Brief Table of Contents

Edited by Hannah L. Klein and Samantha Hoot

Chapter 16. Repair Systems 395
Chapter 17. Transposable Elements and
Retroviruses 424
Edited by Damon Lisch Chapter 18. Somatic Recombination and
Hypermutation in the Immune System 459
Part 3. TRANSCRIPTION
AND POSTTRANSCRIPTIONAL
MECHANISMS 508
Chapter 19. Prokaryotic Transcription 509 Edited by Richard Gourse
Chapter 20. Eukaryotic Transcription 549
Chapter 21. RNA Splicing and Processing 578
Chapter 22. mRNA Stability and
Localization 622
Edited by Ellen Baker
Chapter 23. Catalytic RNA 647 Edited by Douglas J. Briant
Chapter 24. Translation 671
Chapter 25. Using the Genetic Code 714
Edited by John Perona
Part 4. GENE REGULATION 744
Chapter 26. The Operon 745 Edited by Liskin Swint-Kruse
Chapter 27. Phage Strategies 777
Chapter 28. Eukaryotic Transcription
Regulation 804
Chapter 29. Epigenetic Effects Are
Inherited 838
Edited by Trygve Tollefsbol
Chapter 30. Regulatory RNA 872
Glossary 894

Index 920

Contents

Preface xix

References 24

About t	the Authors xxi
CHR	T 1. GENES AND OMOSOMES 1
	ter 1. Genes Are DNA 2
1.2	
1.3	DNA Is the Genetic Material of Eukaryotic Cells 6
1.4	Polynucleotide Chains Have Nitrogenous Bases Linked to a Sugar–Phosphate Backbone 7
1.5	Supercoiling Affects the Structure of DNA 8
1.6	DNA Is a Double Helix 10
1.7	DNA Replication Is Semiconservative 12
1.8	Polymerases Act on Separated DNA Strands at the Replication Fork 13
1.9	Genetic Information Can Be Provided by DNA or RNA 14
1.10	Nucleic Acids Hybridize by Base Pairing 15
1.11	Mutations Change the Sequence of DNA 17
1.12	Mutations May Affect Single Base Pairs or Longer Sequences 18
1.13	The Effects of Mutations Can Be Reversed 19
1.14	Mutations Are Concentrated at Hotspots 20
1.15	Many Hotspots Result from Modified Bases 21
1.16	Some Hereditary Agents Are Extremely Small 22
1.17	Summary 23

Chapter 2. Genes Encode RNAs and Polypeptides 26

- 2.1 Introduction 27
- 2.2 Most Genes Encode Polypeptides 28
- 2.3 Mutations in the Same Gene Cannot Complement 29
- 2.4 Mutations May Cause Loss of Function or Gain of Function 30
- 2.5 A Locus May Have Many Different Mutant Alleles 31
- 2.6 A Locus May Have More Than One Wild-Type Allele 31
- 2.7 Recombination Occurs by Physical Exchange of DNA 32
- 2.8 The Genetic Code Is Triplet 34
- 2.9 Every Coding Sequence Has Three Possible Reading Frames 36
- **2.10** Bacterial Genes Are Colinear with Their Products 37
- **2.11** Several Processes Are Required to Express the Product of a Gene 38
- **2.12** Proteins Are *trans*-Acting but Sites on DNA Are *cis*-Acting 39
- **2.13** Summary 41

References 41

Chapter 3. Methods in Molecular Biology and Genetic Engineering 42

- 3.1 Introduction 43
- 3.2 Nucleases 44
- **3.3** Cloning 46

3.4 Cloning Vectors Can B Different Purposes 4	•	Chapter 5. The Content of the Genome 100
3.5 Nucleic Acid Detection		5.1 Introduction 101
3.6 DNA Separation Techn		5.2 Genomes Can Be Mapped at Several Levels of Resolution 102
3.7 DNA Sequencing 58	14463 54	5.3 Individual Genomes Show Extensive Variation 103
3.8 PCR and RT-PCR 59		5.4 RFLPs and SNPs Can Be Used for Genetic
3.9 Blotting Methods 65		Mapping 104
3.10 DNA Microarrays 69		Eukaryotic Genomes Contain Nonrepetitive and Repetitive DNA Sequences 106
3.11 Chromatin Immunopre	cipitation 72	
3.12 Gene Knockouts and T	ransgenics 74	5.6 Eukaryotic Protein-Coding Genes Can Be Identified by the Conservation of Exons 107
3.13 Summary 79		The Conservation of Genome Organization Helps to Identify Genes 109
Chapter 4. The Interr	upted Gene 81	5.8 Some Organelles Have DNA 111
Edited by Donald Forsdyke 4.1 Introduction 82		5.9 Organelle Genomes Are Circular DNAs That Encode Organelle Proteins 113
4.2 An Interrupted Gene C and Introns 83	consists of Exons	5.10 The Chloroplast Genome Encodes Many Proteins and RNAs 115
4.3 Exon and Intron Base	Compositions Differ 84	5.11 Mitochondria and Chloroplasts Evolved
4.4 Organization of Interro	upted Genes May Be	by Endosymbiosis 116
	Nagative Calaction Are	5.12 Summary 117 References 117
Conserved but Introns	Negative Selection Are Vary 86	References 117
4.6 Exon Sequences Under Introns Are Conserved	Positive Selection Vary but 87	Chapter 6. Genome Sequences and Gene Numbers 120
4.7 Genes Show a Wide Dis		6.1 Introduction 121
Due Primarily to Intro Variation 88		6.2 Prokaryotic Gene Numbers Range Over an Order of Magnitude 122
4.8 Some DNA Sequences I Polypeptide 90	Encode More Than One	6.3 Total Gene Number Is Known for Several Eukaryotes 123
4.9 Some Exons Can Be Eq Domains 92	uated with Protein Functional	6.4 How Many Different Types of Genes Are There? 125
4.10 Members of a Gene Far Organization 93	nily Have a Common	6.5 The Human Genome Has Fewer Genes Than Originally Expected 127
4.11 There Are Many Forms	of Information in DNA 95	6.6 How Are Genes and Other Sequences Distributed in
4.12 Summary 97		the Genome? 129
References 97		6.7 The Y Chromosome Has Several Male-Specific Genes 131
		6.8 How Many Genes Are Essential? 132

