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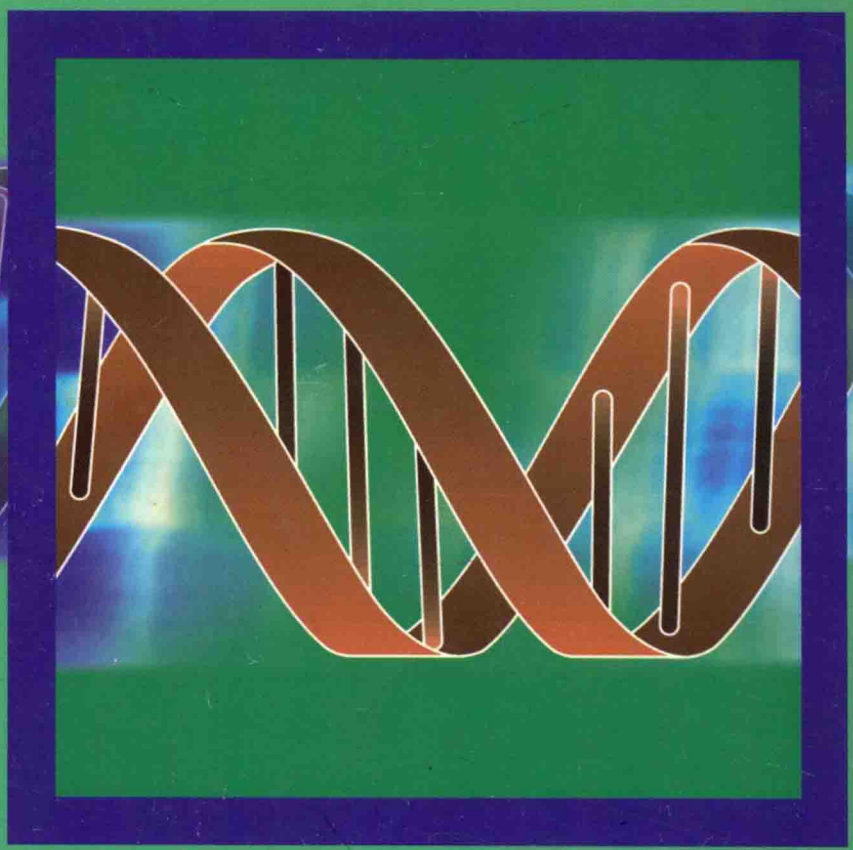
Medical Genetics

Second Edition

Jorde • Carey • Bamshad • White



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Medical Genetics

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Medical Genetics

To our families

Eileen and **Alton Jorde**
Leslie, Patrick, and **Andrew Carey**
Jerry and **Joanne Bamshad**
Joan, Juliette, and **Jeremy White**

Foreword

J.B.S. Haldane titled an anthology of some of his more dyspeptic writings, "Everything Has a History," and this is clearly applicable to the field of medical genetics. More than 200 years ago scientists such as Buffon, Lamarck, Goethe, and Kielmeyer reflected on how the developmental history of each organism related to the history of life on Earth. Based on these ideas, the discipline of biology was born in eighteenth-century Europe, enjoyed adolescence as morphology and comparative anatomy in the nineteenth century, and has reached adulthood in the twentieth century as the field of genetics. However, the late nineteenth century definition of genetics (heredity) as the science of variation (and its causes) is still valid. Thus, human genetics is the science of human variation, medical genetics the science of abnormal human variation, and clinical genetics that branch of medicine that cares for individuals and families with abnormal variation of structure and function.

In the late nineteenth and early twentieth century, the unity of morphology-based science was gradually replaced by a pluralistic view of biology that splintered the field into many different, and often rivalrous, disciplines. However, thanks to the application of novel molecular biological methods to the analysis of development and to the understanding of the materials of heredity (i.e., genes), the various branches of biology are being reunited. This new discipline, termed molecular morphology, may be defined as the study of the form, formation, transformation, and malformation of living organisms. Indeed, ignorant as they may be of the traditional methods of historiography, geneticists have developed their own brilliant and highly effective methods. Consequently, they have achieved a perspective remarkably longer and much better documented than that of historians. This nearly four-billion-year perspective unites living organisms into a single web of life related to each other in unbroken descent to a common ancestor. This makes the phylogenetic (i.e., the genetic relationships of different species to one another) and the ontogenetic perspectives of development (i.e., the genetic basis for the development of individual organisms) not only complementary but inseparable. Thus, it is now possible to effectively explore a key question of biology of the nineteenth and twentieth centuries: what is the relationship between evolution and development?

