
Index

A

ABO locus, 19
Actin, 121–122, 127, 134
Activation, 67
Activator, 157
 AraC, 148–149, 151–152
 catabolite activator protein (CAP), 150
Adams, Alison E.M., 122, 128
Adaptors, 92, 104
Adenosine triphosphate (ATP), 47
AFLPs (amplified fragment length polymorphisms), 12
Age-related macular degeneration, 203
Agglutination of red blood cells, 19
Alkaptonuria, 185–186
Allele frequencies, 183
Alleles, 12–14
 inferring human gene function from
 disease alleles, 195–206
 mutant, 13, 20–22, 24–27
 null, 14, 26, 28–29
 pseudoalleles, 28
 wild-type, 13–14
Allelism, 12–13, 38
Allelomorph, 12
Allosteric activation, 64
Allosteric inhibition, 63
Allosteric interaction, mutations affecting, 200–201
Allosteric modulation, 64
Amber mutations, 110
Ameliorating interaction, 134
Amino acids
 genetic code, 87, 91–92, 92t
 in metabolic pathways, 61
 number in typical proteins, 94
Amorph, 27
Amplified fragment length polymorphisms (AFLPs), 12

Andrews, Brenda J., 135–136
Annotation, genome, 167
Anticodon, 92, 115
Anti-correlation coefficient, 38
Antimorph, 27
Antitermination, 149
Arabinose (*ara*) operon in *E. coli*, 148–150, 151–152
AraC, 148–149, 151–152
Arginine biosynthesis, 124–125, 124f
Autozygosity, 186
Auxotrophs, 49–50, 53, 106–112, 131

B

Backcross, 18
Back mutation, 105
Bacteria, coupling of transcription and translation, 139
Bacteriophage λ , 118–119
Bacteriophage T4
 genome, 71–73
 infection process, 71
 morphogenesis and assembly pathways, 52–55, 54f
 protein biosynthesis regulation, 138
 rII system, 72
 fine-structure mapping, 78–80
 mutations, 71, 74, 78–81, 95, 107, 111–112, 114
 polycistronic mRNA, 144
 r phenotypes, 75
Balanced reciprocal translocations, 97
Base-pairing, 88, 92–93
Bateson, William, 8, 12, 15, 57, 133, 184–185
Benzer, Seymour, 6, 12, 17
 biography, 84
 cis-trans test, 81–83, 82f
 function gene definition, 81–83, 84
 phage studies by, 71–74, 78–81, 83, 95, 111

- Bernard, Claude, 69
 β -galactosidase, 141, 143–146, 159, 207
 β -galactoside permease, 141, 143–145
 β -galactoside transacetylase, 141, 143–145
 β -globin genes/proteins, 20–22, 172–173
Biochemical reactions, 47. *See also* Metabolic pathways
Biotechnology, 157–160
Blood types, human, 19
Boone, Charlie M., 135–136
BRCA1 alleles, 23–24
Breast cancer, 23–24
Brenner, Sydney, 114–115
Bridges, Calvin, 97, 104
Brown, Michael, 198, 206
Bypass suppressors, 124–125, 124f
- C**
- Caenorhabditis elegans*, sex determination in, 127
CAG repeats, 199, 205–206
cAMP (cyclic AMP), 150
Cancer
 amplification of genomic sequences, 101
 applications of genetics and genomics, 209
 causative mutation, 10
 loss of heterozygosity and, 201–202
 oncogenes, 175, 200
 point mutations and, 175
 TP53 gene mutation, 14
 translocations and, 98, 162
 tumor cell selection assays, 161–163
 tumor-suppressor genes, 102, 162, 175, 196, 200, 201–202, 206
 virus integration into genome, 100
Cannon, Walter, 68–69
Catabolite activator protein (CAP), 150, 155
Catalysis, by enzymes, 47, 48, 49f
CCR5 gene, 210
Cell cycle, 123
Centimorgan, 37
Chain-termination mutations, 96
Chaperone protein, 118
Chemokine receptor, 210
Chemostat, 62
Chlamydomonas reinhardtii, flagella of, 125–126
Cholesterol homeostasis, 210
Chorismic acid, 63, 63f
Chromosomal rearrangements, 161–162, 171
Chromosomes
 gain and loss of entire, 162
 recombination, 100–103, 102f
 translocations, 97–98, 98f, 161–162
cis-acting elements, regulation and, 156–157, 162
cis-acting regulatory sites, 177, 202
cis-dominance, 114, 145–146, 157
cis-trans test, 17, 114
 Benzer and, 81–83, 82f
 cis-dominance, 145–146
 Lewis and Pontecorvo, 81, 84
Cistron, 91
 cis-trans test and, 17, 82–83
 defined, 82–84
 polycistronic messenger RNA (mRNA), 142
Coding strand, 87, 92–93, 139
CODIS, 11–12
Codominance, 19, 21, 36
Codons, 87, 91–92, 92f
Coinfections, phage, 75–76, 78
Cold-sensitive (Cs) mutations, 119–121
Combinatorial regulation, 150–151
Combined DNA Index System (CODIS), 11–12
Complementation, 13, 27–29
Complementation group, 28
Complementation tests. *See also cis-trans* test
 araC cistron, 151
 in phage crosses, 75
 suppressor mutations and, 120, 125
 T4 conditional-lethal mutants, 53
Complement factor H, 203
Complex phenotypes, 131–136
 disease phenotypes, 203–205
 epistasis, 133
 gene interactions, 134
 genetic heterogeneity, 131–132
 genome-scale genetic interactions in yeast, 134–136, 135f
 polygenic inheritance, 132
 quantitative traits, 132
 synthetic phenotypes, 132–133
Compound heterozygote, 27–29
Conditional-lethal mutations, 52–53, 74–75, 77, 107, 119–120, 122–123
Consanguinity, 184
Conserved DNA
 conservation of functional sequences, 167–169
 phenotypic effects of mutations in, 174–179