- 6.9 About 10,000 Genes Are Expressed at Widely Differing Levels in a Eukaryotic Cell 135
- **6.10** Expressed Gene Number Can Be Measured En Masse 136
- **6.11** Summary 137

Chapter 7. Clusters and Repeats 141

- 7.1 Introduction 142
- 7.2 Unequal Crossing Over Rearranges Gene Clusters 144
- 7.3 Genes for rRNA Form Tandem Repeats Including an Invariant Transcription Unit 147
- 7.4 Crossover Fixation Could Maintain Identical Repeats 149
- 7.5 Satellite DNAs Often Lie in Heterochromatin 152
- 7.6 Arthropod Satellites Have Very Short Identical Repeats 154
- 7.7 Mammalian Satellites Consist of Hierarchical Repeats 154
- 7.8 Minisatellites Are Useful for Genetic Mapping 158
- 7.9 Summary 159

References 160

Chapter 8. Genome Evolution 161

- 8.1 Introduction 162
- 8.2 DNA Sequences Evolve by Mutation and a Sorting Mechanism 163
- 8.3 Selection Can Be Detected by Measuring Sequence Variation 165
- 8.4 A Constant Rate of Sequence Divergence Is a Molecular Clock 169
- 8.5 The Rate of Neutral Substitution Can Be Measured from Divergence of Repeated Sequences 173
- 8.6 How Did Interrupted Genes Evolve? 174
- 8.7 Why Are Some Genomes So Large? 177
- 8.8 Morphological Complexity Evolves by Adding New Gene Functions 179
- 8.9 Gene Duplication Contributes to Genome Evolution 180

- **8.10** Globin Clusters Arise by Duplication and Divergence 181
- **8.11** Pseudogenes Are Nonfunctional Gene Copies 183
- **8.12** Genome Duplication Has Played a Role in Plant and Vertebrate Evolution 185
- **8.13** What Is the Role of Transposable Elements in Genome Evolution? 186
- 8.14 There May Be Biases in Mutation, Gene Conversion, and Codon Usage 187
- **8.15** Summary 188

References 189

Chapter 9. Chromosomes 192

Edited by Hank W. Bass

- 9.1 Introduction 193
- 9.2 Viral Genomes Are Packaged into Their Coats 194
- 9.3 The Bacterial Genome Is a Nucleoid 197
- 9.4 The Bacterial Genome Is Supercoiled 198
- 9.5 Eukaryotic DNA Has Loops and Domains Attached to a Scaffold 200
- 9.6 Specific Sequences Attach DNA to an Interphase Matrix 201
- 9.7 Chromatin Is Divided into Euchromatin and Heterochromatin 202
- 9.8 Chromosomes Have Banding Patterns 204
- 9.9 Lampbrush Chromosomes Are Extended 205
- 9.10 Polytene Chromosomes Form Bands 206
- **9.11** Polytene Chromosomes Expand at Sites of Gene Expression 208
- 9.12 The Eukaryotic Chromosome Is a Segregation
 Device 209
- 9.13 Regional Centromeres Contain a Centromeric Histone H3 Variant and Repetitive DNA 210
- 9.14 Point Centromeres in *S. cerevisiae* Contain Short, Essential DNA Sequences 212
- 9.15 The *S. cerevisiae* Centromere Binds a Protein Complex 213
- 9.16 Telomeres Have Simple Repeating Sequences 213
- 9.17 Telomeres Seal the Chromosome Ends and Function in Meiotic Chromosome Pairing 214

9.18	Telomeres Are Synthesized by a Ribonucleoprotein Enzyme 216
9.19	Telomeres Are Essential for Survival 218
9.20	Summary 219
Referen	ces 220
Chapt	ter 10. Chromatin 223
10.1	Introduction 225
10.2	DNA Is Organized in Arrays of Nucleosomes 225
10.3	The Nucleosome Is the Subunit of All Chromatin 228
10.4	Nucleosomes Are Covalently Modified 231
10.5	Histone Variants Produce Alternative Nucleosomes 234
10.6	DNA Structure Varies on the Nucleosomal Surface 237
10.7	The Path of Nucleosomes in the Chromatin Fiber 240
10.8	Replication of Chromatin Requires Assembly of Nucleosomes 242
10.9	Do Nucleosomes Lie at Specific Positions? 245
[10.10]	Nucleosomes Are Displaced and Reassembled During Transcription 249
10.11	DNase Sensitivity Detects Changes in Chromatin Structure 252
10.12	Insulators Define Transcriptionally Independent Domains 254
10.13	An LCR May Control a Domain 258
10.14	Summary 260
Referenc	res 261

PART 2. DNA REPLICATION AND RECOMBINATION 265

Chapter 11. Replication Is Connected to the Cell Cycle 266

Edited by Barbara Funnell

- 11.1 Introduction 267
- 11.2 Bacterial Replication Is Connected to the Cell Cycle 269

