

Brief Table of Contents

1 The Molecular Basis of Heredity, Variation, and Evolution 1

2 Transmission Genetics 30

3 Cell Division and Chromosome Heredity 67

4 Gene Interaction 105

5 Genetic Linkage and Mapping in Eukaryotes 145

6 Genetic Analysis and Mapping in Bacteria and Bacteriophages 185

APPLICATION A Human Hereditary Disease and Genetic Counseling 223

7 DNA Structure and Replication 235

8 Molecular Biology of Transcription and RNA Processing 275

9 The Molecular Biology of Translation 314

APPLICATION B Human Genetic Screening 346

10 Eukaryotic Chromosome Abnormalities and Molecular Organization 361

11 Gene Mutation, DNA Repair, and Homologous Recombination 399

12 Regulation of Gene Expression in Bacteria and Bacteriophage 439

13 Regulation of Gene Expression in Eukaryotes 476

14 Analysis of Gene Function by Forward Genetics and Reverse Genetics 507

APPLICATION C The Genetics of Cancer 538

15 Recombinant DNA Technology and Its Applications 552

16 Genomics: Genetics from a Whole-Genome Perspective 593

17 Organellar Inheritance and the Evolution of Organellar Genomes 632

18 Developmental Genetics 663

19 Genetic Analysis of Quantitative Traits 696

20 Population Genetics and Evolution at the Population, Species, and Molecular Levels 725

APPLICATION D Human Evolutionary Genetics 758

APPLICATION E Forensic Genetics 778

Table of Contents



1

The Molecular Basis of Heredity, Variation, and Evolution 1

- 1.1 Modern Genetics Is in Its Second Century 2**
 - The Development of Modern Genetics 2
 - The Four Phases of Modern Genetics 3
 - Genetics—Central to Modern Biology 5
- 1.2 The Structure of DNA Suggests a Mechanism for Replication 6**
 - The Discovery of DNA Structure 6
 - DNA Nucleotides 7
 - DNA Replication 9
 - Genetic Analysis 1.1 10
 - Experimental Insight 1.1 10
- 1.3 DNA Transcription and Messenger RNA Translation Express Genes 11**
 - Transcription 12
 - Translation 13
 - Genetic Analysis 1.2 14
- 1.4 Genetic Variation Can Be Detected by Examining DNA, RNA, and Proteins 15**
 - Gel Electrophoresis 15
 - Stains, Blots, and Probes 16
 - DNA Sequencing and Genomics 18
 - Proteomics and Other “-omic” Analyses 18
- 1.5 Evolution Has a Genetic Basis 19**
 - Darwin’s Theory of Evolution 19
 - Four Evolutionary Processes 20
 - Tracing Evolutionary Relationships 21
 - Genetic Analysis 1.3 24
 - Case Study Ancient DNA: Genetics Looks into the Past 24*
 - Summary 26 • Preparing for Problem Solving 27 • Problems 27*



2

Transmission Genetics 30

- 2.1 Gregor Mendel Discovered the Basic Principles of Genetic Transmission 31**
 - Mendel’s Modern Experimental Approach 31
 - Five Critical Experimental Innovations 33
- 2.2 Monohybrid Crosses Reveal the Segregation of Alleles 34**
 - Identifying Dominant and Recessive Traits 34
 - Evidence of Particulate Inheritance and Rejection of the Blending Theory 36
 - Segregation of Alleles 36
 - Hypothesis Testing by Test-Cross Analysis 37
 - Hypothesis Testing by F_2 Self-Fertilization 38
 - Genetic Analysis 2.1 39
- 2.3 Dihybrid and Trihybrid Crosses Reveal the Independent Assortment of Alleles 40**
 - Dihybrid-Cross Analysis of Two Genes 40
 - Experimental Insight 2.1 41
 - Testing Independent Assortment by Test-Cross Analysis 43
 - Genetic Analysis 2.2 44
 - Testing Independent Assortment by Trihybrid-Cross Analysis 45
 - The Rediscovery of Mendel’s Work 46
 - Experimental Insight 2.2 46
- 2.4 Probability Theory Predicts Mendelian Ratios 47**
 - The Product Rule 47
 - The Sum Rule 47
 - Conditional Probability 47
 - Binomial Probability 48
- 2.5 Chi-Square Analysis Tests the Fit between Observed Values and Expected Outcomes 49**
 - Chi-Square Analysis 50
 - Chi-Square Analysis of Mendel’s Data 50