- Constitutive, 141
Constitutive mutants, 141
 Lac system, 141, 143–145
Copy number variants (CNVs), 98–99, 161–162,
 171, 202, 205
Corepressors, 148, 155
Correns, Carl Erich, 15
Crick, Francis, 92, 100, 104, 114
Cross-feeding, 50–51, 51f, 55, 56
Crossing over, 31, 34, 34f, 36, 101, 102f,
 187–189
Cyclic AMP (cAMP), 150
Cyclins, 123
Cystic fibrosis, 44, 183
Cytological analysis, 97
Cytoskeleton, 121–122, 125–126
- D**
- Darwin, Charles, 10, 15
Databases
 genome sequences, 167
 human mutations, 14, 175
Degeneracy, genetic code, 91–92, 177
Delbrück, Max, 84
Deletions (deletion mutations), 13–14, 175
 definition, 80
 gene knockout, 196
 in laboratory selection assays, 162
 lac operon genes, 146–147, 147f
 nonreverting T4 *rII* mutants, 79–80
 null alleles, 14, 26
De novo mutations, 205
de Vries, Hugo, 9, 15
Dihybrid cross, 32, 33f
Diploid, 5–6, 8, 72
Direct repetition, 101
Disease, inferring human gene function from
 alleles, 195–206
 complex disease phenotypes,
 203–205
 simple Mendelian disease phenotypes,
 195–202
DNA
 replication, 88, 157
 structure, 88, 89f
 transcription, 89–91, 90f
dnaB, 118–119
DNA polymerase, 153
DNA polymorphisms, 10, 11, 38–42, 39f–41f, 44,
 187, 190. *See also* Polymorphisms
 as genetic markers, 13
 haplotype, 42–43
 in *TP53* gene, 14
 linkage mapping, 11, 196
 linkage phase, 42, 43f
 segregation of polymorphic loci
 single locus, 39–40, 39f
 three loci, 41, 41f
 two loci, 40, 40f
DNA recombination. *See* Recombination
DNA repair, 101, 103
DNA sequence variant, 10, 11
DNA variants, 9–14
 alleles, 12–14
 mutations, 9–10
 polymorphisms, 10–12
Dobzhansky, Theodosius, 1, 14, 132
Domain architecture of proteins and their genes,
 163–166, 164f
Dominance, 17–22, 24–27
 biological interpretation of, 24–27
 cis-dominance, 114, 145–146, 157
 codominance, 19, 21
 definition, 18
 gain-of-function, 25
 genomic rearrangements and, 202
 haploinsufficiency, 26
 implicit experiment and determination of,
 17–20
 incomplete (partial) dominance, 19
 loss of heterozygosity and, 201–202
 mutant allele relationship to wild-type allele,
 20–22, 24–27
 nonsense suppressors, 112
 overdominance, 21–22
 in phage crosses, 75
Dominant disease phenotypes, 199
Dominant-negative mutation, 26, 27
Dosage suppression, 122–123
Double crossovers, 37
Double helix, DNA, 88, 89f
Double mutant analysis
 in metabolic pathways, 50–52, 51f, 57
 in regulatory and signal transduction
 pathways, 55–56, 56f, 57
 as test of epistasis, 57
Downstream, 48, 139
Down syndrome, 204
Drosophila melanogaster, genome of, 169
Dulbecco, Renato, 73
Duplication
 gene, 27, 171–172, 202
 whole-genome, 173

E

E. coli

- as prototroph, 48
- genome size, 169
- human protein production in, 157–159
- induction-repression mechanisms in, 67

Edgar, Robert S., 52–53, 57

Effect size, 191

Eisen, Michael, 170, 179

Elongation, 154

End-product inhibition, 62–65, 65f, 66, 67

Energy, 47

Englesberg, Ellis, 148, 152

Enhancers, 151, 157

Enzymes, 47–51

- metabolic regulation at level of enzyme activity, 62–65
- metabolic regulation at level of enzyme synthesis, 65–67

Epidermal growth factor domain, t-PA, 164–165, 164f

Epigenetics, 208

Epistasis, 57, 133

Eugenic laws, 183

Evolution, 1, 4

- as compromise, 163
- consequences of genome architecture, 160–163
- conservation of functional sequences, 167–169
- domain architecture of proteins and their genes, 163–166, 164f
- duplication and divergence of genes, 171–172
- neutral theory of molecular evolution, 170–171
- phenotypic effects of mutations in conserved DNA, 174–179
- of replication, transcription and translation machinery, 153
- tree of life, 168f

