

*Second Edition*

AN INTRODUCTION TO

# Human Molecular Genetics

*Mechanisms of  
Inherited Diseases*

*Jack J. Pasternak*





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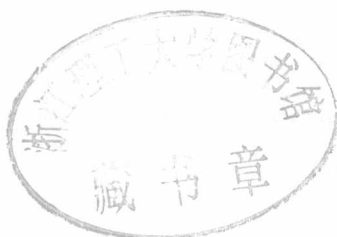
AN INTRODUCTION TO  
**Human  
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*Mechanisms of  
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Second Edition

**Jack J. Pasternak**

University of Waterloo  
Ontario, Canada



 **WILEY-LISS**

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Published by John Wiley & Sons, Inc., Hoboken, New Jersey.  
Published simultaneously in Canada.

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*Library of Congress Cataloging-in-Publication Data is available.*

ISBN: 0-471-47426-6

Printed in the United States of America

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*For my family**Lili (I-1)*

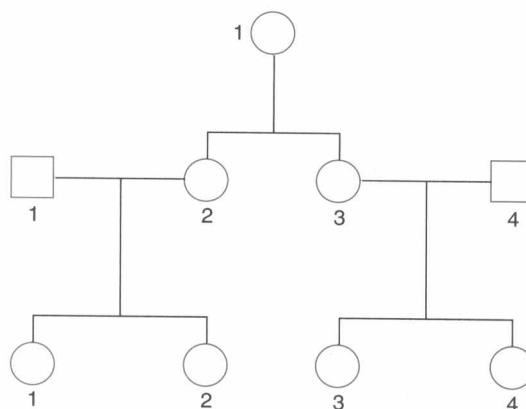
I

*Lisa (II-2)**Dahna (II-3)**Martin (II-1)*

II

*Mike (II-4)**Madelaine (III-1)**Miranda (III-2)**Nina (III-3)**Maya (III-4)*

III



*If we begin with certainties, we shall end in doubts; but if we begin with doubts, and are patient in them, we shall end in certainties.*

FRANCIS BACON (1561–1626)

*Our doubts are traitors,  
And make us lose the good we oft might win,  
By fearing to attempt.*

WILLIAM SHAKESPEARE (1564–1616)

## Preface

Any textbook is a work in progress. Consequently, a second edition provides a rare opportunity to amend, revise, update, elaborate, discard and insert new material. Moreover, specifically for *An Introduction to Human Molecular Genetics*, the first edition preceded completion of the human genome sequence, which is now essential for initiating studies of the molecular basis of human genetic disorders. The human genome is not only accessible online, but clones are available for any region of the human chromosome complement. Both of these resources have made the previous methods of identifying and isolating human disease-causing genes obsolete.

In this edition of *An Introduction to Human Molecular Genetics*, there are new chapters on complex genetic disorders, human population genetics, genomic imprinting, bioinformatics including proteomics, and clinical genetics. Many of the original chapters have been overhauled because of the advances in understanding the molecular genetics of various disorders. As well, the number of review questions for most chapters has been increased. However, the overall rationale for *An Introduction to Human Molecular Genetics*, as described in the previous preface, has not changed significantly.

The advice, comments, and criticisms of many of the anonymous reviewers of the first drafts of some of the new chapters were exceptionally helpful and greatly appreciated. I'm also thankful to the readers of the first edition who pointed out errors. It has been a pleasure working with everyone at J. Wiley and Sons. Finally, I'm exceedingly grateful to all my family for their encouragement and forbearance.