In 1945 the University of Utah established the Laboratory for the Study of Hereditary and Metabolic Disorders (later called the Laboratory of Human Genetics). Here, an outstanding group of scientists performed pioneering studies on clefts of lips and palate, muscular dystrophy, albinism, deafness, hereditary polyposis of the colon (Gardner syndrome), and familial breast cancer. These predecessors would be enormously proud of their current peers at the University of Utah, whose successes have advanced knowledge in every aspect of the field of genetics.

In their attempts to synthesize the story of genetics and its applications to human variability, health and disease, development, and cancer, the authors of this text have succeeded admirably. In the second edition, the authors have extensively revised the previous twelve chapters by adding new research data and human applications. They have also added two new chapters that discuss the fundamental concepts and clinical applications of biochemical genetics and developmental genetics. Thus, this concise, well written and illustrated, carefully edited and indexed book is highly recommended to undergraduate students, new graduate students, medical students, genetic counseling students, nursing students, and students in the allied health sciences. Importantly, it is also a wonderful text for the practicing physician (primary care providers and specialists) who wants an authoritative introduction to the basis and principles of modern genetics as applied to human health and development. This text, by distinguished and internationally respected colleagues and friends who love to teach, is a joy to read in its expression of enthusiasm and of wonder, which Aristotle said was the beginning of all knowledge.

Einstein once said, "The most incomprehensible thing about the world is that it is comprehensible." When I began to work in the field of medical genetics, the gene

was widely viewed as incomprehensible. Indeed, some scientists, such as Goldschmidt, cast doubt on the very existence of the gene, although the great American biologist E.B. Wilson had predicted its chemical nature more than 100 years previous. In this text, genes and their function in health and disease are made comprehensible in a manner that should have wide appeal to all.

John Opitz, MD
Salt Lake City, Utah

Preface

Medical genetics is a rapidly progressing field. No textbook can remain factually current for long, so we have attempted to emphasize the central principles of genetics and their clinical application. In particular, this textbook integrates recent developments in molecular genetics with clinical practice.

This new edition maintains the format and presentation that were well received in the first edition. Basic principles of molecular biology are introduced early in the book so that they can be discussed and applied in subsequent chapters. The chapters on autosomal and X-linked disorders include discussions of recent developments such as genomic imprinting, anticipation, and expanded trinucleotide repeats. The chapter on cytogenetics highlights recent molecular advances in this area. Gene mapping and cloning, a central focus of modern medical genetics, is treated at length. Chapters are included on the rapidly developing fields of immunogenetics and cancer genetics. Departing somewhat from tradition, this book gives special emphasis to the genetics of common adult diseases such as diabetes, cancer, and heart disease. Although such diseases are more refractory to genetic analysis than many of the pediatric diseases usually found in medical genetics textbooks, their impact on public health is enormous. Fortunately, they too are beginning to yield to newer methods of genetic analysis. The book concludes with chapters on genetic diagnosis (again emphasizing current molecular approaches) and clinical genetics and genetic counseling.

A new feature in this edition is the connection of content throughout the text with a Web site. To provide access to the continually changing information in medical genetics, we have developed an Internet Web page at the University of Utah School of Medicine (http://medgen.genetics.utah.edu). The Web page includes many additional patient photographs, other clinical images, hyperlinks to other relevant sites, recent research findings, and other up-to-the-minute changes in the field. The symbol **WWW** will be found throughout the text next to topics that are supplemented by information on the Web page.

