84 The Practice of Genetics in Clinical Medicine

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APPLICATIONS OF MOLECULAR GENETICS IN CLINICAL MEDICINE

Genetic testing for inherited abnormalities associated with disease risk is increasingly used in the practice of clinical medicine. Germline alterations include chromosomal abnormalities (Chap. 83e), specific gene mutations with autosomal dominant or recessive patterns of transmission (Chap. 82), and single nucleotide polymorphisms with small relative risks associated with disease. Germline alterations are responsible for disorders beyond classic Mendelian conditions with genetic susceptibility to common adult-onset diseases such as asthma, hypertension, diabetes mellitus, macular degeneration, and many forms of cancer. For many of these diseases, there is a complex interplay of genes (often multiple) and environmental factors that affect lifetime risk, age of onset, disease severity, and treatment options.

The expansion of knowledge related to genetics is changing our understanding of pathophysiology and influencing our classification of diseases. Awareness of genetic etiology can have an impact on clinical management, including prevention and screening for or treatment of a range of diseases. Primary care physicians are relied upon to help patients navigate testing and treatment options. Consequently, they must understand the genetic basis for a large number of genetically influenced diseases, incorporate personal and family history to determine the risk for a specific mutation, and be positioned to provide counseling. Even if patients are seen by genetic specialists who assess genetic risk and coordinate testing, primary care providers should provide information to their patients regarding the indications, limitations, risks, and benefits of genetic counseling and testing. They must also be prepared to offer risk-based management following genetic risk assessment. Given the pace of genetics, this is an increasingly difficult task. The field of clinical genetics is rapidly moving from single gene testing to multigene panel testing, with techniques such as whole-exome and -genome sequencing on the horizon, increasing the complexity of test selection and interpretation, as well as patient education and medical decision making.

COMMON ADULT-ONSET GENETIC DISORDERS

INHERITANCE PATTERNS

Adult-onset hereditary diseases follow multiple patterns of inheritance. Some are autosomal dominant conditions. These include many common cancer susceptibility syndromes such as hereditary breast and ovarian cancer (due to germline *BRCA1* and *BRCA2* mutations) and Lynch syndrome (caused by germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*). In both of these examples, inherited mutations are associated with a high penetrance (lifetime risk) of cancer, although risk is not 100%. In other conditions, although there is autosomal dominant transmission, there is lower penetrance, thereby making the disorders more difficult to recognize. For example, germline mutations in *CHEK2* increase the risk of breast cancer, but with a moderate lifetime risk in the range of 20–40%, as opposed to 50–70% for mutations in *BRCA1* or *BRCA2*. Other adult-onset hereditary diseases are transmitted in an autosomal recessive fashion where two mutant alleles are necessary to cause disease. Examples include hemochromatosis and *MYH*-associated colon cancer. There are more pediatric-onset autosomal recessive disorders, such as lysosomal storage diseases and cystic fibrosis.

The genetic risk for many adult-onset disorders is multifactorial. Risk can be conferred by genetic factors at a number of loci, which individually have very small effects (usually with relative risks of <1.5). These risk loci (generally single nucleotide polymorphisms [SNPs]) combine with other genes and environmental factors in ways that are not well understood. SNP panels are available to assess risk of disease, but the optimal way of using this information in the clinical setting remains uncertain.

Many diseases have multiple patterns of inheritance, adding to the complexity of evaluating patients and families for these conditions. For example, colon cancer can be associated with a single germline mutation in a mismatch repair gene (Lynch syndrome, autosomal dominant), biallelic mutations in *MYH* (autosomal recessive), or multiple SNPs (polygenic). Many more individuals will have SNP risk alleles than germline mutations in high-penetrance genes, but cumulative lifetime risk of colon cancer related to the former is modest, whereas the risk related to the latter is significant. Personal and family histories provide important insights into the possible mode of inheritance.

FAMILY HISTORY

When two or more first-degree relatives are affected with asthma, cardiovascular disease, type 2 diabetes, breast cancer, colon cancer, or melanoma, the relative risk for disease among close relatives ranges from two- to fivefold, underscoring the importance of family history for these prevalent disorders. In most situations, the key to assessing the inherited risk for common adult-onset diseases is the collection and interpretation of a detailed personal and family medical history in conjunction with a directed physical examination.

Family history should be recorded in the form of a pedigree. Pedigrees should convey health-related data on first- and second-degree relatives. When such pedigrees suggest inherited disease, they should be expanded to include additional family members. The determination of risk for an asymptomatic individual will vary depending on the size of the pedigree, the number of unaffected relatives, the types of diagnoses, and the ages of disease onset. For example, a woman with two first-degree relatives with breast cancer is at greater risk for a specific Mendelian disorder if she has a total of 3 female first-degree relatives (with only 1 unaffected) than if she has a total of 10 female first-degree relatives (with 7 unaffected). Factors such as adoption and limited family structure (few women in a family) should to be taken into consideration in the interpretation of a pedigree. Additional considerations include young age of disease onset (e.g., a 30-year nonsmoking woman with a myocardial infarction), unusual diseases (e.g., male breast cancer or medullary thyroid cancer), and the finding of multiple potentially related diseases in an individual (e.g., a woman with a history of both colon and endometrial cancer). Some adult-onset diseases are more prevalent in certain ethnic groups. For instance, 2.5% of individuals of Ashkenazi Jewish ancestry carry one of three founder mutation in *BRCA1* and *BRCA2*. Factor V Leiden mutations are much more common in Caucasians than in Africans or Asians.

Additional variables that should be documented are nonhereditary risk factors among those with disease (such as cigarette smoking and myocardial infarction; asbestos exposure and lung disease; and mantle radiation and breast cancer). Significant associated environmental exposures or lifestyle factors decrease the likelihood of a specific genetic disorder. In contrast, the absence of nonhereditary risk factors typically associated with a disease raises concern about a genetic association. A personal or family history of deep vein thrombosis in the absence of known environmental or medical risk factors suggests a hereditary thrombotic disorder. The physical examination may also provide important clues about the risk for a specific inherited disorder. A patient presenting with xanthomas at a young age should prompt consideration of familial hypercholesterolemia. The presence of trichilemmomas in a woman with breast cancer raises concern for Cowden syndrome, associated with *PTEN* mutations.

Recall of family history is often inaccurate. This is especially so when the history is remote and families lose contact or separate geographically. It can be helpful to ask patients to fill out family history forms before or after their visits, because this provides them with an opportunity to contact relatives. Ideally, this information should be embedded in electronic health records and updated intermittently. Attempts should be made to confirm the illnesses reported in the family history before making important and, in certain circumstances, irreversible management decisions. This process is often labor