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Hypertrophic Cardiomyopathy: For *Heart Failure Clinics*: Genetics of Cardiomyopathy and Heart Failure

Carolyn Y. Ho, MD[Assistant Professor of Medicine][Medical Director]

Cardiovascular Genetics Center, Cardiovascular Division, Brigham and Women's Hospital,
Harvard Medical School, Boston, MA

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Introduction

Important insights into the molecular basis of hypertrophic cardiomyopathy (HCM) and related diseases have been gained by studying families with inherited cardiac hypertrophy. Integrated clinical and genetic investigations have demonstrated that different genetic defects can give rise to the common phenotype of cardiac hypertrophy. Diverse pathways have been identified, implicating perturbations in force generation, force transmission, intracellular calcium homeostasis, myocardial energetics, and cardiac metabolism in causing disease. Although not fully elucidated, the fundamental mechanisms linking gene mutations to clinical disease are being characterized. Further advances will allow a better understanding of pathogenesis, diagnosis, and treatment, not just of relatively rare inherited cardiomyopathies, but will also be of relevance to more common acquired forms of hypertrophic remodeling.

Hypertrophic Cardiomyopathy

Clinical Phenotype of HCM

Natural History and Clinical Manifestations—Unexplained left ventricular hypertrophy (LVH) which develops in the absence of other inciting factors, including increased hemodynamic load (systemic hypertension, valvular heart disease), infiltrative or storage disorders, is a defining feature of hypertrophic cardiomyopathy (HCM). Myocyte hypertrophy with disarray and fibrosis are pathognomonic histologic features of HCM (Figure 1). A diagnosis of HCM is typically made by identifying unexplained LVH on cardiac imaging studies, as illustrated in the echocardiographic images in figure 2. Clinical evaluation may be triggered in response to symptoms, or in asymptomatic individuals in the course of family screening or after detection of a systolic murmur or an abnormal EKG. The degree and pattern of distribution of LV hypertrophy vary markedly. Asymmetric septal hypertrophy is the most common morphologic pattern, however any configuration, including

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Carolyn Ho, MD Cardiovascular Division Brigham and Women's Hospital 75 Francis Street Boston, MA 02115 T: 617-525-7052 F: 617-264-5265 cho@partners.org.

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concentric, apical, and isolated segmental hypertrophy can be seen (Figure 3).³¹ The morphologic pattern of LVH is not closely predictive of the severity of symptoms or prognosis.^{16,37}

HCM is a complex and heterogeneous disease which demonstrates remarkable diversity in disease course, age of onset, severity of symptoms, left ventricular outflow obstruction, and risk for sudden cardiac death (SCD).⁴¹ While some individuals experience no or only minor symptoms, others may develop refractory symptoms or end stage heart failure requiring cardiac transplantation. Shortness of breath, particularly exertional, is the most common symptom of HCM, and occurs in up to 90% of patients. Other manifestations include chest pain, palpitations, atrial and ventricular arrhythmias, orthostatic lightheadedness, presyncope and syncope, volume overload, and fatigue.^{37,54} Atrial fibrillation develops in approximately 20–25% of patients and is associated with an increased risk of stroke and thromboembolic complications.

Left ventricular outflow tract (LVOT) obstruction is one of the most highly visible features of disease, however its clinical significance has been debated. Obstructive physiology is likely an important contributor to symptomatology, particularly exertional dyspnea, pulmonary congestion, and orthostasis, however, large gradients may be asymptomatic and tolerated for long periods of time. Approximately 25–30% of patients will have evidence of obstruction at rest, but the majority of patients may develop obstruction in response to exercise or maneuvers which decrease preload or afterload or increase contractility or heart rate.⁴⁴ The mechanism for outflow tract obstruction in most patients is systolic anterior motion of the mitral valve (SAM) causing mechanical obstruction to the flow of blood out of the heart. Although older reports have not demonstrated a close relationship with outcomes, a recent large retrospective study indicated that the presence of outflow tract obstruction (>30 mmHg) is associated with increased disease-related morbidity and mortality.⁴³ The magnitude of the gradient did not correlate with clinical outcomes, however patients with obstruction were nearly 5 times more likely to progress to severe symptoms of heart failure and heart failure-related death.

Left ventricular ejection fraction is typically preserved or even hyperdynamic in HCM. However, up to 5–10% of patients may progress to the “burnt-out” or end stage phase of HCM, marked by left ventricular systolic dysfunction, worsening symptoms, and occasionally progressive LV wall thinning, and chamber enlargement. The prognosis of patients who develop this end stage phenotype is worse, with an increased risk of cardiovascular events and need for transplantation as compared to typical HCM.^{8,26} Patients with end stage development are more likely to have a family history of HCM, suggesting a genetic association, however specific genetic factors that predict or correlate with this phenotypic variant have not been identified.

Estimates of annual mortality rates for HCM range from 4–6% in referral-based populations to 1–2% in community-based studies.³⁹ Overall, life expectancy is not dramatically impacted in the majority of patients with HCM. Sudden cardiac death (accounting for approximately half of HCM-related deaths), progressive heart failure, atrial fibrillation, and stroke are leading contributors to the morbidity and mortality associated with HCM.

Management—Strategies to prevent or modify disease progression in asymptomatic patients are not yet available; therefore current treatment focuses on symptom management, assessment for risk of SCD, and family screening as summarized in Box 1. Medical therapy is the first line approach for symptomatic disease, typically utilizing β -blockers or L-type calcium channel blockers (verapamil or diltiazem) to lengthen diastolic filling period and diminish left ventricular gradients. If obstruction is present and symptoms persist, the

addition of disopyramide may provide additional symptomatic benefit by reducing LV pressure gradients via its negative inotropic effects. If symptoms from LV outflow tract obstruction are refractory to medical management, invasive approaches such as ethanol septal ablation or surgical myectomy may be employed to mechanically decrease outflow tract gradients.^{16,37,45} Patients with non-obstructive disease and those with end stage HCM should be managed with appropriate therapy for advanced heart failure and may ultimately require cardiac transplantation.

