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The concept of molecular medicine dates back to Linus Pauling, who in the late 1940s and early 1950s generalized from the ideas that came from the study of the sickle cell hemoglobin molecule. With the first cloning of human genes about 1976, molecular genetics took the molecular perspective of disease to the level of DNA. The term molecular medicine achieved wide currency in the 1980s with the assignment of this designation to journals, at least one society, institutes, and academic divisions of departments of internal medicine. Undoubtedly, molecular medicine has been abetted by the Human Genome Project, which has aided greatly in the molecular characterization of disease. Map-based gene discovery, as in positional cloning of previously unknown genes responsible for “mystery diseases,” could be now replaced by sequence-based gene discovery.

What is molecular medicine? In the first edition of Principles of Molecular Medicine, Francis Collins seems to define it as “molecular genetics and medicine”—the last four words of his Foreword. He was referring to the pervasive relevance of genetics and genomics to all of medicine. In essence, molecular medicine is genetic medicine.

Since the publication of the first edition Principles of Molecular Medicine in 1998, the Human Genome Project has provided a “complete” sequence of the human genome with several surprising revelations relevant to molecular medicine.

As indicated in the Preface of the first edition, the total count of genes was thought to be 50,000 to 80,000. Scrutiny of the complete human sequence leads to a count only half that, perhaps fewer than 30,000. It has come to be realized that each gene can give rise to multiple protein gene products through alternative splicing of pre-messenger RNA, as well as through different posttranscriptional modification of the gene products. Each gene may on the average have as many as 10 different protein products. Mutations in different ones of these can cause quite different clinical disorders. Thus the focus has shifted to the transcriptome and to the proteins that constitute the proteome—a shift from genomics to proteomics.

Compilation of the rapidly expanded topic of molecular medicine since the edition of some 8 years ago is a daunting task. The rate at which new discoveries have been made means that there are many new opportunities and challenges for clinical medicine. One of the effects of the completion of the Human Genome Project is the increasing application of the fields of molecular biology and genetics to the understanding and management of common diseases. Assimilation of the new developments since the first edition has been ably accomplished by Drs. Runge and Patterson with the help of their many knowledgeable authors.

As was evident in the first edition, molecular genetics is involved in every specialty of medicine. A recurrent theme in that edition, perhaps even more striking in the present one, is that information gleaned and research methods designed in one specialty have been highly influential on researchers and physicians in other fields—often in ways that could not have been foreseen. The editors have succeeded in considering all the disciplines while searching for connections and correlations that might otherwise be missed.

The organization selected by the editors allows for the molecular bases of disease, as well as the constantly evolving areas of ethical issues and counseling that affect all disciplines, to be covered in the opening section. Specifics in the several medical disciplines are then handled splendidly in the sections that follow. Each chapter resounds with the amazing detail of what is known and simultaneously probes the many unanswered questions that provide new avenues for research in the 21st century. The state-of-the-art focus in each specialty will be much appreciated by the reader, whether practitioner, researcher or student.

The authors and section editors that participated in this text are recognized leaders in their fields from around the globe. They and Drs. Runge and Patterson, who have led and coordinated this extraordinary effort, deserve commendation. The product is a text that will be useful for all interested in the molecular pathogenesis of disease.

Victor A. McKusick, MD
Foreword to the First Edition

Until recently, medical genetics and molecular medicine were considered the exclusive province of academic specialists in tertiary-care medical centers. Queried about their familiarity with molecular genetic aspects of clinical medicine, most primary-care providers only a few years ago would have responded that such matters were irrelevant to their daily practice.

Yet few could say that today. Few internists or general practitioners have not prescribed recombinant insulin, tPA, or erythropoietin; few pediatricians have not gone through the molecular evaluation of a child with dysmorphology or learning disability; few obstetricians have not performed amniocentesis or CVS for couples at increased genetic risk; and few general surgeons have not faced penetrating questions about the role of genetic testing or prophylactic surgery from women with a strong family history of breast or ovarian cancer.

This level of emergence of molecular genetics into clinical medicine is still quite modest, however, compared to what is coming. As the human genome project hurtles toward completion of the sequence of a reference human genome, and the identification of all human genes, by 2005, the pace of revelations about human illness will continue to accelerate. Until recently, most disease-gene discoveries have related to single-gene disorders (cystic fibrosis, fragile X syndrome, and so on) or to Mendelian subsets of more common illnesses (BRCA1 and BRCA2, the hereditary nonpolyposis colon cancer syndromes, and so on). But with the initiation in 1998 of an aggressive new genome project goal, cataloging all common human sequence variations, it is expected that the weaker polygenic contributors to virtually all diseases will begin to be discerned. Many consequences will result. Individualized preventive medicine strategies, rooted in the gene-based determination of future risk of illness, will become part of the regular practice of medicine. New designer drugs, based not on empiricism but on a detailed understanding of the molecular pathogenesis of disease, will appear. Pharmacogenomics, wherein the efficacy and toxicity of a particular drug regimen can be predicted based on patient genotype, will become a standard component of designing optimum therapy for the individual. And gene therapy, fed by a wealth of disease-gene discoveries, will mature into a significant part of the physician’s armamentarium against disease.