- 11.3 The Septum Divides a Bacterium into Progeny That Each Contain a Chromosome 270
- 11.4 Mutations in Division or Segregation Affect Cell
 Shape 271
- 11.5 FtsZ Is Necessary for Septum Formation 272
- 11.6 min and noc/slm Genes Regulate the Location of the Septum 273
- 11.7 Chromosomal Segregation May Require Site-Specific Recombination 274
- 11.8 Partition Involves Separation of the Chromosomes 276
- 11.9 The Eukaryotic Growth Factor Signal Transduction Pathway 277
- 11.10 Checkpoint Control for Entry Into S Phase: p53, a Guardian of the Checkpoint 280
- 11.11 Checkpoint Control for Entry into S Phase: Rb, a Guardian of the Checkpoint 281
- **11.12** Summary 282

References 283

Chapter 12. The Replicon: Initiation of Replication 286

Edited by Stephen D. Bell

- 12.1 Introduction 287
- 12.2 An Origin Usually Initiates Bidirectional Replication 288
- 12.3 The Bacterial Genome Is (Usually) a Single Circular Replicon 289
- 12.4 Methylation of the Bacterial Origin Regulates
 Initiation 290
- 12.5 Initiation: Creating the Replication Forks at the Origin *oriC* 291
- 12.6 Multiple Mechanisms Exist to Prevent Premature Reinitiation of Replication 294
- 12.7 Archaeal Chromosomes Can Contain Multiple
 Replicons 295
- 12.8 Each Eukaryotic Chromosome Contains Many Replicons 295
- 12.9 Replication Origins Can Be Isolated in Yeast 297
- 12.10 Licensing Factor Controls Eukaryotic
 Rereplication 298

12.11 Licensing Factor Binds to ORC 299 12.12 Summary 301	14.3 Terminal Proteins Enable Initiation at the Ends of Viral DNAs 331
References 302	14.4 Rolling Circles Produce Multimers of a Replicon 332
Chapter 13. DNA Replication 304 Edited by Peter Burgers	Rolling Circles Are Used to Replicate Phage Genomes 334
13.1 Introduction 305	14.6 The F Plasmid Is Transferred by Conjugation Between Bacteria 335
DNA Polymerases Are the Enzymes That Make DNA 306	14.7 Conjugation Transfers Single-Stranded DNA 336
13.3 DNA Polymerases Have Various Nuclease Activities 308	14.8 Single-Copy Plasmids Have a Partitioning System 338
13.4 DNA Polymerases Control the Fidelity of Replication 308	14.9 Plasmid Incompatibility Is Determined by the Replicon 340
13.5 DNA Polymerases Have a Common Structure 310	14.10 The ColE1 Compatibility System Is Controlled by an RNA Regulator 341
13.6 The Two New DNA Strands Have Different Modes of Synthesis 311	14.11 How Do Mitochondria Replicate and Segregate? 343
13.7 Replication Requires a Helicase and a Single-Strand Binding Protein 312	14.12 D Loops Maintain Mitochondrial Origins 344
13.8 Priming Is Required to Start DNA Synthesis 313	14.13 The Bacterial Ti Plasmid Causes Crown Gall Disease in Plants 346
13.9 Coordinating Synthesis of the Lagging and Leading Strands 314	14.14 T-DNA Carries Genes Required for Infection 347
13.10 DNA Polymerase Holoenzyme Consists of Subcomplexes 315	14.15 Transfer of T-DNA Resembles Bacterial Conjugation 349
13.11 The Clamp Controls Association of Core Enzyme with DNA 316	14.16 Summary 351 References 352
13.12 Okazaki Fragments Are Linked by Ligase 319	Chapter 15. Homologous and Site-Specific
13.13 Separate Eukaryotic DNA Polymerases Undertake Initiation and Elongation 321	Recombination 354 Edited by Hannah L. Klein and Samantha Hoot
13.14 Lesion Bypass Requires Polymerase Replacement 323	15.1 Introduction 356
13.15 Termination of Replication 325	15.2 Homologous Recombination Occurs Between
13.16 Summary 325	Synapsed Chromosomes in Meiosis 358 15.3 Double-Strand Breaks Initiate Recombination 359
References 326	15.3 Double-Strand Breaks Initiate Recombination 359 15.4 Gene Conversion Accounts for Interallelic
Chapter 14. Extrachromosomal	Recombination 361
Replicons 328 Edited by Søren Johannes Sørensen and Lars Hestbjerg Hansen	15.5 The Synthesis-Dependent Strand-Annealing Model 363
14.1 Introduction 329	15.6 The Single-Strand Annealing Mechanism Functions at Some Double-Strand Breaks 364