Exacerbating interaction, 134

Exome sequencing, 204

Exons, 91, 165, 176

Experimental organisms, 3–4, 14, 182

Expression microarray, 207

Expressivity, 23–24

Extragenic suppressor, 106

F

Familial hypercholesterolemia, 198

Fanconi anemia, 131–132

FBI Combined DNA Index System (CODIS), 11–12

Feedback inhibition, 61, 66

- allosteric interactions, 63–64
- example, 64–65, 65f
- in tryptophan biosynthesis, 62–63
- speed and reversibility of, 67
- usage of term, 63

Feldman, Marc, 170, 179

Fibrin, 163–165

Fibronectin finger domain, t-PA, 164–165, 164f

Fimbrin, 122, 134

Fine-structure mapping, bacteriophage T4, 78–80

Fisher, Ronald, 43, 46, 133

Fitch, Walter, 172, 179

5' untranslated region (5' UTR), 176, 177

Flagella, 125–126

FlyBase, 167

Fly room at Columbia University, 32, 46

Fragile X syndrome, 199

Frameshift mutations, 96–97, 112–115, 175

Friedreich's ataxia, 199

Function, 5, 6

Functional gene

- complementation and definition of, 27–29
- definition, 81–83, 84
- DNA polymorphisms and, 13
- evolutionary conservation of sequences, 170–174
- locus reconciled with, 80–81

Functional sequences, evolutionary conservation of, 167–179

Functional suppression, 117–128

- bacteriophage λ , 118–119
- dosage suppression, 122–123

Functional suppressors, 109

- bypass, 124–125, 124f
- mutual interaction, 121–122
- protein interaction, 117–119
- recessive, 125–127
- with novel phenotypes, 119–121

G

Gain-of-function mutation, 25, 200

Gametes, 8

Gametogenesis, 33

Garrod, Archibald, 184–185

Gene amplification, 202

Genecards, 14

- Gene conversion, 103
Gene duplication, 27, 171–172, 202
Gene expression, transcriptional regulation of, 137–152
Gene interactions, 134
Gene knock-in, 196
Gene knockout, 196
Genes, 12
 domain architecture of proteins and their genes, 163–166, 164f
 duplication and divergence of genes, 171–172
 functional definition, 6
 inferring human gene function from disease alleles, 195–206
 meaning of term, 6
 modular architecture of, 153–166
 number of, 169, 195
Gene set analysis, 204
Gene therapy, 100
Genetic analysis, 1–6, 8
 actin cytoskeleton, 121–122
 lactose utilization in *E. coli*, 140–141
 suppression and, 106–109
Genetic code, 87, 91–92, 92t
Genetic drift, 182
Genetic heterogeneity, 131–132
Genetic markers, DNA polymorphisms as, 13
Genetics
 applications of, 209–210
 future of, 207–210
 genomics distinguished from, 207
Genetic testing, DNA source for, 38–39
Genetic variation, 4–5
Genome(s)
 evolutionary consequences of genome architecture, 160–163
 modular architecture of, 153–166
 non-protein-encoding sequences, 169
 sequence databases, 167
 size of, 169
 whole-genome duplication, 173
Genome annotation, 167
Genome-wide association study (GWAS), 191–194, 192f, 193f, 203
Genomic rearrangements, 202
Genomics
 applications of, 209–210
 future of, 207–210
 genetics distinguished from, 207
Genomic sequence diversity, recombination and, 100–103, 102f
Genotype
 change (*see* Mutation)
 definition, 7
 penetrance and expressivity, 22–24
 phenotype connection, 22–24
Genotype frequencies, 183–184
Genotyping, 12
Georgopoulos, Costa, 118, 128
GFP (green fluorescent protein), 159–160, 160f
Gilbert, Walter, 90, 104
Globin genes, 172–173, 173f
Glutamic semialdehyde, 124–125, 124f
Goldstein, Joseph, 198, 206
Green fluorescent protein (GFP), 159–160, 160f
groE, 118–119
GTPases, 201
Gusella, James F., 199, 205, 206
GWAS. *See* Genome-wide association study
H
Haldane, J.B.S., 37, 45
Haploid, 6, 8, 72–73, 74
Haploinsufficiency, 26
Haplotype, 42–43, 189–191, 196
Haplotype blocks, 189–191
Hardy, Godfrey Harold, 182, 194
Hardy-Weinberg law (Hardy-Weinberg equilibrium), 182–185, 194
Hawthorne, Donald, 111–112, 115
HBB gene, 20–22, 172
Heat-sensitive mutations, 119–121
Hemizygote, 9
Hemoglobin, 172
 dominance relationships in β -globin (*HBB*) gene, 20–22
 hemoglobin A, 21
 hemoglobin S, 21
Hemophilia A, 10
Hershey, Alfred Day, 72, 74, 84
Herskowitz, Ira, 118, 128
Heterozygote
 compound, 27–29
 dominance and recessiveness, 17–22, 25–26
 codominance, 19, 21
 haploinsufficiency, 26
 human β -globin gene, 20–22
 incomplete (partial) dominance, 19
 simple, 17–18
 dominance via loss of heterozygosity, 201–202