As we watch this train coming down the track, this is an ideal time to collect information about molecular medicine into one authoritative text. Principles of Molecular Medicine aims to do just that, bridging the current gap between basic science and the bedside. It will thus be useful to researchers and clinicians alike. With more than 100 chapters covering a wide variety of topics, its distinguished cohort of section editors, and its abundant tables and illustrations, it provides an accessible and much needed manual to the present and the future of molecular genetics and medicine.

Francis S. Collins
Preface

Since publication of the first edition of *Principles of Molecular Medicine*, dramatic discoveries in molecular medicine along with concomitant rapid technological advances have revolutionized the diagnosis and treatment of a broad range of human diseases. Given the pace of new discovery, genetic- and cell-based therapies may well become a common part of the physicians’ armamentarium in the near future. Direct links between genetic mutations and diseases are being mapped almost routinely. Genomic approaches to diseases such as breast cancer have led to identification of previously unrecognized malignancies and the ability to prognosticate outcomes to therapy. The delicate interplay between adipocytes and regulation of insulin sensitivity, the roles of bone morphogenetic proteins in pulmonary hypertension, and the discovery of mutations involved in an array of cardiomyopathies are but a few of the important recent advances that have direct implications for patient care.

It is virtually impossible to keep track of the breadth of discovery that has led to these biomedical advances. The goal of the many authors and editors of this second edition of the *Principles of Molecular Medicine* has been to present the voluminous discoveries of the past decade in a format that captures the essence of scientific discovery but allows rapid assimilation in each particular area.

This second edition again includes chapters describing advances in fields paralleling traditional medical texts, and will be especially useful to specialists who are updating their education, practicing physicians interested in keeping abreast of new developments, and students appropriately curious about what is known and what lies ahead. Although only 8 years have passed since the first edition was published, we have made every effort to comprehensively update chapters with recent advances and have added chapters for disease entities and areas in which discovery has accelerated during the past five years.

As we have participated in the assembly of this volume, we have had the good fortune to review in depth the molecular discoveries that are transforming medical practice. For example, in the interval since the first edition of this text, stem cell populations have been discovered that regenerate muscle, heart, and neural cell populations, and that have the potential to serve as cell-based therapies in chronic and degenerative diseases. New cell growth and cell death mechanisms that are dysregulated in neoplasia and that may serve as new anticancer targets have been elucidated. Advances have been made in understanding the biology of previously untreatable neurodegenerative diseases such as Huntington’s disease. These and many other important advances in our understanding of human diseases are elucidated in this edition.

In addition, we have been able to note the new epistemologies in the genetic basis of human disease that are rapidly emerging. For instance, characterization of candidate genes for human diseases has expanded well beyond monogenic diseases, the study of late-onset diabetes being a notable example. Molecular alterations can have far-reaching effects on many systems. The identification of genes for epithelial sodium channels has led to a deeper understanding of their role in disorders of total body Na+ homeostasis, blood volume, and blood pressure. As a result of advances like these, views that had been held for much of the 20th century are being reconsidered. For example, hereditary hemochromatosis, a familial disease characterized by excess tissue deposits of iron leading to end-organ damage, has traditionally been thought to result from mutations in a single gene. Very recently, the identification of similar phenotypes associated with mutations of at least four different iron–metabolism genes has expanded our understanding of the pathophysiology of this relatively common genetic disease.

One common theme repeated in the chapters in this text is that the pathophysiology of disease is often a succession of genetic alterations, not just a single mutation. Although understanding these genetic relationships is never simple, their role in human diseases is all the more fascinating to consider. Human health often appears tenuous, but the discovery that a series of genetic missteps is often required to produce many disease states can be reassuring. The presence of several genetic steps in a disease process also suggests that multiple therapeutic targets may exist to modulate the course of these diseases. Less exhilarating is the knowledge that numerous diseases result not just from a complex succession of genetic missteps, but also from an individual’s
interaction with the environment. Abundant examples of this principle are present throughout clinical medicine, and are described in detail in this edition of Principles of Molecular Medicine.

Paradoxically, as new discoveries are made, new mysteries appear. The many advances described in this volume often raise as many new questions as they answer. On the one hand, this indicates that biomedical discovery and medical practice will continue to evolve. On the other hand, the changes in medical care described in the chapters of this text are an indication that the unresolved questions of today may be harbingers of new therapeutic approaches in years to come.

It has been our pleasure to bring together in-depth expositions of the most recent advances in molecular medicine. We invite you to enjoy this magnificent point in biomedical history, as genetics and molecular medicine continue to merge with clinical practice. The compendium of information in Principles of Molecular Medicine: Second Edition, has been made possible by the tireless efforts of our section editors. Without their expertise and commitment to this project, this textbook would not be possible. In addition, we thank the individual authors for sharing their expertise with all of us.

