

Genetic testing in cardiac disease: from bench to bedside

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Over the past 15 years, breakthroughs in basic science have revealed the genetic etiology for several inherited cardiovascular diseases.^{1,2} By studying instructive monogenic diseases, including hypertrophic cardiomyopathy (HCM), and long QT syndrome (LQTS), we have gained valuable insight into critical molecular pathways involved in cardiac remodeling, inherited susceptibility to sudden cardiac death (SCD), and arrhythmias. Since the underlying genetic defects in these monogenic diseases are typically simple base-pair substitutions, mutations can be easily identified by DNA sequence analysis. Although genetic testing for HCM and LQTS is now clinically available, how can genetic testing for heritable cardiovascular disorders improve the care of our patients?

An ideal genetic test would be inexpensive, and provide a definitive diagnosis and valuable information to predict prognosis and tailor treatment. Unfortunately, this is often not the case for the tests now available. As genetic testing moves from the research laboratory into clinical practice, many important issues must be considered to determine how these tests are best applied. Diagnostic yield, clinical impact and the emotional and medical implications for individuals and their families will all affect the value of a test for each patient.

Clinically available genetic tests for inherited cardiovascular disorders use a variety of mutation detection techniques with variable sensitivity and specificity. Commonly, direct DNA sequencing techniques are used and can detect nearly 100% of mutations in genes known to cause disease. We have not yet determined all of the causal genes that give rise to a particular phenotype, however, and even if a gene is successfully identified, the disease course is usually not predicted accurately. Appropriate interpretation requires careful consideration of these limitations, otherwise the clinician and patient can be left with uncertainty rivaling that present before they received their test results, with potentially negative psychological and financial consequences.

HCM is an autosomal dominant disorder characterized by unexplained left ventricular

hypertrophy (LVH) with myocyte disarray and fibrosis. Although highly variable, clinical manifestations include exercise intolerance, chest pain and an increased risk of SCD. The prevalence of unexplained LVH in the general population is approximately 1 in 500;^{1,3} sarcomere mutations can be identified in approximately 55–70% of these individuals,^{4,5} making HCM the most common inherited cardiovascular disorder. Although mutations have been identified in 11 different sarcomere genes, for practical purposes clinical testing is performed on the 8 most prevalent sarcomere genes only. While identifying a mutation can confirm a clinical suspicion of HCM, the implications of failure to identify a mutation are ambiguous. A negative result in a case of clinically suspected HCM could occur if a mutation exists in one of the untested sarcomere genes, or in a nonsarcomere gene that mimics the gross HCM phenotype, or if there is a nongenetic etiology for the patients' unexplained LVH.

Although HCM is a monogenic disease, a benign or malignant phenotype is not invariably predicted by individual genotypes. As no treatment is currently available to reverse or prevent HCM, medical management centers on the treatment of symptoms and assessment of risk for SCD. Practical benefits of sarcomere gene testing, therefore, focus on clarifying diagnosis, performing presymptomatic testing through confirmation of a family mutation, and reproductive counseling. Genetic screening for a known family mutation can remove the anxiety caused by the uncertain future of younger family members. If a mutation is not present, the individual can be reassured that they are not at risk for disease development or transmission and serial clinical evaluation is not required. If a mutation is confirmed, serial clinical assessment for early phenotypic development is recommended and individuals are counseled about the 50% risk of disease transmission to their offspring.

LQTS and Brugada syndrome are associated with an inherited predisposition to arrhythmias and SCD because of mutations in transmembrane

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ion channel proteins and resultant repolarization abnormalities. At least eight distinct genes have been associated with LQTS although three types predominate: LQT1 and LQT2 (caused by potassium channel protein defects) and LQT3 (caused by cardiac sodium channel protein defects).⁶ Sodium channel defects are also associated with Brugada syndrome. For practical purposes, clinical genetic testing consists of sequencing the five most-common genes, estimated to account for approximately 70% of LQTS. For individuals with suspected LQTS, the mutation detection rate is approximately 70%; however, the detection rate specifically for Brugada syndrome is approximated at only 20%, highlighting current limitations of knowledge about the array of causative genes associated with this phenotype.

Although the story continues to evolve, genotype–phenotype correlations have been more robust in LQTS. Arrhythmic triggers, SCD risk, and treatment response are influenced by the underlying genotype. Among individuals with LQT1, for example, the QT interval does not shorten appropriately in response to tachycardia and catecholamine release because of a genetic defect in the slow component of the K^+ rectifier (I_{Ks} , encoded by *KCNQ1*). As a consequence, LQT1 is associated with increased arrhythmic event rates in situations of increased adrenergic activity, and event rates are dramatically decreased by β -blockers.⁷ By contrast, LQT3 is caused by mutations in *SCN5A*, which encodes the cardiac sodium channel, and is associated with QT prolongation when cycle length is increased (e.g. with bradycardia). Although not rigorously tested, β -blockers could theoretically be detrimental because of the associated bradycardia. Ongoing investigation of larger genotyped groups of patients with LQTS will continue to refine genotype–phenotype correlations and increase the impact of genotype on clinical management.

As demonstrated by HCM and LQTS, careful consideration by clinicians is required for appropriate interpretation of gene mutation identification. If the mutation has been demonstrated previously to be disease-causing, it can be considered pathogenic in a patient with a newly recognized case and can confirm the diagnosis. There is substantial genetic heterogeneity in HCM and LQTS, however, and novel mutations are frequently encountered. Determining the significance of a novel sequence variant identified in an index case can be difficult. The clinical context

must be taken into account before concluding that a newly identified sequence variant is pathogenic rather than a coincidental polymorphism. Evaluation of other family members and demonstration that the novel mutation correlates with phenotype can help establish a causal link between genotype and disease.

Genetic testing today benefits patients by clarifying diagnosis, allowing definitive identification of family members at risk for disease development, and by permitting presymptomatic and prenatal diagnosis. In certain instances where predictable genotype–phenotype correlations have been established, the results can provide important information to drive management or assist in reproductive counseling. The best is yet to come, however, for genetic testing in cardiac disease. The greatest promise and power of genetic testing lies in the future as research continues to unravel the molecular basis of genetic cardiovascular disease, critically refine genotype–phenotype relationships and further elucidate key pathways in cardiovascular pathophysiology. These advances will enable a transition from reactive and palliative care to an important new paradigm of rational and pre-emptive treatment to diminish and prevent the expression of gene mutations.

Competing interests

The authors declared they have no competing interests.

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