HCM is associated with an increased risk of sudden cardiac death and rarely, such an event may be the presenting manifestation of disease.^{16,37,45,54} HCM is the leading cause of sudden death among adolescents/young adults, and competitive athletes in the United States.³⁸ Therefore assessment of SCD risk and determination of appropriate therapy are important, although challenging, components of clinical management. Clinical predictors associated with an increased risk of SCD include a family history of sudden death or known malignant genotype, unexplained syncope, hypotensive blood pressure response to exercise, significant spontaneous ventricular ectopy on Holter monitoring, and extreme left ventricular hypertrophy (>30 mm), as summarized in Table 1.^{18,45} Implantable cardioverter-defibrillator (ICD) therapy has been shown to be effective and life saving in appropriate patients.^{17,18,37,45} However, since the positive predictive value of these predictors individually is relatively low, accurate risk assessment is difficult. Making the decision to implant an ICD for primary prevention is therefore guided by the number and nature of predictors, as well as individualized clinical judgment and personal input from well educated and informed patients.⁷⁶ Individuals who do not demonstrate any of these risk predictors are likely not at increased risk and do not require more aggressive management, although longitudinal re-assessment of risk is appropriate. Patients who have survived cardiac arrest or sustained ventricular tachycardia are at high risk for recurrent events and should receive ICDs for secondary prevention.

Genetics of HCM: A disease of the sarcomere

The heritable nature and autosomal dominant pattern of inheritance of HCM have long been appreciated. Family linkage studies in the 1980's led to the discovery of pathogenic mutations in genes encoding different components of the contractile apparatus^{28,67,73} and established the paradigm that HCM is a disease of the sarcomere (Figure 4). The prevalence of unexplained LVH in the general adult population is estimated to be 1 in 500, but not all will have an underlying sarcomere mutation.^{40,77} The proportion of disease caused by sarcomere mutations is estimated to range from 45–70%, with a higher prevalence if a family history of HCM is present.^{60,61,70} As such, HCM is the most common monogenic cardiovascular disorder. However, as with the clinical heterogeneity seen with HCM, there is also substantial genetic heterogeneity, at both allelic and non-allelic levels. Over 800 distinct mutations have been identified in 11 different contractile genes, with no specific racial or ethnic predilections. Genes which have been causally-associated with HCM are summarized in Table 2 and updated data are available at <http://cardiogenomics.med.harvard.edu>. In addition to the genes listed in Table 2, mutations in other sarcomere-associated genes have been described in HCM, including cardiac troponin C (*TNNC1*), telethonin (*TCAP*), and muscle LIM protein (*CRP3*).^{11,21,55} Mutations in these genes are rare and the strength of evidence that they are truly disease-causing is not yet definitive.

Currently, the majority of mutations identified (~30–60% in *MYBPC3* and *MYH7*) are novel sequence variants—not previously identified as pathogenic mutations.^{36,60,61,63} Furthermore, when novel sequence variants are identified, family analysis to confirm appropriate cosegregation is valuable. Demonstrating that the variant is present in other relatives with HCM and not present in clinically unaffected family members provides

further support to allow a more confident conclusion that the variant is clinically significant and responsible for causing disease in the family. A relatively high 3–10% rate of compound heterozygosity (two sarcomere mutations present in a single individual with HCM) has also been observed.^{61,71}

Mutations in the genes encoding cardiac β -myosin heavy chain (*MYH7*), cardiac myosin binding protein C (*MYBPC3*), and cardiac troponin T (*TNNT2*), and cardiac troponin I (*TNNI3*) are the most prevalent and, in aggregate, account for over 80% of HCM.

Cardiac β -Myosin Heavy Chain (MYH7, β -MHC)—In 1989, linkage analysis of a large family led to the discovery of the first mutation associated with HCM, identified in *MYH7*.^{23,28} Since then, almost 200 different *MYH7* mutations have been reported in both familial and sporadic disease, accounting for ~30–40% of cases^{36,60,63} (<http://cardiogenomics.med.harvard.edu>). Myosin heavy chain is an abundant protein that has two functional domains: an amino terminal globular head and a carboxyl terminal rod.⁵⁹ The head domain binds ATP, contains the ATPase activity to power the lever arm, and contains the actin-binding domain to form the actinomyosin complex crucial for force generation. The rod domain interacts with the myosin light chains. Mutations which cause HCM are almost exclusively missense (resulting in amino acid substitution) and clustered within the globular head or head-rod junction, as illustrated in the molecular model shown in Figure 5. In general, *MYH7* mutations have been associated with a gain of function, resulting in increased actin-dependent ATPase activity, in vitro sliding velocity, and force production, as further discussed in the following sections.^{56,69} Gain of function effects have also been suggested in studies on thin filament mutations and *MYBPC3*.^{2,66}

Cardiac Myosin Binding Protein C (MYBPC3, cMyBPC)—The function of cardiac myosin binding protein C is unknown, but it is thought to provide structural integrity to the sarcomere (binding MHC and titin), play a role in sarcomeric assembly,⁶⁶ and may modulate myosin ATPase activity and cardiac contractility in response to adrenergic stimulation.²⁰ Missense mutations occur, however nonsense (leading to premature termination of translation), splice site and small deletion/insertion mutations are common, leading to a truncated protein or null allele.⁶¹ Almost 150 mutations have been reported to date, accounting for ~30–40% of cases of HCM.^{36,60,63} Mutations in *MYBPC3* have been characteristically associated with late-onset disease,⁵³ however they are also a frequent cause of pediatric-onset HCM.⁴⁹

Cardiac Troponin T (TNNT2, cTnT)—Troponin T links the troponin complex to α -tropomyosin, thus playing a central role in the regulation of contraction. Alternative splicing results in multiple isoforms of troponin T, including a cardiac-specific isoform. To date ~30 missense, splice site, and deletion mutations have been reported in *TNNT2*, accounting for approximately 5% of HCM.⁶¹ Initial reports suggested that disease caused by *TNNT2* mutations were associated with an increased risk of sudden death despite only modest hypertrophy,^{46,73} however exceptions have been well-documented.

