

## Hypertrophic Cardiomyopathy – an Overview

### Introduction

Hypertrophic cardiomyopathy (HCM), which occurs at a prevalence of 1 in 500 (0.2%), is characterized by a thickening of the heart muscle that can lead to severe cardiac problems such as progressive heart failure, embolic stroke, and sudden cardiac death (SCD) (1-4). Notably, HCM is the most common cause of SCD in young adults, who are often unaware of their underlying condition. Early diagnosis of HCM is important, since at-risk individuals may be advised not to participate in competitive sports and should undergo regular cardiac screening to assess the risk of SCD (5). In high-risk patients, use of an implantable cardioverter-defibrillator (ICD) may help to prevent SCD (6). Since most cases of HCM are familial, regular screening of family members of known patients can help to identify individuals at increased risk for HCM early in life (5,7). However, cardiac screening cannot reliably identify unaffected family members, because clinical diagnosis is based on the appearance of HCM-related symptoms, which may occur at any age. Since HCM has been associated with dominant mutations in any one of at least 12 genes, genetic testing can facilitate the diagnosis of HCM and allow for accurate identification of both affected and unaffected family members (8,9). Extensive cardiac screening at regular intervals can then be limited to affected family members. In addition, genetic testing can confirm presence of the metabolic subtype of HCM, which may differ in both prognosis and mode of inheritance from the more common sarcomere-related HCM (10).

### Molecular Pathophysiology

Most HCM is caused by defects in the cardiac sarcomere – the contractile unit of the heart muscle (11). The sarcomere is built from thick and thin filaments, which are arranged in an overlapping fashion. Thick filaments are composed primarily of myosin, along with associated myosin binding proteins C, H, and

X. Thin filaments are composed of cardiac actin,  $\alpha$ -tropomyosin, and troponins C, I, and T. A giant protein, titin, provides a scaffold for the thick and thin filaments. When thick filaments slide along thin filaments, the muscle shortens. This contractile motion is driven by interaction of the myosin motor protein with actin and triggered by transient increases in intracellular  $\text{Ca}^{2+}$  concentration. The response to  $\text{Ca}^{2+}$  is regulated by the cardiac troponin-tropomyosin complex in sarcomeric thin filaments. The myosin light chain kinase and myosin-binding protein-C also play a role in the modulation of cardiac contractility.

HCM has been linked to mutations in almost every protein within the sarcomere, including thick filament proteins MYH7, MYL2, MYL3, and MYBPC3 and thin filament proteins ACTC, TNNT2, TNNI3, and TPM1. Mutations in the genes coding for these eight proteins are estimated to account for about 60% of all familial cases of HCM (Table 1).

**Table 1: Genetic Causes of HCM** <sup>4,8,10</sup>

Gene (Protein)	% HCM
<b>Sarcomere-related HCM</b>	
<i>TNNT2</i> (cardiac troponin T)	5-20
<i>TNNI3</i> (cardiac troponin I)	<5
<i>TPM1</i> ( $\alpha$ -tropomyosin)	<5
<i>MYBPC3</i> (myosin binding protein C)	20-40
<i>MYH7</i> (cardiac myosin heavy chain, beta)	30-50
<i>MYL2</i> (cardiac myosin light chain, regulatory)	<3
<i>MYL3</i> (cardiac myosin light chain, essential)	<1
<i>ACTC</i> ( $\alpha$ -cardiac actin)	<1
<b>Metabolic HCM</b>	
<i>PRKAG2</i> (AMP-activated protein kinase)	<1
<i>LAMP2</i> (lysosome-associated membrane protein)	<1

A less common type of HCM, known as metabolic HCM, is not related to defects in the cardiac sarcomere, but due to glycogen accumulation in cardiac myocytes (10). Metabolic HCM is typically associated with ventricular pre-excitation and atrial fibrillation (Wolff-

Parkinson-White syndrome, WPW), presumably because glycogen-filled myocytes can serve as accessory conduction pathways between the atria and the ventricles. Over time, glycogen accumulation may lead to cell death and progressive conduction defects. Mutations in the gamma-2 regulatory subunit of AMP-activated protein kinase 2 or in lysosome-associated membrane protein 2 are believed to account for about 1% of all HCM and for up to 50% of HCM with ventricular pre-excitation (Table 1).

## Clinical Presentation

The initial clinical presentation of patients with HCM is widely variable and includes cardiac arrhythmias, exercise-induced hypotension, systolic heart murmur with bifid arterial pulse, pulmonary congestion and/or fatigue, a history of syncope or near syncope, cardiac arrest, or even SCD (1). In young athletes, the two most common complaints are chest pain and exertional dyspnea (4). Adolescent patients are at higher risk of SCD, while older patients are more likely to develop progressive heart failure or embolic stroke (3). Initial presentation typically occurs during adolescence, but symptoms may also appear during childhood or be delayed to adulthood (5). Most patients exhibit left-ventricular hypertrophy (LVH), and 75-95% of patients show an abnormal EKG pattern. Between 20-25% of affected individuals also suffer from chronic atrial fibrillation, which is associated with an increased risk of embolic stroke. Ventricular arrhythmias, which can lead to SCD, may also occur. Some HCM patients suffer progressive heart failure, and 5-10% of patients experience LV wall thinning and systolic dysfunction that resembles dilated cardiomyopathy. Over time, HCM causes scarring, fibrosis, and cellular disarray in the myocardium and narrowing of the coronary arteries (4).