2.6 Autosomal Inheritance and Molecular Genetics Parallel the Predictions of Mendel's Hereditary Principles 51

Autosomal Dominant Inheritance 52

Autosomal Recessive Inheritance 53

Prospective and Retrospective Predictions in Human Genetics 53

Molecular Genetics of Mendel's Traits 54

Genetic Analysis 2.3 55

Case Study OMIM, Gene Mutations, and Human Hereditary Disease 57

Summary 59 • Preparing for Problem

Solving 60 • Problems 60



3

Cell Division and Chromosome Heredity 67

3.1 Mitosis Divides Somatic Cells 68

The Cell Cycle 68

Substages of M Phase 69

Chromosome Movement and Distribution 72

Completion of Cell Division 73

Cell Cycle Checkpoints 74

3.2 Meiosis Produces Cells for Sexual Reproduction 75

Meiosis Features Two Cell Divisions 75

Meiosis I 76

Meiosis II 79

Meiosis Generates Mendelian Ratios 80

3.3 The Chromosome Theory of Heredity Proposes That Genes Are Carried on Chromosomes 82

Genetic Analysis 3.1 84

X-Linked Inheritance 85

Testing the Chromosome Theory of Heredity 86

3.4 Sex Determination Is Chromosomal and Genetic 87

Sex Determination in *Drosophila* 87

Genetic Analysis 3.2 88

Mammalian Sex Determination 89

Diversity of Sex Determination 89

Experimental Insight 3.1 90

3.5 Human Sex-Linked Transmission Follows Distinct Patterns 91

Expression of X-Linked Recessive Traits 92

X-Linked Dominant Trait Transmission 93

Y-Linked Inheritance 93

Genetic Analysis 3.3 95

3.6 Dosage Compensation Equalizes the Expression of Sex-Linked Genes 96

Case Study The (Degenerative) Evolution of the Mammalian Y Chromosome 97

Summary 99 • Preparing for Problem

Solving 99 • Problems 100



4

Gene Interaction 105

4.1 Interactions between Alleles Produce Dominance Relationships 106

The Molecular Basis of Dominance 106

Functional Effects of Mutation 107

Notational Systems for Genes and Allele Relationships 109

Incomplete Dominance 110

Codominance 110

Dominance Relationships of ABO Alleles 110

Genetic Analysis 4.1 113

Allelic Series 113

Lethal Alleles 116

Delayed Age of Onset 118

4.2 Some Genes Produce Variable Phenotypes 118

Sex-Limited Traits 119

Sex-Influenced Traits 119

Incomplete Penetrance 120

Variable Expressivity 120

Gene-Environment Interactions 121

Pleiotropic Genes 122

4.3 Gene Interaction Modifies Mendelian Ratios 122

Gene Interaction in Pathways 122

The One Gene-One Enzyme Hypothesis 124

Experimental Insight 4.1 125

Genetic Dissection to Investigate Gene Action 127

Genetic Analysis 4.2 128

Epistasis and Its Results 129

4.4 Complementation Analysis Distinguishes Mutations in the Same Gene from Mutations in Different Genes 133

Genetic Analysis 4.3 134

Case Study Complementation Groups in a Human Cancer-Prone Disorder 136

Summary 137 • Preparing for Problem Solving 138 • Problems 138



5

Genetic Linkage and Mapping in Eukaryotes 145

5.1 Linked Genes Do Not Assort Independently 146

Detecting Genetic Linkage 147

The Discovery of Genetic Linkage 149

Detecting Autosomal Genetic Linkage through Test-Cross Analysis 150

Cytological Evidence of Recombination 153

Genetic Analysis 5.1 154

5.2 Genetic Linkage Mapping Is Based on Recombination Frequency between Genes 155

The First Genetic Linkage Map 155

Map Units 156

Chi-Square Analysis of Genetic Linkage Data 156

5.3 Three-Point Test-Cross Analysis Maps Genes 156

Identifying Parental, Single-Crossover, and Double-Crossover Gametes in Three-Point Mapping 157