## Preface to the First Edition

*An Introduction to Human Molecular Genetics: Mechanisms of Inherited Diseases* was written for advanced level undergraduate courses, introductory graduate level courses, and basic medical school courses on human genetics. The text examines how human genes are discovered and, once a gene is known, how the defective version(s) causes a particular disorder. Humans are fascinated with everything to do with being human, and there is a keen interest in how the human genetic system functions and what causes inherited disorders. This book is derived from years of teaching Human Molecular Genetics at both the graduate and undergraduate levels at the University of Waterloo. These courses were initiated in the mid-1980s before any significant number of disease-causing genes had been mapped, isolated, or characterized. At that time, it seemed clear that the new gene technologies, based primarily on recombinant DNA technology, were going to make the direct study of human genes commonplace. To paraphrase one biologist, researchers will no longer need to rely on "breeding fruit flies and counting chiasmata" to appreciate the workings of human genes. Rather, a significant new phase in the study of human genetics was emerging. In the past decade, the developments in this research area have been phenomenal. In Star Trek parlance, human genetics is proceeding at "warp speed." Hardly a week now passes without a report in a major journal or newspaper stating that "The gene for disease X has been discovered!" And with the full flowering of the Human Genome Project, we are indeed in the midst of the genomic age in the life sciences.

This text has been structured to provide flexibility in the way topics might be covered within the time constraints of a traditional academic term. The first three chapters (Part One) review the fundamentals of genetics and focus on basic cytogenetics and Mendelian genetics. Some students, whose knowledge of these topics may be a bit rusty, would need this information as a brief refresher course. Obviously, these chapters can be omitted if an instructor feels that his/her students understand the material. Part Two covers the concepts of molecular genetics (chapter four); the tools, resources, and strategies for manipulating genes (chapter five); genetic and physical mapping of human chromosomes (chapter six); and isolating disease-causing genes (chapter seven). The chapters in Part Three of the book build on the information presented in the earlier chapters and focus on the molecular genetics of selected biological systems. Specifically, gene-based knowledge of inherited disorders of muscle,

the nervous system, and the eye are presented in detail. In these chapters and those that deal with inheritance of mitochondrial disorders and cancer, the biological basis of each particular system is described. Then, the discussion focuses on the mapping, identification, and characterization of genes that contribute to a system and how that system is affected by mutations in different genes. The goal is to familiarize the reader with the anatomical, physiological, and biochemical underpinnings that pertain to these genetic studies. The final chapter covers the exciting field of human gene therapy. Unfortunately, because human molecular genetics is such a broad-ranging scientific discipline, not all basic systems could be handled in this manner. In spite of these "omissions," there is plenty of challenging and interesting material in the book to occupy readers and provide a solid foundation for understanding the many facets of human molecular genetics.

In 1938, Herbert Walter (1867–1945), in the preface to the fourth edition of his book *Genetics* noted ruefully that "Any book concerning the growing subject of genetics is bound to be out of date as soon as it appears, just as every automobile on the road must be classified as a 'used car'." How true! Both Walter's pronouncement and his analogy are applicable today. There is fun and frustration in writing about human molecular genetics. On the one hand, conveying how a gene was discovered (often an arduous process) and explaining how it may function is exciting. On the other hand, by the time the book emerges, statements such as "It has not been established that gene X is responsible for disease Y," which are sprinkled throughout the book, may be passé. Clearly, some excellent candidate disease genes will have been confirmed and others shown not to be causative of the condition in question. Moreover, additional genes will have been found that cause disorders of the systems considered in the book. Undoubtedly, any text in human molecular genetics is "a work in progress" because of the dizzying pace of research in this field. This text is no different; however, the focus on key ideas and scientific principles, and the careful detail in which they are explained will allow students to acquire a solid foothold in human molecular genetics so that they can pursue additional topics in this area.

Because the field of human molecular genetics draws on information from so many scientific disciplines, and because it is based on a number of new technologies, there are many new technical terms in this text that might seem forbidding to students on their initial encounter. This trade language is not meant to mystify or be exclusive; rather, it is used for precision and to streamline communication. As Don DeLillo (B. 1936) warns us in his novel *Underworld*, "You didn't see the thing because you don't know how to look. And you don't know how to look because you don't know the names." For us to be able "to look" at human molecular genetics, we need to "know the names." Throughout this text I have tried to avoid technical jargon, but the use of some specialized nomenclature is inevitable. Each chapter ends with a list of Key Terms that are then discussed in a comprehensive Chapter Summary. Also, an extensive Glossary is included at the end of the text to help students with unfamiliar terminology.

