repressor and the *lac* operator 408
Genetic analysis of the *lac* promoter 408
Molecular characterization of the Lac repressor and the *lac* operator 408
11.3 Catabolite Repression of the *lac* Operon: Positive Control 409
The basics of *lac* catabolite repression: choosing the best sugar to metabolize 410
The structures of target DNA sites 410
A summary of the *lac* operon 411
11.4 Dual Positive and Negative Control: The Arabinose Operon 413
11.5 Metabolic Pathways and Additional Levels of Regulation: Attenuation 414
11.6 Bacteriophage Life Cycles: More Regulators, Complex Operons 417
Molecular anatomy of the genetic switch 421
Sequence-specific binding of regulatory proteins to DNA 422
11.7 Alternative Sigma Factors Regulate Large Sets of Genes 423

12 Regulation of Gene Expression in Eukaryotes 431
12.1 Transcriptional Regulation in Eukaryotes: An Overview 432
12.2 Lessons from Yeast: The GAL System 436
Gal4 regulates multiple genes through upstream activation sequences 436
The Gal4 protein has separable DNA-binding and activation domains 438
Gal4 activity is physiologically regulated 439
Gal4 functions in most eukaryotes 439
Activators recruit the transcriptional machinery 440
The control of yeast mating type: combinatorial interactions 440
12.3 Dynamic Chromatin 443
Chromatin-remodeling proteins and gene activation 444
Modification of histones 445
Histone methylation can activate or repress gene expression 448
The inheritance of histone modifications and chromatin structure 448
Histone variants 449
DNA methylation: another heritable mark that influences chromatin structure 449
12.4 Activation of Genes in a Chromatin Environment 450
The β-interferon enhanceosome 451
Enhancer-blocking insulators 452
12.5 Long-Term Inactivation of Genes in a Chromatin Environment 454
Mating-type switching and gene silencing 454
Heterochromatin and euchromatin compared 455
Position-effect variegation in *Drosophila* reveals genomic neighborhoods 456
Genetic analysis of PEV reveals proteins necessary for heterochromatin formation 457
12.6 Gender-Specific Silencing of Genes and Whole Chromosomes 460
Genomic imprinting explains some unusual patterns of inheritance 460
But what about Dolly and other cloned mammals? 461
Silencing an entire chromosome: X-chromosome inactivation 462
12.7 Post-Transcriptional Gene Repression by miRNAs 463

13 The Genetic Control of Development 469
13.1 The Genetic Approach to Development 471
13.2 The Genetic Toolkit for *Drosophila* Development 474
Classification of genes by developmental function 474
Homeotic genes and segmental identity 474
Organization and expression of *Hox* genes 476
The homeobox 478
Clusters of *Hox* genes control development in most animals 479

13.3 Defining the Entire Toolkit 482
The anteroposterior and dorsoventral axes 483
Expression of toolkit genes 484
13.4 Spatial Regulation of Gene Expression in Development 487
Maternal gradients and gene activation 488
Drawing stripes: integration of gap-protein inputs 489
Making segments different: integration of Hox inputs 491
13.5 Post-transcriptional Regulation of Gene Expression in Development 494
RNA splicing and sex determination in *Drosophila* 494
Regulation of mRNA translation and cell lineage in *C. elegans* 496
Translational control in the early embryo 496
miRNA control of developmental timing in *C. elegans* and other species 499
13.6 From Flies to Fingers, Feathers, and Floor Plates: The Many Roles of Individual Toolkit Genes 500
13.7 Development and Disease 501
Polydactyly 501
Holoprosencephaly 502
Cancer as a developmental disease 502

14 Genomes and Genomics 507
14.1 The Genomics Revolution 510
14.2 Obtaining the Sequence of a Genome 511
Turning sequence reads into an assembled sequence 511
Whole-genome sequencing 513
Traditional WGS 513
Next-generation whole-genome shotgun sequencing 514
Whole-genome-sequence assembly 517
14.3 Bioinformatics: Meaning from Genomic Sequence 519
The nature of the information content of DNA 519
Deducing the protein-encoding genes from genomic sequence 520
14.4 The Structure of the Human Genome 524
Noncoding functional elements in the genome 525
14.5 The Comparative Genomics of Humans with Other Species 527
Phylogenetic inference 527
Of mice and humans 530
Comparative genomics of chimpanzees and humans 532
14.6 Comparative Genomics and Human Medicine 532
The exome and personalized genomics 533
Comparative genomics of nonpathogenic and pathogenic *E. coli* 534
14.7 Functional Genomics and Reverse Genetics 536
"'Omics" 536
Reverse genetics 539

PART III MUTATION, VARIATION, AND EVOLUTION

15 The Dynamic Genome: Transposable Elements 547
15.1 Discovery of Transposable Elements in Maize 549
McClintock's experiments: the *Ds* element 549
Autonomous and nonautonomous elements 550
Transposable elements: only in maize? 552
15.2 Transposable Elements in Prokaryotes 553
Bacterial insertion sequences 553
Prokaryotic transposons 554
Mechanism of transposition 556
15.3 Transposable Elements in Eukaryotes 558
Class 1: retrotransposons 558
Class 2: DNA transposons 562
Utility of DNA transposons for gene discovery 564
15.4 The Dynamic Genome: More Transposable Elements Than Ever Imagined 566
Large genomes are largely transposable elements 567
Transposable elements in the human genome 568
The grasses: LTR-retrotransposons thrive in large genomes 569
Safe havens 569
15.5 Regulation of Transposable Element Movement by the Host 571
Genome surveillance in animals and bacteria 573

16 Mutation, Repair, and Recombination 581
16.1 The Phenotypic Consequences of DNA Mutations 583
Types of point mutation 583
The molecular consequences of point mutations in a coding region 584
The molecular consequences of point mutations in a noncoding region 586
16.2 The Molecular Basis of Spontaneous Mutations 586
Luria and Delbrück fluctuation test 586
Mechanisms of spontaneous mutations 588
Spontaneous mutations in humans: trinucleotide-repeat diseases 591

16.3 The Molecular Basis of Induced Mutations 593
Mechanisms of mutagenesis 593
The Ames test: evaluating mutagens in our environment 595
16.4 Biological Repair Mechanisms 596
Direct reversal of damaged DNA 597
Base-excision repair 598
Nucleotide-excision repair 599
Postreplication repair: mismatch repair 602
Error-prone repair: translesion DNA synthesis 604
Repair of double-strand breaks 606
The involvement of DSB repair in meiotic recombination 608
16.5 Cancer: An Important Phenotypic Consequence of Mutation 609
How cancer cells differ from normal cells 609
Mutations in cancer cells 609

17 Large-Scale Chromosomal Changes 617
17.1 Changes in Chromosome Number 618
Aberrant euploidy 619
Aneuploidy 627
The concept of gene balance 632
17.2 Changes in Chromosome Structure 634
Deletions 637
Duplications 640
Inversions 642
Reciprocal translocations 645
Robertsonian translocations 647
Applications of inversions and translocations 648
Rearrangements and cancer 649
Identifying chromosome mutations by genomics 650
17.3 Overall Incidence of Human Chromosome Mutations 651

18 Population Genetics 665
18.1 Detecting Genetic Variation 666
Single nucleotide polymorphisms (SNPs) 667
Microsatellites 668
Haplotypes 669
Other sources and forms of variation 670
The HapMap Project 671
18.2 The Gene-Pool Concept and the Hardy–Weinberg Law 672
18.3 Mating Systems 677
Assortative mating 677
Isolation by distance 678
Inbreeding 679
The inbreeding coefficient 680
Population size and inbreeding 682
18.4 Genetic Variation and Its Measurement 684
18.5 The Modulation of Genetic Variation 687
New alleles enter the population: mutation and migration 687
Recombination and linkage disequilibrium 689
Genetic drift and population size 691
Selection 696
Forms of selection 698
Balance between mutation and drift 702
Balance between mutation and selection 703
18.6 Biological and Social Applications 704
Conservation genetics 704
Calculating disease risks 705
DNA forensics 706
Googling your DNA mates 707

