A Guide for Clinicians

Hypertrophic Cardiomyopathy

Gene DNA Diagnostic Experts
Introduction

Hypertrophic cardiomyopathy (HCM) is the most common of the genetic cardiovascular diseases, characterized by heterogeneity in its cause, phenotypic expression and management options. The prevalence of HCM in the general population is at least 0.2% (1:500); the disease is transmitted as an autosomal dominant trait, affecting males and females equally. HCM occurs worldwide and has been reported from all continents and more than 60 countries. The disease is caused by mutations in a variety of genes encoding proteins of the cardiac sarcomere.

Clinical Presentation/Course:

HCM is characterized by variable clinical presentation and natural history, ranging from preventable sudden death from ventricular tachyarrhythmias, to progressive heart failure, to the consequences of embolic stroke. Patients with HCM may display a variety of symptoms. Exertional dyspnea, exercise intolerance and fatigue reflect heart failure and may be associated with chest pain (which can be typical angina pectoris, even in the absence of coronary artery disease). Such symptoms of exertional dyspnea are usually due to three possible mechanisms: (1) Left ventricular (LV) outflow obstruction, which produces elevated LV intraventricular pressures and wall stress; (2) diastolic dysfunction and impaired LV filling from noncompliant and thickened wall; and (3) myocardial ischemia from small vessel disease. However, it should be emphasized that HCM is also frequently compatible with normal life expectancy, often without disability or the need for major interventions to achieve that outcome. The diagnosis of HCM is most commonly made following the onset of symptoms.
Phenotypic Expression
HCM is characterized by a hypertrophied, nondilated LV in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident in a given patient (Figure 1). The clinical diagnosis of HCM is conventionally made with two-dimensional echocardiographic imaging (or increasingly with MRI) demonstrating the *sine quo non* of asymmetric LV hypertrophy—i.e., usually wall thickening of 15 mm, which may appear in myriad patterns. However, no absolute wall thickness excludes the diagnosis of HCM (even normal) since some genetically predisposed family members may in fact have normal echocardiograms and not show LV hypertrophy, especially early in life. It may also be difficult to distinguish the LV hypertrophy of HCM from that of systemic pathology. In patients with hypertension or physiologic athlete’s heart, the 12-lead ECG may show a myriad of patterns including increased voltage ST-T changes with T-wave inversion and deep Q waves that mimic HCM.

Pathology
There are three prominent histologic marks of HCM: (1) myocardial disarray in which the cellular architecture is disorganized; (2) small vessel disease, probably responsible for silent ischemia; and (3) scarring. Together these features probably represent the basis of electrical instability and the ventricular arrhythmias which are linked to sudden death.
Management
The heterogeneity of disease expression in HCM translates to the variety of management strategies available to patients with this disease.

Drugs: Medications used to control symptoms of heart failure usually consist of beta-blockers, verapamil and disopyramide, and occasionally diuretics.

Surgery: Septal myectomy is the treatment of choice for most patients with severe symptoms of heart failure due to LV obstruction refractory to medical treatment. Alcohol septal ablation is an alternative option in selected patients.

Implantable defibrillator: An implantable defibrillator is the preferred treatment, either for primary or secondary prevention, for those patients judged to be at high risk for arrhythmias due to the presence of one or more of the six major risk markers.

Lifestyle restriction: Under the guidelines of Bethesda Conference, young athletes with HCM are discouraged from participating in intense, competitive sports. This restriction is based on the premise that intense training and competition can increase sudden death risk in susceptible athletes with HCM (or represent the sole risk factor in an otherwise low-risk individual), and that this risk is likely reduced by withdrawal from sports.

Heart transplant: Occasionally, patients may gradually develop progressive heart failure associated with systolic dysfunction due to widespread scarring of the LV. Such patients may require a heart transplant.

Genetics of HCM
HCM is transmitted in an autosomal dominant pattern of inheritance. Therefore, an individual carrying a disease-causing HCM mutation has a 50% chance of transmitting the mutation to a child, either male or female. Molecular genetic studies have defined HCM as a disease of the sarcomere, the contractile unit within the cardiac myocyte that is comprised of thick and thin filaments.