Sarcomere Gene Mutations Are a Common Etiology for Cardiac Hypertrophy in Different Patient Populations—The clinical diagnosis of HCM is typically made in adolescence or young adulthood, but patients may present at any age. Whether childhood-onset HCM represents the same disease as HCM that presents in adulthood has recently been evaluated. Direct sequence analysis of sarcomere genes was performed in children with isolated, idiopathic LVH diagnosed before the age of 15 years (mean age 7 ± 6.1 years).⁴⁹ The prevalence of sarcomere mutations was found to be essentially the same as that seen in adult-onset HCM. Mutations were identified in 49% of children with apparently sporadic disease and 64% of children with a family history of HCM. Also, as in adult-onset disease,

~75% of cases were attributable to mutations in *MYH7* or *MYBPC3*, although *MYBPC3* mutations in children were more likely to be missense (predicted to result in an amino acid substitution), rather than truncation mutations which predominate in adults. Unrecognized familial disease was also well-documented, where direct family evaluation revealed that one of the parents of an affected child carried the causal sarcomere mutation, but were without symptoms or clinical features of HCM on echocardiography.

At the other end of the age spectrum, sarcomere mutations have been identified in adults with late onset cardiac hypertrophy, presenting after age 40 years.⁵³ Approximately 20% had an underlying sarcomere mutation, however a distinctive feature of this population was the relative under-representation of mutations in *MYH7*, *TNNT2*, and *TNNI3*, which together typically account for >45% of HCM, accounted for only ~5% of late-onset disease. Mutations were most frequently identified in *MYBPC3*, *TPM1* and *MYH6* (encoding alpha-myosin heavy chain).

Sarcomere mutations are also present in individuals in a community-based population with incidentally-identified unexplained LVH, but without a formal clinical diagnosis of HCM. A cohort from the Framingham Heart Study (n=1869, mean age 59 ± 9 years) demonstrated a ~3% prevalence of unexplained increased LVWT. Sarcomere gene mutations were identified in 15% of these subjects, but were notably absent in control subjects without LVH and those with secondary cardiac hypertrophy from hypertension or aortic stenosis.⁴⁸ These studies indicate that sarcomere mutations are an important and shared contribution to HCM throughout different ages and demographic groups. Since a similar genetic contribution to disease is seen, the reasons underlying differences in natural history are unclear and speak to the importance of genetic and environmental modifiers which have not yet been characterized.

Genotype-Phenotype Correlations—The factors that drive the diverse phenotypic spectrum of HCM and the clinical significance of prominent features of disease are unclear. Genetic heterogeneity is equally marked and likely accounts for some of the clinical diversity, however robust genotype-phenotype correlations have not emerged. Although genotype certainly influences phenotype, most mutations are individually rare—private to a particular family and infrequently recurring in unrelated individuals. Furthermore, clinical outcomes of individual mutations are not consistently benign or malignant. There is great diversity in the degree of symptoms, age of onset, extent and location of LVH, and sudden death risk, even amongst family members who have inherited the same causal mutation, indicating that variation in genotype alone does not account for all of the variation in clinical features. In the majority of cases, determining the exact identity of the causal gene mutation confirms the clinical diagnosis, defines the exact genetic etiology and may importantly inform family management, but typically does not alter specific management or provide prognostic insight.

A small number of specific point mutations have recurred more frequently and have demonstrated more consistent phenotypes in unrelated families. For example, the clinical course of *MYH7* mutations Arg403Gln, Arg719Trp, and Arg719Gln have tended to be severe, associated with an increased risk of sudden death or development of end-stage heart failure. Certain *TNNT2* mutations (Arg92Trp, Arg92Gln, Ile79Asn) have been associated with mild LVH but an increased risk of sudden death in certain families.^{36,46,66,73} However, caution must be used in generalizing these specific observations to other patients and families, as exceptions are well documented.

Although the causal sarcomere mutation is inherited or introduced at the time of fertilization, the clinical expression or penetrance of LVH is highly variable and age-

dependent. LV wall thickness is often normal in infancy and early childhood, despite the presence of a sarcomere mutation. LVH more commonly becomes evident in adolescence, in conjunction with the pubertal growth spurt. Genotype may influence the age of onset of LVH, as illustrated in figure 6. The majority of *MYH7* mutation carriers develop demonstrable LVH by the 2nd decade of life. In contrast, mutations in *MYBPC3* may not result in clinically evident hypertrophy until the 4th or 5th decade of life, and mutations in this gene have been associated with elderly-onset HCM.^{52,53} The ultimate phenotype reflects a multitude of factors, including genetic background, comorbid illnesses and lifestyle. Integrating genetic information, family history, and comprehensive clinical assessment will lead to the best patient management. Longitudinal studies to follow genotyped patients, both apparently healthy mutation carriers who have not yet developed LVH, and those with overt disease, will help address important unresolved issues, including more accurate determination of the true lifetime penetrance of sarcomere mutations, characterization of the full phenotypic spectrum, identification of more sensitive and early markers of disease, and description of disease evolution.

Implications of Genetic Discoveries: Refining the Phenotype of HCM—

Although unexplained LVH is the clinically defining feature of HCM, it is not an infallible marker for genetic status or future risk of developing disease or disease-related complications.^{12,42} The steps leading from sarcomere gene mutation to clinical disease are largely unknown, but likely stem from a dominant negative effect in which the mutant protein is incorporated into the sarcomere and interferes with the function of the normal protein, potentially disrupting coordinated mechanics of the sarcomere.² The study of genetically engineered animals and *in vitro* models of disease have identified fundamental abnormalities of contractile function, intracellular calcium homeostasis, and myocardial energetics that are helping to refine understanding of disease phenotype at a molecular level.