19 The Inheritance of Complex Traits 715
19.1 Measuring Quantitative Variation 717
Types of traits and inheritance 717
The mean 718
The variance 719
The normal distribution 721
19.2 A Simple Genetic Model for Quantitative Traits 722
Genetic and environmental deviations 722
Genetic and environmental variances 724
Correlation between variables 725
19.3 Broad-Sense Heritability: Nature Versus Nurture 727
Measuring heritability in humans using twin studies 728
19.4 Narrow-Sense Heritability: Predicting Phenotypes 731
Gene action and the transmission of genetic variation 732
The additive and dominance effects 733
A model with additivity and dominance 734
Narrow-sense heritability 736
Predicting offspring phenotypes 739
Selection on complex traits 740
19.5 Mapping QTL in Populations with Known Pedigrees 742
The basic method 743
From QTL to gene 747
19.6 Association Mapping in Random-Mating Populations 742
The basic method 751
GWA, genes, disease, and heritability 752

20 Evolution of Genes and Traits 761

20.1 Evolution by Natural Selection 764
20.2 Natural Selection in Action: An Exemplary Case 766
The selective advantage of Hb^S 768
The molecular origins of Hb^S 770
20.3 Molecular Evolution: The Neutral Theory 771
The development of the neutral theory 771
The rate of neutral substitutions 772
The signature of purifying selection on DNA 772
20.4 Cumulative Selection and Multistep Paths to Functional Change 774
Multistep pathways in evolution 774
The signature of positive selection on DNA sequences 778
20.5 Morphological Evolution 779
Adaptive changes in a pigment-regulating protein 779
Gene inactivation 781
Regulatory-sequence evolution 782
Loss of characters through regulatory-sequence evolution 783
Regulatory evolution in humans 785
20.6 The Origin of New Genes and Protein Functions 786
Expanding gene number 787
The fate of duplicated genes 788

A Brief Guide to Model Organisms 793
Appendix A: Genetic Nomenclature 809
Appendix B: Bioinformatics Resources for Genetics and Genomics 810
Glossary 813
Answers to Selected Problems 833
Index 845

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Preface

Since its first edition in 1974, *Introduction to Genetic Analysis* has emphasized the power and incisiveness of the genetic approach in biological research and its applications. Over its many editions, the text has continuously expanded its coverage as the power of traditional genetic analysis has been extended with the introduction of recombinant DNA technology and then genomics. In the eleventh edition, we continue this tradition and show how the flowering of this powerful type of analysis has been used for insight into research in biology, agriculture, and human health.

Pedagogical Tools

One of the important new features in this edition is the inclusion of lists of **learning outcomes** at the beginning of each chapter. Learning outcomes are crucial components of understanding. One of the tenets of the constructivist theory of learning is that although understanding might be a series of new mental circuits, the learner can never be sure of what is in his or her brain until called upon for some type of performance. Indeed, understanding has even been defined by some as *flexible performance capacity.* The lists of goals show learners what precise performances are expected of them. The notes that follow show how the benefits of the learning outcomes in this book can be maximized for instructors who wish to use them.

> **LEARNING OUTCOMES**
>
> *After completing this chapter, you will be able to*
>
> - Perform a quantitative analysis of the progeny of a dihybrid testcross to assess whether or not the two genes are linked on the same chromosome.
> - Extend the same type of analysis to several loci to produce a map of the relative positions of loci on a chromosome.
> - In ascomycete fungi, map the centromeres to other linked loci.
> - In asci, predict allele ratios stemming from specific steps in the heteroduplex model of crossing over.

Classroom sessions large and small (for example, lectures and tutorials) should be structured as far as possible on learning outcomes closely paralleling those in these chapters. At various stages in the classes students should be asked to demonstrate their understanding of the material just covered by attaining one or more learning outcomes. In writing examination or test questions, the instructor should try to stick closely to learning outcomes. When reviewing test results, show in what ways the outcomes have been attained or not attained by the learner.

Students should read the list of learning outcomes before embarking on a chapter. Although it will not be possible to understand most of them before reading the chapter, their wording gives a good idea of the lay of the land, and shows the extent of what the instructor's expectations are. Ideally, after reading a section of the chapter, it is a good idea for a student to go back to the list and match the material covered to an outcome. This process should be repeated at the end of the chapter by scanning the sections and making a complete match with each outcome as far as possible. In solving the end-of-chapter problems, try to focus effort on the skills described in the learning outcomes. Students should use the learning outcomes for rapid review when studying for exams; they should try to imagine ways that they will be expected to demonstrate understanding through the application of the outcomes.

The general goal of a course in genetics is to learn how to think and work like a geneticist. The learning outcomes can fractionate this general goal into the many different skills required in this analytical subject.

In this edition we have replaced "Messages" with "**Key Concepts.**" Messages have been in the book since its first edition in 1974. In the 1960s and 1970s, perhaps due to the popularity of Marshall McLuhan's principle "The medium is the message," the word *message* was in common use, and teachers were often asked, "What is your message?" Although with the rise of electronic media it is perhaps time for a resurgence of McLuhan's principle, we felt that the word *message* no longer has the meaning it had in 1974.

New Coverage of Modern Genetic Analysis

One of our goals is to show how identifying genes and their interactions is a powerful tool for understanding biological properties. In the eleventh edition, we present a completely rewritten introductory Chapter 1, with a focus on modern applications of genetics. From there, the student follows the process of a traditional genetic dissection, starting with a step-by-step coverage of single-gene identification in Chapter 2, gene mapping in Chapter 4, and identifying pathways and networks by studying gene interactions in Chapter 6. New genomic approaches to identifying and locating genes are explored in Chapters 10, 14, and 19.

Flood-intolerant and flood-tolerant rice

FIGURE 1-20 An Indian farmer with rice variety *Swarna* that is not tolerant to flooding (*left*) compared to variety *Swarna-sub1* that is tolerant (*right*). This field was flooded for 10 days. The photo was taken 27 days after the flood waters receded. [Ismail et al., "The contribution of submergence-tolerant (Sub 1) rice varieties to food security in flood-prone rainfed lowland areas in Asia," Field Crops Research 152, 2013, 83–93, © Elsevier.]

SUB1 gene increases rice yield under flooding

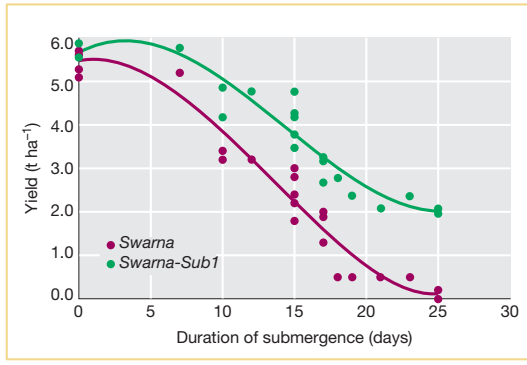

FIGURE 1-21 Yield comparison between variety *Swarna* that is not tolerant to flooding (purple circles) and variety *Swarna-Sub1* that is tolerant (green circles). Yield in tons per hectare (y-axis) versus duration of flooding in days (x-axis). [Data from Ismail et al., "The contribution of submergence-tolerant (Sub 1) rice varieties to food security in flood-prone rainfed lowland areas in Asia," Field Crops Research 152, 2013, 83–93.]

- A reconceptualized Chapter 1 now piques student interest in genetics by presenting a selection of modern applications in biology, evolution, medicine, and agriculture. After a brief history of the study of genetics and a review of some fundamentals, the chapter describes four stories of how genetics is used today.
- Classical genetic dissection is given a more gradual introduction in Chapters 2 and 4. Chapter 2 begins with a new introduction to forward genetics and the role of genetic analysis in identifying traits of single-gene inheritance. Crosses are depicted visually as well as mathematically. The concepts of dominance and recessiveness are explained in terms of haplosufficiency and haploinsufficiency. The use of chi-square analysis in Chapter 4 has been rewritten for clarity.
- The modern application of genetics introduced in Chapter 1 continues in Chapter 14 by applying new genomic techniques such as RNA-seq and exome sequencing, which are introduced to solve problems in medicine. The search for meaning in noncoding segments of the genome is an important frontier in genomics, and the ENCODE project has been added to this chapter to represent that search.

Focus on Key Advances in Genetics

We have enhanced coverage of several cutting-edge topics in the eleventh edition.

Chromatin remodeling and epigenetics: Previously spread among several chapters, the flourishing field of epigenetics is now consolidated and completely updated in Chapter 12. In section 12.3, "Dynamic Chromatin," we discuss the three major mechanisms of altering chromatin structure: chromatin remodeling, histone modification, and histone variants. Changes throughout this section provide more detail and clarity, based on recent advances in the field.