14.2 The Ends of Linear DNA Are a Problem for

Replication 330

15.7 Break-Induced Replication Can Repair Double-Strand

Breaks 364

15.8	15.8 Recombining Meiotic Chromosomes Are Connected		Controlling the Direction of Mismatch Repair 407
45.0	by the Synaptonemal Complex 365	16.8	Recombination-Repair Systems in E. coli 409
	The Synaptonemal Complex Forms After Double-Strand Breaks 367	16.9	Recombination Is an Important Mechanism to Recover from Replication Errors 411
15.10	Pairing and Synaptonemal Complex Formation Are Independent 369	16.10	Recombination-Repair of Double-Strand Breaks in Eukaryotes 413
(15.11)	The Bacterial RecBCD System Is Stimulated by chi Sequences 370	16.11	Nonhomologous End-Joining Also Repairs Double- Strand Breaks 414
15.12	Strand-Transfer Proteins Catalyze Single-Strand Assimilation 371	16.12	DNA Repair in Eukaryotes Occurs in the Context of Chromatin 415
15.13	Holliday Junctions Must Be Resolved 374	16.13	RecA Triggers the SOS System 418
15.14	Eukaryotic Genes Involved in Homologous Recombination 376		Summary 420
15.15	Specialized Recombination Involves Specific Sites 379	Referen	ces 420
15.16	Site-Specific Recombination Involves Breakage and Reunion 380	and R	ter 17. Transposable Elements etroviruses 424
15.17	Site-Specific Recombination Resembles		d by Damon Lisch
	Topoisomerase Activity 381		Introduction 426
	Lambda Recombination Occurs in an Intasome 383	17.2	Insertion Sequences Are Simple Transposition Modules 427
15.19	Yeast Can Switch Silent and Active Loci for Mating Type 384	17.3	Transposition Occurs by Both Replicative and Nonreplicative Mechanisms 429
15.20	Unidirectional Gene Conversion Is Initiated by the Recipient <i>MAT</i> Locus 386	17.4	Transposons Cause Rearrangement of DNA 430
15.21	Antigenic Variation in Trypanosomes Uses Homologous Recombination 387	17.5	Replicative Transposition Proceeds Through a Cointegrate 431
15.22	Recombination Pathways Adapted for Experimental Systems 388	17.6	Nonreplicative Transposition Proceeds by Breakage and Reunion 433
15.23	Summary 391	17.7	Transposons Form Superfamilies and Families 434
Referen	ces 392	17.8	The Role of Transposable Elements in Hybrid Dysgenesis 437
Chapt	ter 16. Repair Systems 395	17.9	P Elements Are Activated in the Germline 438
16.1	Introduction 396	17.10	The Retrovirus Lifecycle Involves Transposition-Like
16.2	Repair Systems Correct Damage to DNA 398		Events 440
16.3	Excision Repair Systems in E. Coli 400		Retroviral Genes Code for Polyproteins 441
16.4	Eukaryotic Nucleotide Excision Repair Pathways 401	17.12	Viral DNA Is Generated by Reverse Transcription 442
16.5	Base Excision Repair Systems Require Glycosylases 404		Viral DNA Integrates into the Chromosome 445 Retroviruses May Transduce Cellular Sequences 446
16.6	Error-Prone Repair and Translesion Synthesis 406		Retroelements Fall into Three Classes 448
	700		NELLUEIEILIN FAIL IIIIO TUTOO LIBECOC 7.7.0

- 17.16 Yeast Ty Elements Resemble Retroviruses 450
- 17.17 The Alu Family Has Many Widely Dispersed Members 452
- 17.18 LINEs Use an Endonuclease to Generate a Priming End 452
- 17.19 Summary 454

Chapter 18. Somatic Recombination and Hypermutation in the Immune System 459

- 18.1 The Immune System: Innate and Adaptive Immunity 462
- 18.2 The Innate Response Utilizes Conserved Recognition
 Molecules and Signaling Pathways 463
- 18.3 Adaptive Immunity 466
- 18.4 Clonal Selection Amplifies Lymphocytes That Respond to a Given Antigen 468
- 18.5 Ig Genes Are Assembled from Discrete DNA Segments in B Lymphocytes 469
- 18.6 L Chains Are Assembled by a Single Recombination Event 471
- 18.7 H Chains Are Assembled by Two Sequential Recombination Events 472
- 18.8 Recombination Generates Extensive Diversity 473
- **18.9** V(D)J DNA Recombination Uses RSS and Occurs by Deletion or Inversion 475
- **18.10** Allelic Exclusion Is Triggered by Productive Rearrangements 476
- **18.11** RAG1/RAG2 Catalyze Breakage and Religation of V(D)J Gene Segments 478
- **18.12** B Cell Differentiation: Early IgH Chain Expression Is Modulated by RNA Processing 480
- 18.13 Class Switching Is Effected by DNA Recombination (Class Switch DNA Recombination [CSR]) 481
- 18.14 CSR Involves AID and Elements of the NHEJ Pathway 483
- 18.15 Somatic Hypermutation (SHM) Generates Additional Diversity 484
- 18.16 SHM Is Mediated by AID, Ung, Elements of the Mismatch DNA Repair (MMR) Machinery, and Translesion DNA Synthesis (TLS) Polymerases 486

- **18.17** Chromatin Modification in V(D)J Recombination, CSR, and SHM 487
- **18.18** Expressed Igs in Avians Are Assembled from Pseudogenes 488
- 18.19 B Cell Differentiation in the Bone Marrow and the Periphery: Generation of Memory B Cells Enables a Prompt and Strong Secondary Response 489
- **18.20** The T Cell Receptor for Antigen (TCR) Is Related to the BCR 492
- **18.21** The TCR Functions in Conjunction with the MHC 493
- 18.22 The Major Histocompatibility Complex (MHC) Locus Comprises a Cohort of Genes Involved in Immune Recognition 495
- **18.23** Summary 498

References 499

PART 3. TRANSCRIPTION AND POSTTRANSCRIPTIONAL MECHANISMS 508

Chapter 19. Prokaryotic Transcription 509

Edited by Richard Gourse

- 19.1 Introduction 511
- 19.2 Transcription Occurs by Base Pairing in a "Bubble" of Unpaired DNA 512
- 19.3 The Transcription Reaction Has Three Stages 513
- 19.4 Bacterial RNA Polymerase Consists of Multiple Subunits 515
- 19.5 RNA Polymerase Holoenzyme Consists of the Core Enzyme and Sigma Factor 516
- 19.6 How Does RNA Polymerase Find Promoter Sequences? 517
- 19.7 The Holoenzyme Goes Through Transitions in the Process of Recognizing and Escaping from Promoters 518
- 19.8 Sigma Factor Controls Binding to DNA by
 Recognizing Specific Sequences in Promoters 519
- 19.9 Promoter Efficiencies Can Be Increased or Decreased by Mutation 521
- 19.10 Multiple Regions in RNA Polymerase Directly Contact Promoter DNA 523