Abnormalities of Diastolic Function: Abnormal diastolic function is a nearly universal feature of overt HCM and may largely account for common symptoms of pulmonary congestion and exercise intolerance. There is compelling data from animal and human studies to indicate that diastolic dysfunction is an early manifestation of sarcomere mutations and an intrinsic feature of the HCM phenotype, present prior to the development of pathologic cardiac remodeling and LVH. A heterozygous knock-in mouse has been developed in which the Arg403Gln missense mutation in *MYH7* (α MHC^{403/+}) is introduced into the mouse genome and recapitulates many phenotypic features of human disease.²² This mouse is a well characterized model of disease and has demonstrated that diastolic abnormalities develop by 6 weeks of age, whereas gross or histopathologic LVH, fibrosis, and disarray are not consistently present until 20–25 weeks of age (figure 7A).^{22,24} The mechanism of impaired relaxation in these animals may relate to alterations in intracellular calcium handling and slowed actin-myosin dissociation kinetics.^{10,19,65} A *TNNT2* I79N transgenic mouse model also develops enhanced systolic function with increased diastolic stiffness in the absence of significant hypertrophy or fibrosis.⁷⁴

More recently, tissue Doppler echocardiographic studies on genotyped human subjects have similarly demonstrated that individuals with sarcomere gene mutations have diastolic abnormalities early in life, prior to the development of LVH. Impaired relaxation is manifested by decreased early myocardial relaxation velocities (Ea velocity), compared to normal controls without sarcomere mutations (figure 7B).^{27,50} These studies provide further evidence that diastolic abnormalities are an early and direct manifestation of the underlying sarcomere mutation, rather than merely a secondary consequence of altered myocardial compliance characteristics due to the distinct changes in myocardial architecture that accompany development of clinically obvious disease.

Altered Intracellular Calcium Handling: Myocardial contraction and relaxation are coordinated by the orchestrated cycling of calcium from the cytoplasm, sarcoplasmic reticulum (SR), and sarcomere through excitation-contraction coupling (Figure 8A). Altered calcium signaling has emerged as a potentially key link between sarcomere mutation, hypertrophic remodeling, contractile abnormalities, and arrhythmias. Biochemical studies using the $\alpha\text{MHC}^{403/+}$ mouse model of HCM indicate that abnormalities in intracellular Ca^{2+} homeostasis (present at 4 weeks of age) are one of the earliest manifestations of sarcomere mutations, preceding the development of diastolic abnormalities (~age 6 weeks), and histologic changes (~age 20 weeks).^{19,64} Evidence for altered intracellular calcium handling has been detected at multiple levels. Biophysical studies across a spectrum of sarcomere genes with HCM-associated mutations have demonstrated increased calcium sensitivity resulting in increased tension generation and ATPase activity.^{10,56} Calcium cycling between the sarcomere and sarcoplasmic reticulum also appears to be altered in HCM. There is blunted release of calcium from the SR in response to caffeine stimulation in $\alpha\text{MHC}^{403/+}$ mice.¹⁹ Furthermore, myocardial extracts from these mice show reduced expression of the cardiac ryanodine receptor (RyR2), as well as SR Ca^{2+} storage protein calsequestrin (CSQ) and associated proteins junctin and triadin.⁶⁴ Taken together, these results suggest that a key early event in HCM is dysregulation of the release of Ca^{2+} from the SR, possibly due to “trapping” in the mutated sarcomere (Figure 8B), and ultimately leading to reduced SR Ca^{2+} stores.

The identification of these early biochemical changes suggests that intracellular Ca^{2+} pathways may be targeted as a means to modify the phenotype of HCM. Pharmacological studies on young, prehypertrophic $\alpha\text{MHC}^{403/+}$ HCM mice demonstrated that treatment with the calcium channel blocker, diltiazem, attenuated phenotypic development with decreased myocyte hypertrophy, disarray, and fibrosis, as compared to placebo-treated animals.⁶⁴ There was no benefit if drug administration was initiated after the development of LVH. These data have intriguing implications for future clinical management of HCM, suggesting that early pharmacologic intervention to counteract biochemical abnormalities, in advance of obvious disease expression, may diminish the expression of the underlying sarcomere gene mutation.

Arrhythmias: The determinants of sudden cardiac death and ventricular arrhythmias in HCM remain incompletely defined and are likely complex and multifactorial. Focal ischemia, abnormalities of intramural arteries, abnormalities of calcium signaling, and changes in myocardial architecture have all been suggested as contributing factors to the atrial and ventricular arrhythmias that accompany HCM. Because myocardial fibrosis and disarray are prominent and characteristic features of HCM, and extrapolating from models of myocardial infarction, these histopathological changes have been hypothesized to represent as the anatomic substrate for electrical instability in HCM, triggering ventricular tachycardia (VT) and SCD.⁷² However, there is little direct evidence linking fibrosis and disarray to arrhythmia. In *TNNT2* R92Q and I79N transgenic HCM mouse models, a strong association between hypertrophy or fibrosis and sudden cardiac death was not demonstrated.^{32,34} Studies on the $\alpha\text{MHC}^{403/+}$ knock-in HCM mouse model did not show a clear correlation between the location or extent of fibrosis and arrhythmic inducibility on programmed stimulation. In contrast, increasing degrees of LVH and contractility correlated with inducibility.⁷⁵

In humans, cardiac MRI studies have been performed to attempt to evaluate the association between delayed enhancement (DE) after administration of the extracellular contrast agent, gadolinium. DE is the presumptive imaging correlate of increased myocardial fibrosis or scar.^{29,30,47} There has been only a modest correlation with presence, but not the degree, of DE and the extent of hypertrophy,¹³ LV mass index, clinical risk factors for sudden death,⁴⁷

and ventricular ectopy on Holter monitoring¹ suggesting that there are additional factors beyond myocardial fibrosis which influence the expression of these important features of disease.