Several pedagogical aids are incorporated in this book:

- Clinical Commentary boxes present detailed coverage of the most important genetic diseases and provide examples of modern clinical management.
- Mini-summaries highlighted in a second color are placed on nearly every page to help the reader understand and summarize important concepts.
- Study questions provided at the end of each chapter assist the reader in review and comprehension.
- A detailed glossary is included at the end of the book.
- Key terms are emphasized in boldface.
- Important references are listed at the end of each chapter.

Many major additions have been incorporated into this revision:

- A new chapter on the biochemical aspects of genetic disease (Chapter 7) provides expanded explanation of the concepts that underlie biochemical genetics.
- A new chapter on developmental genetics (Chapter 10) discusses the many recent advances in our understanding of gene regulation and their clinical consequences.
- Expanded content on gene cloning, gene therapy, and genetic diagnosis stresses some of the fastest growing clinical applications of genetics.
- Forty new clinical photographs have been added.
- Several "vignettes" from patients and families have been added to provide the patient's perspective on genetic disease.
- Additional study questions have been included in each chapter.
- An expanded comprehensive index includes all text citations of all diseases.

This textbook evolved from courses we teach for medical students, nursing students, and graduate and undergraduate students in human genetics. These students are the primary audience for this book, but it should also be useful for students in genetic counseling and biology and for house staff, physicians, and other

health care professionals who wish to become more familiar with medical genetics.

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Many of our colleagues have generously donated their time and expertise in reading and commenting on portions of this book. We extend our sincere gratitude to Arthur Brothman, PhD; Peter Byers, MD; William Carroll, MD; Debbie Dubler, BS; Ruth Foltz, MS; Sandra Hasstedt, PhD; James Kushner, MD; Jean-Marc Lalouel, MD, DSc; Claire Leonard, MD; Mark Leppert, PhD; William McMahon, MD; James Metherall, PhD; Shige Sakonju, PhD; Carl Thummel, PhD; Thérèse Tuohy, PhD; Scott Watkins, BS; John Weis, PhD; H. Joseph Yost, PhD; Maxine J. Sutcliffe, PhD; Leslie R. Schover, PhD; and Craig Smith, medical student. In addition, a number of colleagues provided photographs; they are acknowledged individually in the figure captions. We wish to thank Peeches Cedarholm, RN, and Bridget Kramer, RN, for their help in obtaining and organizing the photographs. The karyotypes in Chapter 6 were provided by Arthur Brothman, PhD, and Bonnie Issa, BS. The illustrations were originally created by Carol Cassidy. Our editors at Mosby, Linda Caldwell and Beverly Copland, offered ample encouragement and understanding. Finally, we wish to acknowledge the thousands of students with whom we have interacted during the past two decades. Teaching involves communication in both directions, and we have undoubtedly learned as much from our students as they have learned from us.

Lynn B. Jorde
John C. Carey
Michael J. Bamshad
Raymond L. White

CLINICAL COMMENTARY BOXES

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Background and History

Genetics is playing an increasingly important role in the practice of clinical medicine. Medical genetics, once largely confined to relatively rare diseases seen by only a few specialists, is now becoming a central component of our understanding of most major diseases. These include not only the pediatric diseases, but also common adult diseases such as heart disease, diabetes, many cancers, and many psychiatric disorders. Because all components of the human body are influenced by genes, genetic disease is relevant to all medical specialties. Today's health care practitioners must understand the science of medical genetics.

WHAT IS MEDICAL GENETICS?

Medical genetics involves any application of genetics to medical practice. It thus includes studies of the inheritance of diseases in families, the mapping of disease genes to specific locations on chromosomes, analyses of the molecular mechanisms through which genes cause disease, and the diagnosis and treatment of genetic disease. As a result of rapid progress in molecular genetics, gene therapy—the insertion of normal genes into patients in order to correct genetic diseases—has recently been initiated. Medical genetics also includes genetic counseling, which involves the communication of information regarding risks, prognoses, and treatment to patients and their families.

WHY IS A KNOWLEDGE OF MEDICAL GENETICS IMPORTANT FOR TODAY'S HEALTH CARE PRACTITIONER?

