New Molecular Genetic Tests in the Diagnosis of Heart Disease

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KEYWORDS

• Cardiac markers • Biomarkers • Cardiovascular genetics • Genetic testing
• Cardiomyopathy • Channelopathy • Thoracic aneurysm • Congenital heart defects

KEY POINTS

- Identification of a genetic cause for cardiovascular disease is increasing at a rapid rate, although even for the most well-understood disorders positive results are still less than 100%, particularly for the cardiomyopathies, which have a high incidence of environmental causes.
- Large screening panels have shown a greater genetic overlap for distinct clinical phenotypes than was originally appreciated, particularly for the cardiomyopathies.
- Testing cardiomyopathies and channelopathies is most informative to identify a pathogenic variant in an affected individual to enable family screening and appropriate management of at-risk individuals and those likely to be unaffected. In some cases, a genetic diagnosis may alter treatment options or prognosis.

CARDIOMYOPATHY

The cardiomyopathy disorders, characterized by disruption of the normal structure or function of the myocardium, are heterogeneous disorders, with 5 to more than 40 genes associated with each of the subphenotypes.[1,2] Furthermore, there is an increased appreciation in the phenotypic overlap of each of the disorders.[1] Together, these argue for sequencing of large panels. At present, this is often done in the context of cardiomyopathies, for which next-generation sequencing has enabled panels of more than 50 genes to be sequenced at less than the cost of 5 genes via traditional sequencing. Clinical sequencing is currently done by sequencing the coding regions and splice sites of the associated genes, although for some genes deletion/duplication analysis is warranted (see http://www.ncbi.nlm.nih.gov/gtr/).[3]

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Key Abbreviations Table	
AF	Atrial fibrillation
AOS	Aneurysm osteoarthritis syndrome
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ASD	Atrial septal defects
ATS	Arterial tortuosity syndrome
AVSD	Atrioventricular septal defects
BAV	Bicuspid aortic valve
BrS	Brugada syndrome
CCA	Congenital contractural arachnodactyly
CCD	Cardiac conduction disease
CHD	Congenital heart defects
CoA	Coarctation of the aorta
CPVT	Catecholaminergic polymorphic ventricular tachycardia
DCM	Dilated cardiomyopathy
EA	Ebstein anomaly
EDS	Ehlers-Danlos syndrome
HCM	Hypertrophic cardiomyopathy
HLH	Hypoplastic left heart
JLNS	Jervell and Lange-Nielsen syndrome
LDS	Loeys-Dietz syndrome
LQTS	Long QT syndrome
LVNC	Left ventricular noncompaction
PS	Pulmonary stenosis
RCM	Restrictive cardiomyopathy
RWS	Romano-Ward syndrome
SIDS	Sudden infant death syndrome
SQTS	Short QT syndrome
SUD	Sudden unexplained death
SVAS	Supravalvular aortic stenosis
TAAD	Thoracic aortic aneurysms and dissections
TOF	Tetralogy of Fallot
VF	Ventricular fibrillation
VSD	Ventricular septal defects

Hypertrophic Cardiomyopathy

Phenotype

HCM is characterized by asymmetric left ventricular hypertrophy (LVH) with myocyte hypertrophy, disarray, and interstitial fibrosis. Although clinical manifestations are variable, they can include severe heart failure and sudden cardiac death (SCD). HCM may present as burnt-out HCM, which is similar in presentation to DCM.

Prevalence and genetic causes

The prevalence is 1 in 500 individuals.[4] More than 20 genes have been implicated in nonsyndromic HCM (**Table 1**), with most identified genetic causes being variants in *MYBPC3* and *MYH7*.[1,5] Additional commonly affected genes are *TPM1*, *TNNT2*, *TNNI3*, *ACTC1*, *MYL2*, and *MYL3*. Inheritance is typically autosomal dominant (AD), although X-linked and autosomal recessive (AR) inheritance can be seen.

Cellular mechanism

Most HCM is thought to be caused by defects in the sarcomere, the contractile unit of myocytes, and the adjacent Z-disc.[6] A high proportion of pathogenic variants in *MYBPC3* are missense or loss of function, suggesting haploinsufficiency as a disease