Etiology of Familial Hypertrophic Cardiomyopathy

Familial hypertrophic cardiomyopathy (FHCM) is a disease in which the dominant and characteristic phenotype is hypertrophy without obvious cause. In adults, the cause of this disease is always genetic; however, the proportion of individuals inheriting the disease as opposed to developing a de novo mutation (sporadic) remains to be determined. Because most sporadic cases transmit the gene to 50% of their offspring and become part of the familial pool, the need for genetic analysis is similar. FHCM is a single-gene disorder inherited in an autosomal-dominant pattern for which 10 genes have been identified. Each of the genes encodes for a sarcomeric protein, as shown in Table 1, with mutations in the βMHC (β-myosin heavy chain) gene, with MYBP-C (myosin-binding protein C) and troponin T probably accounting for 70% to 80% of all cases of FHCM. The total number of mutations is well over 100, and new mutations continue to be identified. The majority of the mutations are single-point missense mutations, meaning a single nucleotide has been substituted, which gives rise to a change in only 1 amino acid of the protein. The remainder of the mutations are small deletions or insertions, with 1 exception being a major deletion of >2000 bases.

Clinical Features

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden cardiac death (SCD) in the young. The recent interest in deciphering the genetics of this disease has also increased our awareness of it, and the true prevalence of the disease is now estimated at 1 in 500. The most common clinical manifestation of HCM is dyspnea followed by chest pain. Unfortunately, all too often, the first symptom is SCD without any warning. Chest pain may be the predominant symptom in the obstructive form of HCM, with or without syncope or presyncope. SCD is a well-recognized manifestation of this form of disease. In most patients, there is a mid-systolic ejection murmur from the outflow tract, but with concentric hypertrophy without obstruction, there is often no murmur. In the obstructive form, 2 murmurs are often present: the systolic murmur is due to the left ventricular outflow tract gradient, and the other murmur is due to mitral incompetence. The mitral murmur varies greatly with a number of interventions, including those designed to change left ventricular cavity size (eg, squatting, Valsalva, and amyl nitrate) and contractility (eg, dobutamine, isoproterenol, and endogenous catecholamines). The change in the intensity of the murmur can often be used to diagnose HCM and detect a left ventricular outflow tract gradient. The ECG is often abnormal, showing the feature of left ventricular hypertrophy and/or nonspecific ST changes with Q waves in II, III, and aVF. The clinical features have been examined in detail in review articles. The diagnosis is confirmed by echocardiogram showing hypertrophy, with the septum or ventricular wall exceeding 1.3 mm without other cause.

Elucidation of the Molecular Basis for the Hypertrophy

Single-gene disorders, when transmitted through subsequent generations, follow a mendelian pattern of inheritance. Although everyone has 2 copies of each gene (referred to as alleles), 1 from each parent, which allele is transmitted to the subsequent generation is determined by random selection. In autosomal-dominant disorders, only 1 allele is required to be defective to induce the disease, whereas in recessive disorders, both alleles are required to be defective to induce the disease. In recessive disorders, both alleles of the causative gene are defective, and there is complete absence of the corresponding protein or the expressed protein is completely defective. In individuals with 1 defective allele (heterozygous) of a recessive disease, there is no risk of ever developing the disease, which indicates the remaining normal allele is adequate for normal cell function. The predominant mechanism accounting for the phenotype in dominant disorders is believed to be that of a dominant-negative or the so-called poison-peptide effect. The wild type (normal allele) and mutant protein are expressed; however, the mutant protein functions as a poison peptide that impairs the function of the normal protein, leading to disease. Another mechanism postulated for dominant disorders is haploinsufficiency. The phenotype results from the absence of 1 allele or its protein product, which indicates that the protein produced solely from the normal allele is insufficient to maintain normal function. The mechanism as to why disease should result despite normal function of the remaining allele is unknown.
HCM is characterized by an abnormality that involves excessive growth (hypertrophy). All of the mutant genes encode for proteins that comprise the sarcomere, which explicitly indicates a defect in contractility. Several in vitro and in vivo studies confirm that mutations in the βMHC gene, troponin T, and MYBP-C impair contractility and induce release of growth factors that stimulate the phenotype of hypertrophy and fibrosis. The phenotype of FHCM has been induced in vitro and in vivo in genetic animal models. The main pathology of human FHCM disease is sarcomeric disarray, increased interstitial fibrosis, and cardiac hypertrophy. Sarcomere disarray is considered the hallmark of FHCM and has been observed consistently in genetic animal models after expression of βMHC, troponin T, and MYBP-C mutations and most recently in the rabbit after expression of βMHC. In all of the genetic animal models, there is sarcomere disarray, increased interstitial fibrosis, and altered myocardial function; however, in the mouse there is very little if any hypertrophy. The heart of the mouse has MHC similar to that of humans. The rabbit exhibits a phenotype that is virtually identical to that observed in human FHCM, which includes sarcomere disarray, increased interstitial fibrosis, hypertrophy, SCD, and impaired myocardial function.