- Heterozygote (*Continued*)
 hemizygote, 9
 usage of term, 8–9
 verification of genotype, 18
HGMD (Human Gene Mutation Database), 14, 175
HIV infection, 210
HLA locus, 193
Hodgkin, Jonathan, 127, 129
Homeostasis, regulation and, 66–67, 137
Homolog, 173, 173f
Homologous chromosomes, 34, 34f
Homologous (legitimate) recombination,
 100–101, 102f, 165
Homozygosity mapping, 186–187
Homozygote
 autozygosity, 186
 usage of term, 8
Host-range mutants, 74
HTT gene, 199
Huang, Bessie, 125–126, 128
Human β -globin (*HBB*) gene, 20–22, 172
Human blood types, 19
Human Gene Mutation Database (HGMD), 14,
 175
Human genome, number of protein-encoding
 genes, 169
Human population genetics, 181–194
Human protein production in *E. coli*, 157–159
Huntington's disease, 199, 205–206
Hybrid organisms, 8
Hypermorph, 27
Hypomorph, 27
Hypothesis testing, multiple, 203–204
Hypoxia, red blood cell sickling under, 21
- I**
- Identity by descent (IBD), 190
Illegitimate recombination, 102–103
Immunoglobulin E (IgE) deficiency, 209
Implicit experiment, 3, 17–29, 108
Inactivation, X chromosome, 178
Inborn error of metabolism, 185
Inbreeding, 184–186, 185f
Incomplete (partial) dominance, 19
Indels, 97. *See also* Deletions (deletion muta-
 tions); Insertion mutations
Independent assortment, 31–33, 41–42
Inducers
 in negative-control systems, 148
 in positive-control systems, 148–149
Inducible, 141
Inducible system, 149
Induction, 66
Informational suppressor, 109
Information flow, 88–94
Informativeness, 40
Inheritance
 complex modes of, 176
 patterns, 1–2
 polygenic, 132
Inherited disease
 genetic lesions causing, 175–176
 inferring human gene function from disease
 alleles, 195–206
Inhibition, 67
Initiation, 154, 155
Insertion mutations, 99, 103, 175
Insulin, human, 157, 159
Interallelic complementation, 29
Intragenic complementation, 29
Intragenic suppressor, 106
Intron-exon boundary elements, 176
Introns, 91, 164f, 165, 176
Inversions, 100, 101
Inverted repetition, 101
In vitro complementation, 53
- J**
- Jacob, François, 66, 68, 84, 139–147, 207
Jarvik, Jonathan W., 119–120, 128
Johannsen, Wilhelm, 6, 7, 15
- K**
- Kimura, Motoo, 170–171, 179
Knudson, Alfred, 200–202, 206
Koshland, Daniel E., Jr., 63, 68
KRAS oncogene, 200–201, 209
Kring domains, t-PA, 164–165, 164f
- L**
- Laboratory selection studies, 161–163
Lac repressor, 143, 144f, 145–148, 151, 155, 202
Lac system in *E. coli* (*lac* operon), 66, 155–157
 cis-dominance, 145–146
 coordinate expression of structural proteins,
 142
 deletions removing *lac* operon genes,
 146–147, 147f

- functional analysis of *lac* operon regulatory elements, 144–146
- genetic structure of *lac* operon, 142–144, 144f
- terminology, 140–141
- Law of mass action, 123
- Leakiness, of mutations, 79
- Lesch–Nyhan syndrome, 45
- Lewis, Edward B., 81, 84
- Li–Fraumeni syndrome, 14
- Likelihood ratio, 46
- Linkage, 31–33, 35
 - likelihood ratio, 46
- Linkage disequilibrium, 190–191, 196
- Linkage mapping, 11
 - disease identification by, 199
 - in human families, 38–43
 - haplotype, 42–43
 - independent assortment, 41–42
 - informativeness, 40
 - linkage phase, 42, 43f
 - Mendelian segregation, 39–40, 39f
 - using DNA polymorphisms, 196
- Linkage phase, 42, 43f, 190–191
- Locus, 12, 78
 - defining by failure to recombine, 38
 - definition and usage of term, 6
 - functional gene reconciled with, 80–81
 - measuring distance between loci by
 - recombination, 35–37
 - polymorphic, 13
- LOD (logarithm of the odds) score, 46, 132
- Logical operators, 156
- Long noncoding RNAs (lncRNAs), 178
- Loss-of-function phenotype/mutation, 25, 27, 49f, 56f, 105, 197–198, 200
 - araC*, 148, 152
 - auxotrophic mutation, 49
 - lac*, 144–145
 - temperature-sensitive mutation, 53
- Loss of heterozygosity, 200, 201–202
- Low-density lipoprotein receptor (*LDLR*) gene/protein, 194, 198–199
- Luria, Salvador, 84, 128
- Lysis, 71
- M**
- Maas, Werner K., 142, 152
- Macular degeneration, age-related, 203
- Major histocompatibility group, 193
- Malaria, 20–22
- Manhattan plots, 192–193, 192f, 193f
- MAPK protein, 123
- Mapping. *See also* Linkage mapping
 - Haldane's mapping function, 37
 - homozygosity, 186–187
 - linkage mapping in human families, 38–43
 - measuring distance between loci by
 - recombination, 35–37
- Maximum likelihood method, 44, 46
- McClintock, Barbara, 97, 99, 104
- Meiosis, 32, 34–35, 34f
 - crossing over, 34, 34f, 187–189
 - homologous recombination, 101
- Mendel, Gregor
 - biography, 15
 - central insight of, 5–6
 - dominance and recessiveness, 17–18
 - independent assortment, 31–33
 - innovations of, 1–2
 - word use by, 3, 5
- Mendelian segregation, 39–40, 39f
- Mendel's First Law, 39
- Mendel's Second Law, 40–41
- Messenger RNA (mRNA), 90–91
 - instability of, 91, 137–138
 - miRNA binding sites, 178
 - polycistronic, 142, 148
 - size, 176
 - splicing, 90–91, 139, 165
 - translation, 89, 90f, 91–94
- Metabolic pathways
 - analysis, 47–52
 - cross-feeding assay, 50–51, 51f, 55, 56
 - double mutants, use of, 50–52, 51f
 - terminology, 47–50
 - order of steps in, 50–52
 - regulation, 59–67
 - example, 64–65, 65f
 - at level of enzyme activity, 62–65
 - at level of enzyme synthesis, 65–67
 - posttranslational protein
 - modification, 64
 - schematic, 60f
- Methionine, 91
- Methylation, 64
- Microarrays, 190, 192, 207–208
- Micro-RNAs (miRNAs), 177, 178
- Microtubules, 125–126
- Missense mutations, 95, 175