[19.11]	RNA Polymerase–Promoter and DNA–Protein Interactions Are the Same for Promoter Recognition	(20.11)	Gene Expression Is Demethylation 56
	and DNA Melting 525	20.12	CpG Islands Are Reg
[19.12]	Interactions Between Sigma Factor and Core RNA Polymerase Change During Promoter Escape 528		Summary 573
19.13	A Model for Enzyme Movement Is Suggested by the Crystal Structure 529		ces 574
[19.14]	A Stalled RNA Polymerase Can Restart 531	Proce	t er 21. RNA Sp ssing 578
19.15	Bacterial RNA Polymerase Terminates at Discrete Sites 531		Introduction 580
19.16	How Does Rho Factor Work? 533	21.2	The 5' End of Eukar
19.17	Supercoiling Is an Important Feature of Transcription 535		Nuclear Splice Sites Splice Sites Are Rea
19.18	Phage T7 RNA Polymerase Is a Useful Model System 536		Pre-mRNA Splicing
19.19	Competition for Sigma Factors Can Regulate Initiation 537	21.6	
19.20	Sigma Factors May Be Organized into Cascades 539		Pathway 588
[19.21]	Sporulation Is Controlled by Sigma Factors 540	21.8	occurred the format of the contract of the con
	Antitermination Can Be a Regulatory Event 542	21.9	An Alternative Splic to Process the Mino
	Summary 544 ces 545	21.10	Pre-mRNA Splicing I with Group II Autoc
Chant	tor 20 Fulsamentia Transportation 5/0	21.11	Splicing Is Tempora

Chapter 20. Eukaryotic Transcription 549

- 20.1 Introduction 550
- 20.2 Eukaryotic RNA Polymerases Consist of Many Subunits 552
- **20.3** RNA Polymerase I Has a Bipartite Promoter 554
- **20.4** RNA Polymerase III Uses Downstream and Upstream Promoters 555
- 20.5 The Start Point for RNA Polymerase II 557
- **20.6** TBP Is a Universal Factor 558
- 20.7 The Basal Apparatus Assembles at the Promoter 561
- 20.8 Initiation Is Followed by Promoter Clearance and Elongation 564
- 20.9 Enhancers Contain Bidirectional Elements That Assist Initiation 567
- 20.10 Enhancers Work by Increasing the Concentration of Activators Near the Promoter 568

- Associated with
- gulatory Targets 571

olicing and

- ryotic mRNA Is Capped 581
- Are Short Sequences 583
- d in Pairs 584
- Proceeds Through a Lariat 585
- d for Splicing 586
- mRNA to the Splicing
- sembly Pathway 591
- eosome Uses Different snRNPs r Class of Introns 593
- Likely Shares the Mechanism catalytic Introns 594
- lly and Functionally Coupled with Multiple Steps in Gene Expression 596
- 21.12 Alternative Splicing Is a Rule, Rather Than an Exception, in Multicellular Eukaryotes 598
- 21.13 Splicing Can Be Regulated by Exonic and Intronic Splicing Enhancers and Silencers 601
- 21.14 trans-Splicing Reactions Use Small RNAs 602
- **21.15** The 3' Ends of mRNAs Are Generated by Cleavage and Polyadenylation 605
- **21.16** 3' mRNA End Processing Is Critical for Termination of Transcription 607
- **21.17** The 3' End Formation of Histone mRNA Requires U7 snRNA 608
- 21.18 tRNA Splicing Involves Cutting and Rejoining in Separate Reactions 609
- 21.19 The Unfolded Protein Response Is Related to tRNA Splicing 612

- **21.20** Production of rRNA Requires Cleavage Events and Involves Small RNAs 613
- **21.21** Summary 616

Chapter 22. mRNA Stability and Localization 622

Edited by Ellen Baker

- 22.1 Introduction 623
- 22.2 Messenger RNAs Are Unstable Molecules 625
- Eukaryotic mRNAs Exist in the Form of mRNPs from Their Birth to Their Death 626
- Prokaryotic mRNA Degradation Involves Multiple Enzymes 627
- 22.5 Most Eukaryotic mRNA Is Degraded via Two
 Deadenylation-Dependent Pathways 629
- 22.6 Other Degradation Pathways Target Specific mRNAs 631
- 22.7 mRNA-Specific Half-Lives Are Controlled by Sequences or Structures Within the mRNA 633
- 22.8 Newly Synthesized RNAs Are Checked for Defects via a Nuclear Surveillance System 635
- Quality Control of mRNA Translation Is Performed by Cytoplasmic Surveillance Systems 636
- **22.10** Translationally Silenced mRNAs Are Sequestered in a Variety of RNA Granules 639
- 22.11 Some Eukaryotic mRNAs Are Localized to Specific Regions of a Cell 640
- **22.12** Summary 643

References 644

Chapter 23. Catalytic RNA 647

Edited by Douglas J. Briant

- 23.1 Introduction 648
- 23.2 Group I Introns Undertake Self-Splicing by Transesterification 649
- 23.3 Group I Introns Form a Characteristic Secondary Structure 651
- 23.4 Ribozymes Have Various Catalytic Activities 653
- 23.5 Some Group I Introns Encode Endonucleases That Sponsor Mobility 655

- 23.6 Group II Introns May Encode Multifunction Proteins 657
- 23.7 Some Autosplicing Introns Require Maturases 658
- 23.8 The Catalytic Activity of RNase P Is Due to RNA 659
- 23.9 Viroids Have Catalytic Activity 659
- 23.10 RNA Editing Occurs at Individual Bases 661
- 23.11 RNA Editing Can Be Directed by Guide RNAs 663
- 23.12 Protein Splicing Is Autocatalytic 665
- **23.13** Summary 667