HCM has proven to be a genetically heterogeneous condition and, to date, 18 disease-causing genes and more than 500 individual mutations have been identified (Figure 2 and Table 1). Mutations in these genes have been identified in 40–60% of HCM cases (the majority of which are missense mutations with amino acid substitution). Many of these mutations have proved to be unique to individual families. Mutations in β-myosin heavy chain (MYH7) and myosin-building protein C (MYBPC 3) account for the majority of identified mutations.
<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>Frequency in Patients with HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td>β-Myosin heavy chain</td>
<td>25–35%</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Cardiac myosin-binding protein C</td>
<td>20–30%</td>
</tr>
<tr>
<td>TNNNT2</td>
<td>Cardiac troponin T</td>
<td>5–15%</td>
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<tr>
<td>TNNI3</td>
<td>Cardiac troponin I</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>TPM1</td>
<td>Tropomyosin 1α</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>MYL2</td>
<td>Regulatory myosin light chain 2</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>ACTC</td>
<td>α-Cardiac actin 1</td>
<td>Rare</td>
</tr>
<tr>
<td>MYL3</td>
<td>Essential myosin light chain 3</td>
<td>Rare</td>
</tr>
<tr>
<td>LAMP2</td>
<td>Lysosome-associated membrane protein 2</td>
<td>Rare</td>
</tr>
<tr>
<td>PRKAG2</td>
<td>Noncatalytic AMP-activated protein kinase gamma 2</td>
<td>Rare</td>
</tr>
<tr>
<td>GLA</td>
<td>Galactosidase alpha (Fabry)</td>
<td>Rare</td>
</tr>
<tr>
<td>CAV3</td>
<td>Caveolin 3 (muscular dystrophy)</td>
<td>Rare</td>
</tr>
<tr>
<td>MTTG</td>
<td>Mitochondrial transfer RNA glycine</td>
<td>Rare</td>
</tr>
<tr>
<td>MTTI</td>
<td>Mitochondrial transfer RNA isoleucine</td>
<td>Rare</td>
</tr>
<tr>
<td>MTTK</td>
<td>Mitochondrial transfer RNA lysine</td>
<td>Rare</td>
</tr>
<tr>
<td>MTTQ</td>
<td>Mitochondrial transfer RNA glutamine</td>
<td>Rare</td>
</tr>
<tr>
<td>TTR</td>
<td>Transthyretin (Amyloidosis)</td>
<td>Rare</td>
</tr>
<tr>
<td>TNNC1</td>
<td>Troponin C</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Figure 2.** Schematic diagram of the cardiac sarcomere. The sarcomere, a fundamental structural and functional unit of the heart muscle, is composed of thick and thin filaments. Muscle contraction is achieved by the sliding and interdigitating of the thick and thin filaments, dependent on complex interactions between sarcomeric proteins, and regulated by calcium via the troponin-tropomyosin complex. Hypertrophic cardiomyopathy can be caused by mutations in genes coding for these proteins.
**Indications and Utility of Genetic Testing**

Genetic testing in a clinically-affected patient with HCM can clarify the diagnosis and assist in the management of family members. Identification of a mutation in the family can lead to genetic identification of at-risk family members who are clinically asymptomatic and who may have normal echocardiograms. Family members who test positive for the familial mutation should receive regular echocardiographic surveillance. Alternatively, a negative genetic test result for the familial mutation would obviate the need for repeated follow-up examinations. Genetic testing may be useful when discerning athlete’s heart from HCM. Genetic testing can be used for prenatal diagnosis.

**Genetic Testing Results and What they Mean**

Diagnostic genetic testing can be considered for patients who clinically manifest with symptoms of HCM and for patients who are asymptomatic but are within a family with a known mutation. Testing should be performed first on the family member who is symptomatic—i.e., has clinical manifestations of HCM. Preferably, the youngest of the most severely affected family members should be tested first. The three possible outcomes of genetic testing are: positive, negative and variant of unknown clinical significance (VOUS). All patients who undergo genetic testing should receive pre-test and post-test genetic counseling so that they can understand the implications of testing. Information about genetic counseling services can be found at www.nsgc.org.