Genome surveillance: Cutting-edge research in transposable elements has uncovered genome surveillance systems in plants, animals, and bacteria similar to that previously identified in *C. elegans*. Chapter 15 now provides an overview of piRNAs in animals and crRNAs in bacteria, and allows students to compare and contrast those approaches to Tc1 elements in worms and MITEs in plants.

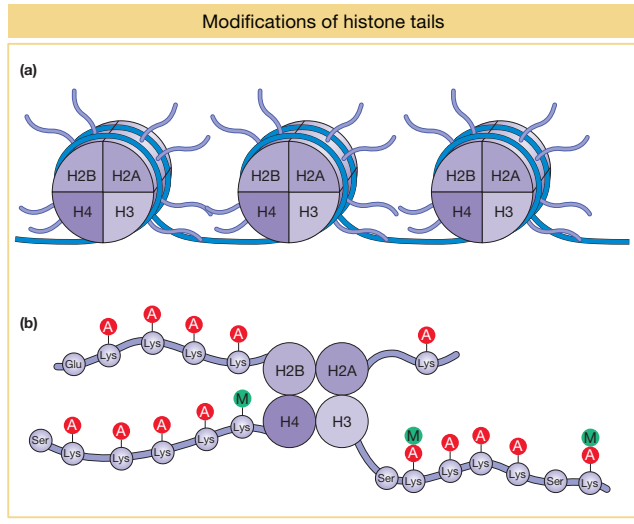

FIGURE 12-13 (a) Histone tails protrude from the nucleosome core (purple). (b) Examples of histone tail modifications are shown. Circles with A represent acetylation while circles with M represent methylation. See text for details.

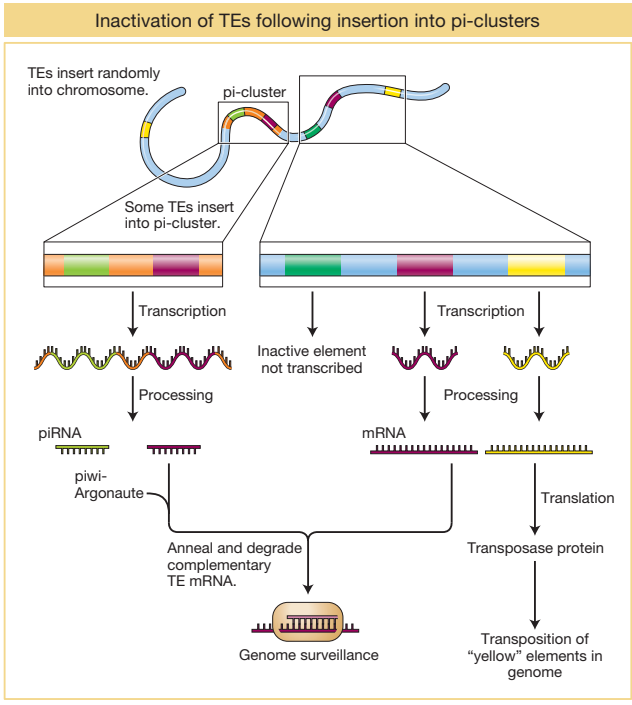

FIGURE 15-27 Insertion of the green and pink transposons into a pi-cluster in the genome results in the degradation of transcripts from these two transposons by the steps shown and described in the text. In contrast, the yellow transposon will remain active until copies insert by chance into a pi-cluster.

Enduring Features

Coverage of model organisms

The eleventh edition retains the enhanced coverage of model systems in formats that are practical and flexible for both students and instructors.

- Chapter 1 introduces some key genetic model organisms and highlights some of the successes achieved through their use.
- Model Organism boxes presented in context where appropriate provide additional information about the organism in nature and its use experimentally.
- A Brief Guide to Model Organisms, at the back of the book, provides quick access to essential, practical information about the uses of specific model organisms in research studies.
- An Index to Model Organisms, on the endpapers at the back of the book, provides chapter-by-chapter page references to discussions of specific organisms in the text, enabling instructors and students to easily find and assemble comparative information across organisms.

Problem sets

No matter how clear the exposition, deep understanding requires the student to personally engage with the material. Hence our efforts to encourage student problem solving. Building on its focus on genetic analysis, the eleventh edition provides students with opportunities to practice problem-solving skills—both in the text and online through the following features.

- **Versatile Problem Sets.** Problems span the full range of degrees of difficulty. They are categorized according to level of difficulty—basic or challenging.
- **Working with the Figures.** An innovative set of problems included at the back of each chapter asks students pointed questions about figures in the chapter. These questions encourage students to think about the figures and help them to assess their understanding of key concepts.
- **Solved Problems.** Found at the end of each chapter, these worked examples illustrate how geneticists apply principles to experimental data.
- **Unpacking the Problems.** A genetics problem draws on a complex matrix of concepts and information. "Unpacking the Problem" helps students learn to approach problem solving strategically, one step at a time, concept on concept.
- **NEW**  Multiple-choice versions of the end-of-chapter problems are available on our online LaunchPad for quick gradable quizzing and easily gradable homework assignments. The **Unpacking the Problem tutorials** from the text have been converted to in-depth online tutorials and expanded to help students learn to solve problems and think like a geneticist. New videos demonstrate how to solve selected difficult problems.

How genetics is practiced today

A feature called "What Geneticists Are Doing Today" suggests how genetic techniques are being used today to answer specific biological questions, such as "What is the link between telomere shortening and aging?" or "How can we find missing components in a specific biological pathway?"

Media and Supplements

The *LaunchPad* is a dynamic, fully integrated learning environment that brings together all the teaching and learning resources in one place. It features the fully interactive e-Book, end-of-chapter practice problems now assignable as homework, animations, and tutorials to help students with difficult-to-visualize concepts.

This learning system also includes easy-to-use, powerful assessment tracking and grading tools, a personalized calendar, an announcement center, and communication tools all in one place to help you manage your course. Some examples:

- **Hundreds of self-graded end-of-chapter problems** allow students to practice their problem-solving skills. Most of the open-ended end-of-chapter questions have been carefully rewritten to create high-quality, analytical multiple-choice versions for assigning.
- **Animations** help students visualize genetics.
- **Unpacking the Problem tutorials** from the text have been converted and expanded to help students learn to solve problems and think like a geneticist. These in-depth online tutorials guide students toward the solution, offering guidance as needed via hints and detailed feedback.
- **NEW Problem-solving videos** walk students through solving difficult problems from the text.

Teaching resources for instructors

Electronic teaching resources are available online at the LaunchPad, at **http://www.whfreeman.com/launchpad/iga11e**

Includes all the electronic resources listed below for teachers. Contact your W. H. Freeman sales representative to learn how to log on as an instructor.

e-Book

The e-Book fully integrates the text and its interactive media in a format that features a variety of helpful study tools (full-text, Google-style searching; note taking; bookmarking; highlighting; and more). Available as a stand-alone item or on the LaunchPad.

Clicker Questions

Jump-start discussions, illuminate important points, and promote better conceptual understanding during lectures.

Layered PowerPoint Presentations

Illuminate challenging topics for students by deconstructing intricate genetic concepts, sequences, and processes step-by-step in a visual format.

All Images from the Text

More than 500 illustrations can be downloaded as JPEGs and PowerPoint slides. Use high-resolution images with enlarged labels to project clearly for lecture hall presentations. Additionally, these JPEG and PowerPoint files are available without labels for easy customization in PowerPoint.

67 Continuous-Play Animations

A comprehensive set of animations, updated and expanded for the eleventh edition, covers everything from basic molecular genetic events and lab techniques to analyzing crosses and genetic pathways. The complete list of animations appears on page xix.

Assessment Bank
This resource brings together a wide selection of genetics problems for use in testing, homework assignments, or in-class activities. Searchable by topic and provided in MS Word format, as well as in LaunchPad and Diploma, the assessment bank offers a high level of flexibility.

Student Solutions Manual
(ISBN: 1-4641-8794-0)

The Student Solutions Manual contains complete worked-out solutions to all the problems in the textbook, including the "Unpacking the Problem" exercises. Available on the LaunchPad and the Instructor's Web site as easy-to-print Word files.

Understanding Genetics: Strategies for Teachers and Learners in Universities and High Schools
(ISBN: 0-7167-5216-6)

Written by Anthony Griffiths and Jolie-Mayer Smith, this collection of articles focuses on problem solving and describes methods for helping students improve their ability to process and integrate new information.