There are several answers to this question. Genetic diseases make up a large proportion of the total disease burden in both the pediatric and adult populations (Table 1-1). This proportion will continue to grow as our understanding of the genetic basis of diseases grows. In addition, modern medicine is placing an increasing emphasis on the importance of prevention. Because genetics provides a basis for understanding the fundamental biological makeup of the organism, it naturally leads to a better understanding of the disease process. In many cases this knowledge can lead to the actual prevention of the disorder. It also leads to more effective disease treatment. Prevention and effective treatment are among the highest goals of medicine. In the chapters that follow, we shall see many examples of the ways in which genetics contributes to these goals. But first, we shall review the foundations upon which current practice is built.

A BRIEF HISTORY

The inheritance of physical traits has been a subject of curiosity and interest for thousands of years. The ancient Hebrews and Greeks, as well as later Medieval scholars, described many genetic phenomena and proposed theories to account for them. Many of these theories were incorrect. Gregor Mendel (Fig. 1-1), an Austrian monk who is usually considered to be the "father" of genetics, advanced the field significantly by performing a series of cleverly designed experiments on living organisms (garden peas). He then used this experimental information to formulate a series of fundamental principles of heredity.

Mendel published the results of his experiments in 1865 in a relatively obscure journal. It is one of the ironies of biological science that his discoveries, which still form the foundation of genetics, received virtually no recognition for 35 years. At about the same time, Charles Darwin formulated his theories of evolution, and his cousin, Francis Galton, performed an extensive series of family studies (concentrating especially on twins) in an effort to understand the influence of heredity on various

TABLE 1-1 A Partial List of Some Important Genetic Diseases

Disease	Approximate prevalence
Chromosome Abnormalities	
Down syndrome	1/700 to 1/1,000
Klinefelter syndrome	1/1,000 males
Trisomy 13	1/10,000
Trisomy 18	1/6,000
Turner syndrome	1/2,500 to 1/10,000 females
Single-Gene Disorders	
Adenomatous polyposis coli	1/6,000
Adult polycystic kidney disease	1/1,000
α-1-Antitrypsin deficiency	1/2,500 to 1/10,000 Caucasians
Cystic fibrosis	1/2,000 to 1/4,000 Caucasians
Duchenne muscular dystrophy	1/3,500 males
Familial hypercholesterolemia	1/500
Fragile X syndrome	1/4,000 males; 1/8,000 females
Hemochromatosis (hereditary)	1/300 Caucasians are homozygotes; approximately 1/1,000 to 1/2,000 are affected
Hemophilia A	1/10,000 males
Hereditary nonpolyposis colorectal cancer	Up to 1/200
Huntington disease	1/20,000 Caucasians
Marfan syndrome	1/10,000 to 1/20,000
Myotonic dystrophy	1/7,000 to 1/20,000 Caucasians
Neurofibromatosis type 1	1/3,000 to 1/5,000
Osteogenesis imperfecta	1/5,000 to 1/10,000
Phenylketonuria	1/10,000 to 1/15,000 Caucasians
Retinoblastoma	1/20,000
Sickle cell disease	1/400 to 1/600 African-Americans; up to 1/50 in central Africa
Tay-Sachs disease	1/3,000 Ashkenazi Jews
Thalassemia	1/50 to 1/100 (South Asian and circum-Mediterranean population)
Multifactorial Disorders	
Congenital malformations	
Cleft lip with/without cleft palate	1/500 to 1/1,000
Club foot (talipes equinovarus)	1/1,000
Congenital heart defects	1/200 to 1/500
Neural tube defects (spina bifida, anencephaly)	1/200 to 1/1,000
Pyloric stenosis	1/300
Adult diseases	
Alcoholism	1/10 to 1/20
Alzheimer disease	1/10 (Americans over age 65)
Bipolar affective disorder	1/100 to 1/200
Cancer (all types)	1/3
Diabetes (types I and II)	1/10
Heart disease/stroke	1/3 to 1/5
Schizophrenia	1/100
Mitochondrial diseases	
Kearns-Sayre disease	Rare
Leber hereditary optic neuropathy (LHON)	Rare
Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS)	Rare
Myoclonic epilepsy and ragged-red fiber disease (MERRF)	Rare