Constructing a Three-Point Recombination Map 158

Determining Gamete Frequencies from Genetic Maps 161

Correction of Genetic Map Distances 162

Genetic Analysis 5.2 163

5.4 Multiple Factors Cause Recombination to Vary 164

Sex Affects Recombination 164

Recombination Is Dominated by Hotspots 165

Genome Sequence Analysis Reveals Recombination Hotspot Distribution 166

5.5 Human Genes Are Mapped Using Specialized Methods 166

Mapping with Genetic Markers 166

The Inheritance of Disease-Causing Genes Linked to Genetic Markers 167

Allelic Phase 168

Lod Score Analysis 169

Experimental Insight 5.1 171

Genetic Analysis 5.3 172

Genome-Wide Association Studies 172

Linkage Disequilibrium and Evolutionary Analysis 174

Case Study Mapping the Gene for Cystic Fibrosis 175

Summary 176 • Preparing for Problem Solving 177 • Problems 177



6

Genetic Analysis and Mapping in Bacteria and Bacteriophages 185

6.1 Specialized Methods Are Used for Genetic Analysis of Bacteria 186

Bacterial Culture and Growth Analysis 186

Characteristics of Bacterial Genomes 188

Plasmids in Bacterial Cells 189

Research Technique 6.1 189

6.2 Bacteria Transfer Genes by Conjugation 191

Conjugation Identified 193

Transfer of the F Factor 194

Formation of an Hfr Chromosome 196

Hfr Gene Transfer 196

Interrupted Mating and Time-of-Entry Mapping 198

Time-of-Entry Mapping Experiments 198

Genetic Analysis 6.1 199

Consolidation of Hfr Maps 200

Conjugation with F' Strains Produces Partial Diploids 201

Plasmids and Conjugation in Archaea 203

6.3 Bacterial Transformation Produces Genetic Recombination 203

Genetic Analysis 6.2 204

Steps in Transformation 205

Mapping by Transformation 205

6.4 Bacterial Transduction Is Mediated by Bacteriophages 205

Bacteriophage Life Cycles 205

Generalized Transduction 208

Cotransduction 209

Cotransduction Mapping 209

Specialized Transduction 211

6.5 Bacteriophage Chromosomes Are Mapped by Fine-Structure Analysis 211

Genetic Analysis 6.3 212

Genetic Complementation Analysis 213

Intragenic Recombination Analysis 213

Deletion-Mapping Analysis 214

6.6 Lateral Gene Transfer Alters Genomes 214

Lateral Gene Transfer and Genome Evolution 215

Identifying Lateral Gene Transfer in Genomes 216

Case Study The Evolution of Antibiotic Resistance and Its Impact on Medical Practice 217

Summary 218 • Preparing for Problem Solving 219 • Problems 219



APPLICATION A Human Hereditary Disease and Genetic Counseling

A.1 Hereditary Disease and Disease Genes 225

Types of Hereditary Disease 225

Genetic Testing and Diagnosis 226

A.2 Genetic Counseling 227

Indicators and Goals of Genetic Counseling 227

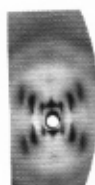
Assessing and Communicating Risks and Options 228