The mutant protein has been shown to be incorporated into the cardiac myofibril in feline cardiomyocytes, transgenic mice, and transgenic rabbits. Contractility of isolated skeletal muscles obtained from patients expressing mutant βMHC exhibited impaired cell shortening. Analysis of a 3D crystalline structure of skeletal myosin heavy chain showed that the βMHC mutations involve several domains critical to contractility of the sarcomere, such as the actin binding site, ATP generation, or calcium sensitivity, which could account for the in vitro observations of impaired contractility. Expression of the βMHC mutant gene in intact feline cardiac myocytes showed sarcomeric disarray after ~72 hours, and expression of a troponin T mutation in cardiac feline myocytes was associated with impaired contractility after 24 to 48 hours, followed by sarcomere disarray in 72 hours. The mutant troponin T expressed in adult cardiac rat myocytes exhibited decreased cell shortening and impaired contractility. In the intact genetic animal model of FHCM expressing a troponin T mutation, cardiac contractility was shown to be impaired before the development of sarcomere disarray.

Thus, the primary genetic defect appears to be impaired contractility, which triggers the release of growth factors that result in compensatory hypertrophy and fibroblast proliferation. Upregulation of growth factors has been confirmed in FHCM mouse models and in humans with FHCM. Furthermore, fetal isoforms of proteins expressed in pressure-overload hypertrophy are also expressed in human FHCM, including c-fos, c-jun, and c-myc; atrial and brain natriuretic peptides; and endothelin 1. Environmental factors such as increased pressure also affect the FHCM phenotype and explain why it is restricted to the left ventricle despite equal abundance of the mutant protein in the right ventricle. Ventricular pressure as a stimulus for the hypertrophy is supported by the results of the 2-year follow-up of FHCM patients after elimination of their outflow tract gradient by septal alcohol injection, which induced a 30% reduction in wall thickness, cardiac mass, and myocardial collagen.

## Insights From Genotype-Phenotype Correlation Studies

The phenotype depends not only on the causal mutation but also on other modifier genes and environmental factors. The incidence of SCD is greater in individuals with FHCM who participate in highly competitive contact sports. There is also a higher incidence of SCD in males with FHCM than in females, although it remains unknown whether this relates to increased physical exercise or a sex-related genetic factor. The DD allele of the angiotensin I converting enzyme gene is associated with more extensive hypertrophy and an increased incidence of SCD in patients with FHCM. In keeping with most autosomal-dominant disorders, the expressivity (variability of the manifestations of the disease) is highly variable, as reflected in the age of onset and clinical severity.

Seldom is any observable disease detected clinically, electrocardiographically, or echocardiographically before puberty. Thus, genetic testing provides the opportunity to detect affected offspring at least a decade before development of the disease. Targeted therapies, if developed, could be initiated as primary prevention, rather than treating the disease after it has developed. Those at risk of developing the

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**TABLE 1. HCM Genes and Their Frequencies**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Frequency, %</th>
<th>Number of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>βMHC</td>
<td>14q1</td>
<td>35–50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>MYBP-C</td>
<td>11q11</td>
<td>15–20</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Cardiac troponin T</td>
<td>1q3</td>
<td>15–20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>α-tropomyosin</td>
<td>15q2</td>
<td>&lt;5</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac troponin I</td>
<td>19q13</td>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>MLC-1</td>
<td>3p</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>MLC-2</td>
<td>12q</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>α-Cardiac actin</td>
<td>15q11</td>
<td>?</td>
<td>2</td>
</tr>
<tr>
<td>Titin</td>
<td>2q31</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Unknown</td>
<td>7q3</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

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Kaplan-Meier Survival Curve

Kaplan-Meier analysis showing prognostic difference between the 2 mutations, based on 1 large family of 4 generations with a total of 20 affected individuals.
disease could be counseled to avoid contact sports, such as basketball.