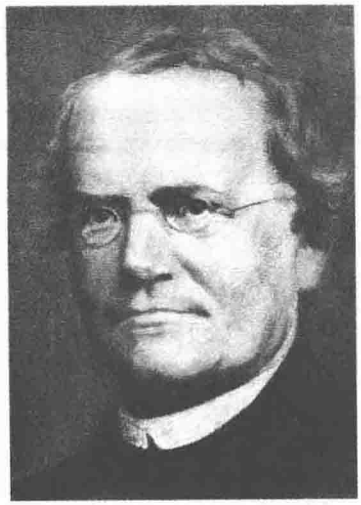

FIG. 1-1 Gregor Johann Mendel
(From Raven PH, Johnson GB [1992] Biology. Ed. 3. Mosby, St Louis. With permission of McGraw-Hill, NY.)

human traits. Neither scientist was aware of Mendel's work.

Genetics as we know it today is largely the result of research performed during the twentieth century. Mendel's principles were independently rediscovered in 1900 by three different scientists working in three different countries. This was also the year in which Landsteiner discovered the ABO blood group. In 1902, Archibald Garrod described alkaptonuria as the first "inborn error of metabolism." In 1909, Johannsen coined the term **gene** to denote the basic unit of heredity.

The next several decades were a period of considerable experimental and theoretical work. Several organisms, including *Drosophila* (fruit flies) and *Neurospora* (bread mold) served as useful experimental systems in which to study the actions and interactions of genes. For example, H.J. Muller demonstrated the genetic consequences of ionizing radiation in the fruit fly. During this period, much of the theoretical basis of population genetics was developed by three central figures: Ronald Fisher, J.B.S. Haldane, and Sewall Wright. In addition, the modes of inheritance of several important genetic diseases, including phenylketonuria, sickle cell disease, Huntington disease, and cystic fibrosis, were established. In 1944, Oswald Avery showed that genes are composed of **DNA (deoxyribonucleic acid).**

Probably the most significant achievement of the 1950s was the specification of the physical structure of DNA by James Watson and Francis Crick in 1953. Their seminal paper, which was only one page in length, formed the basis for what is now known as **molecular genetics** (the study of the structure and function of genes at the molecular level). Another significant accomplishment in this decade was the correct specification of the number of human chromosomes. Since the early 1920s, it had been thought that humans had 48 chromosomes in each cell. Only in 1956 was the correct number, 46, finally determined. The ability to count and identify chromosomes led to a flurry of new findings in cytogenetics, including the discovery in 1959 that Down syndrome is caused by an extra copy of chromosome 21.

Technological developments since 1960 have brought about significant achievements at an ever-increasing rate. The most spectacular have occurred in the field of molecular genetics. During the past decade, nearly 6,000 genes have been mapped to specific chromosome locations. The Human Genome Project, a large collaborative venture begun in 1990, hopes to provide the complete human DNA sequence by the year 2003 (the term **genome** refers to all of the genes in an organism). Important developments in computer technology help to decipher the barrage of data being generated by this and related projects. In addition to mapping genes, molecular geneticists have pinpointed the molecular defects underlying a number of important genetic diseases. This research has contributed greatly to our understanding of the ways in which gene defects can cause diseases, opening the path to more effective treatment and potential cures. The next decade promises to be a time of great excitement and fulfillment.

TYPES OF GENETIC DISEASES

Each human is estimated to have approximately 50,000 to 100,000 different genes. Alterations in these genes, or in combinations of them, can produce genetic disorders. These disorders are classified into several major groups:

1. **Chromosome disorders**, in which entire chromosomes, or large segments of them, are missing, duplicated, or otherwise altered. These disorders include diseases such as Down syndrome and Turner syndrome.
2. Disorders in which single genes are altered (often termed "mendelian" conditions, or **single-gene disorders**). Well-known examples include cystic fibrosis, sickle cell disease, and hemophilia.
3. **Multifactorial disorders**, which are due to a combination of multiple genetic as well as environmental causes. Many birth defects, such as cleft lip and/or cleft palate, as well as many adult disorders, including heart disease and diabetes, belong in this category.
4. **Mitochondrial disorders**, a relatively small number of diseases caused by alterations in the small cytoplasmic mitochondrial chromosome.