In addition to the phenomenal work of the editors and contributors, we would like to extend special thanks to Ms. Katie O’Brien for her commitment to this project; to Ms. Angela Clotfelter-Rego, whose tireless efforts despite numerous obstacles made this project possible; and to Ms. Carolyn Kruse, who synthesized the work of numerous authors to create a blazingly readable text. The editors thank our families, who have tolerated yet another joint effort. Finally, we would like to dedicate this volume to the first chairmen of medicine we had the privilege to serve under, Juha P. Kokko, MD, PhD, and Victor McKusick, MD. As physicians and scientists, these gentlemen nurtured many of the contributors to this edition, and their own work as scientists is frequently cited directly and indirectly in these chapters. It is on the shoulders of men like these that the principles of molecular medicine have been determined.

Marschall S. Runge, MD, PhD
Cam Patterson, MD
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Plate 1 (Fig. 2, Chapter 4). Fluorescent in situ hybridization of a pediatric leukemia sample demonstrating that one chromosome 5 contains a deleted segment that includes the EGR1 gene.

Plate 2 (Fig. 1, Chapter 10). The left side of the figure depicts fetal circulation in the human. The right side of the figure depicts neonatal circulation in the human.

Plate 3 (Fig. 2, Chapter 10). Dosage sensitive role of Tbx1 in the etiology of cardiovascular defects in mice.

Plate 4 (Fig. 1A–C, Chapter 11). Gross pathological specimens of a heart with (A) hypertrophic cardiomyopathy (HCM) and (C) dilated cardiomyopathy (DCM). Note the marked increased in left ventricular hypertrophy (HCM) and chamber dimensions (DCM) as compared with (B) the normal heart.

Plate 5 (Fig. 2, Chapter 11). Histopathology of distinct human cardiomyopathies revealed by hematoxylin and eosin staining.

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## Abbreviations

### I. MOLECULAR GENETICS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAV</td>
<td>adeno-associated virus</td>
</tr>
<tr>
<td>ABGC</td>
<td>American Board of Genetics Counseling</td>
</tr>
<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
</tr>
<tr>
<td>AMKL</td>
<td>acute megakaryocytic leukemia</td>
</tr>
<tr>
<td>AS</td>
<td>Angelman syndrome</td>
</tr>
<tr>
<td>BBS</td>
<td>Bardet-Biedl syndrome</td>
</tr>
<tr>
<td>BNSF</td>
<td>Burlington Northern Santa Fe Railroad</td>
</tr>
<tr>
<td>BWS</td>
<td>Beckwith-Wiedemann syndrome</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>CEERs</td>
<td>Centers of Excellence in ELSI Research</td>
</tr>
<tr>
<td>CF</td>
<td>cystic fibrosis</td>
</tr>
<tr>
<td>cM</td>
<td>centimorgan</td>
</tr>
<tr>
<td>DPD</td>
<td>dihydropyrimidine dehydrogenase</td>
</tr>
<tr>
<td>DS</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>ELSI</td>
<td>ethical, legal, and social implications</td>
</tr>
<tr>
<td>EM</td>
<td>extensive metabolizer</td>
</tr>
<tr>
<td>F1</td>
<td>filial 1</td>
</tr>
<tr>
<td>FAP</td>
<td>familial adenomatous polyposis</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FISH</td>
<td>fluorescent in situ hybridization</td>
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<tr>
<td>HD</td>
<td>Huntington disease</td>
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<tr>
<td>HER2</td>
<td>human epidermal receptor 2</td>
</tr>
<tr>
<td>HGP</td>
<td>Human Genome Project</td>
</tr>
<tr>
<td>HH</td>
<td>hemihyperplasia</td>
</tr>
<tr>
<td>htSNP</td>
<td>haplotype tagging single-nucleotide polymorphism</td>
</tr>
<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>IGF</td>
<td>insulin-like growth factor</td>
</tr>
<tr>
<td>IND</td>
<td>investigational new drug</td>
</tr>
<tr>
<td>LGK</td>
<td>Lander-Green-Kruglyak</td>
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<tr>
<td>LOD</td>
<td>likelihood of the odds</td>
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<tr>
<td>MCMC</td>
<td>Monte-Carlo Markov Chain</td>
</tr>
<tr>
<td>MDR</td>
<td>multidrug resistance</td>
</tr>
<tr>
<td>MELAS</td>
<td>mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes</td>
</tr>
<tr>
<td>MEN</td>
<td>multiple endocrine neoplasia</td>
</tr>
<tr>
<td>MEN1</td>
<td>multiple endocrine neoplasia type 1</td>
</tr>
<tr>
<td>MEN2</td>
<td>multiple endocrine neoplasia type 2</td>
</tr>
<tr>
<td>MTC</td>
<td>medullary thyroid carcinoma</td>
</tr>
<tr>
<td>mtDNA</td>
<td>mitochondrial DNA</td>
</tr>
<tr>
<td>NHGRI</td>
<td>National Human Genome Research Institute</td>
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<tr>
<td>PKU</td>
<td>phenylketonuria</td>
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<tr>
<td>PM</td>
<td>poor metabolizer</td>
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<tr>
<td>PWS</td>
<td>Prader–Willi syndrome</td>
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<tr>
<td>RP</td>
<td>retinitis pigmentosa</td>
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<tr>
<td>SNP</td>
<td>single-nucleotide polymorphism</td>
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<tr>
<td>TDT</td>
<td>transmission/disequilibrium test</td>
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<tr>
<td>UC</td>
<td>ulcerative colitis</td>
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<tr>
<td>UPD</td>
<td>uniparental disomy</td>
</tr>
<tr>
<td>URM</td>
<td>ultra rapid metabolizer</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>WAGR</td>
<td>Wilm’s tumor, aniridia, genital–urinary abnormalities, and mental retardation</td>
</tr>
<tr>
<td>XP</td>
<td>xeroderma pigmentosum</td>
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1 Mendelian Inheritance

