

the principles of human biochemical genetics

Third, Revised Edition

HARRY HARRIS

**University of Pennsylvania School of Medicine,
Philadelphia**

ELSEVIER / NORTH-HOLLAND

Contents

<i>Preface to 1st edition</i>	v
<i>Preface to 2nd edition</i>	vii
<i>Preface to 3rd edition</i>	ix
 <i>Chapter 1. Gene mutations and single aminoacid substitutions</i>	 1
1.1. Introduction: genes, DNA and proteins	1
1.2. The hemoglobin variants	8
1.3. The structures of variant hemoglobins	12
1.4. Single aminoacid substitutions and the genetic code	16
1.5. Single base change mutations	20
1.6. The effects of single aminoacid substitutions	22
1.6.1. Sickle-cell disease	23
1.6.2. Hereditary methemoglobinemias	25
1.6.3. Unstable hemoglobins	28
1.6.4. Altered oxygen affinity	29
1.7. Two separate aminoacid substitutions in a single polypeptide chain	31
1.8. 'Hybrid' proteins in heterozygotes	32
1.8.1. Hemoglobin	32
1.8.2. 'Hybrid' enzymes in heterozygotes	35
1.8.3. Symmetric and asymmetric electrophoretic patterns in heterozygotes ..	40
 <i>Chapter 2. One gene-one polypeptide chain</i>	 46
2.1. The hemoglobin loci	46
2.1.1. The α -, β -, γ -, δ -, ϵ - and ζ -hemoglobin loci	46
2.1.2. Developmental changes in hemoglobin gene expression	51
2.1.3. Double heterozygotes	53
2.1.4. Chromosomal locations	55
2.2. Multilocus enzymes	61
2.2.1. Lactate dehydrogenase	61
2.2.2. Phosphoglucumutase	69
2.2.3. Incidence of multilocus enzyme systems	78
2.2.4. Subunit structure	81
2.2.5. Tissue differences and developmental changes	88
2.2.6. Chromosomal locations	91
2.3. Gene duplication and molecular evolution	92

2.4. Genes and isozymes	98
2.5. Posttranslational modifications	100
2.5.1. Purine nucleoside phosphorylase	101
2.5.2. Causes of 'secondary' isozymes	104
<i>Chapter 3. Unequal crossovers, deletions, chain elongations, partial duplications and other rearrangements</i>	<i>108</i>
3.1. Unequal crossing-over	108
3.1.1. The Lepore hemoglobins	109
3.1.2. Hb Kenya: a γ - β fusion product	112
3.2. Deletions	113
3.3. Chain elongations	117
3.4. The thalassemias	121
3.4.1. α -Thalassemia	122
3.4.2. β -Thalassemia	128
3.5. The immunoglobulins: an exception to the rules	137
3.5.1. Immunoglobulin structure	139
3.5.2. Immunoglobulin genes	142
3.6. The haptoglobin variants	145
<i>Chapter 4. Quantitative and qualitative variation of enzymes</i>	<i>157</i>
4.1. Quantitative variation in enzyme activity	157
4.2. Serum cholinesterase	159
4.2.1. 'Atypical' serum cholinesterase	161
4.2.2. The 'silent' or 'null' allele	165
4.2.3. 'Fluoride resistant' serum cholinesterase	168
4.2.4. Multiple allelism causing 'continuous' variation in activity	168
4.2.5. A second locus — E_2	171
4.3. Glucose-6-phosphate dehydrogenase (G-6-PD)	173
4.3.1. G-6-PD deficiencies	173
4.3.2. The common Black and Mediterranean G-6-PD variants: Gd B, Gd A, Gd A-, and Gd Mediterranean	175
4.3.3. Other G-6-PD variants	181
4.3.4. The Lyon hypothesis	184
4.4. Red cell acid phosphatase	190
4.4.1. The electrophoretic variants	190
4.4.2. Quantitative differences	194
<i>Chapter 5. The inborn errors of metabolism I</i>	<i>198</i>
5.1. Garrod and the concept of 'inborn errors of metabolism'	198
5.2. Phenylketonuria	201
5.3. Galactosemia	207
5.4. Deficiencies in multilocus enzyme systems	210
5.4.1. Aldolase deficiency in hereditary fructose intolerance	210
5.4.2. Pyruvate kinase deficiency	214