Resources for students

at **http://www.whfreeman.com/launchpad/iga11e**

LaunchPad 6-month Access Card (ISBN: 1-4641-8793-2)

The LaunchPad contains the following resources for students:

- *Self-Graded End-of-Chapter Problems:* To allow students to practice their problem-solving skills, most of the open-ended end-of-chapter questions have been carefully rewritten to create high-quality, analytical multiple-choice versions for assigning.
- *Online Practice Tests:* Students can test their understanding and receive immediate feedback by answering online questions that cover the core concepts in each chapter. Questions are page referenced to the text for easy review of the material.
- *Animations:* A comprehensive set of animations, updated and expanded for the eleventh edition, covers everything from basic molecular genetic events and lab techniques to analyzing crosses and genetic pathways. The complete list of animations appears on the facing page.
- *Interactive "Unpacking the Problem":* An exercise from the problem set for many chapters is available online in interactive form. As with the text version, each Web-based "Unpacking the Problem" uses a series of questions to step students through the thought processes needed to solve a problem. The online version offers immediate feedback to students as they work through the problems as well as convenient tracking and grading functions. Authored by Craig Berezowsky, University of British Columbia.
- **NEW** *Problem-Solving Videos:* Twenty-five problem-solving videos walk students through solving difficult problems from the text.

Student Solutions Manual (ISBN: 1-4641-8794-0)
The Solutions Manual contains complete worked-out solutions to all the problems in the textbook, including the "Unpacking the Problem" exercises. Used in conjunction with the text, this manual is one of the best ways to develop a fuller appreciation of genetic principles.

Other genomic and bioinformatic resources for students:
Text Appendix A, *Genetic Nomenclature,* lists model organisms and their nomenclature.

Text Appendix B, *Bioinformatic Resources for Genetics and Genomics,* builds on the theme of introducing students to the latest genetic research tools by providing students with some valuable starting points for exploring the rapidly expanding universe of online resources for genetics and genomics.

Animations

Sixty-seven animations are fully integrated with the content and figures in the text chapters. These animations are available on the LaunchPad and the Book Companion site.

CHAPTER 1
A Basic Plant Cross (Figure 1-3)
The Central Dogma (Figure 1-10)

CHAPTER 2
Mitosis (Chapter Appendix 2-1)
Meiosis (Chapter Appendix 2-2)
X-Linked Inheritance in Flies (Figure 2-17)

CHAPTER 3
Punnett Square and Branch Diagram Methods for Predicting the Outcomes of Crosses (Figure 3-4)
Meiotic Recombination Between Unlinked Genes by Independent Assortment (Figures 3-8 and 3-13)
Analyzing a Cross: A Solved Problem (Solved Problem 2)

CHAPTER 4
Crossing Over Produces New Allelic Combinations (Figures 4-2 and 4-3)
Meiotic Recombination Between Linked Genes by Crossing Over (Figure 4-7)
A Molecular Model of Crossing Over (Figure 4-21)
A Mechanism of Crossing Over: A Heteroduplex Model (Figure 4-21)
A Mechanism of Crossing Over: Genetic Consequences of the Heteroduplex Model
Mapping a Three-Point Cross: A Solved Problem (Solved Problem 2)

CHAPTER 5
Bacterial Conjugation and Mapping by Recombination (Figures 5-11 and 5-17)

CHAPTER 6
Interactions Between Alleles at the Molecular Level, *RR:* Wild-Type
Interactions Between Alleles at the Molecular Level, *rr:* Homozygous Recessive, Null Mutation
Interactions Between Alleles at the Molecular Level, *r′r′*: Homozygous Recessive, Leaky Mutation
Interactions Between Alleles at the Molecular Level, *Rr:* Heterozygous, Complete Dominance
Screening and Selecting for Mutations
A Model for Synthetic Lethality (Figure 6-20)

CHAPTER 7
DNA Replication: The Nucleotide Polymerization Process (Figure 7-15)
DNA Replication: Coordination of Leading and Lagging Strand Synthesis (Figure 7-20)
DNA Replication: Replication of a Chromosome (Figure 7-23)

CHAPTER 8
Transcription in Prokaryotes (Figures 8-7 to 8-10)
Transcription in Eukaryotes (Figures 8-12 and 8-13)
Mechanism of RNA Splicing (Figures 8-16 and 8-17)

CHAPTER 9
Peptide-Bond Formation (Figure 9-2)
tRNA Charging (Figure 9-7)
Translation (Figure 9-14 to 9-16)
Nonsense Suppression at the Molecular Level: The *rod*^{ns} Nonsense Mutation (Figure 9-18)
Nonsense Suppression at the Molecular Level: The tRNA Nonsense Suppressor (Figure 9-18)
Nonsense Suppression at the Molecular Level: Nonsense Suppression of the *rod*^{ns} Allele (Figure 9-18)

CHAPTER 10
Polymerase Chain Reaction (Figure 10-3)
Plasmid Cloning (Figure 10-9)
Finding Specific Cloned Genes by Functional Complementation: Functional Complementation of the Gal$^-$ Yeast Strain and Recovery of the Wild-Type *GAL* gene
Finding Specific Cloned Genes by Functional Complementation: Making a Library of Wild-Type Yeast DNA
Finding Specific Cloned Genes by Functional Complementation: Using the Cloned *GAL* Gene as a Probe for *GAL* mRNA
SDS Gel Electrophoresis and Immunoblotting
Dideoxy Sequencing of DNA (Figure 10-17)
Creating a Transgenic Mouse (Figures 10-29 and 10-30)

CHAPTER 11
Regulation of the Lactose System in *E. coli:* Assaying Lactose Presence/Absence Through the Lac Repressor (Figure 11-6)
Regulation of the Lactose System in *E. coli:* O^C *lac* Operator Mutations (Figure 11-8)
Regulation of the Lactose System in *E. coli:* I$^-$ Lac Repressor Mutations (Figure 11-9)
Regulation of the Lactose System in *E. coli:* I^S Lac Superrepressor Mutations (Figure 11-10)

CHAPTER 12
Three-Dimensional Structure of Nuclear Chromosomes (Figure 12-11)
Gal4 Binding and Activation (Figures 12-6 through 12-9)
Chromatin Remodeling (Figures 12-13 and 12-14)

CHAPTER 13
Drosophila Embryonic Development
Sex Determination in Flies (Figure 13-23)

CHAPTER 14
DNA Microarrays: Using an Oligonucleotide Array to Analyze Patterns of Gene Expression (Figure 14-20)
DNA Microarrays: Synthesizing an Oligonucleotide Array
Yeast Two-Hybrid Systems (Figure 14-21)

CHAPTER 15
Replicative Transposition (Figure 15-9)
Life Cycle of a Retrovirus (Figure 15-11)
The *Ty1* Mechanism of Retrotransposition (Figures 15-13 and 15-14)

CHAPTER 16
Replication Slippage Creates Insertion or Deletion Mutations (Figure 16-8)
UV-Induced Photodimers and Excision Repair (Figure 16-19)
Base-Excision Repair, Nucleotide Excision Repair, and Mismatch Repair (Figures 16-20, 16-22, and 16-23)

CHAPTER 17
Autotetraploid Meiosis (Figure 17-6)
Meiotic Nondisjunction at Meiosis I (Figure 17-12)
Meiotic Nondisjunction at Meiosis II (Figure 17-12)
Chromosome Rearrangements: Paracentric Inversion, Formation of Paracentric Inversions (Figure 17-27)
Chromosome Rearrangements: Paracentric Inversion, Meiotic Behavior of Paracentric Inversions (Figure 17-28)
Chromosome Rearrangements: Reciprocal Translocation, Formation of Reciprocal Translocations (Figure 17-30)
Chromosome Rearrangements: Reciprocal Translocation, Meiotic Behavior of Reciprocal Translocations (Figure 17-30)
Chromosome Rearrangements: Reciprocal Translocation, Pseudolinkage of Genes by Reciprocal Translocations (Figure 17-32)

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CHAPTER

1

The Genetics Revolution

DNA (deoxyribonucleic acid) is the molecule that encodes genetic information. The strings of four different chemical bases in DNA store genetic information in much the same way that strings of 0's and 1's store information in computer code. [*Sergey Nivens/Shutterstock.*]

OUTLINE

1.1 The birth of genetics

1.2 After cracking the code

1.3 Genetics today

LEARNING OUTCOMES

After completing this chapter, you will be able to

- Describe the way in which modern genetics developed.
- List the main cellular constituents involved in gene expression and action.
- Give some examples of how genetics has influenced modern medicine, agriculture, and evolution.