Ethical Issues in Genetic Medicine 231

Genetic Counseling and Ethical Issues 232

In Closing 233

Problems 234



7 DNA Structure and Replication 235

7.1 DNA Is the Hereditary Molecule of Life 236

Chromosomes Contain DNA 236

A Transformation Factor Responsible for Heredity 236

DNA Is the Transformation Factor 238

DNA Is the Hereditary Molecule 238

7.2 The DNA Double Helix Consists of Two Complementary and Antiparallel Strands 240

DNA Nucleotides 240

The DNA Duplex 241

Genetic Analysis 7.1 244

7.3 DNA Replication Is Semiconservative and Bidirectional 244

Three Competing Models of Replication 245

The Meselson-Stahl Experiment 245

Origin and Directionality of Replication in Bacterial DNA 247

Multiple Replication Origins in Eukaryotes 248

7.4 DNA Replication Precisely Duplicates the Genetic Material 249

DNA Sequences at Replication Origins 249

Molecular Biology of Replication Initiation 253

Continuous and Discontinuous Strand Replication 253

RNA Primer Removal and Okazaki Fragment Ligation 254

Synthesis of Leading and Lagging Strands at the Replication Fork 255

DNA Proofreading 256

Supercoiling and Topoisomerases 257

Replication at the Ends of Linear Chromosomes 257

Genetic Analysis 7.2 258

7.5 Methods of Molecular Genetic Analysis Make Use of DNA Replication Processes 260

The Polymerase Chain Reaction 261

Separation of PCR Products 262

Dideoxynucleotide DNA Sequencing 263

New Generations of DNA Sequencing Technology 266

Genetic Analysis 7.3 267

Case Study DNA Helicase Gene Mutations and Human Progeroid Syndrome 269

Summary 270 • Preparing for Problem Solving 271 • Problems 271



8 Molecular Biology of Transcription and RNA Processing 275

8.1 RNA Transcripts Carry the Messages of Genes 276

RNA Nucleotides and Structure 276

Experimental Discovery of Messenger RNA 277

Categories of RNA 278

8.2 Bacterial Transcription Is a Four-Stage Process 279

Bacterial RNA Polymerase 280

Bacterial Promoters 280

Transcription Initiation 281

Genetic Analysis 8.1 283

Transcription Elongation and Termination 284

Transcription Termination Mechanisms 284

8.3 Eukaryotic Transcription Is More Diversified and Complex than Bacterial Transcription 286

Polymerase II Transcription of mRNA in Eukaryotes 287

Research Technique 8.1 288

Pol II Promoter Recognition 289

Detecting Promoter Consensus Elements 290

Other Regulatory Sequences and Chromatin-Based

Regulation of RNA Pol II Transcription 291

RNA Polymerase I Promoters 292

RNA Polymerase III Promoters 292

Archaeal Promoters and Transcription 292

The Evolutionary Implications of Comparative Transcription 293

8.4 Posttranscriptional Processing Modifies RNA Molecules 294

Capping 5' Pre-mRNA 294

Polyadenylation of 3' Pre-mRNA 295

The Torpedo Model of Transcription Termination 296

Introns 296

Pre-mRNA Splicing 297

Splicing Signal Sequences 298

A Gene Expression Machine Couples Transcription and Pre-mRNA Processing 298

Alternative Patterns of RNA Transcription and Alternative RNA Splicing 301

Self-Splicing Introns 302

Genetic Analysis 8.2 303

Ribosomal RNA Processing 304

Transfer RNA Processing 304

RNA Editing 307

Case Study *Sexy Splicing: Alternative mRNA Splicing and Sex Determination in Drosophila* 307

Summary 308 • *Preparing for Problem Solving* 309 • *Problems* 309



9

The Molecular Biology of Translation 314

9.1 Polypeptides Are Amino Acid Chains That Are Assembled at Ribosomes 315

Amino Acid Structure 315

Polypeptide and Transcript Structure 315

Ribosome Structures 317

A Three-Dimensional View of the Ribosome 319

Research Technique 9.1 319

9.2 Translation Occurs in Three Phases 320

Translation Initiation 320

Polypeptide Elongation 324

Genetic Analysis 9.1 326

Translation Termination 327

9.3 Translation Is Fast and Efficient 327

The Translational Complex 327

Translation of Polycistronic mRNA 329

9.4 The Genetic Code Translates Messenger RNA into Polypeptide 329

The Genetic Code Displays Third-Base Wobble 330

The (Almost) Universal Genetic Code 331

Genetic Analysis 9.2 332

Charging tRNA Molecules 333

Protein Folding and Posttranslational Polypeptide Processing 333

The Signal Hypothesis 334

9.5 Experiments Deciphered the Genetic Code 334

No Overlap in the Genetic Code 335

A Triplet Genetic Code 336

No Gaps in the Genetic Code 336

Deciphering the Genetic Code 337

Genetic Analysis 9.3 339

Case Study *Antibiotics and Translation Interference* 340

Summary 340 • *Preparing for Problem Solving* 341 • *Problems* 342



APPLICATION B Human Genetic Screening

B.1 Presymptomatic Diagnosis of Huntington's Disease 348

Trinucleotide Repeat Expansion 348

Detecting the Number of Repeats 348

B.2 Newborn Genetic Screening 349

Phenylketonuria and the First Newborn Genetic Test 349

Living with PKU 350

The Recommended Uniform Screening Panel 351

B.3 Genetic Testing to Identify Carriers 353

Testing Blood Proteins 353
 DNA-Based Carrier Screening and Diagnostic Verification 353
 Carrier Screening Criteria 353
 Pharmacogenetic Screening 354

B.4 Prenatal Genetic Testing 354

Invasive Screening Using Amniocentesis or Chorionic Villus Sampling 354
 Noninvasive Prenatal Testing 356
 Maternal Serum Screening 356
 Preimplantation Genetic Screening 356

B.5 Direct-to-Consumer Genetic Testing 357**B.6 Opportunities and Choices 359**

Problems 359

**10****Eukaryotic Chromosome Abnormalities and Molecular Organization 361****10.1 Chromosome Number and Shape Vary among Organisms 362**

Chromosomes in Nuclei 362
 Chromosome Visualization 363
 Chromosome Banding 364
 Heterochromatin and Euchromatin 365

10.2 Nondisjunction Leads to Changes in Chromosome Number 366

Chromosome Nondisjunction 366
 Gene Dosage Alteration 366
Genetic Analysis 10.1 368
 Aneuploidy in Humans 368
 Mosaicism 370
 Uniparental Disomy 371

10.3 Changes in Euploid Content Lead to Polyploidy 371

Causes of Autopolyploidy and Allopolyploidy 371
Genetic Analysis 10.2 372
 Consequences of Polyploidy 373
 Polyploidy and Evolution 374

10.4 Chromosome Breakage Causes Mutation by Loss, Gain, and Rearrangement of Chromosomes 375

Partial Chromosome Deletion 375
 Unequal Crossover 376
 Detecting Duplication and Deletion 377
 Deletion Mapping 377

10.5 Chromosome Breakage Leads to Inversion and Translocation of Chromosomes 378

Chromosome Inversion 378
Genetic Analysis 10.3 379
Experimental Insight 10.1 382
 Chromosome Translocation 383

