

Contents

1 Introduction to Statistical Genetics and Background in Molecular Genetics	1
1.1 Basic Concepts in Genetic Disease	2
1.2 Review of Molecular Genetics	6
1.3 Types of Genetic Variants	9
1.4 Effects of Genetic Variants on Disease	12
2 Principles of Inheritance: Mendel's Laws and Genetic Models	15
2.1 Mendel's Experiments	15
2.2 A Framework for Genetic Models	19
2.3 The Biology Underlying Mendelian Inheritance	24
2.4 Exercises	28
3 Some Basic Concepts from Population Genetics	31
3.1 Estimation of Allele Frequencies	31
3.2 Population Substructure	33
3.2.1 Population Stratification	33
3.2.2 Population Admixture	34
3.2.3 Population Inbreeding	35
3.3 Hardy-Weinberg Equilibrium	36
3.3.1 Testing for HWE	38
3.3.2 Some Causes of the Failure of HWE	39
3.3.3 Measuring the Departure from HWE	41
3.4 Exercises	42
4 Aggregation, Heritability and Segregation Analysis: Modeling Genetic Inheritance Without Genetic Data	45
4.1 Preliminaries	46
4.2 Aggregation Analysis	48
4.2.1 Estimating Recurrence Risk Ratios	51
4.2.2 Further Simplifications	51
4.3 Heritability Analysis	54

4.4	Segregation Analysis	57
4.4.1	Segregation Analysis for Dominant Mendelian Diseases	58
4.4.2	Segregation Analysis for Recessive Mendelian Diseases	62
4.4.3	Summary	63
4.5	Exercises	63
5	The General Concepts of Gene Mapping: Linkage, Association, Linkage Disequilibrium and Marker Maps	67
5.1	Introduction	67
5.2	Genetic Markers and Marker Maps	72
5.3	Testing for Linkage or Association: Basic Concepts	75
5.4	A Formal Definition of Linkage Disequilibrium and Related Measures Used to Describe Linkage Disequilibrium	77
5.5	The Origin and Extent of LD in the Human Genome	81
5.6	The Human Genome and HapMap Projects	82
5.7	Exercises	84
6	Basic Concepts of Linkage Analysis	87
6.1	Basic Approach to Assessing Linkage Between Two Loci	88
6.2	The Direct Counting Method	90
6.3	The Interpretation of LOD Scores	94
6.4	Exercises	95
7	The Basics of Genetic Association Analysis	99
7.1	Testing Association with Dichotomous Disease Traits: Codominant, Recessive and Dominant Models	101
7.2	The Additive Genetic Model: The Alleles Test and the Trend Test	103
7.3	Small Sample and Permutation Tests	106
7.4	Which Mode of Inheritance Should We Assume for Testing?	107
7.5	Estimating Effect Sizes and Confidence Intervals	108
7.6	Examples of Testing Association with Diallelic Markers	109
7.7	The Regression Approach: Extensions to Covariate Adjustment and to Other Phenotypes	111
7.8	Association Analysis with Complex Traits: An Association Between INSIG2 and BMI	114
7.9	Sample Size and Power Considerations for Case-Control Design	116
7.10	Power and Effect Estimation: Testing a Marker in LD with the DSL	120
7.11	Exercises	122

8	Population Substructure in Association Studies	125
8.1	The Impact of Population-Admixture and Stratification on Genetic Association Tests	127
8.2	Genomic Control Approaches	132
8.3	Modeling the Effects of Population Admixture and Stratification	133
8.4	Regression-Based and Principal Component Approaches	133
8.5	Exercises	136
9	Association Analysis in Family Designs	139
9.1	The Trio Design and the TDT	139
9.2	Family Based Association Tests: FBAT	142
9.2.1	Missing Parents	145
9.2.2	Comparative Power for Family-Based and Case-Control Designs	147
9.3	Applications	148
9.3.1	Using FBAT to Obtain the TDT	149
9.3.2	Deriving a TDT for a Recessive Mode of Inheritance	150
9.3.3	Informative Families	150
9.3.4	Codominant Mode of Inheritance	151
9.3.5	Multiallelic Test	151
9.3.6	Using Unaffected Offspring	152
9.3.7	Missing Parental Information	153
9.3.8	Quantitative Traits	156
9.4	Exercises	158
10	Advanced Topics	161
10.1	The Multiple Testing Problem in Association Studies	161
10.1.1	Methods Based on P-Value Adjustment	161
10.1.2	Permutation and Monte Carlo Tests	164
10.2	Other Methods for the Analysis of Multiple SNPs, Including Haplotypes	165
10.3	Gene–Environment/Gene–Drug Interaction	170
10.4	Exercises	174
11	Genome Wide Association Studies	175
11.1	Introduction	175
11.2	Quality–Control for the Genotype Data	176
11.3	Multi-Stage Designs	182
11.4	Testing Strategies for Family-Based Studies	185
11.5	Replication, Non-replications and Meta-analysis	186
11.6	Exercises	189

12 Looking Toward the Future	191
A Basic Concepts of Linkage Analysis (Continued from Chapter 6)	193
A.1 General Issues with Parametric Linkage Analysis	193
A.2 Non-parametric Linkage Analysis	195
A.3 Multipoint Linkage Analysis	199
B A Class of Score Tests for Family Designs	203
Properties of the Score Test	204
Missing Parents	205
C The TDT Tests for Both Linkage and Association (LD)	207
Bibliography	211
Index	219