- Mitotic recombination, 102
Model organisms, 195–196. *See also* Experimental organisms
Modular architecture of genes and genomes, 153–166
 biotechnology and, 157–160
 domain architecture of proteins and their genes, 163–166, 164f
 evolutionary consequences of genome architecture, 160–163
 initiation, elongation, and specificity in macromolecular synthesis, 153–156
 separable regulatory sites and coding sequences, 156–157
Moir, Donald T., 120, 128
Molecular biology, 87
Monod, Jacques, 63, 66, 68, 139–147, 207
Morgan, Thomas Hunt, 32, 37, 45, 104
Morphogenesis
 assembly pathways and, 52–55, 54f
 phage experiments, 119–120
Mortimer, Robert K., 111–112, 115
Mouse Genome Informatics, 167
mRNA. *See* Messenger RNA
Muller, Hermann, 9, 15, 27, 85
Multicellular organisms, genomes of, 169
Multiple hypothesis testing, 203–204
Mutant alleles
 dominance relationships, 20–22, 24–27
 null alleles, 26
 sources of, 13
Mutant phenotype, 10, 14
Mutation(s), 94–100
 auxotrophic, 49–50, 53, 106–112, 131
 back, 105
 causative, 9–10
 chain-termination, 96
 chromosomal rearrangements, 161–162, 171
 cis-acting, 157
 complementation analysis, 27–29
 conditional-lethal, 52–53, 74–75, 77, 107, 119–120, 122–123
 constitutive mutants, 141
 copy number variants (CNVs), 98–99, 161–162, 171, 202, 205
 databases on human, 14
 definition and usage of term, 9–10
 deleterious, 171
 deletions, 13–14, 26, 79–80, 146–147, 147f, 162, 175, 196
 de novo, 205
 dominant-negative, 26, 27
 dominant to wild type, 25
 enhancer and silencer, 151
 fixation of, 170–171
 frameshift, 96–97, 112–115, 175
 gain-of-function, 25, 200
 haploinsufficiency and, 26
 human gene, 14
 indels, 97
 insertion, 99, 103, 175
 inversions, 100
 loss-of-function, 25, 27, 49, 49f, 56f, 105, 197–198
 missense, 95, 175
 molecular taxonomy of simple, 94–97
 multipoint, 94
 neutral, 170–171, 174, 176
 nonsense, 96, 175
 nonsense suppressors, 109–112
 nucleotide expansion, 199
 null, 26, 28–29, 49–50, 49f, 96–97, 99
 nutritional, 106–112
 passenger, 196
 phage mutant phenotypes, 73–74
 phenotypic effects of mutations in conserved DNA, 174–179
 plaque morphology mutants, 73–74, 76–77, 76f
 point, 94–97, 161, 174–175
 promoter, 139–140, 146
 recessive, 24–25, 27–29, 151
 revertant frequency, 79
 RNA-splicing defects, 175, 176
 signal transduction and allosteric interaction, 200–201
 silent, 96
 somatic, 14
 strength of phenotype, 79
 substitution, 95
 synonymous, 95–96
 temperature-sensitive (Ts), 74–75, 119–121, 122, 127, 134
 translocations, 97–98, 98f, 161–162
 transposons, 99–100, 103, 202
 trinucleotide repeat alleles, 199–200, 205–206
Mutation rate, 105, 106, 182
Muton, 80
Mutual interaction suppressors, 121–122
Myopia, 192, 192f
Myotonic dystrophy, 199