10.6 Eukaryotic Chromosomes Are Organized into Chromatin 385

Chromatin Compaction 386
 Histone Proteins and Nucleosomes 386
 Higher Order Chromatin Organization and Chromosome Structure 389
 Nucleosome Disassembly, Synthesis, and Reassembly during Replication 389
 Position Effect Variegation: Effect of Chromatin State on Transcription 390

Case Study Human Chromosome Evolution 392
Summary 393 • Preparing for Problem Solving 394 • Problems 394

**11****Gene Mutation, DNA Repair, and Homologous Recombination 399****11.1 Mutations Are Rare and Random and Alter DNA Sequence 400**

Proof of the Random Mutation Hypothesis 400
 Germ-Line and Somatic Mutations 401
 Point Mutations 401
 Base-Pair Substitution Mutations 401
 Frameshift Mutations 402
 Regulatory Mutations 402
Experimental Insight 11.1 404
 Forward Mutation and Reversion 405

11.2 Gene Mutations May Arise from Spontaneous Events 405

Spontaneous DNA Replication Errors 405

Genetic Analysis 11.1 407

Spontaneous Nucleotide Base Changes 409

11.3 Mutations May Be Caused by Chemicals or Ionizing Radiation 410

Chemical Mutagens 410

Radiation-Induced DNA Damage 412

The Ames Test 413

11.4 Repair Systems Correct Some DNA Damage 415

Direct Repair of DNA Damage 415

Genetic Analysis 11.2 416

DNA Damage-Signaling Systems 419

11.5 Proteins Control Translesion DNA Synthesis and the Repair of Double-Strand Breaks 420

Translesion DNA Synthesis 420

Double-Strand Break Repair 420

11.6 DNA Double-Strand Breaks Initiate Homologous Recombination 422

The Holliday Model 422

The Bacterial RecBCD Pathway 422

The Double-Stranded Break Model of Homologous Recombination 422

11.7 Transposable Genetic Elements Move throughout the Genome 425

The Characteristics and Classification of Transposable Elements 425

The Mutagenic Effect of Transposition 426

Transposable Elements in Bacterial Genomes 426

Transposable Elements in Eukaryotic Genomes 427

The Discovery of *Ds* and *Ac* Elements in Maize 427

Genetic Analysis 11.3 428

Drosophila P Elements 429

Retrotransposons 430

Case Study *Mendel's Peas Are Shaped by Transposition* 431

Summary 432 • **Preparing for Problem**

Solving 434 • **Problems** 434



12

Regulation of Gene Expression in Bacteria and Bacteriophage 439

12.1 Transcriptional Control of Gene Expression Requires DNA-Protein Interaction 440

Negative and Positive Control of Transcription 441

Regulatory DNA-Binding Proteins 441

12.2 The *lac* Operon Is an Inducible Operon System under Negative and Positive Control 443

Lactose Metabolism 443

lac Operon Structure 444

lac Operon Function 444

12.3 Mutational Analysis Deciphers Genetic Regulation of the *lac* Operon 447

Analysis of Structural Gene Mutations 447

lac Operon Regulatory Mutations 448

Molecular Analysis of the *lac* Operon 451

Genetic Analysis 12.1 452

Experimental Insight 12.1 453

12.4 Transcription from the Tryptophan Operon Is Repressible and Attenuated 454

Feedback Inhibition of Tryptophan Synthesis 455

Attenuation of the *trp* Operon 456

Attenuation Mutations 459

Attenuation in Other Amino Acid Operon Systems 459

12.5 Bacteria Regulate the Transcription of Stress Response Genes and Also Translation 459

Alternative Sigma Factors and Stress Response 459

Genetic Analysis 12.2 460

Translational Regulation in Bacteria 461

12.6 Riboswitches Regulate Bacterial Transcription, Translation, and mRNA Stability 462

Riboswitch Regulation of Transcription 462

Riboswitch Regulation of Translation 463

Riboswitch Control of mRNA Stability 464

12.7 Antiterminators and Repressors Control Lambda Phage Infection of *E. coli* 464

The Lambda Phage Genome 465

Early Gene Transcription 465

Cro Protein and the Lytic Cycle 466

The λ Repressor Protein and Lysogeny 468

Resumption of the Lytic Cycle following Lysogeny Induction 468

Case Study *Vibrio cholerae*—Stress Response Leads to Serious Infection Through Positive Control of Transcription 469