The "from the Human Genetics files" feature in each chapter provides additional material dealing with experimental procedures or other aspects of human



molecular genetics that are not covered in the main body of the chapter. Some of the “files,” for example, provide information about the important human genetics Internet site, On-line Mendelian Inheritance in Man (OMIM); spectral karyotyping; comparative genomic hybridization; DNA chips; and transgenic animal models. The Review Questions at the end of each chapter are usually of a general nature to ensure that the reader has grasped the various topics and that he/she is able to convey these concepts in writing without the aid of the book. The Reference sections contain most of the sources for the information presented in each chapter. Some of the references are highly technical research papers; others are review articles. Because human molecular genetics is such a rapidly changing discipline, it may be more helpful for the reader who wishes to pursue specialized items in the literature to conduct an up-to-date search of published articles. The complete author citations are presented for each reference not only to give full credit to all those who participated in a particular research project, but also to underscore the collaborative nature of modern genetics research.

## Acknowledgments

*An Introduction to Human Molecular Genetics* would not exist if it weren't for the invaluable contributions of a large number of people. The entire manuscript was converted into computer files from less-than-legible long-hand drafts and then read for “sense” and commas by my wife, Lili. Critical reviews of sections and chapters by Edward Berger of Dartmouth College, Geoffrey M. Cooper of Boston University, Paula Gregory of Ohio State University, John Hardy of the Mayo Clinic, J. Fielding Hejtmancik of the National Eye Institute (NIH), Louis Kunkel of Harvard Medical School and the Howard Hughes Medical Institute, Marie Lott of Emory University, Donald Nash of Colorado State University, Hesed Padilla-Nash of the National Cancer Institute (NIH), Thomas R. Ried of the National Cancer Institute (NIH), Mark Sanders of the University of California, Davis, Alan Schecter of the National Institute for Digestive Diseases and Kidney Disorders (NIH) and Steven Wood of the University of British Columbia helped enormously to improve the presentation of the material. Most importantly, the reviewers—all of whom were exceptionally thorough and diligent—pointed out errors, misleading statements, and both minor and major problems pertaining to scientific matters. Needless to say, errors of any kind that remain are entirely my responsibility. K. Hesselmeier-Haddad, H. Padilla-Nash, T. Ried, S. Stenke, H.-Ulli Weier, and D. Winkler kindly provided the magnificent fluorescent in situ hybridization (FISH) images found in the color insert; C. Lengauer furnished the FISH image on the cover. Michael Goldberg and Jeff Holtmeier of the American Society for Microbiology Press graciously allowed material from *Molecular Biotechnology: Principles and Applications of Recombinant DNA*, 2nd ed. by Bernard R. Glick and Jack J. Pasternak to be used here. Nancy Knight did a thorough and impressive job of converting “final” manuscript copies into publishable versions. Susan Graham coordinated the production process with efficiency, aplomb, and patience. The book was designed by Susan Schmidler with her usual deft touch. The team headed by Karen Hawk at Precision Graphics produced the book



and created its “look.” Thanks to Hope Page, who is more adept at sending and opening attachments than her boss. Last, but not least (as the cliché goes), I am grateful to Patrick Fitzgerald, who nurtured the book from its conception, assembled the team to bring it to fruition, was an unflagging source of encouragement, and contributed ideas by the bushelful. If it can be believed, Patrick makes all phases of writing a book pleasurable!

