

Contents

About the Online Resources

	v
1 Introduction	1
1.1 Genetics: the universal research language	1
1.2 What will you get in the subsequent pages?	2
1.3 An historical sketch: genetics as a four-act play	2
1.4 Genetic terminology	5
2 The genetic epidemiology of schizophrenia	6
2.1 What is schizophrenia?	6
2.2 Does schizophrenia run in families?	7
2.3 Traditional assumptions about heredity, mental illness, and behavior	9
2.4 Diagnosing schizophrenia	9
2.5 Adoption, heredity, and environment	11
2.6 Twins	14
2.7 Should we rely on twin and adoption studies?	20
Summary	20
3 Molecular biology of nucleic acids	22
3.1 DNA	22
3.2 RNA	25
3.3 The genetic code	26
3.4 The polymerase chain reaction	28
3.5 DNA sequencing	29
3.6 Genome sequence and the problem of repetitive DNA	31
3.7 What is a gene?	32
3.8 Genetic variation: genotyping versus sequencing	34
3.9 Genome variation: sequence variants, polymorphisms, mutations, and their functional consequences	35
Summary	38
4 Epigenetics, gene regulation, and 'omic technologies	39
4.1 What is 'epigenetics'?	39
4.2 The regulation of gene expression	40
4.3 Epigenetic explanations of behavior	43
4.4 Prader–Willi and Angelman syndromes	45

4.5	Epigenetic transgenerational inheritance	47
4.6	Not every cellular mechanism is epigenetic	48
4.7	'Omics	49
	Summary	51
5	Linkage and association	52
5.1	Linkage analysis	52
5.2	Genetic association analysis	58
5.3	Endophenotypes	64
	Summary	66
6	Genome-wide association studies	67
6.1	Genome-wide association is a more powerful strategy than linkage	67
6.2	Reading human history in our DNA	68
6.3	The nature and number of genetic variants needed for GWAS	69
6.4	Linkage disequilibrium and the HapMap Consortium	70
6.5	The first results of GWAS of common complex disease	72
6.6	How to interpret a GWAS result	74
6.7	GWAS developments since 2008: more SNPs (both real and imaginary)	77
6.8	Three axioms that emerge from GWAS results	79
6.9	Turning genetic loci into genes	81
6.10	Transcriptome-wide association studies	83
6.11	A conversation about genetic architecture	84
	Summary	85
7	Molecular genetics of schizophrenia	86
7.1	Genome-wide association studies of schizophrenia	86
7.2	Polygenic risk scores	87
7.3	The Psychiatric Genomics Consortium	89
7.4	GWAS for schizophrenia identifies hundreds of risk loci	90
7.5	SNP-based heritability	93
7.6	Schizophrenia and the problem of missing heritability	96
7.7	Copy-number variants	97
7.8	Exomes and rare variants as a cause of schizophrenia	98
	Summary	101
8	Autism spectrum disorder	102
8.1	What is autism?	102
8.2	The heritability of autism, and autism spectrum disorder	103
8.3	Molecular genetics of ASD	104
8.4	Copy-number variants	105
8.5	<i>De novo</i> mutations in genes that cause ASD	106
8.6	Rare variant analysis: how do we know that a mutation causes ASD?	108
8.7	Mosaicism	109
8.8	Common variants that contribute to the risk of ASD	109

172	8.9	Altering the consequences of mutations	111
172	8.10	Causes of autism	111
176		Summary	112
178			
181	9	Intellectual disability and developmental disorders	113
184	9.1	Intellectual disability, developmental delay, or neurodevelopmental disorder?	113
185	9.2	Chromosomal abnormalities as a cause of intellectual disability: Down syndrome	114
185	9.3	Small chromosomal abnormalities: a question of dosage	115
186	9.4	X chromosome abnormalities	116
187	9.5	Single-nucleotide variants as a cause of intellectual disability	118
187	9.6	The biology of intellectual disability	120
188	9.7	The nonspecificity of genetic action	122
190		Summary	123
191			
197	10	Anxiety, depression, and eating disorders	124
199	10.1	Major depression	124
200	10.2	Bipolar disorder	129
202	10.3	Anxiety disorders	131
204	10.4	Eating disorders	134
208		Summary	135
209			
209	11	Alcoholism	136
209	11.1	Alcohol-dependence syndrome	136
210	11.2	A twin study of alcoholism in Sweden	137
214	11.3	The molecular genetics of alcoholism	140
217		Summary	142
218			
221	12	The genetics of intelligence, personality, and personality disorders	143
222	12.1	Intelligence	143
223	12.2	Personality	153
223	12.3	Personality disorders	157
223	12.4	The three laws of behavior genetics	160
225		Summary	161
225			
225	13	Genes for what?	163
227	13.1	Depression and anxiety	163
229	13.2	Seven common disorders	164
241	13.3	Major depression and personality	165
243	13.4	Polygenic risk scores and genetic correlations	166
245	13.5	Mendelian randomization	167
246	13.6	Genes and sex	169
246	13.7	Genes and development	169
246		Summary	170