Summary 470 • **Preparing for Problem**

Solving 471 • **Problems** 471



13

Regulation of Gene Expression in Eukaryotes 476

13.1 Cis-Acting Regulatory Sequences Bind Trans-Acting Regulatory Proteins to Control Eukaryotic Transcription 478

Overview of Transcriptional Regulatory Interactions in Eukaryotes 479

Integration and Modularity of Eukaryotic Regulatory Sequences 480

Locus Control Regions 481

Enhancer-Sequence Conservation 482

Yeast as a Simple Model for Eukaryotic Transcription 482

Insulator Sequences 484

13.2 Chromatin Remodeling and Modification Regulates Eukaryotic Transcription 484

PEV Mutations 485

Overview of Chromatin Remodeling and Chromatin Modification 486

Open and Covered Promoters 486

Mechanisms of Chromatin Remodeling 487

Chemical Modifications of Chromatin 488

Genetic Analysis 13.1 490

An Example of Inducible Transcriptional Regulation in *S. cerevisiae* 493

Facultative Heterochromatin and Developmental Genes 494

Epigenetic Heritability 494

lncRNAs and Inactivation of Eutherian Mammalian Female X Chromosomes 496

Genomic Imprinting 497

Nucleotide Methylation 498

13.3 RNA-Mediated Mechanisms Control Gene Expression 498

Gene Silencing by Double-Stranded RNA 499

Constitutive Heterochromatin Maintenance 501

The Evolution and Applications of RNAi 502

Case Study *Environmental Epigenetics* 502

Summary 503 • **Preparing for Problem**

Solving 504 • **Problems** 504



14

Analysis of Gene Function by Forward Genetics and Reverse Genetics 507

14.1 Forward Genetic Screens Identify Genes by Their Mutant Phenotypes 509

General Design of Forward Genetic Screens 509

Specific Strategies of Forward Genetic Screens 509

Analysis of Mutageneses 513

Identifying Interacting and Redundant Genes Using Modifier Screens 514

Genetic Analysis 14.1 515

14.2 Genes Identified by Mutant Phenotype Are Cloned Using Recombinant DNA Technology 516

Cloning Genes by Complementation 516

Genome Sequencing to Determine Gene Identification 517

14.3 Reverse Genetics Investigates Gene Action by Progressing from Gene Identification to Phenotype 519

Genome Editing 519

Use of Homologous Recombination in Reverse Genetics 522

Use of Insertion Mutants in Reverse Genetics 524

RNA Interference in Gene Activity 525

Reverse Genetics by TILLING 525

Genetic Analysis 14.2 527

14.4 Transgenes Provide a Means of Dissecting Gene Function 527

Monitoring Gene Expression with Reporter Genes 528

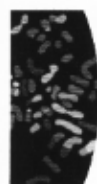
Enhancer Trapping 531

Investigating Gene Function with Chimeric Genes 532

Case Study *Reverse Genetics and Genetic Redundancy in Flower Development* 533

Summary 535 • **Preparing for Problem**

Solving 535 • **Problems** 535



APPLICATION C The Genetics of Cancer

- C.1 Cancer Is a Somatic Genetic Disease that Is Only Occasionally Inherited** 540
- C.2 What Is Cancer and What Are the Characteristics of Cancer?** 540
Progression of Abnormalities 540
The Hallmarks of Cancer Cells and Malignant Tumors 541
- C.3 The Genetic Basis of Cancer** 543
Single Gene Mutations and Cancer Development 543
The Genetic Progression of Cancer Development and Cancer Predisposition 546
Breast and Ovarian Cancer and the Inheritance of Cancer Susceptibility 548
- C.4 Cancer Cell Genome Sequencing and Improvements in Therapy** 549
The Cancer Genome Atlas 549
Epigenetic Irregularities 549
Targeted Cancer Therapy 550
Problems 550



15 Recombinant DNA Technology and Its Applications

- 15.1 Specific DNA Sequences Are Identified and Manipulated Using Recombinant DNA Technology** 553
Restriction Enzymes 553
Experimental Insight 15.1 554
Genetic Analysis 15.1 556
Molecular Cloning 557
DNA Libraries 562
Advances in Altering and Synthesizing DNA Molecules 564
- 15.2 Introducing Foreign Genes into Genomes Creates Transgenic Organisms** 565
Expression of Heterologous Genes in Bacterial and Fungal Hosts 565
Experimental Insight 15.2 569
Transformation of Plant Genomes by *Agrobacterium* 570
Transgenic Animals 574
Manipulation of DNA Sequences in Vivo 578

15.3 Gene Therapy Uses Recombinant DNA Technology

- Two Forms of Gene Therapy 579
Somatic Gene Therapy Using ES Cells 579
Genetic Analysis 15.2 580

15.4 Cloning of Plants and Animals Produces Genetically Identical Individuals

- Case Study Gene Drive Alleles Can Rapidly Spread Through Populations* 585
Summary 587 • Preparing for Problem Solving 588 • Problems 588