# Contents

*Preface* xvii

*Preface to the First Edition* xix

## chapter 1

### **Understanding Human Disease 1**

**Human Genetic Disease 2**

**Human Genetics from 1900 to 1957 5**

Eugenics: Genetics Misinterpreted 9

The Molecularization of Genetics 11

**Genes and Phenotypes 12**



**from the human genetics files**

*OMIM: An Important Online Source of Information About Human Genetic Disorders 14*

**Key Terms 17**

**Summary 17**

**References 18**

**Review Questions 18**

## chapter 2

### **The Genetic System: Chromosomes 19**

**Human Chromosomes 19**

Maintaining the Chromosome Number 19

Cell Division Cycle: The Mitotic Process 20

The Meiotic Process 22

**Characterizing Human Chromosomes 24**

**Chromosome Abnormalities 28**

Whole Chromosome Changes: Aneuploidy 28

Chromosome Structural Changes 30



**from the human genetics files**

*Determining the Phases of the Cell Cycle 32*

**Key Terms 35**

**Summary 35**

**References 36**

**Review Questions 36**

**chapter 3****The Genetic System: Mendel's Laws of Inheritance and Genetic Linkage 37**

Dominance, Recessiveness, and Segregation 38

Independent Assortment 41

Genetic Linkage 44

Constructing Genetic Maps 47

Three-Point Cross 48

Chi-Square Distribution: Testing for Significance 52

Multiple Alleles 54

Human Genetics 55

Autosomal Dominant Inheritance 58

Autosomal Recessive Inheritance 59

X-Linked Inheritance 60

Using Pedigrees to Study Human Genetic Disorders 61



from the human genetics files

*Calculating Mendelian Frequencies* 65

Detection and Estimation of Genetic Linkage in Humans 66

The Logarithm of the Likelihood Ratio Method of Linkage Analysis:  
LOD Score 67

Key Terms 71

Summary 72

References 72

Review Questions 73

**chapter 4****The Molecular Biology of the Gene 75**

Properties of Genetic Material 75

Structure of DNA 76

DNA Replication 79

Decoding Genetic Information: RNA and Protein 79

Translation 85

Regulation of mRNA Transcription 89



from the human genetics files

*Hemoglobinopathies and Thalassemias: An Abundance of Mutations* 92

Nucleotide Sequence Alteration: Mutation 94

Mutations of Structural Genes 95

Nomenclature for Mutations 100

Dominant Mutations and Genetic Disorders 102

Key Terms 104

Summary 104

References 105

Review Questions 106

## chapter 5

### **Recombinant DNA Technology 107**

Restriction Endonucleases 108

Cloning Vectors 115

Plasmid Cloning Vector pUC19 116

Screening DNA Constructs by DNA Hybridization 119

In Situ Hybridization 122

Chemical Synthesis of DNA 122

Sequencing DNA 124

Polymerase Chain Reaction 130

Human-Rodent Somatic Cell Hybrids 131

Human DNA Libraries 137

Genomic Libraries 137

Chromosome DNA Libraries 139

 **from the human genetics files**  
*Multicolor Karyotyping: Coloring Chromosomes 143*

Region-Specific Chromosome Libraries 144

Constructing a cDNA Library 145

Key Terms 149

Summary 149

References 151

Review Questions 151

## chapter 6

### **Genetic and Physical Mapping of the Human Genome 153**

Genetic Mapping of Human Chromosomes 153

Genetic Polymorphism 153

Restriction Fragment Length Polymorphism 155

Short Tandem Repeat Polymorphism 158

Mapping of a Genetic Disease Locus to a Chromosome Location 159

Multilocus Mapping of Human Chromosomes 163

Inserting a Disease Gene into a Linkage Map 165

Homozygosity Mapping 168

Linkage Disequilibrium Mapping 169

Radiation Hybrid Mapping 171

Genotyping Single-Nucleotide Polymorphisms 174

Physical Mapping of the Human Genome 181

Assembling Contigs from BAC Libraries 181

 **from the human genetics files**  
*Comparative Genetic Maps 182*

Integration of Cytogenetic, Genetic, and Physical Maps 184

Key Terms 186

Summary 186

References 186

Review Questions 187

**chapter 7****Discovering Human Disease Genes 189****Cloning Human Disease Genes 190**

Functional/Candidate Gene Cloning 190

Positional-Candidate Gene Cloning 191