N

Nasmyth, Kim A., 123, 128
Nearsightedness, 192, 192f
Negative control, 148
Neomorph, 27
Neurofibromatosis type 1, 23–24
Neurotransmitters, 61
Neutral mutation, 170–171, 174, 176
Neutral theory of molecular evolution, 170–171
NFI gene, 23–24
Noncoding RNAs, 177–179
Nonhomologous end joining, 102
Nonpermissive condition, 53, 75–79
Nonsense codons, 154
Nonsense mutations, 96, 175
Nonsense suppressors, 109–112
Novick, Aaron, 62–63, 68
Novick, Peter Jay, 127, 129, 134
Nucleotide expansion mutations, 199
Null alleles, 14, 26, 28–29, 198
Null mutation, 26, 28–29, 49–50, 49f, 96–97, 99
Null phenotype, 26, 174, 196
Nutritional mutation, 106–112

O

Ochre mutations, 110
Ohno, Susumu, 171, 179
Omalizumab, 209
OMIM (Online Mendelian Inheritance in Man), 14
Oncogenes, 175, 200
 KRAS, 200–201, 209
 proto-oncogenes, 200
 recessive, 102, 162, 200
Online Mendelian Inheritance in Man (OMIM), 14, 195
Opal mutations, 110
Open reading frame (ORF), 94
Operator, 155
 cis-acting mutations, 157
 lac, 143, 144f, 145, 147–148, 156
Operons
 arabinose (*ara*) operon in *E. coli*, 148–150, 151–152
 definition, 142
 Lac system in *E. coli*, 140–147, 144f, 147f
 positive control by antitermination, 149
Ortholog, 172–173, 173f, 195–196, 202
Ovarian cancer, 23–24
Overdominance, 21–22

P

Paralogs, 65, 122, 172, 173f, 174
Parental gametes, 36
Partial diploids, 144–146
Passenger mutations, 196
Pathways, 47–57. *See also* Metabolic pathways
 epistasis, 57
 morphogenesis and assembly pathways, 52–55, 54f
 regulatory and signal transduction, 55–57, 56f
Patterns of inheritance, 1–2
PCR (polymerase chain reaction), 12
PCSK9 gene, 210
Penetrance, 23–24
Permissive condition, 52–53, 75–78
Phage, 71–84. *See also specific bacteriophages*
 advantages of phage system for study, 73
 cistrons, 82–84
 coinfections, 75–76, 78
 complementation and recombination
 assessments in, 75–78, 76f
 gene and locus in T4, 72–73
 morphogenesis and assembly pathways, 52–55, 54f
 morphogenesis experiments, 119–120
 mutant phenotypes, 73–74
 recombination frequency, 76–77
 selective crosses, 77–78
Phenotypes. *See also specific phenotypes*
 causative mutation, 9–10
 complementation analysis, 27–29
 complex, 131–136
 complex disease, 203–205
 definition, 7
 dominance and recessiveness, 17–22, 24–27
 genotype connection, 22–24
 haploinsufficient, 26
 loss-of-function, 25, 105
 null, 26, 174, 196
 penetrance and expressivity, 22–24
 qualitative differences in, 23
 simple Mendelian disease phenotypes, 195–202
 strength of mutant, 79
 synthetic, 132–135
 wild type, 10
Phenotypic effects of mutations in conserved DNA, 174–179
 cis-acting regulatory sites, 177

- Phenotypic effects of mutations in conserved DNA (*Continued*)
 long noncoding RNAs (lncRNAs), 178
 micro-RNAs, 178
 noncoding RNAs, 177–179
 protein-coding sequences, 174–176
 transcribed noncoding sequences in genes that encode proteins, 176–177
- Philadelphia chromosome, 98, 98f, 162
- Phosphorylation, 64
- Phylogenetic tree, 168f
- PKD database, 201–202
- PKD1/PKD2* genes, 201–202
- Plaque, 74
- Plaque assay, 73–74, 75–77
- Plaque morphology mutants, 73–74, 76–77, 76f
- Plasmid, 158
- Plasmin, 163–164
- Plasminogen, 163–165
- Plasmodium falciparum*, 20–21
- Point mutations, 94–97, 161, 174–175
- Polycistronic messenger RNA (mRNA), 142, 148
- Polycystic kidney disease, 201–202
- Polygenic inheritance, 132
- Polymerase chain reaction (PCR), 12
- Polymorphisms, 10–12, 38–42, 39f–41f, 44, 187, 190
 amplified fragment length polymorphisms (AFLPs), 12
 definition and usage of term, 10
 DNA polymorphisms, 10, 11, 13, 14, 38–42, 39f–41f, 44, 187, 190
 as genetic markers, 13
 haplotype, 42–43
 linkage mapping, 11, 196
 linkage phase, 42, 43f
 restriction fragment length polymorphisms (RFLPs), 11, 13, 39
 segregation of polymorphic loci
 single locus, 39–40, 39f
 three loci, 41, 41f
 two loci, 40, 40f
 short tandem repeat (STR), 11–12, 13
 single-nucleotide polymorphism (SNP), 12, 186–192, 192f, 193f, 203–204
 variable number tandem repeat (VNTR), 11–12, 13, 39
- Polypeptide, cistron and, 83–84, 91
- Pontecorvo, Guido, 81, 84, 85
- Population genetics, human, 181–194
- Positive control, 148–149
- Positive selection, 171
- Posttranslational protein modification, 64
- Precursor (pre-) mRNA, 176
- Pringle, John, 128
- Proline biosynthesis, 124–125, 124f
- Promoter fusions, 159–160
- Promoters, 139–140
 human protein production in *E. coli*, 157–159
 lac, 143, 144f, 146, 156
 mutations, 146
 cis-acting, 157
 in laboratory selection assays, 162
 transcription initiation and, 154, 155
- Protease domain, t-PA, 164–165, 164f
- Protein fusions, 160
- Protein interaction suppressors, 117–119
- Proteins
 domain architecture of proteins and their genes, 163–166, 164f
 human protein production in *E. coli*, 157–159
 mRNA translation, 89, 90f, 91–94
 number of amino acids in typical, 94
 number of genes encoding, 169
 posttranslational protein modification, 64
 stability of, 138
 transcriptional regulation of gene expression, 137–152
- Proto-oncogenes, 200
- Prototrophs, 48–49, 107
- Pseudoalleles, 28
- Pseudo-revertants, 105, 108, 111–112, 120
- Punnett, Reginald Crandall, 183, 194
- Punnett square, 33f, 183
- Purifying (negative) selection, 171, 176, 177
- Purine auxotrophs, 146–147
- Purine biosynthesis, 149, 155
- Purine repressor, 148, 155
- Q**
- Quantitative analysis, 1–3
- Quantitative trait loci (QTLs), 132, 191
- R**
- Random assortment, 31–33
- Random drift, 171
- Reading frame, 93–94
- Recessive, definition of, 18
- Recessive disease phenotypes, 196–199
- Recessive mutations, 24–25
 complementation analysis, 27–29