Genetics is a form of information science. Geneticists seek to understand the rules that govern the transmission of genetic information at three levels—from parent to offspring within families, from DNA to gene action within and between cells, and over many generations within populations of organisms. These three foci of genetics are known as transmission genetics, molecular-developmental genetics, and population-evolutionary genetics. The three parts of this text examine these three foci of genetics.

The science of genetics was born just over 100 years ago. Since that time, genetics has profoundly changed our understanding of life, from the level of the individual cell to that of a population of organisms evolving over millions of years. In 1900, William Bateson, a prominent British biologist, wrote presciently that an "exact determination of the laws of heredity will probably work more change in man's outlook on the world, and in his power over nature, than any other advance in natural knowledge that can be foreseen." Throughout this text, you will see the realization of Bateson's prediction. Genetics has driven a revolution in both the biological sciences and society in general.

In this first chapter, we will look back briefly at the history of genetics, and in doing so, we will review some of the basic concepts of genetics that were discovered over the last 100 years. After that, we will look at a few examples of how genetic analysis is being applied to critical problems in biology, agriculture, and human health today. You will see how contemporary research in genetics integrates concepts discovered decades ago with recent technological advances. You will see that genetics today is a dynamic field of investigation in which new discoveries are continually advancing our understanding of the biological world.

Like begets like

FIGURE 1-1 Family groups in the gray wolf show familial resemblances for coat colors and patterning. [*(Top) altrendo nature/Getty Images; (bottom) Bev McConnell/Getty Images.*]

1.1 The Birth of Genetics

Throughout recorded history, people around the world have understood that "like begets like." Children resemble their parents, the seed from a tree bearing flavorful fruit will in turn grow into a tree laden with flavorful fruit, and even members of wolf packs show familial resemblances (Figure 1-1). Although people were confident in these observations, they were left to wonder as to the underlying mechanism. The Native American Hopi tribe of the Southwestern United States understood that if they planted a red kernel of maize in their fields, it would grow into a plant that also gave red kernels. The same was true for blue, white, or yellow kernels. So they thought of the kernel as a message to the gods in the Earth about the type of maize the Hopi farmers hoped to harvest. Upon receiving this message, the gods would faithfully return them a plant that produced kernels of the desired color.

In the 1800s in Europe, horticulturalists, animal breeders, and biologists also sought to explain the resemblance between parents and offspring. A commonly held view at that time was the **blending theory** of inheritance, or the belief that inheritance worked like the mixing of fluids such as paints. Red and white paints, when mixed, give pink; and so a child of one tall parent and one short parent could be expected to grow to a middling height. While blending theory seemed to work at times, it was also clear that there were exceptions, such as tall children born to parents of average height. Blending theory also provided no mechanism by which the "heredity fluids" it imagined, once mixed, could be separated—the red and white paints cannot be reconstituted from the pink. Thus, the long-term expectation of blending theory over many generations of intermating among individuals is that all members of the population will come to express the same average value of a trait. Clearly, this is not how nature works. Human populations have people with a range of

heights, from short to tall, and we have not all narrowed in on a single average height despite the many generations that human populations have dwelled on Earth.

Gregor Mendel—A monk in the garden

While the merits and failings of blending theory were being debated, Gregor Mendel, an Austrian monk, was working to understand the rules that govern the transmission of traits from parent to offspring after hybridization among different varieties of pea plants (Figure 1-2). The setting for his work was the monastery garden in the town of Brünn, Austria (Brno, Czech Republic, today). From 1856 to 1863, Mendel cross-pollinated or intermated different varieties of the pea plant. One of his experiments involved crossing a pea variety with purple flowers to one with white flowers (Figure 1-3). Mendel recorded that the first hybrid generation

Gregor Mendel

FIGURE 1-2 Gregor Mendel was an Austrian monk who discovered the laws of inheritance. [*James King-Holmes/Science Source.*]

One of Mendel's experiments

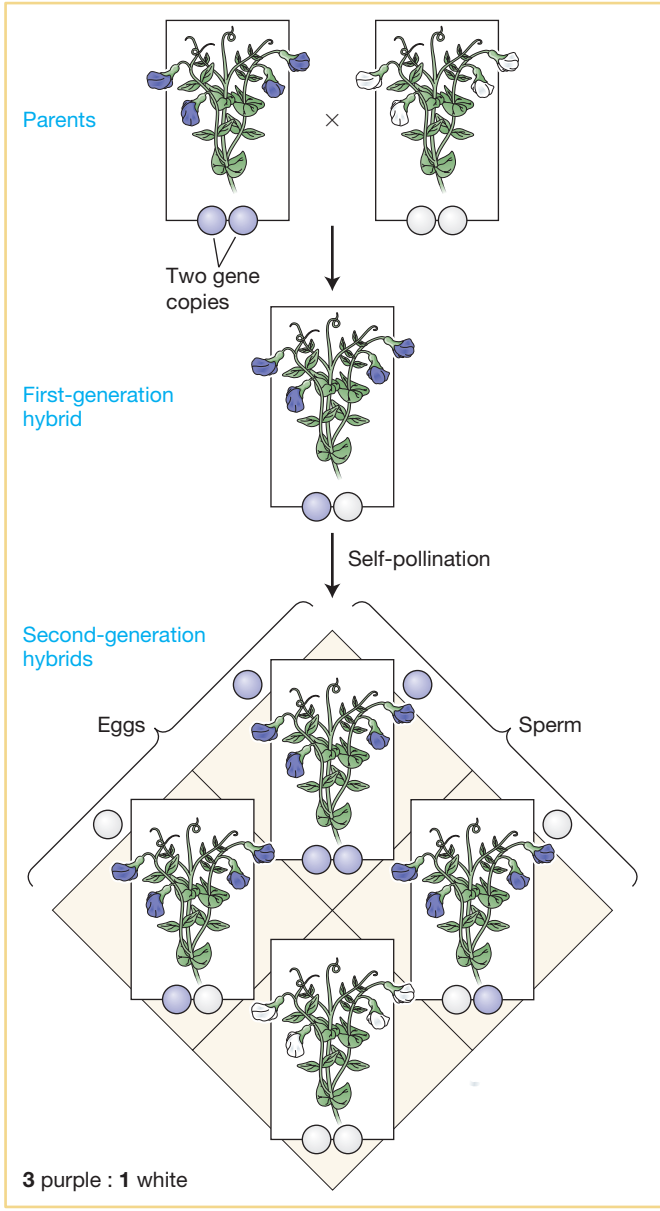
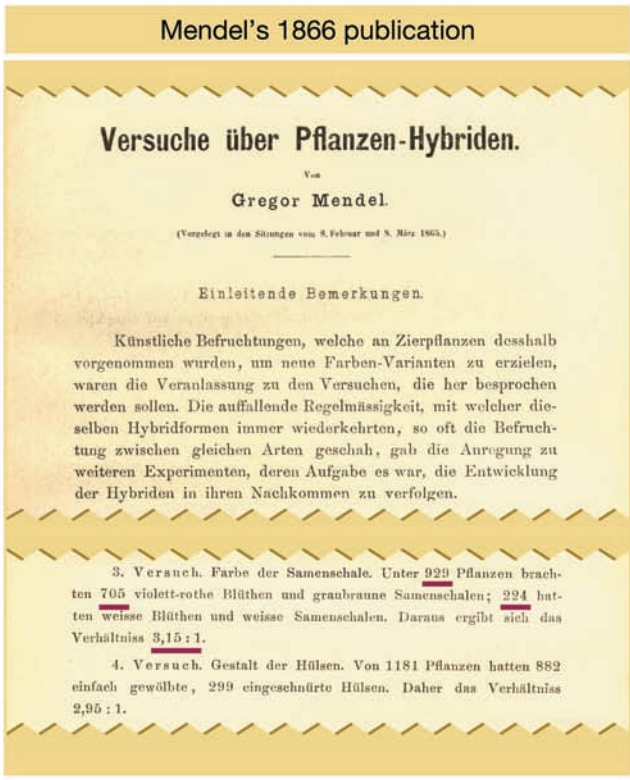


FIGURE 1-3 The mating scheme for Mendel's experiment involving the crossing of purple- and white-flowered varieties of pea plants. The purple and white circles signify the gene variants for purple vs. white flower color. Gametes carry one gene copy; the plants each carry two gene copies. The "×" signifies a cross-pollination between the purple- and white-flowered plants.


Mendel's 1866 publication

Versuche über Pflanzen-Hybriden.

