Preface

The past half-century has witnessed a breathtaking series of advances in genetic research, beginning with Watson and Crick's description of the structure of the DNA molecule and culminating recently with the finished human DNA sequence. Along the way, fields have emerged, developed, and matured, including cytogenetics, genetic epidemiology, epigenetics, and molecular population genetics. Applications of genetic research, including genetic diagnosis and gene therapy, are playing increasingly important roles in medicine. Although the phrase "genetic revolution" has become a cliché, it uniquely captures the excitement and hope that have pervaded the science of genetics as these advances have occurred.

Because genetics is essentially the science of variation among individuals, it is appropriate that the first section of this volume deals with *Genetic Variation and Evolution*. Evolutionary genetics has been transformed by our ability to assay thousands of genetic variants in individuals and populations. Comparative analyses of variation in the DNA of mitochondria, Y chromosomes, and autosomes have contributed immensely to our understanding of the origins and history of our species. A better appreciation of population differences and similarities is leading to a more sophisticated view of the controversial concept of "race" and its social and biomedical implications. Forensic analysis of DNA owes its widespread acceptance to informed analyses of genetic variation. Studies of human genetic variation are helping in propelling the emerging science of pharmacogenomics, and they are proving critical to the appropriate design and implementation of large-scale projects that seek the genes that underlie complex diseases.

Another major beneficiary of our increasing ability to assay large numbers of DNA variants has been the field of gene mapping (*see* Section *Gene Mapping*). The development of hundreds of restriction fragment length polymorphisms (RFLPs) in the 1980s was followed by the discovery of thousands of short tandem repeat polymorphisms (STRPs) and, most recently, by the description of millions of single-nucleotide polymorphisms (SNPs). This wealth of marker data, combined with dramatic advances in statistical and computer analysis, has enabled the mapping and cloning of genes responsible for virtually all of the most clinically significant Mendelian diseases. As our attention turns increasingly to the genetic underpinnings of complex disease, many questions and controversies remain. Which statistical techniques (e.g., parametric vs. nonparametric) are most powerful in specific contexts? Which types of markers (e.g., STRPs vs. SNPs) are most informative and useful? When should we study families, and when should we study unrelated individuals in populations? These and other critical gene-mapping issues are reviewed in the section on *Gene Mapping*.

While gene-mapping efforts have been impressively successful in defining the genes that cause Mendelian diseases, the rate of progress in defining genes that cause complex diseases (e.g., heart disease, common cancer, and diabetes) has been understandably slower. Because of the enormous public health impact of

these diseases, much attention is being focused on them, as outlined in the section on *Complex Traits and Diseases*. A fundamental question is whether common diseases are largely the result of DNA variants that are common in populations. The alternative possibility—that these diseases are primarily caused by many relatively rare variants—would pose significant and possibly insurmountable challenges. Fortunately, there are now several examples of complex diseases in which important causal DNA variants have been identified (e.g., *PPARγ* in type 2 diabetes, *CARD15* in Crohn's disease, *APOE* in Alzheimer's disease, and several important loci in asthma). As discussed in the section on *Complex Traits and Diseases*, there is now considerable potential for pinpointing genes that underlie susceptibility to many common, complex diseases.

Although gene-mapping discoveries have probably received the lion's share of attention during the past two decades, the field of cytogenetics has also undergone many changes and improvements (*see* Section *Cytogenetics*). The advent of modern human cytogenetics is usually dated to 1956, when it first became possible to accurately count the number of human chromosomes. This capability, along with the development of staining techniques that revealed banding patterns on chromosomes, helped to establish that major chromosome abnormalities (extra or missing chromosomes or microscopically visible alterations of chromosome structure) are seen in about 1 in 150 live births. These conditions are much more common at conception and constitute the leading known cause of spontaneous pregnancy loss. Although the microscopic visualization of metaphase chromosomes is a mainstay of clinical cytogenetics, this field has also taken advantage of new developments in molecular technology. As described in detail in the section on *Cytogenetics*, fluorescence *in situ* hybridization (FISH) is now used routinely to diagnose chromosome abnormalities such as aneuploidy, deletions, and duplications. Molecular analysis also forms the basis of comparative genomic hybridization (CGH), which, in combination with microarrays, is used increasingly to detect the gains and losses of genes that characterize most cancers.

One of the more intriguing observations of the past few decades is that some inherited diseases are not the result of changes in the DNA sequence but instead are caused by epigenetic modifications such as methylation and histone acetylation. Epigenetics, the focus of the *Epigenetics* section, plays a key role in X inactivation and in the phenomenon of genomic "imprinting", in which some genes are either transcriptionally active or inactive, depending on which parent transmits the gene. Imprinting helps explain how, for example, a paternally transmitted 4-Mb deletion of chromosome 15 can produce Prader–Willi syndrome in the offspring, while the same deletion, when maternally transmitted, produces a completely different phenotype, Angelman syndrome. As discussed in this section, imprinting may have evolved as an expression of parental conflict, wherein fathers attempt to increase the expression of genes that will produce large fetuses, while mothers, in an effort to conserve resources during pregnancy, try to decrease their expression.

The final two sections of this volume, which deal with genetic medicine, genetic diagnosis, and gene therapy, show how recent genetic discoveries are leading to significant clinical applications. Genetic diagnosis is commercially available for about 500 single-gene diseases, and this number will continue to increase

as more disease-causing mutations are discovered. The section *Genetic Medicine and Clinical Genetics* reviews the progress in genetic diagnostic techniques and their applications in carrier screening, newborn screening, and prenatal diagnosis. Genetic counseling, whereby genetic information is delivered to patients and families, is discussed, as are aspects of physical examination and patient interview that are especially pertinent to genetic disease (e.g., taking family histories and assessing risk based on pedigree analysis). Genetic testing poses special challenges such as the potential for discrimination on the part of insurance companies and/or employers. These and other legal and ethical issues are also discussed in this section.

Perhaps no other area of modern human genetics has received as much attention—both favorable and unfavorable—as gene therapy (*see* Section *Gene Therapy*). Thousands of patients worldwide are enrolled in hundreds of gene therapy protocols, some of which are now in Phase III trials. Encouraging results are beginning to emerge for a handful of inherited diseases, such as X-linked severe combined immune deficiency (SCID) and hemophilia A and B. Notable progress is being made in the therapy of noninherited diseases, including ischemic heart disease and many cancers. At the same time, well-publicized failures, such as the death of a patient with OTC deficiency and the discovery that retroviral therapy for X-linked SCID caused T-cell leukemia in two patients, have prompted necessary caution and scrutiny. The section on *Gene Therapy* provides useful reviews of the technology of gene therapy and some current, promising applications.

The articles in this volume demonstrate the breadth and diversity of current genetic research. They also demonstrate the enormous potential of this research to help fulfill the goals of understanding disease and, most importantly, improving human health.

Genetics Editor
Lynn B. Jorde
Salt Lake City