- enhancer and silencer mutations, 151
 - Recessiveness, 17–22, 24–27
 - biological interpretation of, 24–27
 - implicit experiment and determination of, 17–20
 - loss of function, 25
 - Mendel's description of, 18
 - non-absolute nature of, 21
 - null alleles, 26
 - Recessive oncogenes, 102, 162, 200
 - Recessive suppressors, 125–127
 - Reciprocal translocation, 162
 - Recombinant DNA technology, 157–160
 - Recombinant gametes, 35–36
 - Recombination, 31–34, 100–103, 102f
 - definition and usage of term, 33, 35
 - frequency of, 35–38, 76–77, 103, 187
 - gene conversion, 103
 - homologous (legitimate), 100–101, 102f, 165
 - illegitimate, 102–103
 - in meiosis, 187–189
 - loci defined by failure to recombine, 38
 - measuring distance between loci by, 35–37
 - mitotic, 102
 - in phage, 76–78, 76f
 - transposition, 103
 - Recon, 80
 - Reduction division, 34. *See also* Meiosis
 - Regulation
 - cis*-acting elements, 156–157, 162
 - combinatorial, 150–151
 - definition and usage of term, 61–62
 - enhancers, 151
 - homeostasis and, 66–67, 137
 - initiation, elongation, and specificity
 - in macromolecular synthesis, 153–156
 - at level of enzyme activity, 62–65
 - at level of enzyme synthesis, 65–67
 - by multiple inputs, 149–151
 - negative control, 148
 - of metabolic pathways, 59–67
 - operon (*see* Operons)
 - positive control, 148–149
 - posttranscriptional by miRNAs, 178
 - separable regulatory sites and coding sequences, 156–157
 - silencers, 151
 - transcriptional regulation of gene expression, 137–152, 156
 - Regulatory pathways, 55–57, 56f
 - Regulon, 142, 155
 - Replication, DNA, 88, 157
 - Repressible, 141
 - Repressible system, 149
 - Repression, 66
 - Repressors
 - cis*-acting mutations, 157
 - corepressors, 148, 155
 - definition, 148
 - Lac repressor, 143, 144f, 145–148, 151, 155, 202
 - purine repressor, 148, 155
 - Restriction fragment length polymorphisms (RFLPs), 11, 13, 39
 - Retinoblastoma, 201–202
 - Revertant frequency, of mutations, 79
 - Revertants. *See also* Suppression
 - pseudo-revertants, 105, 108, 111–112, 120
 - true, 105, 108, 113
 - RFLPs. *See* Restriction fragment length polymorphisms
 - Rheumatoid arthritis, 193, 193f
 - Ribosomal ambiguity suppressors, 115
 - Ribosomal RNAs, 177
 - Ribosome-binding site, 158
 - Ribosomes, 91, 139, 153
 - RNA
 - structure, 88
 - transcription, 89–91, 90f
 - translation, 89, 90f, 91–94
 - RNA polymerase, 90f, 118–119, 138
 - as multisubunit structure, 83–84
 - catalytic subunits, 153
 - cis*-dominant phenotypes and, 157
 - promiscuity of, 155
 - promoter interaction, 139–140
 - RNA polymerase II holoenzyme, 156
 - transcription factors, 151
 - RNA splicing. *See* Splicing
 - RNA-splicing defects, 175, 176
 - Rotman, Raquel (Sussman), 72, 74, 84
 - rpoB*, 118–119
- ## S
- Saccharomyces cerevisiae*
 - as prototroph, 48
 - genome size, 169
 - introns, 176
 - Saccharomyces* Genome Database (SGD), 167
 - Saliva sample, for genetic testing, 38–39
 - Schekman, Randy, 129