The alterations in intracellular Ca^{2+} homeostasis seen in HCM may be a common factor linking sarcomere mutations to both hypertrophy as well as increased risk for arrhythmias and SCD. Biophysical and genetic data from other inherited cardiac disease associated with an increased occurrence sudden death has provided support for the role of calcium in arrhythmic risk. Calcium dysregulation and diastolic leak of Ca^{2+} from the SR have been implicated in catecholaminergic polymorphic ventricular tachycardia (CPVT), a familial syndrome of exercise-induced sudden death, as well as arrhythmogenic right ventricular cardiomyopathy (ARVC), a disease with fibrofatty infiltration of the right ventricular myocardium and increased ventricular arrhythmias.³⁵ Mutations in key calcium binding proteins have been implicated in both of these disorders, specifically mutations in the cardiac ryanodine receptor (RyR2) have been identified in association with autosomal dominant ARVD and CPVT,^{35,58} mutations in calsequestrin (CSQ) have been associated with autosomal recessive CPVT.¹⁵ Studies on patients and animal models suggest that the mechanism may involve delayed after-depolarizations which may trigger membrane depolarization and arrhythmias.⁷

Abnormalities in Myocardial Energetics: Impaired myocardial energetics has been proposed as a unifying mechanism by which sarcomere mutations may result in both cardiac hypertrophy and heart failure.^{5,14,65} ³¹P magnetic resonance spectroscopy (MRS) studies on the $\alpha\text{MHC}^{403/+}$ mouse model have indicated that less force is generated per molecule of ATP hydrolyzed which may result in reduced mechanical efficiency and compensatory hypertrophy.⁶⁵ ³¹P MRS studies performed on a genotyped human population have also demonstrated impaired myocardial energetics, both in the early, prehypertrophic stage, and with clinically overt disease. Subjects with overt HCM and family members who carry sarcomere mutations but have not yet developed diagnostic clinical features had a significantly decreased ratio of phosphocreatine to ATP ($\text{P}_{\text{Cr}}/\text{ATP}$), indicating a compromised energetic state. These data lend further support to the primary role energy deficiency and increased energy cost of force production in the pathogenesis of HCM.¹⁴ Energy depletion may also be a common mechanism underlying the shared phenotype of cardiac hypertrophy, seen in HCM, mitochondrial disease, and in disease caused by mutations in genes involved in myocardial metabolism (reviewed below).

Other paradigms of Genetic Cardiac Hypertrophy

Sarcomere mutations are not identified in ~30–50% of individuals with a clinical diagnosis of HCM. This incomplete detection rate is partially explained by methodologic limitations. Although DNA sequencing technology is highly robust and reliable, in frame deletions and promoter mutations which alter gene expression will not be detected by current candidate gene sequencing strategies. Furthermore, clinical genetic testing is not available for certain sarcomere genes (titin, myozenin, α -myosin heavy chain) in which mutations have been rarely reported, but are known to cause HCM. The genetic basis of unexplained LVH in the absence of a sarcomere mutation has not yet been fully elucidated, either in familial or sporadic disease. Such subjects tend to be slightly older at presentation and lack a clear family history of HCM, but otherwise are difficult to differentiate from those with HCM from underlying sarcomere mutations.

Metabolic Cardiomyopathies

Phenocopies of HCM have been identified where cardiac hypertrophy is caused by mutations in genes distinct from those which encode sarcomere proteins (Table 3). By

identifying these genes, different pathways leading to the common final disease phenotype can be discovered. Genetic studies in families and sporadic cases of unexplained LVH with conduction abnormalities (progressive atrioventricular block, atrial fibrillation, ventricular pre-excitation) have led to the discovery of a separate category of metabolic cardiomyopathies: genetic cardiac hypertrophy caused by mutations in *PRKAG2*, encoding the $\gamma 2$ regulatory subunit of adenosine monophosphate-activated protein kinase (AMPK), and in the X-linked lysosome associated membrane protein (*LAMP2*) gene. Mutations in these genes may be present in roughly 2–12% of individuals who carry a clinical diagnosis of HCM in whom a sarcomere mutation is not identified, and 40% of individuals with combined features of LVH and pre-excitation.^{3,4,9,25}

Histopathologically, cardiac hypertrophy caused by *PRKAG2* and *LAMP2* mutations do not display the prominent myocardial disarray or interstitial fibrosis as pathognomonic for HCM. Instead, myocardial vacuolization with glycogen-filled myocytes (*PRKAG2*) or autophagic vacuoles (*LAMP2*) are seen (Figure 9). Although incompletely defined, the molecular pathways triggered by *PRKAG2* and *LAMP2* mutations are almost certainly distinct from those triggered by sarcomere gene mutations. As such, practice guidelines developed for HCM may not be appropriate or applicable for treating these metabolic cardiomyopathies. Genetic testing for both *PRKAG2* and *LAMP2* is clinically available and may be considered when unexplained LVH is accompanied by preexcitation, or if marked LVH is present in young males (*LAMP2*). In the case of *LAMP2* cardiomyopathy, genetic diagnosis provides important prognostic information by identifying individuals who may be destined for worse outcomes and warrant more aggressive management.

Fabry disease is an X-linked recessive disorder caused by mutations in the gene encoding the lysosomal hydrolase, α -galactosidase (GLA), and thus is etiologically similar to the less common *LAMP2* cardiomyopathy. Mutations cause enzyme deficiency and glycosphingolipid accumulation in the heart, kidneys, nervous system and skin. Classic Fabry disease occurs at a prevalence of ~1/40,000 and commonly presents in childhood or adolescence. A cardiac-predominant variant of Fabry disease has been described and may present later in life. Studies suggest that at least 2–3% of unexplained LVH in adult males may be due to underlying Fabry disease.^{51,62} Measuring plasma or leukocyte α -galactosidase activity can reliably diagnose males. GLA mutation testing is also available and is particularly helpful to diagnose heterozygous females who may have normal α -galactosidase activity but nonetheless develop clinical disease due to unfavorable X-inactivation. Identifying patients with Fabry disease is important due to the availability of potentially effective α -galactosidase enzyme replacement therapy.⁶

From Bench to Bedside: Integrating Genetic Information into Clinical Practice

Incorporating genetic information into clinical practice will be increasingly important in the molecular era of medicine both to refine diagnosis and prognosis, and to provide optimal management for families with inherited disease.