Von

Gregor Mendel.

(Vorgelegt in den Sitzungen vom 8. Februar und 8. März 1865.)

Einleitende Bemerkungen.

Künstliche Befruchtungen, welche an Zierpflanzen desshalb vorgenommen wurden, um neue Farben-Varianten zu erzielen, waren die Veranlassung zu den Versuchen, die hier besprochen werden sollen. Die auffallende Regelmässigkeit, mit welcher dieselben Hybridformen immer wiederkehrten, so oft die Befruchtung zwischen gleichen Arten geschah, gab die Anregung zu weiteren Experimenten, deren Aufgabe es war, die Entwicklung der Hybriden in ihren Nachkommen zu verfolgen.

3. Versuch. Farbe der Samenschale. Unter 929 Pflanzen brachten 705 violett-rothe Blüthen und graubraune Samenschalen; 224 hatten weisse Blüthen und weisse Samenschalen. Daraus ergibt sich das Verhältniss 3,15 : 1.

4. Versuch. Gestalt der Hülsen. Von 1181 Pflanzen hatten 882 einfach gewölbte, 299 eingeschnürte Hülsen. Daher das Verhältniss 2,95 : 1.

FIGURE 1-4 Excerpts from Mendel's 1866 publication, *Versuche über Pflanzen-Hybriden* (Experiments on plant hybrids). [*Augustinian Abbey in Old Brno, Courtesy of the Masaryk University, Mendel Museum.*]

of offspring from this cross all had purple flowers, just like one of the parents. There was no blending. Then, Mendel self-pollinated the first-generation hybrid plants and grew a second generation of offspring. Among the progeny, he saw plants with purple flowers as well as plants with white flowers. Of the 929 plants, he recorded 705 with purple flowers and 224 with white flowers (Figure 1-4). He observed that there were roughly 3 purple-flowered plants for every 1 white-flowered plant.

How did Mendel explain his results? Clearly, blending theory would not work since that theory predicts a uniform group of first-generation hybrid plants with light purple flowers. So Mendel proposed that the factors that control traits act like *particles* rather than fluids and that these particles do not blend together but are passed intact from one generation to the next. Today, Mendel's particles are known as **genes.**

Mendel proposed that each individual pea plant has two copies of the gene controlling flower color in each of the cells of the plant body (**somatic cells**). However, when the plant forms sex cells, or **gametes** (eggs and sperm), only one copy of the gene enters into these reproductive cells (see Figure 1-3). Then, when egg and sperm unite to start a new individual, once again there will be two copies of the flower color gene in each cell of the plant body.

Mendel had some further insights. He proposed that the gene for flower color comes in two gene variants, or **alleles**—one that conditions purple flowers and one that conditions white flowers. He proposed that the purple allele of the flower color gene is **dominant** to the white allele such that a plant with one purple allele and one white allele would have purple flowers. Only plants with two white alleles would have white flowers (see Figure 1-3). Mendel's two conclusions, (1) that genes behaved like particles that do not blend together and (2) that one allele is dominant to the other, enabled him to explain the lack of blending in the first-generation hybrids and the reappearance of white-flowered plants in the second-generation hybrids with a 3:1 ratio of purple- to white-flowered plants. This revolutionary advance in our understanding of inheritance will be fully discussed in Chapter 2.

How did Mendel get it right when so many others before him were wrong? Mendel chose a good organism and good traits to study. The traits he studied were all controlled by single genes. Traits that are controlled by several genes, as many traits are, would not have allowed him to discover the laws of inheritance so easily. Mendel was also a careful observer, and he kept detailed records of each of his experiments. Finally, Mendel was a creative thinker capable of reasoning well beyond the ideas of his times.

Mendel's particulate theory of inheritance was published in 1866 in the *Proceedings of the Natural History Society of Brünn* (see Figure 1-4). At that time, his work was noticed and read by some other biologists, but its implications and importance went unappreciated for over 30 years. Unlike Charles Darwin, whose discovery of the theory of evolution by natural selection made him world-renowned virtually overnight, when Mendel died in 1884, he was more or less unknown in the world of science. As biochemist Erwin Chargaff put it, "There are people who seem to be born in a vanishing cap. Mendel was one of them."

KEY CONCEPT Gregor Mendel demonstrated that genes behave like particles and not fluids.

Mendel rediscovered

As the legend goes, when the British biologist William Bateson (Figure 1-5) boarded a train bound for a conference in London in 1900, he had no idea how profoundly his world would change during the brief journey. Bateson carried with him a copy of Mendel's 1866 paper on the hybridization of plant varieties. Bateson had recently learned that biologists in Germany, the Netherlands, and Austria had each independently reproduced Mendel's 3:1 ratio, and they each cited Mendel's original work. This trio had rediscovered Mendel's laws of inheritance. Bateson needed to read Mendel's paper. By the time he stepped off the train, Bateson had a new mission in life. He understood that the mystery of inheritance had been solved. He soon became a relentless apostle of Mendel's laws of inheritance. A few years later in 1905, Bateson coined the term **genetics**—the study of inheritance. The genetics revolution had begun.

When Mendel's laws of inheritance were rediscovered in 1900, a flood of new thinking and ideas was unleashed. Mendelism became the organizing principle for much of biology. There were many new questions to be asked about inheritance. Table 1-1 summarizes the chronology of seminal discoveries made over the coming decades and the chapters of this text that cover each of these topics. Let's look briefly at a few of the questions and their answers that transformed the biological sciences.

Where in the cell are Mendel's genes? The answer came in 1910, when Thomas H. Morgan at Columbia University in New York demonstrated that Mendel's genes are located on chromosomes—he proved the **chromosome theory** of inheritance. The idea was not new. Walter Sutton, who was raised on a farm in Kansas and later served as a surgeon for the U.S. army during WWI had proposed the chromosome theory of inheritance in 1903. Theodor Boveri, a German biologist, independently proposed it at the same time. It was a compelling hypothesis, but there were no experimental data to support it. This changed in 1910, when Morgan proved the chromosome theory of inheritance using Mendelian genetics and the fruit fly as his experimental organism. In Chapter 4, you will retrace Morgan's experiments that proved genes are on chromosomes.

Can Mendelian genes explain the inheritance of continuously variable traits like human height? While 3:1 segregation ratios could be directly observed for simple traits like flower color, many traits show a continuous range of values in second-generation hybrids without simple ratios like 3:1. In 1918, Ronald Fisher, the British statistician and geneticist, resolved how Mendelian genes explained the inheritance of continuously variable traits like height in people (Figure 1-6). Fisher's core idea

William Bateson gave genetics its name

FIGURE 1-5 William Bateson, the British zoologist and evolutionist who introduced the term *genetics* for the study of inheritance and promoted Mendel's work. [*SPL/Science Source.*]

Continuous variation for height

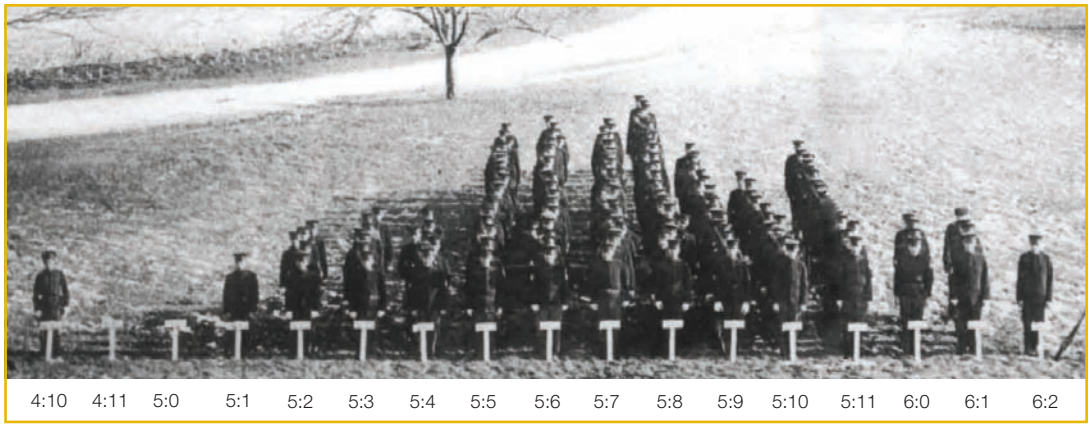


FIGURE 1-6 Students at the Connecticut Agriculture College in 1914 show a range of heights. Ronald Fisher proposed that continuously variable traits like human height are controlled by multiple Mendelian genes. [*A. F. Blakeslee, "Corn and Men," Journal of Heredity 5, 11, 1914, 511–518.*]