**Detection of Mutations in Human Genes 191**

Single-Strand Conformation Polymorphism Analysis 191

Denaturing Gradient Gel Electrophoresis 193

Heteroduplex Analysis 193

**from the human genetics files***Rapid Detection of Unknown Mutations: Capillary Electrophoresis 197*

Chemical Mismatch Cleavage 197

Direct DNA Sequencing 199

Protein Truncation Test 199

Key Terms 201

Summary 202

References 202

Review Questions 202

**chapter 8****Bioinformatics: Genomics, Functional Genomics, and Proteomics 203****Similarity Search of a DNA Database 204****Functional Genomics 207**

DNA Microarray Technology 208

Serial Analysis of Gene Expression 211

**Proteomics 213**

Separation and Identification of Proteins 214

Protein Expression Profiling 217

Protein-Protein Interaction Mapping 219

**from the human genetics files***How Many Genes Do We Have? 220*

Key Terms 226

Summary 226

References 227

Review Questions 228

**chapter 9****Human Population Genetics 229****Alleles, Genotypes, and Hardy–Weinberg Equilibrium 230**

Hardy–Weinberg Equilibrium with X-Linked Genes 236

Hardy–Weinberg Equilibrium with Two Loci 238

**Processes That Alter Allele and Genotype Frequencies in Populations 239****Population Size 239**

Genetic Structure of Isolated Human Populations 241

Founder Effect 243

**Migration 244****Mating Systems 248**

Assortative Mating 248

Inbreeding 250

Effect of Inbreeding on Populations 256

**Mutation 260****Fitness and Selection 262**

Directional Selection 265

Balancing Selection 269

Disruptive Selection 272

**Mutation, Selection, and Founder Effect: A Case Study 273**

from the human genetics files

*Dysgenics: Fact or Fiction* 276

from the human genetics files

*Coalescence* 278**Neutral Theory 279**

Testing for Selection 280

Wright's  $F_{ST}$  Statistic 284

from the human genetics files

*Using DNA Polymorphisms to Infer Human History* 286**Key Terms 288****Summary 289****References 290****Review Questions 292****chapter 10****Molecular Genetics of Complex Disorders 295****Phenotypic Variation of Monogenic Disorders 300**

Oculocutaneous Albinism Type 1 300

Glucose-6-Phosphate Dehydrogenase Deficiency 301

Cystic Fibrosis 303

**Oligogenic Disorders 305**

Autosomal Recessive Nonsyndromic Deafness 306

Bardet-Biedl Syndrome 306

**Polygenic Inheritance 307**

Familial Risk Ratio 309

Twin Studies 311

**Locating Quantitative Trait Loci 319**

Case-Control Association Studies 319



from the human genetics files

*Genetics of Human Intelligence* 320

Genome Scans 321

Transmission/Disequilibrium Test 324


Affected Sib Pair Linkage Analysis 325

**Key Terms 327****Summary 327**

References	328
Review Questions	330


chapter 11

**Genomic Imprinting: An Epigenetic Modification    333**

Parent-of-Origin Effect	333
Gene Silencing	335
Genomic Imprinting and Human Disease	339
Prader–Willi Syndrome	340
Angelman Syndrome	343
 from the human genetics files <i>X-Chromosome Inactivation</i>	344
Beckwith–Wiedemann Syndrome	345
Key Terms	346
Summary	346
References	347
Review Questions	348

chapter 12


**Molecular Genetics of Mitochondrial Disorders    349**

Mitochondria and Oxidative Phosphorylation	349
Mitochondrial Genetics	352
Mitochondrial Disorders	354
Myoclonus Epilepsy and Ragged Red Fibers	355
Mitochondrial Encephalomyopathy with Lactic Acidosis and Strokelike Episodes	355
Leber Hereditary Optic Neuropathy	357
Neuropathy, Ataxia, and Retinitis Pigmentosa	358
Kearns–Sayre Syndrome	358
Nuclear-Encoded Mitochondrial Disorders	359
Mitochondrial Protein Importation Defects	360
Substrate Transport Defects	360
Substrate Utilization Defects	360
Iron Transport Defect	361
Electron Transport Chain Defects	361
 from the human genetics files <i>Revelations From the Grave: Using Mitochondrial DNA Analysis to Resolve Historical Mysteries</i>	362
Mitochondrial DNA Defects	363
Key Terms	365
Summary	365
References	366
Review Questions	367




