8th Annual Women's Heart & Vascular Symposium

Genetic Testing in Cardiovascular Medicine

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Genetic discoveries are leading to new therapies that target specific disease mechanisms. Such discoveries have ushered in the era of modern medicine and are expected to change the future of clinical practice.

Elucidation of the molecular genetic basis of hereditary cardiovascular disease (CVD), along with advances in nucleic acid sequencing technologies, has enabled routine application of genetic testing to cardiomyopathies, cardiac arrhythmias, hereditary causes of aortic aneurysm, and aspects of congenital heart disease (Table I). Genetic testing is currently most useful in screening patients and their families for causal genetic variants. Interpreting test results necessitates expertise in modern molecular genetics and the phenotypic characteristics of the disease of interest.

The Human Genome and Its Sequencing

The human genome comprises approximately 6.4 billion nucleotides (3.2 billion base pairs) and about 20,000 genes that code for proteins (~2% of the genome). The rest of the genome is pervasively transcribed into RNA, including microRNAs and long noncoding RNAs involved in various biological processes. Exons are the protein-coding segments of genes. All the exons in a genome are called an exome. The exome in the human genome (~30 million base pairs) contains most known disease-causing mutations and pathologic variants. These variants affect protein sequence, structure, and function, and genetic testing focuses primarily on identifying them.

Modern technologies have enabled efficient, accurate sequencing of the entire human genome. Accordingly, a typical human genome differs from the reference sequence in approximately 4 to 5 million sites (out of 3.2 billion pairs).[1] The variations, called polymorphisms, are inherited from parents or are introduced during cell division. In each genome, 3.5 to 4 million variants involve one nucleotide and are called single-nucleotide polymorphisms or variants (SNVs). The rest are small insertions or deletions, or, less frequently, large deletions. Approximately 10,000 to 12,000 SNVs in each genome are nonsynonymous—that is, they affect the amino acid sequence in the encoded protein. Some genetic variants are considered pathogenic because they substantially change the structure of the encoded protein and lead to its premature truncation, elongation, or alternative splicing. These variants are typically rare in the general population (prevalence, <1%).

During the last 3 decades, advances in nucleic acid sequencing technologies and partial elucidation of the molecular genetic basis of hereditary CVD have ushered in the era of molecular genetic testing,[2] which is usually performed by means of whole exome sequencing. The sequences are typically analyzed for the presence of pathogenic variants in specific genes that are associated with a heritable CVD of interest. The chief focus is on variants that are known to cause the particular phenotype. Because each exome comprises numerous pathogenic variants, focusing on the known gene minimizes false conclusions. Research environments uniquely enable the identification of pathogenic variants in genes not previously implicated in a disease, and thus new genes that cause CVD are discovered.

★ ***CME Credit***

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TABLE I. Cardiovascular Conditions Often Analyzed by Means of Genetic Testing

Aortic aneurysms
Marfan syndrome
Loeys-Dietz syndrome
Ehlers-Danlos syndrome
Cardiac arrhythmias
QT interval disorders (long- and short-QT syndromes)
Brugada syndrome
Catecholaminergic ventricular tachycardia
Cardiomyopathies
Hypertrophic
Dilated
Restrictive
Arrhythmogenic, including right ventricular
Left ventricular noncompaction syndrome
Occurring in conjunction with skeletal myopathies
Congenital heart disease
Familial hypercholesterolemia
Pulmonary hypertension

Applying Genetic Testing in Cardiovascular Disease

The strongest application of genetic testing for CVD is in families. A detailed family medical history and pedigree—essential before testing—can lead to the early identification of family members who do or do not carry the causal variant. In carriers, periodic and focused clinical evaluation is indicated; in other family members, evaluation is performed as though they were part of the general public. It is rewarding to identify family members who have not inherited the causal mutation and are therefore not at increased risk of the disease. Of equal importance, early intervention can reduce the risk of sudden cardiac death in mutation carriers when phenotypes such as asymptomatic hypertrophy or arrhythmias are detected during periodic evaluation.

Genetic testing can enable diagnosis of a disease and its distinction from phenocopy conditions. For example, hypertrophic cardiomyopathy caused by mutations in genes coding for sarcomere proteins can be distinguished from cardiac hypertrophy caused by storage diseases, such as Fabry disease. Accurate diagnosis has substantial clinical implications because storage or infiltrative disorders might benefit from specific interventions, such as enzyme replacement therapy. Conversely, genetic testing for prognostication and for devising individual therapy is of less clinical benefit, because many factors influence outcomes.[3] However, when we better understand genetic determinants of positive and adverse responses to therapy, the knowledge might be used to increase drug efficacy and eliminate adverse effects.

One shortcoming of genetic testing is the null finding—that is, the failure to identify a pathogenic or causal mutation. This happens often, to the disappointment of patients and physicians. In part, it is because one third to one half of the causal genes for single-gene CVDs are unknown. In addition, neither clinical outcome nor disease severity can be reliably predicted by knowing the causal mutation. Overall, mutations exhibit variable phenotypic expression because of many contributory genetic and nongenetic factors.

Looking Ahead

In single-gene CVD and other disorders, one pathogenic variant can cause disease, albeit with variable severity. Recent whole-exome sequencing data show pathogenic variants in multiple genes associated with a phenotype, implying that subsets of the conventionally defined single-gene disorders are oligogenic in origin.[4] Genetic testing for complex diseases, such as coronary artery disease, is currently limited to research environments only. Finally, an important contribution of genetic discoveries is in delineating novel molecular mechanisms responsible for a disease. This may lead to preventive and therapeutic targeting of pathogenic pathways, thus changing the future practice of medicine.

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