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Genetic Considerations in Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy (LVH) that develops in the absence of pressure overload or storage/infiltrative processes. Approximately 20 years ago, mutations in genes encoding sarcomere proteins were identified as the cause of HCM. Although there are limitations to current clinical application, genetic testing can identify the specific gene mutation responsible for causing HCM in a patient and their family. This provides a definitive means to identify at-risk relatives, as well as new opportunities to study pathogenesis, and to develop strategies for disease prevention and modification.

Keywords

Genetics; Hypertrophy; Cardiomyopathy

Hypertrophic cardiomyopathy has been recognized to be a familial disease with autosomal dominant inheritance for over half a century.¹ In the 1980s, linkage studies were performed in families, comparing the genetic background of family members with HCM to those without disease. These efforts led to the seminal discovery that HCM is caused by mutations in genes encoding sarcomere proteins, including beta-myosin heavy chain (*MYH7*), cardiac myosin binding protein C (*MYBPC3*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), cardiac actin (*ACTC*), alpha-tropomyosin (*TPMI*), essential myosin light chain (*MYL3*), and regulatory myosin light chain (*MYL2*).² Sarcomere mutations can be found in ~50% of patients referred for clinical genetic testing, however this yield is strongly influenced by family history. Approximately 60% of adult and pediatric patients with a family history of HCM will have a sarcomere mutation identified (positive genetic testing results). In contrast only ~30% of patients without a family history will have positive results, often due to sporadic or *de novo* mutations that may be passed on to the next generation.² Over 1000 distinct mutations have been identified, most commonly involving myosin heavy chain and myosin binding protein C. Most mutations are unique to a single family, rarely recurring in unrelated patients.

Symptoms, age of onset, pattern and extent of LVH, degree of obstruction, and risk for sudden cardiac death (SCD) can vary considerably, even within the same family. Given the heterogeneity of both genotype and phenotype, identifying the exact mutation responsible for disease usually does not substantially influence management or provide insight into

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Conflict of Interest Disclosures

None

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prognosis, including risk for sudden death. However, more severe consequences (cardiovascular death, stroke, progressive symptoms, systolic dysfunction) have been demonstrated in HCM patients with sarcomere mutations than patients who do not have a sarcomere mutation identified.³ Gene dosage effects have also been described, as patients with >1 mutation (~5% incidence) may have more severe disease, particularly in rare situations where >2 mutations are present in a single individual, or if patients are homozygous and do not express any normal protein.⁴

Family Evaluation

The goal of family screening is to identify relatives with unrecognized HCM, and to follow at-risk individuals for disease development, assessing risk for sudden death as appropriate. HCM follows autosomal dominant inheritance; therefore each 1st degree relative of an affected patient has a 50% chance of carrying the mutation and potentially developing HCM. Since diagnosis and SCD risk are both linked to the presence of LVH, and because the penetrance of LVH is age-dependent, clinical evaluation must continue longitudinally. Screening is most frequent (annually) during adolescence and early adulthood (age 12–21 years) when LVH most commonly emerges. Early childhood screening is appropriate if there is a family history of early onset disease or other concerns. During adulthood, screening is recommended every ~5 years, or in response to clinical change, as LVH can develop late in life.^{5, 6} Genetic testing can provide important insights into family management by definitively identifying at-risk relatives-- those that have inherited the family's pathogenic mutation.

Genetic Testing

Although originally available only through specialized academic research laboratories, the development of faster and less expensive DNA sequencing methodology has fostered the transition of genetic testing for HCM to the clinic (see www.genetests.org for further information). Commercially available testing was introduced in 2003. Currently all laboratories employ a candidate-gene strategy, analyzing the sequence of sarcomere genes as well as a small number of genes associated with metabolic/storage and mitochondrial disease that may mimic HCM by causing increased LV wall thickness.⁷ Genetic testing typically falls into 2 categories: diagnostic (comprehensive sequence analysis to identify a disease-causing mutation in a patient with HCM) and predictive (focused genetic testing to determine if the mutation previously identified in the family is present in a relative).

Although genetic testing can provide valuable information, accurate interpretation is complex. Unlike more familiar types of laboratory testing, genetic testing results are probabilistic rather than binary or quantitative. This is a key consideration because the clinical utility of genetic testing rest almost entirely on the predicted probability that the variant is disease causing. However, it may be difficult to accurately predict if a DNA variant identified in a patient is truly disease causing (pathogenic), disease modifying, or merely a benign polymorphism or rare variant present in a small proportion of the general population. If the clinical significance of the variant is unclear and not confidently predicted to be the cause of HCM, genetic testing results are non-informative and cannot be used in a predictive manner to identify at-risk relatives. Negative genetic testing results are also non-informative. Failing to identify a mutation does not exclude the possibility of genetic disease or obviate the need for longitudinal clinical screening in at-risk relatives. Furthermore, results may evolve over time. As we gain more experience in sequencing reference populations in different ethnic backgrounds, and in sequencing more patients and families with HCM, new information may emerge. As a result, a variant's classification as benign or pathogenic may change substantially.

Guidelines for the management of HCM give a Class I recommendation for genetic testing in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause.⁶ Genetic testing is considered “reasonable” to facilitate identification of at-risk family members (Class IIa recommendation). Figure 1 reviews practical considerations to guide the use of genetic testing, focusing on familial disease since the yield and impact of genetic testing is typically highest in this setting.

Genetic testing should be considered a family test, rather than a test for an individual patient. Indeed, the management of the family member with HCM that undergoes initial comprehensive genetic testing may not be substantially changed by the results. The implications of downstream, predictive genetic testing in family members may be more dramatic because it allows definitive identification of relatives who are at risk for developing HCM from those who are not at risk. Thus, if a pathogenic sarcomere mutation is identified in the family proband, predictive genetic testing provides a cost effective and definitive means of family screening. Longitudinal evaluation can be focused on mutation carriers since only they are at risk for developing disease.