Family Screening- Clinical Evaluation

HCM follows autosomal dominant inheritance, therefore clinical screening of first degree relatives of affected individuals is recommended, consisting of history, physical examination, 12-lead EKG, and echocardiography. Since the penetrance of LVH is age-dependent, the absence of diagnostic clinical findings on initial assessment does not exclude the possibility of future disease development or the presence of an underlying sarcomere mutation, particularly in children since LV wall thickness is often normal early in life. Serial

follow up of apparently healthy members of families with HCM is required. The strategy outlined in Fig10 has been proposed for following members of families with HCM for the development of clinical disease.⁴²

Genetic Testing

The identification of a sarcomere gene mutation, in the appropriate clinical setting, can provide a definitive diagnosis of HCM, establish the exact genetic etiology of disease, and importantly guide the management of families. Testing can be fruitful in the context of familial disease, since a sarcomere mutation may be identified in ~60% of probands, and 50% of their 1st degree relatives are predicted to carry the mutation. Mutation confirmation testing in relatives can definitively identify which currently unaffected family members at risk for disease. Longitudinal clinical follow up to be appropriately focused on these genotype positive individuals, and this knowledge may relieve anxiety associated with the otherwise uncertain future risk of disease development. Family members who have not inherited the mutation can be reassured that they are not at risk for disease development or transmission to children, and do not require serial clinical evaluation. Family members who have inherited the causal mutation require serial clinical follow up as well as counseling regarding the 50% risk of transmission to offspring.

Currently, genetic testing relies on DNA sequence analysis of candidate genes, and an important caveat to this strategy is that the failure to identify a causal mutation via candidate gene sequencing is an inconclusive, non-informative result. It does not exclude the possibility of familial disease due to rare genetic causes of HCM or other types of inherited LVH.

Novel Treatment Strategies to Modify Disease

Greater understanding of the molecular pathogenesis of HCM will foster the development of new therapeutic approaches to disease, designed to modify or prevent phenotypic development, rather than merely palliating symptoms or counteracting established hemodynamic abnormalities. As described above, early treatment of mice carrying the Arg403Gln mutation in MYH7 with the L-type calcium channel blocker, diltiazem, prior to overt disease development, appeared to mitigate development of hypertrophy and fibrosis.⁶⁴ Other strategies have been trialed in animal models to reverse the effects of established disease by decreasing myocardial fibrosis, a prototypic feature of HCM. Administration of angiotensin II receptor blockers (losartan),³³ HMG-CoA reductase inhibitors (simvastatin),⁵⁷ and aldosterone antagonists (spironolactone)⁶⁸ have shown encouraging results in decreasing myocardial fibrosis and collagen content, and identify other new targets for intervention in human studies.

Conclusions

Elucidating the genetic basis of inherited cardiac hypertrophy will provide important insights into the myriad of mechanisms involved in hypertrophic remodeling of the heart. Clinical translation of basic discoveries will improve the practical management of our patients by enabling precise diagnosis, identification of at-risk individuals, and determination of early markers of disease. These efforts will ultimately foster development of novel treatment paradigms designed to change the natural history of disease.

Box 1. Standard Management Strategies for Hypertrophic Cardiomyopathy

All Patients

Family screening

Genetic counseling

Periodic assessment for SCD risk

Education on recommended exercise restrictions

Mild to Moderate Symptoms (Exercise intolerance, SOB, CP)

β -blockers

Calcium channel blockers (Diltiazem or Verapamil)

Symptomatic Volume Overload

Add Diuretics (Caution: hypovolemia may worsen obstructive physiology)

Persistent or Worsening Symptoms + Obstructive Physiology

Consider adding Disopyramide

Medically Refractory Symptoms + Obstructive Physiology

Septal myectomy

Alcohol septal ablation

Heart Failure/ End Stage HCM

Diuretics

ACE-inhibitors/ Angiotensin receptor blockers (if LV systolic dysfunction)

β -blockers

Consider cardiac transplantation

References

1. Adabag AS, Maron BJ, Appelbaum E, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. *J Am Coll Cardiol* 2008;51:1369. [PubMed: 18387438]
2. Ahmad F, Seidman JG, Seidman CE. The genetic basis for cardiac remodeling. *Annu Rev Genomics Hum Genet* 2005;6:185. [PubMed: 16124859]
3. Arad M, Benson DW, Perez-Atayde AR, et al. Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. *J Clin Invest* 2002;109:357. [PubMed: 11827995]
4. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med* 2005;352:362. [PubMed: 15673802]
5. Ashrafian H, Watkins H. Reviews of translational medicine and genomics in cardiovascular disease: new disease taxonomy and therapeutic implications cardiomyopathies: therapeutics based on molecular phenotype. *J Am Coll Cardiol* 2007;49:1251. [PubMed: 17394955]
6. Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med* 2007;146:77. [PubMed: 17179052]
7. Bauce B, Rampazzo A, Basso C, et al. Screening for ryanodine receptor type 2 mutations in families with effort-induced polymorphic ventricular arrhythmias and sudden death: early diagnosis of asymptomatic carriers. *J Am Coll Cardiol* 2002;40:341. [PubMed: 12106942]
8. Biagini E, Coccolo F, Ferlito M, et al. Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. *J Am Coll Cardiol* 2005;46:1543. [PubMed: 16226182]

