82 Principles of Human Genetics

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IMPACT OF GENETICS AND GENOMICS ON MEDICAL PRACTICE

The prevalence of genetic diseases, combined with their potential severity and chronic nature, imposes great human, social, and financial burdens on society. Human genetics refers to the study of individual genes, their role and function in disease, and their mode of inheritance. Genomics refers to an organism's entire genetic information, the *genome*, and the function and interaction of DNA within the genome, as well as with environmental or nongenetic factors, such as a person's lifestyle. With the characterization of the human genome, genomics complements traditional genetics in our efforts to elucidate the etiology and pathogenesis of disease and to improve therapeutic interventions and outcomes. Following impressive advances in genetics, genomics, and health care information technology, the consequences of this wealth of knowledge for the practice of medicine are profound and play an increasingly prominent role in the diagnosis, prevention, and treatment of disease (Chap. 84).

Personalized medicine, the customization of medical decisions to an individual patient, relies heavily on genetic information. For example, a patient's genetic characteristics (genotype) can be used to optimize drug therapy and predict efficacy, adverse events, and drug dosing of selected medications (*pharmacogenetics*) (Chap. 5). The mutational profile of a malignancy allows the selection of therapies that target mutated or overexpressed signaling molecules. Although still investigational, genomic risk prediction models for common diseases are beginning to emerge.

Genetics has traditionally been viewed through the window of relatively rare single-gene diseases. These disorders account for ~10% of pediatric admissions and childhood mortality. Historically, genetics has focused predominantly on chromosomal and metabolic disorders, reflecting the long-standing availability of techniques to diagnose these conditions. For example, conditions such as trisomy 21 (Down's syndrome) or monosomy X (Turner's syndrome) can be diagnosed using cytogenetics (Chap. 83e). Likewise, many metabolic disorders (e.g., phenylketonuria, familial hypercholesterolemia) are diagnosed using biochemical analyses. The advances in DNA diagnostics have extended the field of genetics to include virtually all medical specialties and have led to the elucidation of the pathogenesis of numerous monogenic disorders. In addition, it is apparent that virtually every medical condition has a genetic component. As is often evident from a patient's family history, many common disorders such as hypertension, heart disease, asthma, diabetes mellitus, and mental illnesses are significantly influenced by the genetic background. These polygenic or multifactorial (complex) disorders involve the contributions of many different genes, as well as environmental factors that can modify disease risk (Chap. 84). Genome-wide association studies (GWAS) have elucidated numerous disease-associated loci and are providing novel insights into the allelic architecture of complex traits. These studies have been facilitated by the availability of comprehensive catalogues of human single-nucleotide polymorphism (SNP) haplotypes generated through the HapMap Project. The sequencing of whole genomes or exomes (the exons within the genome) is increasingly used in the clinical realm in order to characterize individuals with complex undiagnosed conditions or to characterize the mutational profile of advanced malignancies in order to select better targeted therapies.

Cancer has a genetic basis because it results from acquired somatic mutations in genes controlling growth, apoptosis, and cellular differentiation (Chap. 101e). In addition, the development of many cancers is associated with a hereditary predisposition. Characterization of the genome (and epigenome) in various malignancies has led to fundamental new insights into cancer biology and reveals that the genomic profile of mutations is in many cases more important in determining the appropriate chemotherapy than the organ in which the tumor originates. Hence, comprehensive mutational profiling of malignancies has increasing impact on cancer taxonomy, the choice of targeted therapies, and improved outcomes.

Genetic and genomic approaches have proven invaluable for the detection of infectious pathogens and are used clinically to identify agents that are difficult to culture such as mycobacteria, viruses, and parasites, or to track infectious agents locally or globally. In many cases, molecular genetics has improved the feasibility and accuracy of diagnostic testing and is beginning to open new avenues for therapy, including gene and cellular therapy (Chaps. 90e and 91e). Molecular genetics has also provided the opportunity to characterize the *microbiome*, a new field that characterizes the population dynamics of bacteria, viruses, and parasites that coexist with humans and other animals (Chap. 86e). Emerging data indicate that the microbiome has significant effects on normal physiology as well as various disease states.

Molecular biology has significantly changed the treatment of human disease. Peptide hormones, growth factors, cytokines, and vaccines can now be produced in large amounts using recombinant DNA technology. Targeted modifications of these peptides provide the practitioner with improved therapeutic tools, as illustrated by genetically modified insulin analogues with more favorable kinetics. Lastly, there is reason to believe that a better understanding of the genetic basis of human disease will also have an increasing impact on disease prevention.

The astounding rate at which new genetic information is being generated creates a major challenge for physicians, health care providers, and basic investigators. Although many functional aspects of the genome remain unknown, there are many clinical situations where sufficient evidence exits for the use of genetic and genomic information to optimize patient care and treatment. Much genetic information resides in databases or is being published in basic science journals. Databases provide easy access to the expanding information about the human genome, genetic disease, and genetic testing (Table 82-1). For example, several thousand monogenic disorders are summarized in a large, continuously evolving compendium, referred to as the *Online Mendelian Inheritance in Man* (OMIM) catalogue (Table 82-1). The ongoing refinement of bioinformatics is simplifying the analysis and access to this daunting amount of new information.

THE HUMAN GENOME

Structure of the Human Genome • ***HUMAN GENOME PROJECT*** The Human Genome Project was initiated in the mid-1980s as an ambitious effort to characterize the entire human genome. Although the prospect of determining the complete sequence of the human genome seemed daunting several years ago, technical advances in DNA sequencing and bioinformatics led to the completion of a draft human sequence in 2000 and the completion of the DNA sequence for the last of the human chromosomes in May 2006. Currently, facilitated by rapidly decreasing costs for comprehensive sequence analyses and improvement of bioinformatics pipelines for data analysis, the sequencing of whole genomes and exomes is used with increasing frequency in the clinical setting. The scope of a whole genome sequence analysis can be illustrated by the following analogy. Human DNA consists of ~3 billion base pairs (bp) of DNA per haploid genome, which is nearly 1000-fold greater than that of the *Escherichia coli* genome. If the human DNA sequence were printed out, it would correspond to about 120 volumes of *Harrison's Principles of Internal Medicine*.

In addition to the human genome, the genomes of numerous organisms have been sequenced completely (~4000) or partially (~10,000) (Genomes Online Database [GOLD]; Table 82-1). They include, among others, eukaryotes such as the mouse (*Mus musculus),*