Other than serial clinical screening to assess for the emergence of clinically overt disease, optimal management of mutation carriers who have not yet developed LVH has not been established. The natural history of this pre-hypertrophic stage is not well characterized but is likely variable, depending on the specific mutation, as well as environmental and genetic modifiers. Family history and individual factors, such as lifestyle and comorbidities, are important considerations in determining follow up. For example, earlier screening may be appropriate if there is a family history of childhood-onset disease or sudden death. More extensive evaluation may be considered if an apparently healthy, young mutation carrier is a serious athlete. Formal exercise restrictions for preclinical mutation carriers are not advocated by US consensus guidelines, although European Society of Cardiology recommendations are more restrictive due to the unknown impact of strenuous athletics in this context.⁸

Future Directions: Characterizing Early Phenotypes and Developing Preventive Treatment

Identifying the genetic basis of disease allows unique opportunities to identify risk and prevent disease. Extraordinary advances have been made in characterizing the genetics underlying HCM. For true preventive medicine to be developed, more knowledge is needed to define the precise steps that lead from mutation to disease, including steps that could be targeted to interrupt phenotypic progression. With this knowledge, we will be able to achieve the ultimate goal: changing the natural history of sarcomere mutations to prevent the development of HCM.

Rudimentary disease prevention based on genetic testing is currently available in the form of assisted reproduction using preimplantation genetic diagnosis (PGD). With PGD *in vitro* fertilization is performed and a single cell is removed from early-stage embryos for genetic testing to determine if the family’s pathogenic mutation is present or absent (Figure 2). Only embryos without evidence of the mutation are used to initiate pregnancy. The decision to pursue PGD is clearly a highly personal one. It requires confidence that the DNA variant identified in the family is the cause of HCM and it mandates the use of *in vitro* fertilization. This option may be a particular consideration for families in whom disease expression is consistently malignant.

Disease-modifying studies are in active development in animal models of HCM. For example, mouse models of HCM have demonstrated that abnormalities in intracellular

calcium handling may be one of the earliest manifestations of sarcomere mutations.^{9, 10} These abnormalities are demonstrable at ~4 weeks of age; far in advance of diastolic abnormalities (~age 6 weeks), and microscopic LVH, fibrosis and disarray (~age 20–25 weeks). Early treatment with the L-type calcium channel blocker, diltiazem, appeared to attenuate the development of LVH and fibrosis if started early in life while cardiac morphology was still normal.¹⁰ These studies have several intriguing clinical implications. They suggest a mechanistic link between calcium imbalance and disease development. Moreover, they provide some of the first evidence that mechanism-based pharmacological therapy may influence the natural history of HCM. To test the feasibility of this strategy, a pilot human randomized control trial was initiated, comparing diltiazem to placebo in sarcomere mutation carriers who have not yet developed LVH (<http://clinicaltrials.gov/ct2/show/NCT00319982>).

More recently, early treatment with the angiotensin II receptor blocker (ARB), losartan, in prehypertrophic HCM mice has also shown promise in decreasing the development of fibrosis and LVH. This effect may be mediated through its inhibition of TGF- β -mediated pathways.¹¹ In these studies, losartan was also unable to reverse established hypertrophy, again emphasizing the potential importance of early treatment and preventive strategies.

Progress is being made in translating these basic discoveries to human disease. By studying sarcomere mutation carriers prior to clinical diagnosis with HCM, we can more precisely characterize the early consequences of these mutations, improving our understanding of how HCM develops. Such studies have demonstrated that diastolic abnormalities,¹² impaired myocardial energetics,¹³ and increased collagen synthesis¹⁴ are present in sarcomere mutation carriers when LV wall thickness is normal. Confirmatory studies and longitudinal evaluation are needed to clarify how these early phenotypes relate to disease development and to serious consequences of HCM, such as heart failure and sudden death. Such collaborative basic science and clinical investigation will help us use genetic insights to truly transform medicine by identifying at-risk individuals early in life, prior to clinical diagnosis; refining understanding of disease pathogenesis; and ultimately developing new treatment paradigms to slow or prevent disease development, rather than simply palliating symptoms.

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Abbreviations

HCM	Hypertrophic cardiomyopathy
LVH	left ventricular hypertrophy
SCD	sudden cardiac death

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- - **Considerations in Specific Patients (Class I)**
 - Severe phenotypes
 - Ambiguous or atypical phenotypes
 - Suspected phenocopy of HCM (Fabry, amyloid, Danon disease, etc)
- - **To Assess Familial Disease (Class IIa)**
 - Genetic testing in the family member with the most clear diagnosis can establish a molecular diagnosis and definitive identification of at-risk relatives through predictive genetic testing
 - If a pathogenic mutation is identified, longitudinal clinical screening can be focused only on mutation carriers
- - **Testing should not be performed:**
 - At-risk family members who do not have a clinical diagnosis
 - Predictive genetic testing on relatives when the family's variant is of unknown significance

Figure 1.

Considerations for genetic testing. Genetic testing may provide important information when trying to differentiate HCM from other genetic causes of cardiac hypertrophy. Additionally, genetic testing can be highly informative in assessing families with HCM. Genetic testing should be avoided in the absence of diagnostic clinical features (for example testing an apparently child following the sudden death of a parent who did not have a prior diagnosis of HCM). Predictive testing should only be performed if there is a high degree of confidence that the family's mutation is disease causing (pathogenic).

Figure 2. Preimplantation genetic testing (PGD). Genetic testing is performed on embryos prior to implantation to attempt achieving a pregnancy that does not carry the family's pathogenic mutation.