9. Blair E, Redwood C, Ashrafian H, et al. Mutations in the gamma(2) subunit of AMP-activated protein kinase cause familial hypertrophic cardiomyopathy: evidence for the central role of energy compromise in disease pathogenesis. *Hum Mol Genet* 2001;10:1215. [PubMed: 11371514]
10. Blanchard E, Seidman C, Seidman JG, et al. Altered crossbridge kinetics in the alphaMHC403/+ mouse model of familial hypertrophic cardiomyopathy. *Circ Res* 1999;84:475. [PubMed: 10066683]
11. Bos JM, Poley RN, Ny M, et al. Genotype-phenotype relationships involving hypertrophic cardiomyopathy-associated mutations in titin, muscle LIM protein, and telethonin. *Mol Genet Metab* 2006;88:78. [PubMed: 16352453]
12. Charron P, Heron D, Gargiulo M, et al. Genetic testing and genetic counselling in hypertrophic cardiomyopathy: the French experience. *J Med Genet* 2002;39:741. [PubMed: 12362031]
13. Choudhury L, Mahrholdt H, Wagner A, et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;40:2156. [PubMed: 12505229]
14. Crilley JG, Boehm EA, Blair E, et al. Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy. *J Am Coll Cardiol* 2003;41:1776. [PubMed: 12767664]
15. Eldar M, Pras E, Lahat H. A missense mutation in the CASQ2 gene is associated with autosomal-recessive catecholamine-induced polymorphic ventricular tachycardia. *Trends Cardiovasc Med* 2003;13:148. [PubMed: 12732448]
16. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet* 2004;363:1881. [PubMed: 15183628]
17. Elliott PM, Gimeno Blanes JR, Mahon NG, et al. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;357:420. [PubMed: 11273061]
18. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000;36:2212. [PubMed: 11127463]
19. Fatkin D, McConnell BK, Mudd JO, et al. An abnormal Ca(2+) response in mutant sarcomere protein-mediated familial hypertrophic cardiomyopathy. *J Clin Invest* 2000;106:1351. [PubMed: 11104788]
20. Freiburg A, Gautel M. A molecular map of the interactions between titin and myosin-binding protein C. Implications for sarcomeric assembly in familial hypertrophic cardiomyopathy. *Eur J Biochem* 1996;235:317. [PubMed: 8631348]
21. Geier C, Perrot A, Ozcelik C, et al. Mutations in the human muscle LIM protein gene in families with hypertrophic cardiomyopathy. *Circulation* 2003;107:1390. [PubMed: 12642359]
22. Geisterfer-Lowrance AA, Christe M, Conner DA, et al. A mouse model of familial hypertrophic cardiomyopathy. *Science* 1996;272:731. [PubMed: 8614836]
23. Geisterfer-Lowrance AA, Kass S, Tanigawa G, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. *Cell* 1990;62:999. [PubMed: 1975517]
24. Georgakopoulos D, Christe ME, Giewat M, et al. The pathogenesis of familial hypertrophic cardiomyopathy: early and evolving effects from an alpha-cardiac myosin heavy chain missense mutation [see comments]. *Nat Med* 1999;5:327. [PubMed: 10086390]
25. Gollob MH, Green MS, Tang AS, et al. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. *N Engl J Med* 2001;344:1823. [PubMed: 11407343]
26. Harris KM, Spirito P, Maron MS, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation* 2006;114:216. [PubMed: 16831987]
27. Ho CY, Sweitzer NK, McDonough B, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. *Circulation* 2002;105:2992. [PubMed: 12081993]
28. Jarcho JA, McKenna W, Pare JA, et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. *N Engl J Med* 1989;321:1372. [PubMed: 2811944]

29. Kim RJ, Judd RM. Gadolinium-enhanced magnetic resonance imaging in hypertrophic cardiomyopathy: in vivo imaging of the pathologic substrate for premature cardiac death? *J Am Coll Cardiol* 2003;41:1568. [PubMed: 12742299]
30. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;343:1445. [PubMed: 11078769]
31. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *Journal of the American College of Cardiology* 1995;26:1699. [PubMed: 7594106]
32. Knollmann BC, Blatt SA, Horton K, et al. Inotropic stimulation induces cardiac dysfunction in transgenic mice expressing a troponin T (I79N) mutation linked to familial hypertrophic cardiomyopathy. *J Biol Chem* 2001;276:10039. [PubMed: 11113119]
33. Lim DS, Lutucuta S, Bachireddy P, et al. Angiotensin II blockade reverses myocardial fibrosis in a transgenic mouse model of human hypertrophic cardiomyopathy. *Circulation* 2001;103:789. [PubMed: 11171784]
34. Maass AH, Ikeda K, Oberdorf-Maass S, et al. Hypertrophy, fibrosis, and sudden cardiac death in response to pathological stimuli in mice with mutations in cardiac troponin T. *Circulation* 2004;110:2102. [PubMed: 15466629]
35. MacRae CA, Birchmeier W, Thierfelder L. Arrhythmogenic right ventricular cardiomyopathy: moving toward mechanism. *J Clin Invest* 2006;116:1825. [PubMed: 16823481]
36. Marian AJ, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 2001;33:655. [PubMed: 11273720]
37. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *Jama* 2002;287:1308. [PubMed: 11886323]
38. Maron BJ. Sudden death in young athletes. *N Engl J Med* 2003;349:1064. [PubMed: 12968091]
39. Maron BJ, Casey SA, Hauser RG, et al. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. *J Am Coll Cardiol* 2003;42:882. [PubMed: 12957437]
40. Maron BJ, Gardin JM, Flack JM, et al. Prevalence of Hypertrophic Cardiomyopathy in a General Population of Young Adults- Echocardiographic analysis of 4111 subjects in the CARDIA study. *Circulation* 1995;92:785. [PubMed: 7641357]
41. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;42:1687. [PubMed: 14607462]
42. Maron BJ, Seidman JG, Seidman CE. Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2004;44:2125. [PubMed: 15582308]
43. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348:295. [PubMed: 12540642]
44. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;114:2232. [PubMed: 17088454]
45. McKenna WJ, Behr ER. Hypertrophic cardiomyopathy: management, risk stratification, and prevention of sudden death. *Heart* 2002;87:169. [PubMed: 11796562]
46. Moolman JC, Corfield VA, Posen B, et al. Sudden death due to troponin T mutations. *J Am Coll Cardiol* 1997;29:549. [PubMed: 9060892]
47. Moon JC, McKenna WJ, McCrohon JA, et al. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. *J Am Coll Cardiol* 2003;41:1561. [PubMed: 12742298]
48. Morita H, Larson MG, Barr SC, et al. Single-gene mutations and increased left ventricular wall thickness in the community: the Framingham Heart Study. *Circulation* 2006;113:2697. [PubMed: 16754800]