References 667

Chapter 24. Translation 671

- 24.1 Introduction 673
- Translation Occurs by Initiation, Elongation, and Termination 674
- 24.3 Special Mechanisms Control the Accuracy of Translation 676
- 24.4 Initiation in Bacteria Needs 30S Subunits and Accessory Factors 677
- 24.5 Initiation Involves Base Pairing Between mRNA and rRNA 679
- 24.6 A Special Initiator tRNA Starts the Polypeptide
- Use of fMet-tRNA_f Is Controlled by IF-2 and the Ribosome 681
- 24.8 Small Subunits Scan for Initiation Sites on Eukaryotic mRNA 683
- **24.9** Eukaryotes Use a Complex of Many Initiation Factors 684
- **24.10** Elongation Factor Tu Loads Aminoacyl-tRNA into the A Site 687
- 24.11 The Polypeptide Chain Is Transferred to Aminoacyl-tRNA 688
- 24.12 Translocation Moves the Ribosome 689
- **24.13** Elongation Factors Bind Alternately to the Ribosome 690
- 24.14 Three Codons Terminate Translation 692
- **24.15** Termination Codons Are Recognized by Protein Factors 693

24.16 Ribosomal RNA Pe	ervades Both Ribosomal	25.16 Frameshifting Occurs at Slippery Sequences 738
Subunits 694	Constant Control Con	25.17 Other Recoding Events: Translational Bypassing and
	Several Active Centers 698	the tmRNA Mechanism to Free Stalled Ribosomes 740
	n Active Role in Translation 700	25.18 Summary 741
	otidyl Transferase Activity 702	References 742
24.20 Ribosomal Structu Come Together	ures Change When the Subunits 704	PART 4. GENE REGULATION 744
24.21 Translation Can B	e Regulated 704	FART 4. GENE REGULATION 744
24.22 The Cycle of Bacto	erial Messenger RNA 705	Chapter 26. The Operon 745
24.23 Summary 708		Edited by Liskin Swint-Kruse
References 709		26.1 Introduction 747
Chapter 25. Using	the Genetic Code 714	26.2 Structural Gene Clusters Are Coordinately Controlled 750
25.1 Introduction 71	E	26.3 The <i>lac</i> Operon Is Negative Inducible 751
	epresent Chemically Similar	26.4 lac Repressor Is Controlled by a Small-Molecule Inducer 752
25.3 Codon–Anticodon Wobbling 717		26.5 cis-Acting Constitutive Mutations Identify the Operator 754
	sed from Longer Precursors 719	26.6 <i>trans</i> -Acting Mutations Identify the Regulator Gene 754
25.5 tRNA Contains Mo	dified Bases 720	26.7 <i>lac</i> Repressor Is a Tetramer Made of Two Dimers 756
	fect Anticodon–Codon Pairing 722	26.8 <i>lac</i> Repressor Binding to the Operator Is Regulated by an Allosteric Change in Conformation 758
Code 723	c Alterations of the Universal	
25.8 Novel Amino Acids	s Can Be Inserted at Certain Stop	<pre>26.9 lac Repressor Binds to Three Operators and Interacts with RNA Polymerase 759</pre>
25.9 tRNAs Are Charged	d with Amino Acids by Aminoacyl-	26.10 The Operator Competes with Low-Affinity Sites to Bind Repressor 760
tRNA Synthetases 25.10 Aminoacyl-tRNA S		26.11 The <i>lac</i> Operon Has a Second Layer of Control: Catabolite Repression 762
Classes 728		26.12 The <i>trp</i> Operon Is a Repressible Operon with Three Transcription Units 764
25.11 Synthetases Use P Accuracy 730	roofreading to Improve	26.13 The <i>trp</i> Operon Is Also Controlled by
25.12 Suppressor tRNAs Read New Codons	Have Mutated Anticodons That 732	Attenuation 766 26.14 Attenuation Can Be Controlled by Translation 767
25.13 There Are Nonsens Termination Codon		26.15 Stringent Control by Stable RNA Transcription 770
25.14 Suppressors May Co	ompete with Wild-Type Reading of	26.16 r-Protein Synthesis Is Controlled by Autoregulation 771
the Code 734		26.17 Summary 773
25.15 The Ribosome Influence Translation 736	uences the Accuracy of	References 774

Contents

xvi

Chapter 27. Phage Strategies 777

- **27.1** Introduction 779
- 27.2 Lytic Development Is Divided into Two Periods 780
- **27.3** Lytic Development Is Controlled by a Cascade 781
- 27.4 Two Types of Regulatory Events Control the Lytic Cascade 782
- **27.5** The Phage T7 and T4 Genomes Show Functional Clustering 783
- 27.6 Lambda Immediate Early and Delayed Early Genes Are Needed for Both Lysogeny and the Lytic Cycle 784
- **27.7** The Lytic Cycle Depends on Antitermination by pN 785
- 27.8 Lysogeny Is Maintained by the Lambda Repressor Protein 787
- **27.9** The Lambda Repressor and Its Operators Define the Immunity Region 788
- **27.10** The DNA-Binding Form of the Lambda Repressor Is a Dimer 788
- **27.11** Lambda Repressor Uses a Helix-Turn-Helix Motif to Bind DNA 790
- **27.12** Lambda Repressor Dimers Bind Cooperatively to the Operator 791
- 27.13 Lambda Repressor Maintains an Autoregulatory Circuit 792
- **27.14** Cooperative Interactions Increase the Sensitivity of Regulation 793
- **27.15** The cII and cIII Genes Are Needed to Establish Lysogeny 795
- 27.16 A Poor Promoter Requires cII Protein 796
- 27.17 Lysogeny Requires Several Events 796
- 27.18 The Cro Repressor Is Needed for Lytic Infection 798
- **27.19** What Determines the Balance Between Lysogeny and the Lytic Cycle? 800
- **27.20** Summary 801