Bruce R. Korf

SUMMARY

The basic patterns of genetic transmission in humans have been known for about a century, but are now coming to be understood at the molecular level. In addition to classical dominant, recessive, and sex-linked inheritance, more complex patterns have also been identified. These include maternal transmission of traits encoded in the mitochondrial genome, digenic traits determined by two distinct genes, and genomic imprinting. It is becoming clear that both rare and common genetic traits are determined by a complex interaction of multiple genetic and nongenetic factors.

Key Words: Digenic; dominant; expressivity; imprinting; Mendelian; mitochondrial inheritance; penetrance; recessive; X-linked.

INTRODUCTION

The existence of human traits that are transmitted from generation to generation in accordance with Mendel’s laws was first recognized early in the 20th century. Understanding the mechanisms that underlie Mendelian inheritance has unfolded over the ensuing decades, and forms the basis for knowledge of human genetics. With increasing sophistication it has become clear that the seemingly straightforward rules of inheritance—for example, dominance and recessiveness—are in fact complex. With more nuanced understanding, however, comes recognition of genetic principles that have a critical role in diagnosis and counseling. This chapter reviews the basics of Mendelian inheritance and explores how insights in molecular genetics are both explicating and changing views of these fundamental principles.

PATTERNS OF GENETIC TRANSMISSION

The patterns of Mendelian transmission ensue from the fact that humans are diploid organisms, inheriting a complete set of genes from each parent. The two individual copies of a specific gene are referred to as alleles. The alleles on homologous chromosomes segregate at meiosis and new combinations are paired together on fertilization. The specific alleles at a locus comprise the genotype; the physical characteristic that results from action of the alleles is the phenotype.

Dominant and Recessive Inheritance

The first instance of Mendelian transmission in humans was recognized by Archibald Garrod, working in the early years of the 20th century. He originated the term “inborn errors of metabolism” to describe a set of disorders in which specific biochemical pathways were deranged, leading to accumulation of toxic substrates or deficiency of end products. He recognized that these conditions are familial and behave as Mendelian recessive traits. A recessive trait is only expressed in a homozygous individual who inherits a mutant allele from both parents (Fig. 1-1A). The parents are heterozygous carriers, who are asymptomatic because of the action of the dominant allele. A couple consisting of two carriers faces a 25% risk of transmission of homozygosity to any offspring.

The basis of recessive inheritance of inborn errors of metabolism is that the responsible genes encode enzymes required to catalyze specific biochemical reactions. Enzymes function in a catalytic manner, so the 50% level of activity that may occur in a heterozygote is sufficient to complete the reaction and thereby avoid the phenotype. Only a homozygote will lack sufficient activity to manifest the disorder. An example is the disorder phenylketonuria, which is because of mutation in the gene that encodes the enzyme phenylalanine hydroxylase, required to convert phenylalanine to tyrosine. Homozygotes accumulate phenylalanine to toxic levels, and also have a deficiency of phenylalanine metabolites such as dopamine and melanin. Children with this disorder detected by newborn screening can be spared the severe developmental impairment of this disorder by treatment with a low-phenylalanine diet. Carrier parents are asymptomatic, but have a 25% risk of additional affected children.

Dominant traits are expressed in both homozygous and heterozygous individuals (Fig. 1-1B). If the trait is rare, most affected individuals will be heterozygous. Moreover, many dominantly inherited medical conditions are lethal in the homozygous state, technically indicating that they are not “true” dominants. An individual who is heterozygous for a dominant trait has a 50% chance of passing either allele to any offspring.

A prototypical autosomal-dominant disorder is Marfan syndrome, resulting from mutation in the connective tissue protein fibrillin. Affected individuals are tall, lanky, and experience complications such as joint dislocation, lens subluxation, and aortic aneurysms because of weakness of connective tissue. The disorder is compatible with survival to reproductive age, and affected individuals have a 50% risk of transmitting the mutant allele to any offspring. The molecular basis for dominance is reviewed later.

Sex Linkage

Sex determination occurs by inheritance of two X chromosomes in females or an X and a Y in males. The Y carries a limited repertoire of genes, including those involved

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in testes determination and spermatogenesis. The X carries a larger set, most of which lack counterparts on the Y. Therefore, for these genes, females have two alleles, but males only one. There are regions at the two ends of the X chromosome where homologous loci exist on the Y. These are referred to as pseudoautosomal. For the other loci found only on the X males are said to be hemizygous.