- Schizophrenia, 205
- Segregation
- Mendelian, 39–40
 - of polymorphic loci
 - single locus, 39–40, 39f
 - three loci, 41, 41f
 - two loci, 40, 40f
- Selection, 174
- extreme, 183
 - laboratory selection assays, 161–163
 - positive, 171
 - purifying (negative), 171, 176, 177
- Selective crosses, 77–78
- Sequence databases, 167
- Sequence homology, 100
- Sex chromosomes, 8–9
- Sex determination in *Caenorhabditis elegans*, 127
- SGD (*Saccharomyces* Genome Database), 167
- Short tandem repeat (STR) polymorphism, 11–12, 13
- Sickle cell anemia, 20–22, 172, 198
- Sickle cell trait, 20–21
- Signal sequence, 164–165, 164f
- Signal transduction
- mutations affecting, 200–201
 - pathways, 55–57, 56f, 127
 - recessive functional suppression and, 127
- Silencers, 151
- Silent mutations, 96
- Single-nucleotide polymorphism (SNP), 12, 39, 42, 186–192, 192f, 193f, 203–204
- Snapdragons, flower color in, 19
- SNPs, 39, 42
- Somatic mutation, 14
- Spinocerebellar ataxia, 199
- Spliceosome, 176
- Splicing, 90–91, 139, 154, 165
- defects, 175, 176
- Statistical significance, 3
- Statistics, 43–45
- likelihood ratio, 46
 - LOD score, 46
- Stop codons, 91, 92t, 94, 154, 158
- nonsense suppressors, 109–112
- STR (short tandem repeat) polymorphism, 11–12, 13
- Structure, 5, 6
- Sturtevant, Alfred, 32, 45, 97, 104
- Substitution mutations, 95
- Suppression
- by frameshift mutations, 112–115
 - definition, 105–106
 - dosage, 122–123
 - functional, 117–128
 - genetics, 105–115
 - genetic test for, 109
- Suppressors
- bypass, 124–125, 124f
 - extragenic, 106
 - functional, 109
 - genetic properties of, 106–112
 - informational, 109
 - intragenic, 106
 - mutual interaction, 121–122
 - nonsense, 109–112
 - with novel phenotypes, 119–121
 - protein interaction, 117–119
 - recessive, 125–127
 - ribosomal ambiguity, 115
 - tRNA-based frameshift, 115
- Swiss Prot Diseases and Variants (database), 14
- Synergistic interaction, 134
- Synonymous mutations, 95–96
- Synthetic lethality, 132, 134, 135
- Synthetic phenotype, 132–135
- Szilard, Leo, 62–63, 68
- T**
- T4. *See* Bacteriophage T4
- Temperature-sensitive (Ts) mutations, 74–75, 119–121, 122, 134
- Template strand, 93, 138
- Termination codons, 154, 158
- Termination factors, 154
- Test cross, 18
- Thought experiment, 17
- 3' untranslated region (3' UTR), 176, 177, 178
- Tissue-type plasminogen activator (t-PA), 163–165, 164f, 173
- TMG, 207
- TP53* gene mutation, 14, 196–197, 197f
- Transcription, 89–91, 90f
- basics of, 138–140
- Transcriptional regulation of gene expression, 137–152
- Transcription factors, 151
- Transfer RNA (tRNA), 92, 177
- Translation, 89, 90f, 91–94, 139, 154
- Translocations, 97–98, 98f, 161–162
- Transmission coefficient, 79
- Transporters, 162, 172
- Transposition, 103

Transposons, 99–100, 103, 202
Tree of life, evolutionary, 168f
Trinucleotide repeat alleles, 199–200, 205–206
Trios, 205
tRNA-based frameshift suppressors, 115
tRNAs, 92, 177
True breeding, 2
Tryptophan
 auxotrophs, 62, 65, 107–109, 111–112, 131
 biosynthesis regulation, 62–63,
 65–66
 chemical structure, 63f
Tryptophanase, 207–208
Tschernek von Seysenegg, Erich, 15
Tubulin, 125
Tumor cells, in laboratory selection assays, 161–
 163
Tumor-suppressor genes, 102, 162, 175, 196, 200,
 201–202, 206
Two-factor cross, 35–37

U

Umber mutations, 110
Upstream, 48, 139

V

Variable number tandem repeat (VNTR) poly-
 morphism, 11–12, 13, 39
Vector, 158
Virus integration into genome, 100

W

Watson, James, 100, 104
Weinberg, Wilhelm, 182, 194
Wexler, Nancy, 199, 205
Wild type, 10, 13–14
Wood, William B., 52–53, 57
WormBase, 167

X

X chromosome, 8–9
 fragile X syndrome, 199
 inactivation, 178

Y

Y chromosome, 8
Yeast
 actin mutations, 121–122, 127, 134
 auxotrophs, 107–112
 conditional-lethal mutations, 122–123
 dosage suppression, 123
 genome-scale genetic interactions, studying,
 134–136, 135f
 genome size, 169
 laboratory selection assays, 161–163
 MAPK protein, 123
 network of functional relationships among
 genes, 135f
 suppressor mutations and, 120–121
 synthetic lethality, 134
 transporters, 162, 172