References 802

Chapter 28. Eukaryotic Transcription Regulation 804

- 28.1 Introduction 805
- 28.2 How Is a Gene Turned On? 807

- 28.3 Mechanism of Action of Activators and Repressors 808
- 28.4 Independent Domains Bind DNA and Activate Transcription 811
- 28.5 The Two-Hybrid Assay Detects Protein-Protein Interactions 812
- 28.6 Activators Interact with the Basal Apparatus 813
- 28.7 There Are Many Types of DNA-Binding Domains 815
- 28.8 Chromatin Remodeling Is an Active Process 817
- 28.9 Nucleosome Organization or Content May Be Changed at the Promoter 820
- **28.10** Histone Acetylation Is Associated with Transcription Activation 822
- 28.11 Methylation of Histones and DNA Is Connected 825
- **28.12** Promoter Activation Involves Multiple Changes to Chromatin 826
- **28.13** Histone Phosphorylation Affects Chromatin Structure 827
- 28.14 Yeast GAL Genes: A Model for Activation and Repression 829
- **28.15** Summary 831

References 833

Chapter 29. Epigenetic Effects Are Inherited 838

Edited by Trygve Tollefsbol

- 29.1 Introduction 839
- **29.2** Heterochromatin Propagates from a Nucleation Event 841
- 29.3 Heterochromatin Depends on Interactions with Histones 842
- **29.4** Polycomb and Trithorax Are Antagonistic Repressors and Activators 845
- 29.5 X Chromosomes Undergo Global Changes 847
- 29.6 Chromosome Condensation Is Caused by Condensins 850
- 29.7 CpG Islands Are Subject to Methylation 853
- **29.8** DNA Methylation Is Responsible for Imprinting 856

xvii

- 29.9 Oppositely Imprinted Genes Can Be Controlled by a Single Center 858
- 29.10 Epigenetic Effects Can Be Inherited 859
- 29.11 Yeast Prions Show Unusual Inheritance 861
- 29.12 Prions Cause Diseases in Mammals 864
- **29.13** Summary 865

Chapter 30. Regulatory RNA 872

- **30.1** Introduction 873
- 30.2 A Riboswitch Can Alter Its Structure According to Its Environment 874
- 30.3 Noncoding RNAs Can Be Used to Regulate Gene Expression 875

- **30.4** Bacteria Contain Regulator RNAs 878
- 30.5 MicroRNAs Are Widespread Regulators in Eukaryotes 881
- 30.6 How Does RNA Interference Work? 884
- 30.7 Heterochromatin Formation Requires
 MicroRNAs 887
- **30.8** Summary 888

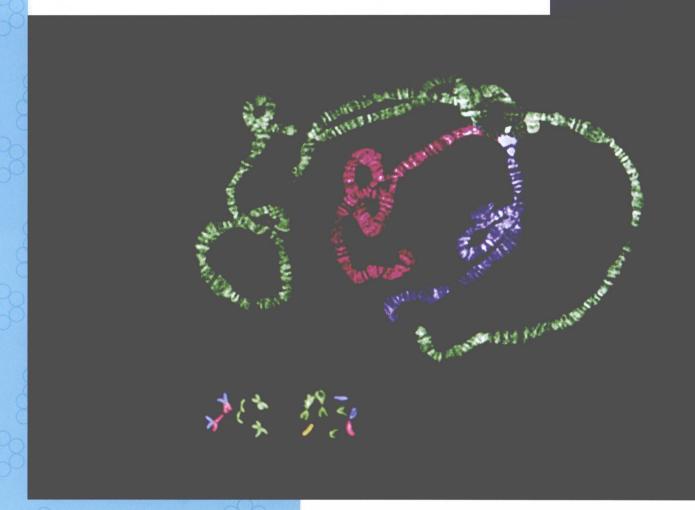
References 890

Glossary 894

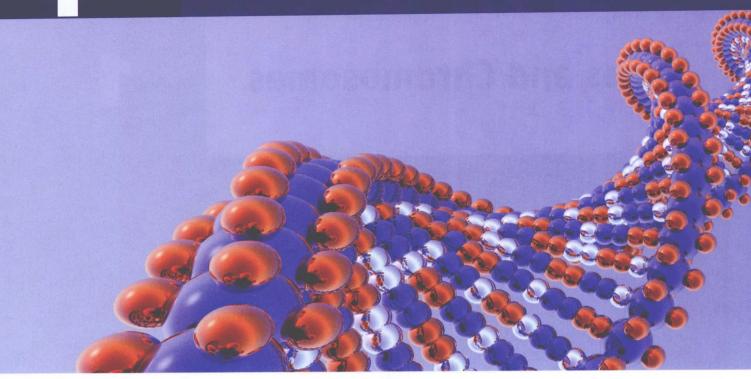
Index 920

1

Genes and Chromosomes



CHAPTER 1 Genes Are DNA CHAPTER 2 Genes Encode RNAs and Polypeptides CHAPTER 3 Methods in Molecular Biology and Genetic Engineering **CHAPTER 4** The Interrupted Gene CHAPTER 5 The Content of the Genome CHAPTER 6 Genome Sequences and Gene Numbers CHAPTER 7 Clusters and Repeats **CHAPTER 8** Genome Evolution CHAPTER 9 Chromosomes CHAPTER 10 Chromatin



Genes Are DNA

CHAPTER OUTLINE

- 1.1 Introduction
- 1.2 DNA Is the Genetic Material of Bacteria and Viruses
 - Bacterial transformation provided the first support that DNA is the genetic material of bacteria. Genetic properties can be transferred from one bacterial strain to another by extracting DNA from the first strain and adding it to the second strain.
 - Phage infection showed that DNA is the genetic material of viruses. When the DNA and protein components of bacteriophages are labeled with different radioactive isotopes, only the DNA is transmitted to the progeny phages produced by infecting bacteria.
- 1.3 DNA Is the Genetic Material of Eukaryotic Cells
 - DNA can be used to introduce new genetic traits into animal cells or whole animals.
 - In some viruses, the genetic material is RNA.
- 1.4 Polynucleotide Chains Have Nitrogenous Bases Linked to a Sugar-Phosphate Backbone
 - A nucleoside consists of a purine or pyrimidine base linked to the 1' carbon of a pentose sugar.
 - The difference between DNA and RNA is in the group at the 2' position of the sugar. DNA has a deoxyribose sugar (2'-H); RNA has a ribose sugar (2'-OH).