Genotype-phenotype correlations, although only performed for a limited number of mutations in the βMHC gene,13 show a high correlation with prognosis (Figure). In general, FHCM due to mutations in the βMHC gene manifests at a younger age and is associated with more extensive hypertrophy and a higher incidence of SCD than FHCM arising from mutations in the MYBP-C or α-tropomyosin genes.33 In contrast, individuals with FHCM due to mutations in the cardiac troponin T (cTnT) gene exhibit mild hypertrophy despite a high incidence of SCD.34 Mutations in the βMHC gene, known as Arg403Gln, Arg453Cys, and Arg719Trp, have been associated with a high incidence of SCD.13 The Arg403Gln mutation is also the most commonly reported mutation and has been described in multiple families.35–37 Pooled data from these families show that ~50% of affected individuals with the Arg403Gln mutation die prematurely, primarily of SCD, and have an average life span of 28 years. These mutations are also associated with high penetrance, early onset of symptoms, severe hypertrophy, and a high incidence of SCD. The mutations Arg453Cys and Arg719Trp are also associated with high penetrance, severe hypertrophy, and a high incidence of SCD.13 The average life expectancy of patients with the Glu930Lys and Arg249Gln mutations is ~40 years. In contrast, 3 mutations (Gly256Glu, Val606Met, and Leu908Val) in the βMHC gene are associated with a benign prognosis and a near-normal life expectancy.13 These exhibit a low penetrance, mild hypertrophy, and usually later onset of the disease. The cumulative rate of SCD in patients with FHCM due to the above mutations is <5% at the age of 50 years. Most mutations in the α-tropomyosin and MYBP-C genes are associated with a low penetrance, mild hypertrophy, and a low incidence of SCD.13 Recent detection of a new mutation (Val95Ala) in the α-tropomyosin gene shows a high incidence of SCD despite minimal hypertrophy.13 A summary of important observations is given in Tables 2 and 3.

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**References**


**TABLE 2. Insights From Genotype/Phenotype Studies**

1. FHCM is inherited as an autosomal-dominant disease that affects males and females equally.
2. Only 50% of the offspring of affected individuals will be at risk of inheriting the gene and developing the disease.
3. The offspring of unaffected family members carry no risk of inheriting the gene and developing the disease.
4. In any one family with FHCM, all affected members have the same mutation.
5. The onset of clinical manifestations is usually delayed until adolescence or early adulthood.
6. Clinical features of the phenotype are not predictive of sudden death; however, in certain genes, there is a high correlation between the extent of ventricular hypertrophy and the incidence of sudden death.
7. FHCM due to the myosin-binding protein C gene is often associated with late onset of the disease.
8. Certain mutations are highly predictive of sudden death and are likely to be included in the future management of FHCM.

**TABLE 3. Mutations and Prognosis in HCM**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Good</th>
<th>Intermediary</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>βMHC</td>
<td>Gly256Glu</td>
<td>Arg249Gln</td>
<td>Arg403Gln</td>
</tr>
<tr>
<td></td>
<td>Leu908Val</td>
<td>Glu930Lys</td>
<td>Arg719Trp</td>
</tr>
<tr>
<td></td>
<td>Val606Met</td>
<td>Val606Met</td>
<td>Arg453Cys</td>
</tr>
<tr>
<td></td>
<td>Phe615Cys</td>
<td>Arg723Glu</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asn232Ser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac troponin T</td>
<td>Ser179Phe</td>
<td>Phe110lle</td>
<td>Arg92Gln</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arg92Trp</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ile79Gln</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ΔGlu160</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ser179Phe (homozygous)</td>
</tr>
<tr>
<td>MYBP-C</td>
<td>All unless listed</td>
<td>SASint20</td>
<td></td>
</tr>
<tr>
<td>α-Tropomyosin</td>
<td>Asp175An</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLC</td>
<td>Insufficient data</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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