## chapter 13

### **Molecular Genetics of Muscle Disorders 369**

- Structure of Skeletal Muscle 369
- Dystrophin and Associated Muscle Proteins 371
- Cardiac and Smooth Muscle 373
- Studying Inherited Muscle Disorders 373
- Skeletal Muscle Disorders 374
  - Duchenne Muscular Dystrophy 374
  - Limb-Girdle Muscular Dystrophy 376
  - Congenital Muscular Dystrophy 378
  - Facioscapulohumeral Muscular Dystrophy 380
- Cardiac Muscle Disorders 382
  - Dilated Cardiomyopathy 382
-  **from the human genetics files**  
*Discovering the DMD Gene* 385
- Hypertrophic Cardiomyopathy 388
- Key Terms 390
- Summary 390
- References 391
- Review Questions 392

## chapter 14

### **Molecular Genetics of Neurological Disorders 393**

- Neurons 394
- Nonneuronal Cells of the Nervous System 395
- Resting Membrane Potential 396
- Initiation, Propagation, and Synaptic Transmission of a Nerve Impulse 397
- Parts of the Brain 400
- Neuronal Channelopathies 402
- Alzheimer Disease 403
  - Biochemistry of Senile Plaques and Neurofibrillary Tangles 405
  - Genetics of Alzheimer Disease 409
  - Mutations of the Amyloid Precursor Protein Gene 409
  - Mutations in the Presenilin Genes 410
  - Genetic Risk Factor for Alzheimer Disease 411
- Huntington Disease and Other Trinucleotide Repeat Expansion Diseases 412
- Amyotrophic Lateral Sclerosis 420
- Charcot-Marie-Tooth Disease 422
- Inherited Prion Diseases 425
-  **from the human genetics files**  
*Genetically Engineered Animal Models for Studying Inherited Human Disorders* 426
- Schizophrenia 430
- Key Terms 433

Summary	433
References	435
Review Questions	437

## chapter 15

### **Molecular Genetics of the Eye 439**

#### **Human Visual System 440**

Structure of the Eye 440

Phototransduction: Conversion of Radiant Energy into Nerve Impulses 442

#### **Studying the Molecular Basis of Inherited Disorders of the Human Eye 444**

#### **Genetic Disorders of the Human Eye 445**

Corneal Dystrophies 445

Glaucoma 447

Aniridia 450

Cataracts 452

Retinitis Pigmentosa 455

Congenital Stationary Night Blindness 459

Choroideremia 460

#### **Color Vision Defects 461**



**from the human genetics files**

*Searching for the Genetic Basis of Myopia 462*

Isolation of Human Rhodopsin and Color Opsin Genes 462

Molecular Genetics of Red and Green Color Vision Defects 463

Blue Cone Monochromacy 466

Blue Color Vision Defects 467

Rod Monochromacy 467

**Key Terms 468**

**Summary 468**

**References 469**

**Review Questions 470**

## chapter 16

### **Molecular Genetics of Cancer Syndromes 471**

#### **Cell Proliferation and Cancer 472**

Signal Transduction Pathway for Cell Proliferation 473

Regulation of the Cell Division Cycle 477

Apoptosis: Programmed Cell Death 480

Tumor Metastasis 481

Oncogenes 482

Alteration of Oncogenes in Cancer Cells 485

Tumor Suppressor Genes 487

#### **Neurofibromatoses 488**

Neurofibromatosis Type 1 488

Neurofibromatosis Type 2 490

#### **Breast Cancer 490**

#### **Retinoblastoma 493**