14	Genes and the environment	172
14.1	Gene–environment interaction	172
14.2	Gene–environment correlation	176
14.3	Using genetics to distinguish correlation from cause	178
14.4	Indirect genetic effects	182
	Summary	184
15	Mapping mouse behavior	186
15.1	The heritability of mouse behavior	186
15.2	Locomotor activity	187
15.3	Inbred strains: heritability and gene–environment interactions	187
15.4	Selection and realized heritability	188
15.5	Genetic models and experimental systems	190
15.6	Mapping behavior in rodents	191
15.7	Two problems of analysis: population structure and haplotypes	197
15.8	Comparing mapping populations	199
15.9	The genetic architecture of behavior in rodents	200
15.10	Some features of the genetic architecture depend on the population in which the loci are mapped	202
15.11	Progressing from locus to gene	204
	Summary	208
16	Reverse genetics	209
16.1	Forward versus reverse genetics	209
16.2	Genetic engineering	210
16.3	Constitutive mutations and the genetic architecture of behavior	214
16.4	Genes involved in learning and memory	217
16.5	A primer in the neurobiology of learning and memory	218
16.6	Memory genes	221
16.7	Inducible mutations	224
16.8	Genetically encoded reagents	228
16.9	Next steps	233
	Summary	233
17	Mutagenesis and the molecular dissection of circadian rhythms	235
17.1	Invertebrate genetics	235
17.2	Random mutagenesis	236
17.3	Finding a circadian rhythm mutant	237
17.4	Molecular clockworks	239
17.5	More clock genes	241
17.6	The mouse's clock	243
17.7	Human clock genes and unquiet sleep	245
17.8	Lessons from fly rhythms	246
17.9	Love on the fly (sex-specific development in the nervous system)	246

17.10	Mutagenesis, and forward and reverse genetics	247
17.11	A Nobel for the little fly	248
	Summary	249
18	Many versus one: genetic variation in flies and worms	251
18.1	Evolving behavior in the laboratory: <i>Drosophila</i>	251
18.2	Finding the genes	253
18.3	Genes for geotaxis?	255
18.4	Aggression	255
18.5	Genes for aggression?	256
18.6	Behavior, the single gene, and the mind of a worm	257
18.7	The first complete anatomy and developmental history	257
18.8	The first complete animal genome	258
18.9	Worm behavior genetics	258
18.10	Wanderlust in fly larvae	260
18.11	So which is it? Pluribus or unum?	261
	Summary	261
19	Comparative genomics	263
19.1	Finding out what makes us human: genetic comparisons with great apes	263
19.2	The genetic basis of fidelity	265
19.3	The genetics of real estate	269
19.4	Social behavior	270
19.5	Supergenes	272
	Summary	274
20	How genes influence behavior	276
20.1	The work of the behavioral geneticist	276
20.2	Two ways of explaining genetic effects	277
20.3	The single-gene perspective ignores background effects	278
20.4	Small-effect genes will tell us little about mechanism	279
20.5	Single genes in genetic architecture terms	279
20.6	Genetic architecture in single-gene terms	280
20.7	How genes influence behavior	280
20.8	The relative contributions of genes differ	281
20.9	How should we use our new-found knowledge of genetic effects?	282
20.10	How to understand an explanation	282
20.11	Should I write back to the prisoners?	283
	Summary	284
21	How do we know a finding is true? Quantitative approaches	286
21.1	The reproducibility crisis	286
21.2	Was the right test used?	287

21.3	Was the correct significance threshold applied?	290
21.4	Could the result be attributable to some unacknowledged confound?	291
21.5	Did the experiment have sufficient power to deliver the result reported?	292
21.6	Was the <i>P</i> value interpreted correctly?	294
21.7	Abandon statistical significance!	296
21.8	Model-fitting approaches	297
21.9	Bayesian approaches	297
Appendix		303
A1	Statistics terminology	303
A2	Genetic models: a single locus and the Hardy–Weinberg principle	305
A3	Genetic models: multiple loci	306
A4	Regression to the mean and the calculation of heritability	308
A5	Twin methodology	309
A6	Effect sizes in categorical tests of association	312
A7	Statistical tests: please use the R statistical programming language!	312
A8	Differences between two samples of quantitative scores (<i>t</i> -test)	312
A9	Analysis of variance (ANOVA)	314
A10	Regression analysis	315
A11	Logistic regression	318
A12	Power	320
A13	Meta-analysis	322
A14	Contingency tables, and Fisher's and χ^2 tests	324
A15	Bayesian terminology	325
References		327
Index		363