Gene dosage is finely controlled, and, therefore, a mechanism exists to compensate for the dosage differences in males and females for X-linked genes. Most genes on the X chromosome are inactivated on one of the two X’s in female cells early in development. The choice of X to be inactivated is random, but once an X is “turned off,” that chromosome remains off in all descendents of a particular cell. Some genes, especially those in the pseudoautosomal regions escape inactivation. The molecular basis for X chromosome inactivation is becoming understood. It includes selection of the chromosome to be inactivated by an RNA molecule encoded by an X-linked gene called Xist and subsequent methylation of DNA on the inactive chromosome.

There are few Y-linked traits of medical significance. A Y-linked gene is transmitted from a male to all his sons and none of his daughters. X-linked traits are transmitted by a heterozygous female to half her offspring; a hemizygous male passes the gene to all his daughters and none of his sons (Fig. 1-1C). The concepts of dominance and recessiveness are meaningless when applied to genes on the X chromosome, which are subject to inactivation, because only one allele is expressed in any cell in either a male or a female. Whether or not a trait is expressed in a heterozygous female depends on whether expression of the mutant gene in approx 50% of cells is sufficient to cause the phenotype, or whether expression of the wild-type allele in 50% is insufficient. Classic “X-linked-recessive” traits such as Duchenne muscular dystrophy and hemophilia A tends not to lead to a phenotype in heterozygous females, unless X chromosome inactivation has somehow been skewed toward inactivation of the wild-type allele. “X-linked-dominant” traits, such as hypophosphatemic rickets, are expressed in both sexes. X-linked traits such as Rett syndrome or incontinentia pigmenti are lethal in hemizygous males and, therefore, only are seen in heterozygous females (Fig. 1-1D).

MATERNAL TRANSMISSION Although not a “Mendelian” pattern, maternal inheritance is another form of single gene transmission. Maternal inheritance applies to a set of genes found on the 16.5-kb circular double-stranded DNA molecules found within mitochondria. These encode 13 peptides involved in mitochondrial oxidative phosphorylation, as well as a set of transfer RNAs and ribosomal RNAs. There are thousands of DNA molecules within mitochondria in every cell. If there is a mutation in some, the cell is said to be heteroplasmic (Fig. 1-2A). Because mitochondrial DNA molecules segregate at random during cell division, the proportion of mutant and wild-type DNA molecules can vary widely between cells. Mitochondrial DNA mutations tend to interfere with cellular energy production. Because of heteroplasmy there can be a wide range of phenotypic effects, depending on the proportion of mutant mitochondria in different tissues.
Most, if not all, mitochondria are transmitted through the oocyte. As a result, a female with a mitochondrial mutation will pass it to all of her offspring, whereas a male will not transmit it at all (Fig. 1-2B). Once again, however, heteroplasm will account for variability, in this case among members of a sibship. This creates a challenge in recurrence risk counseling for mitochondrial disorders, because the likelihood that an offspring will inherit sufficient mutant DNA molecules to produce a phenotype cannot be predicted.

COMPLEXITIES OF MENDELIAN TRAITS

Although single gene traits are transmitted in accordance with Mendel’s laws, a number of phenomena may lead to deviation from the expected segregation ratios. These include nonpenetrance, new mutation, mosaicism, anticipation, imprinting, and digenic inheritance.

**Penetrance and Expressivity** Individuals who have the genotype associated with a particular phenotype yet do not display the phenotype are said to be nonpenetrant. For a dominant trait this may lead to a skipped generation (i.e., a trait is seen in a child and a grandparent, but the parent is not affected). Some phenotypes display age-dependent penetrance, so the probability of phenotypic expression increases with age. This is typical of disorders such as Huntington disease or adult polycystic kidney disease. Penetrance is an all-or-none phenomenon for an individual; the phenotype is either present or not at a particular time. Penetration should not be confused with expressivity, which refers to the degree of phenotypic expression from individual to individual. The possibility of nonpenetration or of age-dependent penetrance needs to be considered when counseling an individual at risk of a dominant trait. The lack of phenotype does not necessarily preclude one from occurring at a later age or exclude the possibility of transmission of the trait to an offspring.

**Mutation and Mosaicism** Sporadically affected individuals with a dominant or an X-linked trait may occur because of a new mutation in the sperm or egg cell. Neither parent will be found to carry the trait, and the affected child will be the first affected member of the family. That child, however, will be at risk of transmitting the trait to his or her offspring. Mutation rates vary among different loci, usually hovering in the range of $10^{-4}$ to $10^{-6}$/gamete/generation. Few distinct risk factors have been identified, although there is a slight increase in the risk of mutation with advancing paternal age.

Mutation may occur in somatic cells as well as in the germline. Somatic mutation during early development results in somatic mosaicism, in which an individual has a mixture of mutant and nonmutant cells. This may manifest as milder expression of a phenotype, or as expression of the phenotype in a limited region of the body. A dramatic example is segmental neurofibromatosis, where café-au-lait spots and neurofibromas may be restricted to part of the body. Germline mosaicism results in multiple sperm or egg cells carrying a new mutation. A parent with germline mosaicism can have multiple affected children despite not carrying the mutation in somatic cells.

