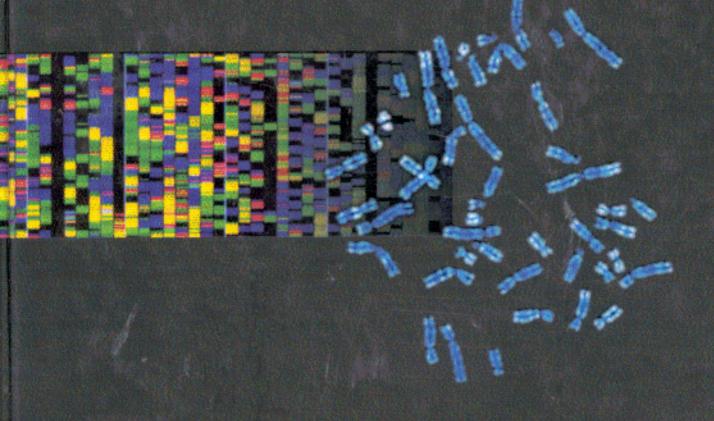
# PETER J. RUSSELL



# *i*GENETICS

## **Detailed Contents**

#### Preface xiii

## CHAPTER 1

#### Genetics: An introduction 1

#### Classical and Modern Genetics 2

#### **Basic Concepts of Genetics 3**

DNA, Genes, and Chromosomes 3 Transmission of Genetic Information 4 Expression of Genetic Information 5 Sources of Genetic Variation 6

#### Geneticists and Genetic Research 6

The Subdisciplines of Genetics 6 Basic and Applied Research 7 Genetic Databases and Maps 8 Model Organisms 9

#### Cellular Reproduction 9

Eukaryotic Cells 9 Eukaryotic Chromosomes 13 Mitosis 15 Meiosis 19

Summary 25

Questions and Problems 25

## Part 1 Genes and Their Functions 29

## CHAPTER 2

## DNA: The Genetic Material 31

## The Search for the Genetic Material 33

Griffith's Transformation Experiment 33 Avery's Transformation Experiment 34 The Hershey-Chase Bacteriophage Experiments 34 The Discovery of RNA as Viral Genetic Material 36

## The Composition and Structure of DNA and RNA $\,38$

The Discovery of the DNA Double Helix 40 Different DNA Structures 43 DNA in the Cell 44

RNA Structure 45

## The Organization of DNA in Chromosomes 45

Viral Chromosomes 45 Prokaryotic Chromosomes 47 Eukaryotic Chromosomes 50 Unique-Sequence and Repetitive-Sequence DNA 55