Metabolic HCM is typically associated with ventricular pre-excitation and frequently presents with WPW (10). Chronic atrial fibrillation leads to an increased risk of embolic stroke, and progression to conduction defects requiring pacemaker implantation is common (12). HCM due to mutations in *LAMP2* – also known as Danon disease – presents differently in males and females, probably due to its un-

usual X-linked dominant mode of inheritance (13). In males, clinical symptoms typically first appear in childhood or adolescence and, in addition to cardiac manifestations such as HCM, WPW, and atrioventricular block, include skeletal myopathy, ophthalmic abnormalities, mild mental retardation, and hepatic involvement (14). Females typically first present in their thirties or forties, with either hypertrophic or dilated cardiomyopathy and few extra-cardiac manifestations. Prognosis is poor in both males and females, with rapid progression to heart failure.

## Diagnosis

Diagnosis of HCM is most commonly based on an observation of left ventricular hypertrophy (LVH), often disproportionately affecting the ventricular septum, that cannot be explained by another disease such as aortic stenosis (1). LVH associated with outflow obstruction is indicated by a heart murmur and/or bifid arterial pulse, while LVH without outflow obstruction is most reliably diagnosed by 2-dimensional echocardiography or MRI. LVH can range from mild (~13-15 mm) to severe (30-60 mm) and may increase or decrease significantly throughout life. “Athlete’s heart,” a mild, benign thickening of the heart muscle often observed in trained athletes, can complicate the diagnosis of HCM because it resembles mild LVH caused by HCM. Diagnosis of WPW is based on the characteristic EKG pattern caused by ventricular pre-excitation – a shortened PR interval and/or a widened QRS complex with a delta wave (10). Presence of skeletal myopathy and elevated creatine kinase levels in males may be indicative of Danon disease (10,13). Since published studies have established a causal relationship between HCM and certain variants of the genes *TNNT2*, *TNNI3*, *TPM1*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *ACTC*, *PRKAG2*, and *LAMP2*, genetic testing not only can confirm a diagnosis of HCM in an affected index patient, but also distinguish family members who are affected but presymptomatic from those who are not affected. In addition, genetic testing can identify cases of metabolic HCM and clarify the mode of inheritance, with important implications for prognosis and genetic counseling.

Once patients have been diagnosed with HCM, they should undergo periodic risk assessment for SCD to guarantee timely recognition of risk factors (2,4,5,7). The two strongest risk factors are prior cardiac arrest and spontaneous sustained ventricular tachycardia; patients who have experienced either are at high risk of SCD (1). Additional risk factors include severe LVH (>30 mm), LVH outflow tract obstruction of >30mm Hg, abnormal blood pressure response during exercise, non-sustained ventricular tachycardia, and history of syncope along with a family history of SCD. HCM patients with two or more of these risk factors are also considered high risk; those with just one are moderate risk; and those with none are low risk (15).

## Treatment

Treatment depends on symptoms and/or risk of SCD. Chronic atrial fibrillation is treated with anticoagulant therapy to prevent clotting and embolic stroke and with electrical or pharmaceutical cardioversion to control arrhythmias. Ventricular pre-excitation can be controlled by medication and may be cured by surgical or radiofrequency catheter ablation of the acces-

sory pathway. Severe outflow obstruction is treated surgically by ventricular septal myotomy-myectomy or non-surgically by alcohol septal ablation or chronic dual chamber pacing. Atrioventricular block can be effectively controlled by pacemaker implantation. Progressive heart failure is treated pharmacologically with ACE inhibitors or  $\beta$ -blockers or, at its end stage, surgically by heart transplantation, which presents the only effective treatment for *LAMP2*-related cardiomyopathy (13). For patients at high risk for SCD, an ICD may be advised (6).

Of note, autosomal dominant mutations in *MYH7*, *MYBPC3*, *TNNT2*, *TPM1*, and *ACTC* are also associated with familial dilated cardiomyopathy; autosomal dominant mutations in *TNNI3* have been linked to familial restrictive cardiomyopathy; and at least one autosomal recessive mutation in *TNNI3* has been associated with familial dilated cardiomyopathy (11,16) *PRKAG2*-related cardiac disease is phenotypically variable and can range from late-life onset of conduction defects to fatal congenital cardiac glycogenosis (17,18)

## References

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