**Anticipation** It has long been noted that in some families with particular dominant traits, severity increases, and age of onset decreases, from generation to generation. This phenomenon is referred to as anticipation. Although initially thought to be an artifact owing to bias of ascertainment, it is now known to be a real event that is the signature of a specific type of mutation, the triplet repeat expansion (Fig. 1-3). A number of genes include repeated triplets of bases, such as CAG/CAG. The exact number of repeats is a heritable polymorphism, as there is no phenotypic impact regardless of the number, up to a point. Individuals with mutations, however, have expanded numbers of repeats that lead to aberrant gene expression. Anticipation results from two characteristics of repeat expansion mutations. First, the larger the number of repeats, the more severe and earlier is the onset of the disorder. Second, the larger the repeat size, the more unstable it is, creating risk of further expansion in the next generation. The expansion, therefore, increases from generation to generation, leading to anticipation. Disorders associated with triplet repeat expansion tend to affect the nervous system, and include Huntington disease, fragile X syndrome, myotonic dystrophy, spinocerebellar ataxia, and others.

**Imprinting** A subset of genes is expressed only from the maternal or paternal allele, but not both, and is referred to as imprinting. The “imprint” that identifies an allele as being of maternal or paternal origin is “erased” each generation. For example, if it is the maternally derived allele that is expressed, a maternally inherited allele will be turned on in a male, but will be turned off when he transmits it to the next generation. It appears that only
a relatively small number of genes are subject to imprinting, but these account for some distinct phenotypes and unusual patterns of transmission. A dominant trait because of an imprinted gene will only result in a phenotype when the transmitting parent is the one who transmits the expressed allele (Fig. 1-4). This gives rise to multiple examples of nonpenetrance. For example, this is the case in familial glomus tumors. Prader–Willi and Angelman syndromes result from deletions on chromosome 15 from a region that contains imprinted genes. The gene involved in Angelman syndrome is expressed from the maternal allele, so deletion of this allele results in the disorder. In contrast, paternal deletion of the same region produces Prader–Willi syndrome, reflecting the presence of one or more paternally expressed genes in the region. The same phenotypes can result from the inheritance of both copies of chromosome 15 from the same parent, referred to as uniparental disomy. In this case there will be absence of either maternally or paternally expressed genes, depending on whether there are two copies of mother’s or father’s chromosomes. Uniparental disomy results when a trisomic zygote produces an embryo in which disomy is restored by a second nondisjunction event. If the chromosomes that remain are from the parent in whom nondisjunction occurred, uniparental disomy will result. Aside from accounting for some cases of Prader–Willi or Angelman syndromes, uniparental disomy for several other chromosomes has been associated with a phenotype.

DIGENIC INHERITANCE In rare instances, it has been found, for example, in some cases of the eye disorder retinitis pigmentosum. Parents who are heterozygous for two different genes can have doubly heterozygous offspring. If the genes are on different chromosomes, an affected child can transmit both mutant alleles to an offspring, producing apparent dominant transmission. Genes that are subject to digenic inheritance tend to encode proteins that interact with one another in the same pathway.

MOLECULAR BASIS OF MENDELIAN INHERITANCE

The patterns of single gene transmission have been known for a long time, but only recently the phenomena have begun to be understood at the molecular level. The bases for the Mendelian patterns as well as the complexities noted in the previous section are gradually emerging.

RECESSIVE VS DOMINANT ALLELES Recessive alleles, by definition, only exert a phenotypic effect in a homozygous state. In general, this implies that a mutation has resulted in loss of function of the gene product, and that partial loss of function is not sufficient to result in a phenotype. As noted, this is the case for most enzyme deficiencies. The mutations responsible for such disorders tend to be those that cause premature termination of translation, such as frame shifts or stop mutations, nonsense mutations, deletions, or splicing mutations, which significantly disrupt the coding sequence. Missense mutations may also cause a phenotype if they significantly disrupt the function of the gene product.

The basis for dominance can be a diverse set of genetic changes. Some mutations lead to gain of function, for example,
constitutive activation of a cell membrane receptor as occurs in the
FGFR3 gene in achondroplasia. Activation of just one allele is
sufficient to alter the behavior of a cell. Another mechanism is
referred to as dominant negative. Here, a single mutant allele pro-
duces sufficient abnormal product to disrupt cellular function.
This is the hallmark of mutations in genes that encode products of
multimeric proteins. Although only 50% of the protein may be
abnormal, abnormal subunits may contribute to a higher propor-
tion of proteins, resulting in a heterozygous phenotype. This is the
case for some types of collagen mutations responsible for osteo-
genesis imperfecta. Dominant transmission may also occur with
loss-of-function mutations if 50% levels of gene product are insuf-
cient for normal function. This occurs in mild forms of Marfan
syndrome because of loss-of-function fibrillin gene mutations.
Interestingly, dominant negative mutations in this gene cause
more severe disease, because the presence of abnormal fibrillin
molecules has a more pervasive effect on connective tissue
integrity than does 50% reduction of quantity.