- A nucleotide consists of a nucleoside linked to a phosphate group on either the 5' or 3' carbon of the (deoxy)ribose.
- Successive (deoxy)ribose residues of a polynucleotide chain are joined by a phosphate group between the 3' carbon of one sugar and the 5' carbon of the next sugar.
- One end of the chain (conventionally written on the left) has a free 5' end and the other end of the chain has a free 3' end.
- DNA contains the four bases adenine, guanine, cytosine, and thymine; RNA has uracil instead of thymine.
- 1.5 Supercoiling Affects the Structure of DNA
 - Supercoiling occurs only in "closed" DNA with no free ends.
 - Closed DNA is either circular DNA or linear DNA in which the ends are anchored so that they are not free to rotate.
 - A closed DNA molecule has a linking number (L), which is the sum of twist (T) and writhe (W).
 - The linking number can be changed only by breaking and reforming bonds in the DNA backbone.

DNA Is a Double Helix

 The B-form of DNA is a double helix consisting of two polynucleotide chains that run antiparallel.

CHAPTER OUTLINE, CONTINUED

- The nitrogenous bases of each chain are flat purine or pyrimidine rings that face inward and pair with one another by hydrogen bonding to form only A-T or G-C pairs.
- The diameter of the double helix is 20 Å, and there is a complete turn every 34 Å, with 10 base pairs per turn (~10.4 base pairs per turn in solution).
- The double helix has a major (wide) groove and a minor (narrow) groove.
- 1.7 DNA Replication Is Semiconservative
 - The Meselson-Stahl experiment used "heavy" isotope labeling to show that the single polynucleotide strand is the unit of DNA that is conserved during replication.
 - Each strand of a DNA duplex acts as a template for synthesis of a daughter strand.
 - The sequences of the daughter strands are determined by complementary base pairing with the separated parental strands.
- Polymerases Act on Separated DNA Strands at the Replication Fork
 - Replication of DNA is undertaken by a complex of enzymes that separate the parental strands and synthesize the daughter strands.
 - The replication fork is the point at which the parental strands are separated.
 - The enzymes that synthesize DNA are called DNA polymerases.
 - Nucleases are enzymes that degrade nucleic acids; they include DNases and RNases and can be categorized as endonucleases or exonucleases.
- Genetic Information Can Be Provided by DNA or RNA
 - Cellular genes are DNA, but viruses may have genomes of RNA.
 - DNA is converted into RNA by transcription, and RNA may be converted into DNA by reverse transcription.
 - The translation of RNA into protein is unidirectional.
- 1.10 Nucleic Acids Hybridize by Base Pairing
 - Heating causes the two strands of a DNA duplex to separate.
 - The T_m is the midpoint of the temperature range for denaturation.
 - Complementary single strands can renature when the temperature is reduced.
 - Denaturation and renaturation/hybridization can occur with DNA-DNA, DNA-RNA, or RNA-RNA combinations and can be intermolecular or intramolecular.

- The ability of two single-stranded nucleic acids to hybridize is a measure of their complementarity.
- 1.11 Mutations Change the Sequence of DNA
 - All mutations are changes in the sequence of DNA.
 - Mutations may occur spontaneously or may be induced by mutagens.
- 1.12 Mutations May Affect Single Base Pairs or Longer Sequences
 - · A point mutation changes a single base pair.
 - Point mutations can be caused by the chemical conversion of one base into another or by errors that occur during replication.
 - A transition replaces a G-C base pair with an A-T base pair or vice versa.
 - A transversion replaces a purine with a pyrimidine, such as changing A-T to T-A.
 - Insertions and/or deletions can result from the movement of transposable elements.
- 1.13 The Effects of Mutations Can Be Reversed
 - Forward mutations alter the function of a gene, and back mutations (or revertants) reverse their effects.
 - Insertions can revert by deletion of the inserted material, but deletions cannot revert.
 - Suppression occurs when a mutation in a second gene bypasses the effect of mutation in the first gene.
- 1.14 Mutations Are Concentrated at Hotspots
 - The frequency of mutation at any particular base pair is statistically equivalent, except for hotspots, where the frequency is increased by at least an order of magnitude.
- 1.15 Many Hotspots Result from Modified Bases
 - A common cause of hotspots is the modified base 5-methylcytosine, which is spontaneously deaminated to thymine.
 - A hotspot can result from the high frequency of change in copy number of a short, tandemly repeated sequence
- 1.16 Some Hereditary Agents Are Extremely Small
 - Some very small hereditary agents do not encode polypeptide, but consist of RNA or protein with heritable properties.
- 1.17 Summary

1.1 Introduction

The hereditary basis of every living organism is its **genome**, a long sequence of deoxyribonucleic acid (DNA) that provides the complete set of hereditary information carried by the organism as well as its individual cells.

The genome includes chromosomal DNA as well as DNA in plasmids and (in eukaryotes) organellar DNA, as found in mitochondria and chloroplasts. We use the term *information* because the genome does not itself perform an active role in the development of