Analytical Approaches for Solving Genetics Problems 57 Questions and Problems 59

## CHAPTER 3

#### DNA Replication 62

#### Semiconservative DNA Replication 63

The Meselson-Stahl Experiment 63

Semiconservative DNA Replication in Eukaryotes 64

#### Enzymes Involved In DNA Synthesis 67

DNA Polymerase I 67

Roles of DNA Polymerases 67

#### Molecular Model of DNA Replication 69

Initiation of Replication 70

Semidiscontinuous DNA Replication 71

Replication of Circular DNA and the Supercoiling Problem 74

Rolling Circle Replication 75

#### **DNA Replication in Eukaryotes** 76

DNA Replication and the Cell Cycle 77

Eukaryotic Replication Enzymes 79

Replicons 80

Origins of Replication 81

Replicating the Ends of Chromosomes 81

Assembling New DNA into Nucleosomes 83

#### Summary 84

Analytical Approaches for Solving Genetics Problems 84

Questions and Problems 85

## CHAPTER 4

#### **Gene Control of Proteins 88**

#### Gene Control of Enzyme Structure 89

Garrod's Hypothesis of Inborn Errors

of Metabolism 89

The One Gene-One Enzyme Hypothesis 89

## Genetically Based Enzyme Deficiencies in Humans 94

Phenylketonuria 94

Albinism 96

Lesch-Nyhan Syndrome 96

Tay-Sachs Disease 96

#### Gene Control of Protein Structure 97

Sickle-Cell Anemia 97

Other Hemoglobin Mutants 99

Biochemical Genetics of the Human ABO

Blood Group 100

Cystic Fibrosis 101

#### Genetic Counseling 103

Carrier Detection 104

Fetal Analysis 104

Summary 105

Analytical Approaches for Solving Genetics Problems 105

Questions and Problems 106

## CHAPTER 5

#### Gene Expression: Transcription 109

Gene Expression: An Overview 111

#### The Transcription Process 111

RNA Synthesis 111

Initiation of Transcription at Promoters 112

Elongation and Termination of an RNA Chain 115

#### Transcription in Eukaryotes 116

Eukaryotic RNA Polymerases 116

Transcription of Protein-Coding Genes by RNA

Polymerase II 116

Eukaryotic mRNAs 119

Transcription of Other Genes 126

#### Summary 134

Analytical Approaches for Solving Genetics Problems 135

Ouestions and Problems 136

## CHAPTER 6

#### Gene Expression: Translation 138

**Proteins** 139

Chemical Structure of Proteins 139

Molecular Structure of Proteins 141

#### The Nature of the Genetic Code 142

The Genetic Code Is a Triplet Code 142

Deciphering the Genetic Code 144

Characteristics of the Genetic Code 145

#### Translation: The Process of Protein Synthesis 147

The mRNA Codon Recognizes the tRNA

Anticodon 147

Charging tRNA 147

Initiation of Translation 148

Elongation of the Polypeptide Chain 151

Termination of Translation 153

#### Protein Sorting in the Cell 155

Summary 156

Analytical Approaches for Solving Genetics Problems 157

Questions and Problems 158

## Part 2 Gene Manipulation and Genomic Analysis 161

## CHAPTER

#### Recombinant DNA Cloning Technology 163

#### DNA Cloning 165

Restriction Enzymes 165 Cloning Vectors and DNA Cloning 168

#### **Recombinant DNA Libraries 173**

Genomic Libraries 173 Chromosome Libraries 175 cDNA Libraries 175

#### Finding a Specific Clone in a Library 176

Screening a cDNA Library 177 Screening a Genomic Library 177 Identifying Genes in Libraries by Complementation of Mutations 181 Identifying Specific DNA Sequences in Libraries Using Heterologous Probes 181 Identifying Genes or cDNAs in Libraries Using

## Analyzing Genes and Gene Transcripts 182

Oligonucleotide Probes 182

Restriction Enzyme Analysis of Cloned DNA Sequences 183 Restriction Enzyme Analysis of Genes in the Genome 185 Analysis of Gene Transcripts 185 DNA Sequencing 187

Polymerase Chain Reaction (PCR) 190

Summary 192

Analytical Approaches for Solving Genetics Problems 192**Ouestions and Problems** 193

## CHAPTER 8

## Applications of Recombinant DNA Technology 196

#### Analysis of Biological Processes 197

Regulation of Transcription: Glucose Repression of the Yeast GAL1 Gene 197 Alternative Pre-mRNA Splicing: A Role in Sexual Behavior in Drosophila 198

Protein-Protein Interaction in the Cell: The Yeast Two-Hybrid System 199

#### **DNA Molecular Testing for Human Genetic** Disease Mutations 200

Concept of DNA Molecular Testing 200 Purposes of Human Genetic Testing 201 Examples of DNA Molecular Testing 201 Availability of DNA Molecular Testing 204

#### Isolation of Human Genes 204

Cloning the Cystic Fibrosis Gene 204

#### **DNA Typing 208**

DNA Typing in a Paternity Case 208 Other Applications of DNA Typing 210

Gene Therapy 211

Commercial Products 212

## Genetic Engineering of Plants 213

Transformation of Plant Cells 214 Applications for Plant Genetic Engineering 215

Summary 217

Analytical Approaches for Solving Genetics Problems 217 Questions and Problems 218

## CHAPTER 9

## **Genome Analysis** 220

#### Structural Genomics 221

Genome Sequencing Using a Mapping Approach 222 Genome Sequencing Using a Direct Shotgun Approach 234

Overview of Genomes Sequenced 234

#### Functional Genomics 240

Identifying Genes in DNA Sequences 241 Homology Searches to Assign Gene Function 241 Assigning Gene Function Experimentally 242 Describing Patterns of Gene Expression 242

**Comparative Genomics 246** 

Ethics and the Human Genome Project 246

Summary 247

Analytical Approaches for Solving Genetics Problems 247**Ouestions and Problems** 249

## Part 3 Principles of Gene Segregation Analysis 253

## CHAPTER 10

**Mendelian Genetics** 255

**Genotype and Phenotype 256** 

Mendel's Experimental Design 257

Monohybrid Crosses and Mendel's Principle of Segregation 258

The Principle of Segregation 262

Representing Crosses with a Branch Diagram 262 Confirming the Principle of Segregation:

onlirming the Principle of Segregation:

The Use of Testcrosses 264

# Dihybrid Crosses and Mendel's Principle of Independent Assortment 266

The Principle of Independent Assortment 266 Branch Diagram of Dihybrid Crosses 267 Trihybrid Crosses 268

The "Rediscovery" of Mendel's Principles 269

Statistical Analysis of Genetic Data:

The Chi-Square Test 270

Mendelian Genetics in Humans 271

Pedigree Analysis 271

Examples of Human Genetic Traits . 272

Summary 275

Analytical Approaches for Solving Genetics Problems 275

**Questions and Problems** 276

## CHAPTER 11

## Chromosomal Basis of Inheritance, Sex Linkage, and Sex Determination 282

#### **Chromosome Theory of Inheritance 283**

Sex Chromosomes 283

Sex Linkage 284

Nondisjunction of X Chromosomes 288

#### **Sex Determination** 291

Genotypic Sex Determination Systems 291 Environmental Sex Determination Systems 297

#### Analysis of Sex-Linked Traits in Humans 298

X-Linked Recessive Inheritance 298

X-Linked Dominant Inheritance 299

Y-Linked Inheritance 300

Summary 301

Analytical Approaches for Solving Genetics Problems 301

Questions and Problems 303

## CHAPTER 12

#### Extensions of Mendellan Genetic Analysis 308

#### **Multiple Alleles 309**

ABO Blood Groups 309

Drosophila Eye Color 310

Relating Multiple Alleles to Molecular Genetics 311

#### **Modifications of Dominance Relationships 312**

Incomplete Dominance 312

Codominance 313

Molecular Explanations of Incomplete Dominance and Codominance 314

#### Gene Interactions and Modified Mendellan Ratios 314

Gene Interactions That Produce New

Phenotypes 315

Epistasis 317

#### **Essential Genes and Lethal Alleles 320**

#### Gene Expression and the Environment 322

Penetrance and Expressivity 322

Effects of the Environment 324

Nature Versus Nurture 327

Summary 328

Analytical Approaches for Solving Genetics Problems 329

Questions and Problems 330

#### CHAPTER 13

#### **Gene Mapping in Eukaryotes** 336

**Discovery of Genetic Linkage 337** 

Morgan's Linkage Experiments with Drosophila 337

## Gene Recombination and the Role of Chromosomal Exchange 339

Corn Experiments 339
Drosophila Experiments 340
Crossing-Over at the Four-Chromatid Stage of Meiosis 342

#### Constructing Genetic Maps 345

Detecting Linkage Through Testcrosses 345 Gene Mapping Using Two-Point Testcrosses 347 Generating a Genetic Map 348 Gene Mapping Using Three-Point Testcrosses 349 Calculating Accurate Map Distances 354

## Tetrad Analysis in Certain Haploid Eukaryotes 356

Using Random-Spore Analysis to Map Genes in Haploid Eukaryotes 357

Using Tetrad Analysis to Map Two Linked Genes 357

Calculating Gene-Centromere Distance in Organisms with Linear Tetrads 362

#### Mitotic Recombination 364

Discovery of Mitotic Recombination 364 Mechanism of Mitotic Crossing-Over 365 Retinoblastoma, a Human Tumor That Can Be Caused by Mitotic Recombination 366

**Summary** 368

Analytical Approaches for Solving Genetics Problems 368 Ouestions and Problems 370

#### CHAPTER 14

# Gene Mapping in Bacteria and Bacteriophages 377

**Genetic Analysis of Bacterla 378** 

#### Genetic Mapping in Bacteria by Conjugation 380

Discovery of Conjugation in E. coli 380

The Sex Factor F 381

High-Frequency Recombination Strains of E. coli 381 F' Factors 383

Using Conjugation to Map Bacterial Genes 384 Circularity of the E. coli Map 386

## Genetic Mapping in Bacteria by Transformation $\ 387$

## Genetic Mapping in Bacteria by Transduction 389

Bacteriophages 389

Transduction Mapping of Bacterial Chromosomes 389

#### Mapping Genes of Bacterlophages 395

#### Fine-Structure Analysis of a Bacteriophage Gene 397

Recombination Analysis of rII Mutants 397
Deletion Mapping 399
Defining Genes by Complementation
(Cis-Trans) Tests 401