A special case of dominant inheritance is accounted for by
tumor suppressor genes. These genes account for familial suscep-
tibility to cancers such as retinoblastoma, colon cancer, and breast
or ovarian cancer. In families with an inherited susceptibility, the
risk is transmitted as a dominant trait. Within a tumor cell, however,
both alleles of the tumor suppressor are mutated, usually with a loss
of function type mutation (Fig. 1-6). The mutation of one allele in
such families is transmitted from generation to generation. An
individual with heterozygous mutation faces an increased risk of
cancer because somatic mutation of the remaining wild-type allele
is all that is required to start a cell on the path to malignancy.

GENETIC HETEROGENEITY There is a wide diversity of
different mutation types, with a range of effects on gene function,
including mutations that increase or decrease levels of gene prod-
uct expression, or change the functional properties of the protein.
Different mutations in the same gene may have differing impacts
on phenotype. The consequence is that different individuals with
a dominant trait may have distinct mutations. Furthermore, the two
mutant alleles in an individual who is homozygous for a recessive
mutation may differ. There are exceptions; in some cases only a
very specific mutation will cause a specified phenotype. This is
ture for the FGFR3 mutation in achondroplasia. In other instances,
a specific mutation may have arisen in an isolated population and
remain relatively common there. This is called the founder effect,
and accounts, for example, for the high prevalence of specific
mutations responsible for Tay-Sachs disease in the Ashkenazi
Jewish population.

Other than these instances, allelic heterogeneity is more a rule
than an exception. In some cases, variable expressivity is
explained by the occurrence of different mutations causing
slightly different phenotypes. Study of genotype–phenotype cor-
relations can sometimes provide information predictive of disease
severity useful in genetic counseling. The difference between
severe Duchenne muscular dystrophy and the milder Becker form
can be predicted from whether the mutation causes complete loss
of the gene product, dystrophin (Duchenne), or production of an
aberrant protein (Becker). In still other cases, the different mutations
result in phenotypes that would not have been regarded as the
same disease. For example, different mutations in the CFTR
gene can cause cystic fibrosis, chronic sinusitis, or male infertility
resulting from congenital bilateral absence of the vas deferens.

Genetic heterogeneity extends not only to different alleles, but
also to different loci. Studies to identify genes responsible for dis-
ease often reveal multiple distinct genes that are associated with
the same phenotype in different individuals. In some instances,
such as congenital deafness, this locus heterogeneity reflects that
a large number of genes contribute to normal hearing. Many of
these genes can be disrupted by mutation, all leading to deafness.
In other cases, genes that encode proteins that interact with one
another in the same pathway result in an indistinguishable phenoty-
pe when mutated. This is the case in tuberous sclerosis, associ-
ated with mutation in either the TSC1 or TSC2 genes. The protein
products, hamartin and tuberin, interact with one another to form
a complex that is involved in the control of cell growth. Locus
heterogeneity is important in clinical genetics, because testing of
the incorrect gene will fail to reveal an underlying mutation and
could lead to incorrect exclusion of a diagnosis. For a recessive
disorder, locus heterogeneity explains why two affected parents
may have unaffected children. This is a common occurrence in
ereditary deafness.

MODIFYING GENES Although some phenotypes are reli-
ably associated with specific genotypes, such as sickle cell anemia
with the substitution of valine for glutamin acid at position 6 β-globin
mutation, mutations should not be thought of as totally determi-
stic of any specific phenotype. All mutations act within a context
that is specified by factors including genetic background and the

Figure 1-5 Pedigree illustrating digenic inheritance. Each parent is
heterozygous for a different gene. The child who is heterozygous for
both expresses the phenotype.

Figure 1-6 Tumor suppressor concept. A tumor suppressor gene is
homozygously mutated in a tumor cell. Those who inherit a heterozy-
gous mutation as a dominant trait are at increased risk of cancer if the
remaining wild-type allele is mutated.
environment. Although a distinction is often made between mono-
genetic and multilaterial phenotypes, in a sense all phenotypes are multifactorial. In some instances, a single gene exerts a major effect and in others many genes exert a more modest effect, but in virtually all cases genetic background and environment play some role.

Modifying loci may be intragenic or may occur as interactions between different gene loci. The poly T polymorphism with the CFTR gene exerts a modifying effect in the expression of mutations within this gene. Individuals may have an allele with 5, 7, or 9T’s with this polymorphic site, which resides within the interval between exons 7 and 8. The 5T allele is associated with skipping of exon 9, whereas the 9T allele leads to normal splicing. Genotype at the poly T site influences phenotype associated with another CFTR mutation, R117H. This mutation is associated with CBAVD when in cis with 9T and opposite another CFTR mutation, but with mild cystic fibrosis if in cis with a 5T allele.