**Positive Result**

A positive test result indicates that a disease-causing mutation was identified in that individual. This finding confirms the diagnosis of HCM and provides valuable information to family members. All first-degree relatives (children, siblings, parents) of the proband can then be offered predictive genetic testing to determine their risk for HCM. If a family member is found to be positive for the familial mutation, this individual is considered to be at risk for HCM and should be monitored regularly. Mutation-positive family members should have a baseline echocardiogram, an annual echocardiogram between the ages of 10–20, an echocardiogram every 2–3 years between the ages of 20–30 and an echocardiogram every five years for individuals over 30. It is important to note that there is phenotypic variability even within families who have been identified with the same mutation.

**Negative Result**

A negative result in an affected individual does not rule out HCM, and the patient should be managed according to his or her clinical symptoms. Possible reasons for a negative result could be: (1) patient may have a mutation in a gene not covered in the testing panel, or (2) patient may have a mutation in a part of an HCM gene that was not covered in the test. Predictive genetic testing of family members when the affected family member’s test is negative will not be informative and is not warranted. Family members of a clinically affected individual with negative test results are still at risk for HCM and thus should be regularly screened by a cardiologist. In addition, cardiac clearance prior to participation in competitive sports is highly recommended.
If an asymptomatic individual is negative for a mutation identified in a family member, this person is considered a true negative and is not at increased genetic risk for familial hypertrophic cardiomyopathy. HCM clinical monitoring for this individual is not necessary, but this patient could, of course develop other types of cardiac disease in the future.

If there are no symptomatic members of an HCM family available for testing, an asymptomatic individual may pursue predictive genetic testing prior to identification of the familial mutation. However, if the asymptomatic family member is found to have a negative test result, this result is considered an uninformative negative, and this asymptomatic family member should still be followed by serial echocardiograms and clinical evaluation because the genetic test identifies mutations in only 60–70% of families with HCM.

**Variant of Unknown Clinical Significance (VOUS)**
A VOUS result indicates that the pathogenicity of the gene variant cannot clearly be established. A VOUS has been tested in a panel of normal individuals and was not identified in any of the normal individuals. To further clarify the clinical significance of this variant, testing of family members is helpful. If an affected adult relative is found to have the same variant, it is more likely that the variant is disease-causing. The greater the number of affected family members who carry the VOUS, the greater is the likelihood that the VOUS is pathogenic. With consistent linkage of the VOUS with symptomatic family members, the variant found would be reclassified as a family-specific mutation and extended family members can be offered predictive genetic testing.

**Resources for patients**
You can find more information at the following websites:
- Hypertrophic Cardiomyopathy Association (HCMA): Patient support organization [www.4hcm.org](http://www.4hcm.org)
- National Society of Genetic Counselors: Search for a counselor or genetic center specializing in cardiology genetics [www.nsgc.org](http://www.nsgc.org)
- Children’s Cardiomyopathy Foundation: Patient support organization for children with cardiomyopathy [www.childrenscardiomyopathy.org](http://www.childrenscardiomyopathy.org)

**References**

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References (continued)


About GeneDx

GeneDx is a highly respected company in genetic testing for rare inherited disorders. Two scientists from the National Institutes of Health (NIH) founded the company in the year 2000 to address the needs of patients and clinicians concerned with rare inherited disorders.

Currently, GeneDx offers testing for over 300 rare Mendelian disorders using DNA sequencing and deletion/duplication analysis of the associated gene(s). GeneDx also offers oligonucleotide microarray-based testing for detecting chromosomal abnormalities, testing for autism spectrum disorders and testing for various forms of inherited cardiac disorders. At GeneDx, our technical services are matched by our expertise and customer support. Our growing staff includes over 12 experts in molecular and clinical genetics and five genetic counselors, who are just a phone call or email away. We invite you to visit our website www.genedx.com to learn more about us and the services we offer.

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