Expanding the Genetic Spectrum of Hypertrophic Cardiomyopathy: X Marks the Spot

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During the past 25 years, major advances have been made in our understanding of the genetic basis of hypertrophic cardiomyopathy (HCM). Although being a disease that was defined as a tumor of the heart by Donald Teare in 1958, our genetic advances have led to a complete redefinition of HCM as a complex nonsyndromic genetic disorder characterized by unexplained left ventricular hypertrophy, in the absence of loading conditions. To date, >1300 mutations in ≥13 disease genes have been identified in patients with HCM. These disease genes encode primarily sarcomere and sarcomere-related proteins and are almost exclusively inherited in an autosomal dominant pattern, with some isolated reports of autosomal recessive HCM. Collectively, these findings have led to the description of HCM as a disease of the sarcomere. Although current genetic testing strategies in HCM lead to an overall pathogenic mutation detection rate of ≤50%, the presence of a family history of HCM and sudden death because of HCM can increase the mutation detection rate to >75%. However, many families with HCM have no causative mutation identified. To this end, efforts to identify the remaining as yet unidentified genes are to be commended and are at the forefront of novel gene discoveries in HCM.

In this issue of Circulation: Cardiovascular Genetics, Hartmannova et al present findings from a large 4-generation Czech family characterized by 4 male individuals with nonobstructive HCM with severe left ventricular diastolic dysfunction and evidence of end-stage disease. Two of these 4 men required heart transplantation. In an attempt to identify a genetic cause of disease in this family, whole exome sequencing was performed, and a novel frameshift mutation of the four-and-a-half LIM domain 1 (FHL1) gene was detected in all 4 affected men. Interestingly, 4 female carriers of the FHL1 mutation had abnormal ECG findings, with 1 female carrier having apical variant form of HCM. None of the family members had any evidence of skeletal myopathies. The findings support the notion of nonsyndromic X-linked HCM.

The study by Hartmannova et al presents several interesting insights. To date, HCM has been considered an autosomal dominant disorder. The X-linked cardiomyopathies, in which hypertrophy occurs, have mainly involved the group of diseases referred to as HCM phenocopies, such as Fabry disease, glycogen storage disorders, and Danon disease. Although these X-linked disorders are characterized by a variety of extracardiac disease manifestations and so represent true syndromes, the current study supports the existence of nonsyndromic X-linked HCM. None of the family members had evidence of any systemic extracardiac manifestations, and importantly, affected individuals and 1 female carrier demonstrated either classical asymmetrical septal hypertrophy or apical HCM. The findings expand the genetic spectrum of HCM, adding to the known autosomal dominant and rarer recessive forms of genetic transmission (Figure).

The identification of FHL1 as the disease gene in this family raises many questions about its role in disease pathogenesis, specifically related to why in this family the phenotype is cardiac specific and why the skeletal muscles are spared. FHL1 is a member of the FHL protein family and is the main isoform in striated muscles, contributing to sarcomere synthesis, assembly, and stress sensing. Interestingly, FHL1 has also been shown to interact with key sarcomere and sarcomere-related proteins, such as myosin-binding protein c and titin. Mutations in the FHL1 gene have previously been described, primarily in X-linked skeletal muscle disorders, such as Emery–Dreifuss muscular dystrophy and reducing body myopathy. In some of these skeletal myopathy cases, cardiac phenotypes have been described, including HCM, dilated cardiomyopathy, and abnormal arrhythmias. In 2012, the group led by Lucie Carrier described 7 small HCM families (from a total of 121 families) in which FHL1 mutations were identified in isolated HCM patients, using a candidate gene approach based on biological plausibility. In cell culture systems, the FHL1 mutants identified in these families supported the possibility that FHL1 may accumulate and act as poison peptides, leading to hypertrophy, diastolic dysfunction, and altered contractility.

The current study provides significant additional support to the link between FHL1 and isolated HCM in 2 main ways. First, the family described is a large, well-phenotyped, and extensively studied 4-generation family, thereby providing scope for informative cosegregation analysis. The family pedigree alone, before blood collection for DNA extraction and analysis, is suggestive of an X-linked pathogenesis, with no male-to-male disease transmission. Second, the use of whole exome sequencing to investigate the genetic basis of disease

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in this family is nonbiased, robust, and comprehensive. Whole exome sequencing, that is, the ability to use next-generation sequencing platforms to analyze all protein-coding exons in >22,000 genes, is emerging as a powerful genetic tool to investigate genetic causes of human diseases. In the cardiovascular field, several studies have already emerged demonstrating the use of exome sequencing in genetic discoveries in both primary arrhythmogenic disorders and inherited cardiomyopathies. Using an appropriate bioinformatics pipeline and analysis, Hartmannova et al performed exome sequencing on only 3 affected individuals. Looking for potential pathogenic variants common to all 3 affected individuals, the vast list of variants was narrowed down to 51 rare coding variants, with the variant in the FHL1 gene emerging as the most likely pathogenic variant.

The exome sequencing approach not only provides unparalleled amounts of genomic data in patients and families but also provides us with the challenge of sorting the wheat from the chaff, that is, determining which of the final list of variants is the pathogenic mutation, and whether perhaps there is a cumulative effect of several genetic variants leading to disease. This determination of pathogenicity remains the Achilles heel of the exome sequencing approach and is a particular issue in families where the disease is inherited as an autosomal dominant condition and so more common variants exist. Serendipity will always play a role. In the current study by Hartmannova et al, the likely X-linked transmission, based on the family history alone, played a major role in refining the DNA variant list to those changes present on the X-chromosome. As shown in Table I in the online-only Data Supplement in the current study, the FHL1 variant was the only one that fulfilled both the pathogenic criteria and was present on the X-chromosome!

Significant advances have been made in defining the genetic basis of HCM. The study by Hartmannova et al provides additional evidence for an X-linked form of isolated HCM caused by a mutation in the FHL1 gene. The study reminds us of the importance of taking a detailed family history, which may provide clues about the disease transmission pattern as well as the diversity of the clinical phenotype. The study also presents a successful implementation of the whole exome sequencing approach in cardiovascular disease and its utility in defining genetic causation, particularly in X-linked disorders. The absence of a skeletal myopathy phenotype despite the expression of FHL1 in all striated muscle is an intriguing finding and may reflect some selectivity in terms of cardiac-specific variants in the FHL1 gene. The findings have some tantalizing parallels to the laminopathies and dilated cardiomyopathy, where mutations in the lamin A/C gene can lead to a variety of clinical disease phenotypes, including cardiac disease both with and without skeletal myopathy and other extracardiac manifestations. More detailed functional studies, as well as studies of the FHL1 gene in other cohorts of HCM families, are required to further define the precise role and molecular mechanisms underpinning FHL1 mutations in HCM.

Disclosures

None.

References


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