A dramatic example of gene–gene interaction is the phenomenon of epitasis, wherein the phenotype of one gene masks that of another. Individuals will only secrete A or B blood group antigens into saliva if they have at least one dominant Se alleles at the secretor locus. Someone with the se/se genotype will not have A or B antigen in saliva regardless of ABO genotype. Modifier loci with more subtle effects are likely to play a role in a large number of phenotypes. At least some degree of variable expression is probably the consequence of interactions between genes. Any single locus can be visualized as a node in a network. Changing the state of a single node will influence, and be influenced by, a large number of other nodes. In rare and common disorders, expression of a phenotype is a consequence of a complex web of interactions, and genetic analysis will increasingly require such complex systems.

CONCLUSIONS

The rules of Mendelian inheritance have provided the basis for the study of human genetics for a century. Studies at the molecular level have provided an understanding of the basis for single gene inheritance and have uncovered some unexpected mechanisms. With new tools of genomics, exploration is beginning of the complexities of gene interactions as they relate to rare and common phenotypes, and knowledge of the elements of genetics is being integrated into a broader picture of biology.

SELECTED REFERENCES


SUMMARY

The “rules” of segregation of alleles originally defined by Gregor Mendel explained much of the phenomena associated with inheritance and have been dogmatically applied in the field of genetics. However, there are situations in which the rules of Mendelian inheritance cannot explain observed phenomena. A variety of molecular mechanisms have been identified that explain certain phenomena that are not easily explained by traditional Mendelian patterns of inheritance. These non-Mendelian mechanisms differ on a molecular basis, but can be described as a group by the term “nontraditional mechanisms of inheritance” or “nontraditional inheritance.” Stated simply, nontraditional inheritance refers to the pattern of inheritance of a trait or phenotype that occurs predictably, recurrently, and in some cases familiarly, but does not follow the rules of typical Mendelian autosomal or sex chromosome inheritance. Examples discussed in this chapter are the triplet repeat expansion mutations, and genomic disorders including genetic imprinting, mitochondrial inheritance, and multi-allelic inheritance.

Key Words: Angelman syndrome (AS); fragile X; Mendelian; mitochondrial inheritance; multifactorial inheritance; non-Mendelian; Prader–Willi syndrome (PWS).

INTRODUCTION

The “rules” of segregation of alleles originally defined by Gregor Mendel explained much of the phenomena associated with inheritance and have been dogmatically applied in the field of genetics. However, there are situations in which the rules of Mendelian inheritance cannot explain observed phenomena. A variety of concepts have been suggested to explain such phenomena, including the idea that individual genes may function in cooperation with each other and with environmental factors to produce a given phenotype. This concept of multifactorial inheritance is well accepted; however, specific examples for which the various factors can be well defined have been difficult to identify. Other natural phenomena, such as anticipation, in which genetic traits or disorders become more severe or pronounced in successive generations, or genetically determined conditions that appear to depend on the sex of the parent of origin of the involved chromosome, have been difficult to explain, even using concepts of multifactorial inheritance.

A variety of molecular mechanisms have been identified, which explain certain phenomena that are not easily explained by traditional Mendelian patterns of inheritance. These non-Mendelian mechanisms differ on a molecular basis, but can be described as a group by the term “nontraditional mechanisms of inheritance” or “nontraditional inheritance.” Stated simply, nontraditional inheritance refers to the pattern of inheritance of a trait or phenotype that occurs predictably, recurrently, and in some cases familial, but does not follow the rules of typical Mendelian autosomal or sex chromosome inheritance. Examples discussed in this chapter are the triplet repeat expansion mutations and genomic disorders including genetic imprinting, mitochondrial inheritance, and multi-allelic inheritance.

TRIPLET REPEAT EXPANSION

The first disorder identified as resulting from this form of nontraditional inheritance is fragile X syndrome (FRAXA). FRAXA is a well-recognized disorder that causes mental retardation, autistic-like behaviors, and a subtle, but characteristic, external phenotype in all males and many females possessing the mutation. Early studies confirmed that the locus of interest was on the X chromosome, and that in some cases the trait was associated with a cytogenetically visible fragile site on the X chromosome, seen only when cells were grown in a folic acid-deficient medium. The mental retardation syndrome was inherited in a classic pattern of X-linked inheritance, with carrier mothers who might have affected brothers or uncles passing the trait on to half of their male offspring. However, some unusual families caused confusion because of a pedigree pattern demonstrating what came to be known as the Sherman paradox. Specifically, there were families identified in which a male appeared to have passed the trait on to his daughters, but he himself was not affected, even though he might have affected brothers or uncles. This pattern could not be explained by typical X-linked inheritance.

The solution to the Sherman paradox became apparent when the molecular basis of the FRAXA was found to be a unique type of mutation that occurs in a region of repeated nucleotides in the genetic sequence. Specifically, in the FMR1 gene (Xq27.3) there is a repeated sequence of CGG nucleotides, a “triplet repeat” (Fig. 2-1). In normal individuals this sequence is repeated 5–44 times, but in an affected individual the sequence is repeated more than 200 times. Even more interesting, the mothers of the affected individuals were found to have triplet repeats with 60–200 copies. The normal allele is stably copied during the process of meiosis,