16 Genomics: Genetics from a Whole-Genome Perspective

16.1 Structural Genomics Provides a Catalog of Genes in a Genome

- Whole-Genome Shotgun Sequencing 596
Reference Genomes and Resequencing 599
Metagenomics 600
Experimental Insight 16.1 601

16.2 Annotation Ascribes Biological Function to DNA Sequences

- Experimental Approaches to Structural Annotation 602
Computational Approaches to Structural Annotation 602
Functional Gene Annotation 603
Research Technique 16.1 604
Related Genes and Protein Motifs 605
Variation in Genome Organization among Species 605
Three Insights from Genome Sequences 606

16.3 Evolutionary Genomics Traces the History of Genomes

- The Tree of Life 608
Interspecific Genome Comparisons: Gene Content 608
Research Technique 16.2 610
Genetic Analysis 16.1 614
Interspecific Genome Comparisons: Genome Annotation 615
Interspecific Genome Comparisons: Gene Order 616

16.4 Functional Genomics Aims to Elucidate Gene Function

- Transcriptomics 619

Other “-omes” and “-omics” 621
 Use of Yeast Mutants to Categorize Genes 624
 Genetic Networks 625

Case Study *Genomic Analysis of Insect Guts May Fuel the World* 627
Summary 628 • *Preparing for Problem Solving* 628 • *Problems* 629

Continual DNA Transfer from Organelles 654
 Encoding of Organellar Proteins 655
 The Origin of the Eukaryotic Lineage 656
 Secondary and Tertiary Endosymbioses 656

Case Study *Ototoxic Deafness: A Mitochondrial Gene–Environment Interaction* 658
Summary 659 • *Preparing for Problem Solving* 660 • *Problems* 660



17

Organellar Inheritance and the Evolution of Organellar Genomes 632

17.1 Organellar Inheritance Transmits Genes Carried on Organellar Chromosomes 633

The Discovery of Organellar Inheritance 633
 Homoplasmy and Heteroplasmy 634
 Genome Replication in Organelles 635
 Replicative Segregation of Organelle Genomes 635

17.2 Modes of Organellar Inheritance Depend on the Organism 636

Mitochondrial Inheritance in Mammals 637
Genetic Analysis 17.1 639
 Mating Type and Chloroplast Segregation in *Chlamydomonas* 640
 Biparental Inheritance in *Saccharomyces cerevisiae* 641
Genetic Analysis 17.2 643
 Summary of Organellar Inheritance 644

17.3 Mitochondria Are the Energy Factories of Eukaryotic Cells 644

Mitochondrial Genome Structure and Gene Content 645
 Mitochondrial Transcription and Translation 646

17.4 Chloroplasts Are the Sites of Photosynthesis 648

Chloroplast Genome Structure and Gene Content 648
 Chloroplast Transcription and Translation 649
 Editing of Chloroplast mRNA 650

17.5 The Endosymbiosis Theory Explains Mitochondrial and Chloroplast Evolution 651

Separate Evolution of Mitochondria and Chloroplasts 651
Experimental Insight 17.1 652



18

Developmental Genetics 663

18.1 Development Is the Building of a Multicellular Organism 664

Cell Differentiation 665
 Pattern Formation 665

18.2 *Drosophila* Development Is a Paradigm for Animal Development 666

The Developmental Toolkit of *Drosophila* 667
 Maternal Effects on Pattern Formation 669
 Coordinate Gene Patterning of the Anterior–Posterior Axis 669
 Domains of Gap Gene Expression 670
 Regulation of Pair-Rule Genes 671
 Specification of Parasegments by *Hox* Genes 673
 Downstream Targets of *Hox* Genes 675
Hox Genes throughout Metazoans 676
Genetic Analysis 18.1 677
 Stabilization of Cellular Memory by Chromatin Architecture 678

18.3 Cellular Interactions Specify Cell Fate 679

Inductive Signaling between Cells 679
 Lateral Inhibition 682
 Cell Death During Development 682

18.4 “Evolution Behaves Like a Tinkerer” 683

Evolution through Co-option 683
 Constraints on Co-option 685

18.5 Plants Represent an Independent Experiment in Multicellular Evolution 685

Development at Meristems 685
 Combinatorial Homeotic Activity in Floral-Organ Identity 686

Genetic Analysis 18.2 689

Case Study *Cyclopia and Polydactyly—Different Shh Mutations with Distinctive Phenotypes* 690

Summary 691 • **Preparing for Problem Solving** 692 • **Problems** 692

**19****Genetic Analysis of Quantitative Traits 696****19.1 Quantitative Traits Display Continuous Phenotype Variation 697**