TABLE 1-1 Key Events in the History of Genetics

Year	Event	Chapters
1865	Gregor Mendel showed that traits are controlled by discrete factors now known as genes.	2, 3
1869	Friedrich Miescher isolated DNA from the nuclei of white blood cells.	7
1903	Walter Sutton and Theodor Boveri hypothesized that chromosomes are the hereditary elements.	4
1905	William Bateson introduced the term “genetics” for the study of inheritance.	2
1908	G. H. Hardy and Wilhelm Weinberg proposed the Hardy–Weinberg law, the foundation for population genetics.	18
1910	Thomas H. Morgan demonstrated that genes are located on chromosomes.	4
1913	Alfred Sturtevant made a genetic linkage map of the *Drosophila X* chromosome, the first genetic map.	4
1918	Ronald Fisher proposed that multiple Mendelian factors can explain continuous variation for traits, founding the field of quantitative genetics.	19
1931	Harriet Creighton and Barbara McClintock showed that crossing over is the cause of recombination.	4, 16
1941	Edward Tatum and George Beadle proposed the one-gene—one-polypeptide hypothesis.	6
1944	Oswald Avery, Colin MacLeod, and Maclyn McCarty provided compelling evidence that DNA is the genetic material in bacterial cells.	7
1946	Joshua Lederberg and Edward Tatum discovered bacterial conjugation.	5
1948	Barbara McClintock discovered mobile elements (transposons) that move from one place to another in the genome.	15
1950	Erwin Chargaff showed DNA composition follows some simple rules for the relative amounts of A, C, G, and T.	7
1952	Alfred Hershey and Martha Chase proved that DNA is the molecule that encodes genetic information.	7
1953	James Watson and Francis Crick determined that DNA forms a double helix.	7
1958	Matthew Meselson and Franklin Stahl demonstrated the semiconservative nature of DNA replication.	7
1958	Jérôme Lejeune discovered that Down syndrome resulted from an extra copy of the 21st chromosome.	17
1961	François Jacob and Jacques Monod proposed that enzyme levels in cells are controlled by feedback mechanisms.	11
1961–1967	Marshall Nirenberg, Har Gobind Khorana, Sydney Brenner, and Francis Crick "cracked" the genetic code.	9
1968	Motoo Kimura proposed the neutral theory of molecular evolution.	18, 20
1977	Fred Sanger, Walter Gilbert, and Allan Maxam invented methods for determining the nucleotide sequences of DNA molecules.	10
1980	Christiane Nüsslein-Volhard and Eric F. Wieschaus defined the complex of genes that regulate body plan development in *Drosophila.*	13
1989	Francis Collins and Lap-Chee Tsui discovered the gene causing cystic fibrosis.	4, 10
1993	Victor Ambrose and colleagues described the first microRNA.	13
1995	First genome sequence of a living organism (*Haemophilus influenzae*) published.	14
1996	First genome sequence of a eukaryote (*Saccharomyces cerevisiae*) published.	14
1998	First genome sequence of an animal (*Caenorhabditis elegans*) published.	14
2000	First genome sequence of a plant (*Arabidopsis thaliana*) published.	14
2001	The sequence of the human genome first published.	14
2006	Andrew Fire and Craig Mello win the Nobel prize for their discovery of gene silencing by double-stranded RNA.	8
2012	John Gurdon and Shinya Yamanaka win the Nobel prize for their discovery that just four regulatory genes can convert adult cells into stem cells.	8, 12

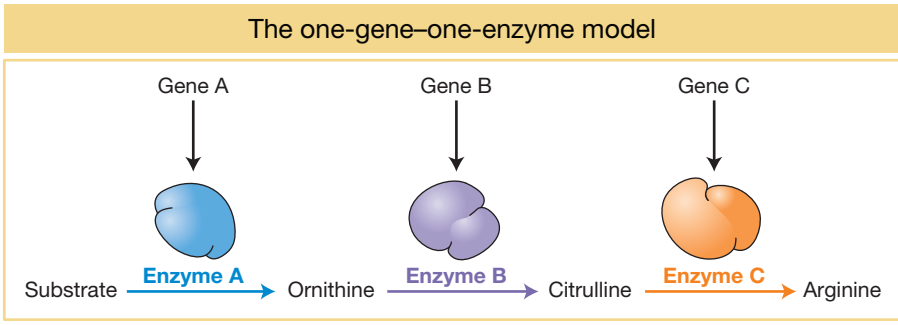


FIGURE 1-7 The one-gene–one-enzyme model proposed that genes encode enzymes that carry out biochemical functions within cells. Tatum and Beadle proposed this model based on the study of the synthesis of arginine (an amino acid) in the bread mold *Neurospora crassa.*

was that continuous traits are each controlled by multiple Mendelian genes. Fisher's insight is known as the **multifactorial hypothesis.** In Chapter 19, we will dissect the mathematical model and experimental evidence for Fisher's hypothesis.

How do genes function inside cells in a way that enables them to control different states for a trait like flower color? In 1941, Edward Tatum and George Beadle proposed that genes encode enzymes. Using bread mold (*Neurospora crassa*) as their experimental organism, they demonstrated that genes encode the enzymes that perform metabolic functions within cells (Figure 1-7). In the case of the pea plant, there is a gene that encodes an enzyme required to make the purple pigment in the cells of a flower. Tatum and Beadle's breakthrough became known as the **one-gene–one-enzyme hypothesis.** You'll see how they developed this hypothesis in Chapter 6.

What is the physical nature of the gene? Are genes composed of protein, nucleic acid, or some other substance? In 1944, Oswald Avery, Colin MacLeod, and Maclyn McCarty offered the first compelling experimental evidence that genes are made of deoxyribonucleic acid (DNA). They showed that DNA extracted from a virulent strain of bacteria carried the necessary genetic information to transform a nonvirulent strain into a virulent one. You'll learn exactly how they demonstrated this in Chapter 7.

How can DNA molecules store information? In the 1950s, there was something of a race among several groups of geneticists and chemists to answer this question. In 1953, James Watson and Francis Crick working at Cambridge University in England won that race. They determined that the molecular structure of DNA was in the form of a double helix—two strands of DNA wound side-by-side in a spiral. Their structure of the double helix is like a twisted ladder (Figure 1-8). The sides of the ladder are made of sugar and phosphate groups. The rungs of the ladder are made of four bases: **adenine (A), thymine (T), guanine (G),** and **cytosine (C).** The bases face the center, and each base is hydrogen bonded to the base facing it in the opposite strand. Adenine in one strand is always paired with thymine in the other by a *double hydrogen bond,* whereas guanine is always paired with cytosine by a *triple hydrogen bond.* The bonding specificity is based on the **complementary** shapes and charges of the bases. The sequence of A, T, G, and C represents the coded information carried by the DNA molecule. You will learn in Chapter 7 how this was all worked out.

How are genes regulated? Cells need mechanisms to turn genes on or off in specific cell and tissue types and at specific times during development. In 1961, François Jacob and Jacques Monod made a conceptual breakthrough on this question. Working on the genes necessary to metabolize the sugar lactose in the bacterium *Escherichia coli,* they demonstrated that genes have **regulatory elements** that regulate **gene expression**—that is, whether a gene is turned on or off (Figure 1-9). The regulatory elements are specific DNA sequences to which a regulatory protein binds and acts as either an activator or repressor of the expression of the gene. In Chapter 11, you will explore the logic behind the experiments of Jacob and Monod with *E. coli,* and in Chapter 12, you will explore the details of gene regulation in eukaryotes.