Table 1-1 provides some examples of each of these types of diseases.

Of these major classes of diseases, the single-gene disorders have probably received the greatest amount of attention. These disorders are classified according to the

way in which they are inherited in families (autosomal dominant, autosomal recessive, and X-linked). These modes of inheritance will be discussed extensively in Chapters 4 and 5. As Table 1-2 shows, the number of defined single-gene traits has grown considerably during recent years, with a total of more than 11,000 conditions presently defined. With continued advances, this number is certain to increase.

While some genetic disorders, particularly the single-gene conditions, are strongly determined by genes, many others are the result of multiple genetic and nongenetic factors. We can therefore think of genetic diseases as lying along a continuum (Fig. 1-2), with disorders such as cystic fibrosis and Duchenne muscular dystrophy situated at one end (strongly determined by genes), and conditions such as measles situated at the other (strongly determined by environment). Many of the most prevalent disorders, such as many birth defects and common diseases like diabetes, hypertension, heart disease, and cancer, lie somewhere in the middle of the continuum. These diseases are the products of varying degrees of both genetic and environmental influences.

THE CLINICAL IMPACT OF GENETIC DISEASE

Genetic diseases are sometimes perceived as being so rare that the average health care practitioner will seldom encounter them. This is far from the truth, which is becoming increasingly evident as our knowledge and technology progress. Less than a century ago, diseases of largely nongenetic causation (diseases caused by malnutrition, unsanitary conditions, and pathogens) accounted for the great majority of deaths in children. During the twentieth century, however, public health has vastly improved. As a result, genetic diseases have come to account for an ever-increasing proportion of pediatric deaths in developed countries. For example, the percentage of deaths due to genetic causes in various hospitals in the United Kingdom has increased from 16.5% in 1914 to 50% in 1976 (Table 1-3).

In addition to contributing to a large proportion of childhood deaths, genetic diseases also account for a large share of admissions into pediatric hospitals. For example, a survey of Seattle hospitals showed that 27% of all pediatric inpatients presented with a genetic disorder, and a survey of admissions into a major pediatric hospital in Mexico showed that 37.8% had a disease that was either genetic or "partly genetic."

Another way to assess the importance of genetic diseases is to ask, "What proportion of individuals in the population will be diagnosed with a genetic disorder?" This is not as simple a question as it may seem. A variety of factors can influence the answer. For example, some diseases are found more frequently in certain ethnic groups. Cystic fibrosis is especially common among Europeans, while sickle cell disease is especially common among Africans. Some diseases are more common in older individuals. Colon cancer, breast cancer, and Alzheimer disease, for instance, are each caused by dominant genes in a small proportion (5% to 10%) of cases

TABLE 1-2 Number of Entries Representing Loci Identified Mainly by Mendelizing Phenotypes

MIM edition	Phenotype autosomal dominant	Autosomal recessive	X-linked	Y-linked	Mitochondrial	Total
1966 (1st ed)	837	531	119			1,487
1968 (2nd ed)	793	629	123			1,545
1971 (3rd ed)	943	783	150			1,876
1975 (4th ed)	1,218	947	171			2,336
1978 (5th ed)	1,489	1,117	205			2,811
1983 (6th ed)	1,827	1,298	243			3,368
1986 (7th ed)	2,201	1,420	286			3,907
1988 (8th ed)	2,559	1,477	310			4,346
1990 (9th ed)	3,047	1,554	336			4,937
1992 (10th ed)	3,711	1,631	368			5,710
1994 (11th ed)	4,457	1,730	412	19	59	6,677
1997 (12th ed)	8,005*		495	27	60	8,587†
2000 (online edition)	10,671*		624	38	60	11,393

From McKusick VA (1998) Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes. Ed 12. Johns Hopkins University Press, Baltimore.

*Represents all entries that relate to loci on autosomes.

†Includes 425 entries with a number sign (#) signifying phenotype descriptions, not independent additional gene loci.