Genetic Potential 697

Major Gene Effects 698

Additive Gene Effects 698

Continuous Phenotypic Variation from Multiple Additive Genes 699

Allele Segregation in Quantitative Trait Production 701

Effects of Environmental Factors on Phenotypic Variation 702

Genetic Analysis 19.1 703

Threshold Traits 704

19.2 Quantitative Trait Analysis Is Statistical 706

Statistical Description of Phenotypic Variation 706

Partitioning Phenotypic Variance 707

Partitioning Genetic Variance 708

19.3 Heritability Measures the Genetic Component of Phenotypic Variation 708

Genetic Analysis 19.2 709

Broad Sense Heritability 710

Twin Studies 710

Narrow Sense Heritability and Artificial Selection 712

19.4 Quantitative Trait Loci Are the Genes That Contribute to Quantitative Traits 713

QTL Mapping Strategies 714

Identification of QTL Genes 716

Genome-Wide Association Studies 717

Case Study *The Genetics of Autism Spectrum Disorders* 718

Summary 719 • **Preparing for Problem Solving** 720 • **Problems** 720

**20****Population Genetics and Evolution at the Population, Species, and Molecular Levels 725****20.1 The Hardy–Weinberg Equilibrium Describes the Relationship of Allele and Genotype Frequencies in Populations 726**

Populations and Gene Pools 727

The Hardy–Weinberg Equilibrium 727

Determining Autosomal Allele Frequencies in Populations 729

The Hardy–Weinberg Equilibrium for More than Two Alleles 731

The Chi-Square Test of Hardy–Weinberg Predictions 731

Genetic Analysis 20.1 732

20.2 Natural Selection Operates through Differential Reproductive Fitness within a Population 732

Differential Reproductive Fitness and Relative Fitness 733

Directional Natural Selection 733

Natural Selection Favoring Heterozygotes 735

Genetic Analysis 20.2 736

20.3 Mutation Diversifies Gene Pools 736

Quantifying the Effects of Mutation on Allele Frequencies 737

Mutation–Selection Balance 737

20.4 Gene Flow Occurs by the Movement of Organisms and Genes between Populations 737

Effects of Gene Flow 738

Allele Frequency Equilibrium and Equalization 739

20.5 Genetic Drift Causes Allele Frequency Change by Sampling Error 739

The Founder Effect 740

Genetic Bottlenecks 740

20.6 Inbreeding Alters Genotype Frequencies but Not Allele Frequencies 741

The Coefficient of Inbreeding 741

Inbreeding Depression 743

20.7 New Species Evolve by Reproductive Isolation 743

Genetic Analysis 20.3 744

Processes of Speciation 744

Reproductive Isolation and Speciation 746

The Molecular Genetics of Evolution in Darwin's Finches 748

20.8 Molecular Evolution Changes Genes and Genomes through Time 748

Vertebrate Steroid Receptor Evolution 749

Case Study Sickle Cell Disease Evolution and Natural Selection in Humans 750

Summary 751 • Preparing for Problem Solving 752 • Problems 753



APPLICATION D
Human Evolutionary Genetics

D.1 Genome Sequences Reveal Extent of Human Genetic Diversity 759

SNP Variation in Humans 760

Variation in CNVs 761

D.2 Diversity of Extant Humans Suggests an African Origin 761

Mitochondrial Eve 762

Y Chromosome Phylogeny 762

Autosomal Loci 763

D.3 Comparisons between Great Apes Identify Human-Specific Traits 763

Revelations of Great Ape Genomes 763

Comparing the Human and Chimpanzee Genomes 765

D.4 Ancient DNA Reveals the Recent History of Our Species 766

Neandertals 768

Denisovans 769

Finding Genes that Make Us Human 770

D.5 Human Migrations around the Globe 770

Europe 770

Australia 771

D.6 Genetic Evidence for Adaptation to New Environments 772

Lactose Tolerance 772

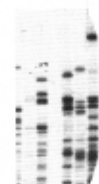
Skin Pigmentation 774

High Altitude 774

D.7 Domestication of Plants and Animals: Maize 775

D.8 The Future 776

Problems 777



APPLICATION E
Forensic Genetics

E.1 CODIS and Forensic Genetic Analysis 780

CODIS History and Markers 780

Electrophoretic Analysis 781

Forensic Analysis Using CODIS 782

Paternity Testing 784

Individual Identification 785

Remains Identified following the 9-11 Attack 785

Identification of the Disappeared in Argentina 786

E.2 DNA Analysis for Genealogy, Genetic Ancestry, and Genetic Health Risk Assessment 786

Assessing Genealogical Relationships 786

Assessing Genetic Ancestry 787

Genetic Health Risk Assessment 788

Late-Onset Alzheimer Disease 788

Celiac Disease 789

One Side of the Equation 789

Problems 789

References and Additional Reading R-1

Appendix: Answers A-1

Glossary G-1

Credits C-1

Index I-1