The structure of DNA

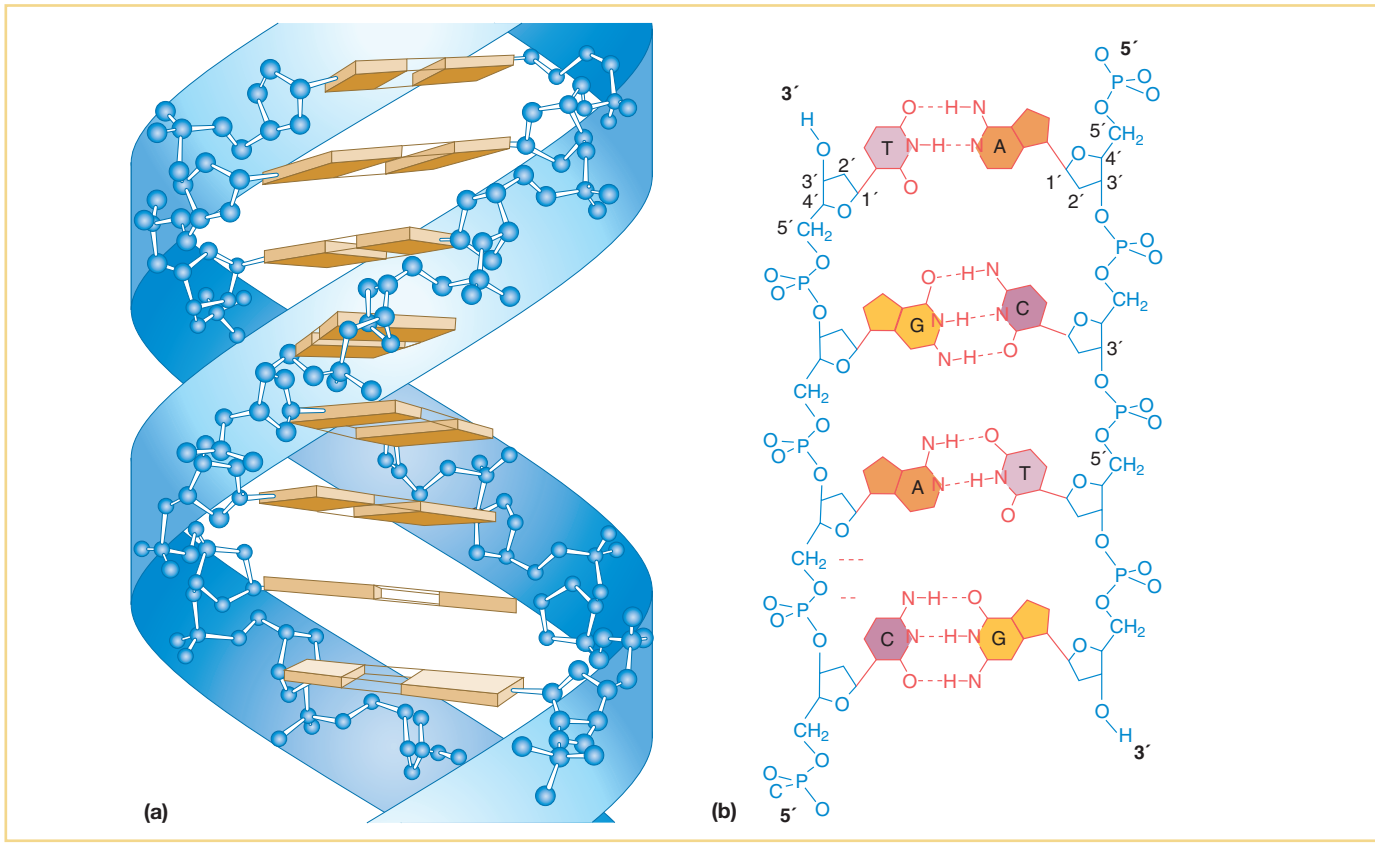


FIGURE 1-8 (a) The double-helical structure of DNA, showing the sugar–phosphate backbone in blue and paired bases in brown. (b) A flattened representation of DNA showing how A always pairs with T and G with C. Each row of dots between the bases represents a hydrogen bond.

How is the information stored in DNA decoded to synthesize proteins? While the discovery of the double-helical structure of DNA was a watershed for biology, many details were still unknown. Precisely how information was encoded into DNA and how it was decoded to form the enzymes that Tatum and Beadle had shown to be the workhorses of gene action remained unknown. Over the years 1961 through 1967, teams of molecular geneticists and chemists working in several countries answered these questions when they "cracked the genetic code." What this means is that they deduced how a string of DNA nucleotides, each with one of four different bases (A, T, C, or G), encodes the set of 20 different amino acids that are the building blocks of proteins. They also discovered that there is a messenger molecule made of ribonucleic acid (RNA) that carries information in the DNA in the nucleus to the cytoplasm where proteins are synthesized. By 1967, the basic flowchart for information transmission in cells was known. This flowchart is called the central dogma of molecular biology.

KEY CONCEPT The rediscovery of Mendel's laws launched a new era in which geneticists resolved many fundamental questions about the nature of the gene and the flow of genetic information within cells. During this era, geneticists learned that genes reside on chromosomes and are made of DNA. Genes encode proteins that conduct the basic enzymatic work within cells.

Genes have regulatory and coding regions

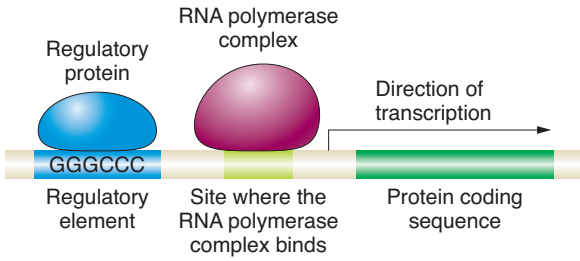


FIGURE 1-9 The structure of a protein-coding gene showing a regulatory DNA element (GGGCCC) to which a regulatory protein binds, the promoter region where the RNA polymerase complex binds to initiate transcription, and a protein-coding region

The central dogma of molecular biology

In 1958, Francis Crick introduced the phrase "central dogma" to represent the flow of genetic information within cells from DNA to RNA to protein, and he drew a simple diagram to summarize these relationships (Figure 1-10a). Curiously, Crick chose the word *dogma* thinking that it meant "hypothesis," which was his intention, unaware that its actual meaning is "a belief that is to be accepted without doubt." Despite this awkward beginning, the phrase had an undeniable power and it has survived.

Figure 1-10b captures much of what was learned about the biochemistry of inheritance from 1905 until 1967. Let's review the wealth of knowledge that this simple figure captures. At the left, you see DNA and a circular arrow representing **DNA replication,** the process by which a copy of the DNA is produced. This process enables each of the two daughter cells that result from cell division to have a

Information transfer among biological molecules

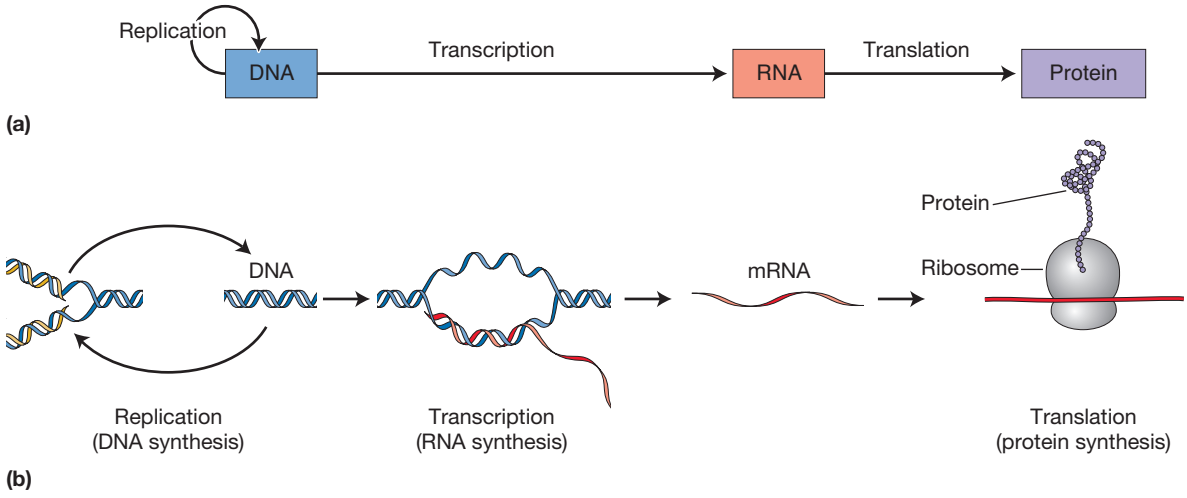


FIGURE 1-10 (a) One version of Francis Crick's sketch of the central dogma, showing information flow between biological molecules. The circular arrow represents DNA replication, the central straight arrow represents the transcription of DNA into RNA, and the right arrow the translation of RNA into protein. (b) More detailed sketch showing how the two strands of the DNA double helix are independently replicated, how the two strands are disassociated for transcription, and how the messenger RNA (mRNA) is translated into protein at the ribosome.