5.5. Partial enzyme deficiencies and their metabolic consequences. The urea cycle enzymes	215
5.6. Glycogen disease	223
5.6.1. Defects in glycogen synthesis	226
5.6.2. Defects in glycogen mobilization	227
5.7. The lysosomal storage diseases	232
5.7.1. Mucopolysaccharidoses	233
5.7.2. Sphingolipidoses	234
5.7.3. Tissue variations	237
5.7.4. Genetic heterogeneity in lysosomal diseases	238
5.7.5. Cell culture studies	244
 <i>Chapter 6. The inborn errors of metabolism II</i>	 247
6.1. Heterozygotes	247
6.1.1. Partial enzyme deficiencies in heterozygotes	247
6.1.2. Acute intermittent porphyria: a 'dominant' inborn error of metabolism	256
6.1.3. Heterozygotes in X-linked inborn errors of metabolism	259
6.2. Receptor defects	260
6.2.1. Familial hypercholesterolemia	261
6.2.2. Low-density lipoprotein (LDL)	261
6.2.3. Heterozygous and 'homozygous' familial hypercholesterolemia	263
6.2.4. The LDL pathway in normal human fibroblasts	264
6.2.5. Defective LDL receptors in familial hypercholesterolemia	268
6.2.6. Heterozygotes	271
6.2.7. Pathological changes in familial hypercholesterolemia	273
6.2.8. Other mutants affecting the LDL pathway	274
6.3. Defects in active transport systems	275
6.3.1. Cystinuria	275
6.3.2. Other aminoacid transport defects	279
6.4. 'Inborn errors' of drug metabolism	281
6.4.1. Enzyme deficiencies and pharmacological aberrations	281
6.4.2. Isoniazid inactivation	282
6.5. 'Inborn errors' with increased enzyme activity	286
 <i>Chapter 7. The blood group substances</i>	 290
7.1. The ABO blood groups	290
7.2. The 'secretor' and 'H' loci	297
7.3. The H, A and B specific glycosyltransferases	300
7.4. The 'Lewis' or Le locus	304
7.5. The biosynthetic pathways for the group specific glycoproteins	307
7.6. Concluding remarks	313

Chapter 8. Enzyme and protein diversity in human populations 316

8.1 'Common' and 'rare' alleles	316
8.1.1. How many alleles occur?	316
8.1.2. Hemoglobin	319
8.1.3. Glucose-6-dehydrogenase (G-6-PD)	326
8.1.4. Haptoglobin	327
8.2. Polymorphism	329
8.2.1. The ubiquity of polymorphism	329
8.2.2. Definition of polymorphism	331
8.2.3. Enzyme polymorphism	332
8.2.4. The average degree of heterozygosity	336
8.2.5. The uniqueness of the individual	338
8.2.6. Quantitative differences in enzyme activity	338
8.2.7. Rare alleles	343
8.2.8. Alleles not detected by electrophoresis	349
8.2.9. Incidence of alleles determining inborn errors of metabolism	355
8.2.10. Plasma protein polymorphisms	358
8.2.11. Tissue protein polymorphisms	359
8.2.12. Polymorphisms detected by immunologic techniques – the HLA system	363
8.2.13. Polymorphism at the DNA level	372
8.3. The extent of allelic variation: summary	377
8.4. The causes of allelic diversity	379
8.4.1. Natural selection and random genetic drift	379
8.4.2. Molecular evolution	382
8.4.3. The 'neutral' gene hypothesis: the question of functional equivalence	388
8.4.4. The random drift versus differential selection controversy: some further aspects	391
8.4.5. The neutralist-selectionist controversy: concluding remarks	405

Chapter 9. Gene mutations and inherited disease 407

9.1. The molecular pathology of inherited disease	408
9.1.1. Defining mutational changes at the DNA level	408
9.1.2. Molecular properties of protein variants	410
9.1.3. Metabolic and clinical consequences	412
9.2. Dominance and recessivity	414
9.3. Heterogeneity of inherited disease	417
9.3.1. Heterogeneity due to multiple allelism at a single locus	417
9.3.2. Heterogeneity due to mutants at different loci	422
9.3.3. Congenital methemoglobinemia: a model example	428
9.3.4. Therapeutic implications of genetic heterogeneity	429
9.3.5. Other causes of variation in inherited disease	431
9.4. Heredity and environment	435

<i>Appendix 1. Disorders due to specific enzyme deficiencies (inborn errors of metabolism)</i>	441
A1.1. Disorders of carbohydrate metabolism	441
A1.2. Lysosomal enzyme deficiencies	446
A1.3. Disorders of aminoacid metabolism	450
A1.4. Miscellaneous disorders	458
<i>Appendix 2. Enzyme and protein polymorphisms</i>	469
<i>References</i>	473
<i>Subject index</i>	547