Summary 404

Analytical Approaches for Solving Genetics Problems 406Questions and Problems 408

## CHAPTER 15

#### Non-Mendelian Inheritance 412

Origin of Mitochondria and Chioroplasts 413

#### Organization of Extranuclear Genomes 414

Mitochondrial Genome 414 Chloroplast Genome 418

#### Rules of Non-Mendellan Inheritance 420

#### Examples of Non-Mendellan Inheritance 421

Shoot Variegation in the Four O'Clock 421
The [poky] Mutant of Neurospora 422
Yeast petite Mutants 424
Non-Mendelian Inheritance in Chlamydomonas 427

Human Genetic Diseases and Mitochondrial
DNA Defects 428

Exceptions to Maternal Inheritance 429 Infectious Heredity: Killer Yeast 429

#### Contrasts to Extranuclear Inheritance 430

Maternal Effect 430 Genomic Imprinting 431

Summary 433

Analytical Approaches for Solving Genetics Problems 433

Questions and Problems 434

## Part 4 Regulation of Gene Expression 439

## CHAPTER 16

# Regulation of Gene Expression in Bacteria and Bacteriophages 441

#### The lac Operon of E. coli 442

Lactose as a Carbon Source for E. coli 442
Experimental Evidence for the Regulation of lac Genes 444
Jacob and Monod's Operon Model for the Regulation of lac Genes 446
Positive Control of the lac Operon 451
Molecular Details of lac Operon Regulation 452

#### The trp Operon of E. coli 455

Gene Organization of the Tryptophan Biosynthesis Genes 455 Regulation of the trp Operon 456

## Regulation of Gene Expression in Phage Lambda 459

Early Transcription Events 459 The Lysogenic Pathway 459 The Lytic Pathway 460

Summary 462

Analytical Approaches for Solving Genetics Problems 462 Questions and Problems 464

## CHAPTER 17

## Regulation of Gene Expression in Eukaryotes 467

Levels of Control of Gene Expression in Eukaryotes 469

Transcriptional Control 469 RNA Processing Control 481 mRNA Transport Control 482 mRNA Translation Control 485

mRNA Degradation Control 485 Protein Degradation Control 486

# Gene Regulation In Development and Differentiation 487

Genomic Activity in Multicellular Eukaryotes 487
Constancy of DNA in the Genome During
Development 487
Differential Gene Activity Among Tissues
and During Development 488
Immunogenetics and Chromosome Rearrangements During Development 492

#### Genetic Regulation of Development in Drosophila 496

Drosophila Developmental Stages 496 Embryonic Development 497 Imaginal Discs 500 Homeotic Genes 500

Summary 504

Analytical Approaches for Solving Genetics Problems 505Questions and Problems 506

## CHAPTER 18

#### **Genetics of Cancer** 511

Relationship of the Cell Cycle to Cancer 513The Two-Hit Mutation Model for Cancer 514

Genes and Cancer 516

Oncogenes 516
Tumor Suppressor Genes 526
Mutator Genes 531

The Multistep Nature of Cancer 531

Chemicals and Radiation as Carcinogens 532

Chemical Carcinogens 533 Radiation 533

Summary 534

Analytical Approaches for Solving Genetics Problems 535Questions and Problems 535

## Part 5 Genetic Change 539

## CHAPTER 19

## DNA Mutation and Repair 541

Adaptation Versus Mutation 543

#### **Mutations Defined** 544

Types of Point Mutations 544

Reverse Mutations and Suppressor Mutations 546

#### **Spontaneous and Induced Mutations 548**

Spontaneous Mutations 548

Induced Mutations 551

Chemical Mutagens in the Environment 557

#### **DNA Repair Mechanisms** 558

Direct Correction of Mutational Lesions 559 Repair Involving Excision of Base Pairs 559

#### **Human Genetic Diseases Resulting from DNA Mutations** 562

#### **Detecting Mutations** 564

Visible Mutations 564

Nutritional Mutations 564

Conditional Mutations 565

Resistance Mutations 565

Molecular Screens 565

Summary 566

Analytical Approaches for Solving Genetics Problems 566

**Questions and Problems** 568

## CHAPTER 20

#### **Transposable Elements 573**

#### **General Features of Transposable Elements 574**

#### **Transposable Elements in Prokaryotes** 574

Insertion Sequences 574

Transposons 575

IS Elements and Transposons in Plasmids 578

Bacteriophage Mu 579

#### **Transposable Elements in Eukaryotes** 581

Transposons in Plants 584

Ty Elements in Yeast 587

Drosophila Transposons 588

Human Retrotransposons 590

**Summary** 591

Analytical Approaches for Solving Genetics Problems 592

**Questions and Problems** 592

## CHAPTER 21

#### **Chromosomal Mutations** 595

Types of Chromosomal Mutations 596

Variations in Chromosome Structure 596

Deletion 597

Duplication 599

Inversion 601

Translocation 604

Position Effect 606

Fragile Sites and Fragile X Syndrome 608

#### Variations in Chromosome Number 609

Changes in One or a Few Chromosomes 609

Changes in Complete Sets of Chromosomes 613

Summary 616

Analytical Approaches for Solving Genetics Problems 616

Questions and Problems 61%

#### Part 6 Genetics of Populations 623

#### CHAPTER 22

#### **Population Genetics** 625

#### **Genetic Structure of Populations** 628

Genotypic Frequencies 628 Allelic Frequencies 628

#### The Hardy-Weinberg Law 630

Assumptions of the Hardy-Weinberg Law 632

Predictions of the Hardy-Weinberg Law 633

Derivation of the Hardy-Weinberg Law 633 Extensions of the Hardy-Weinberg Law to Loci

with More Than Two Alleles 635

Extensions of the Hardy-Weinberg Law

to Sex-Linked Alleles 635

Testing for Hardy-Weinberg Proportions 636

Using the Hardy-Weinberg Law to Estimate

Allelic Frequencies 637

#### **Genetic Variation in Space and Time 637**

#### **Genetic Variation in Natural Populations** 639

Measuring Genetic Variation at the Protein Level 639

Measuring Genetic Variation at the DNA Level 642

#### **Forces That Change Gene Frequencies** in Populations 645

Mutation 645

Random Genetic Drift 647

Migration 653

Natural Selection 655
Balance Between Mutation and Selection 662
Assortative Mating 663
Inbreeding 663

# Summary of the Effects of Evolutionary Forces on the Genetic Structure of a Population 664

Changes in Allelic Frequency Within a Population 665
Genetic Divergence Among Populations 665
Increases and Decreases in Genetic Variation Within Populations 665

#### The Role of Genetics in Conservation Biology 665

**Speciation** 666

Barriers to Gene Flow 666 Genetic Basis for Speciation 666

Summary 667

Analytical Approaches for Solving Genetics Problems 667

Ouestions and Problems 668

## CHAPTER 23

#### **Quantitative Genetics** 673

#### The Nature of Continuous Traits 675

Why Some Traits Have Continuous Phenotypes 676 Questions Studied in Quantitative Genetics 676

#### **Statistical Tools** 677

Samples and Populations 677
Distributions 677
The Mean 678
The Variance and the Standard Deviation 678
Correlation 680
Regression 681
Analysis of Variance 683

#### Polygenic Inheritance 684

Inheritance of Ear Length in Corn 684 Polygene Hypothesis for Quantitative Inheritance 685 Quantitative Trait Loci 687

## Heritability 688

Components of the Phenotypic Variance 690 Broad-Sense and Narrow-Sense Heritability 692 Understanding Heritability 693 How Heritability Is Calculated 694

#### **Response to Selection** 696

Estimating the Response to Selection 697 Genetic Correlations 698

Summary 700

Analytical Approaches for Solving Genetics Problems 700Ouestions and Problems 702

## CHAPTER 24

#### **Molecular Evolution** 707

#### Patterns and Modes of Substitutions 709

Nucleotide Substitutions in DNA Sequences 709
Rates of Nucleotide Substitutions 710
Variation in Evolutionary Rates Between Genes 712
Rates of Evolution in Mitochondrial DNA 713
Molecular Clocks 715

#### Molecular Phylogeny 716

Phylogenetic Trees 717
Reconstruction Methods 718
Phylogenetic Trees on a Grand Scale 721

#### Acquisition and Origins of New Functions 723

Multigene Families 723 Gene Duplication and Gene Conversion 724 Arabidopsis Genome Results 724 Domain (Exon) Shuffling 725

Summary 725

Analytical Approaches for Solving Genetics Problems 725 Questions and Problems 726

Glossary 728

Suggested Readings 747

**Solutions to Selected Questions and Problems** 764

Credits 799

**Index** 803