49. Morita H, Rehm HL, Menesses A, et al. Shared genetic causes of cardiac hypertrophy in children and adults. *N Engl J Med* 2008;358:1899. [PubMed: 18403758]
50. Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation* 2001;104:128. [PubMed: 11447072]
51. Nakao S, Takenaka T, Maeda M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med* 1995;333:288. [PubMed: 7596372]
52. Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy [see comments]. *N Engl J Med* 1998;338:1248. [PubMed: 9562578]
53. Niimura H, Patton KK, McKenna WJ, et al. Sarcomere protein gene mutations in hypertrophic cardiomyopathy of the elderly. *Circulation* 2002;105:446. [PubMed: 11815426]
54. Nishimura RA, Holmes DR Jr. Clinical practice. Hypertrophic obstructive cardiomyopathy. *N Engl J Med* 2004;350:1320. [PubMed: 15044643]
55. Osio A, Tan L, Chen SN, et al. Myozenin 2 is a novel gene for human hypertrophic cardiomyopathy. *Circ Res* 2007;100:766. [PubMed: 17347475]
56. Palmiter KA, Tyska MJ, Haeberle JR, et al. R403Q and L908V mutant beta-cardiac myosin from patients with familial hypertrophic cardiomyopathy exhibit enhanced mechanical performance at the single molecule level. *J Muscle Res Cell Motil* 2000;21:609. [PubMed: 11227787]
57. Patel R, Nagueh SF, Tsybouleva N, et al. Simvastatin induces regression of cardiac hypertrophy and fibrosis and improves cardiac function in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circulation* 2001;104:317. [PubMed: 11457751]
58. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001;103:196. [PubMed: 11208676]
59. Rayment I, Holden HM, Whittaker M, et al. Structure of the actin-myosin complex and its implications for muscle contraction. *Science* 1993;261:58. [PubMed: 8316858]
60. Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation* 2003;107:2227. [PubMed: 12707239]
61. Richard P, Villard E, Charron P, et al. The genetic bases of cardiomyopathies. *J Am Coll Cardiol* 2006;48:A79.
62. Sachdev B, Takenaka T, Teraguchi H, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation* 2002;105:1407. [PubMed: 11914245]
63. Seidman JG, Seidman C. The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. *Cell* 2001;104:557. [PubMed: 11239412]
64. Semsarian C, Ahmad I, Giewat M, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. *J Clin Invest* 2002;109:1013. [PubMed: 11956238]
65. Spindler M, Saupe KW, Christie ME, et al. Diastolic dysfunction and altered energetics in the alphaMHC403/+ mouse model of familial hypertrophic cardiomyopathy. *J Clin Invest* 1998;101:1775. [PubMed: 9541509]
66. Tardiff JC. Sarcomeric proteins and familial hypertrophic cardiomyopathy: linking mutations in structural proteins to complex cardiovascular phenotypes. *Heart Fail Rev* 2005;10:237. [PubMed: 16416046]
67. Thierfelder L, Watkins H, MacRae C, et al. Alpha-tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere. *Cell* 1994;77:701. [PubMed: 8205619]
68. Tsybouleva N, Zhang L, Chen S, et al. Aldosterone, through novel signaling proteins, is a fundamental molecular bridge between the genetic defect and the cardiac phenotype of hypertrophic cardiomyopathy. *Circulation* 2004;109:1284. [PubMed: 14993121]
69. Tyska MJ, Hayes E, Giewat M, et al. Single-molecule mechanics of R403Q cardiac myosin isolated from the mouse model of familial hypertrophic cardiomyopathy. *Circ Res* 2000;86:737. [PubMed: 10764406]

70. Van Driest SL, Ellsworth EG, Ommen SR, et al. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy. *Circulation* 2003;108:445. [PubMed: 12860912]
71. Van Driest SL, Vasile VC, Ommen SR, et al. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2004;44:1903. [PubMed: 15519027]
72. Varnava AM, Elliott PM, Mahon N, et al. Relation between myocyte disarray and outcome in hypertrophic cardiomyopathy. *Am J Cardiol* 2001;88:275. [PubMed: 11472707]
73. Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* 1995;332:1058. [PubMed: 7898523]
74. Westermann D, Knollmann BC, Steendijk P, et al. Diltiazem treatment prevents diastolic heart failure in mice with familial hypertrophic cardiomyopathy. *Eur J Heart Fail* 2006;8:115. [PubMed: 16214409]
75. Wolf CM, Moskowitz IP, Arno S, et al. Somatic events modify hypertrophic cardiomyopathy pathology and link hypertrophy to arrhythmia. *Proc Natl Acad Sci U S A* 2005;102:18123. [PubMed: 16332958]
76. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e385. [PubMed: 16935995]
77. Zou Y, Song L, Wang Z, et al. Prevalence of idiopathic hypertrophic cardiomyopathy in China: a population-based echocardiographic analysis of 8080 adults. *Am J Med* 2004;116:14. [PubMed: 14706660]

Figure 1. Pathologic features of HCM

A. Gross pathology showing hypertrophic cardiomyopathy (left) as compared to normal cardiac morphology (right).

B. Histologic sections stained with hematoxylin and eosin demonstrate myocyte disarray, where myocytes are oriented at bizarre and variable angles to each other, as well as increased myocardial fibrosis (left), the pathognomonic features of HCM. In contrast, normal myocardium demonstrates a very orderly arrangement of myocytes (right). Courtesy of Dr. Robert Padera, Department of Pathology, Brigham and Women's Hospital, Boston, MA.

Figure 2. Echocardiographic appearance of HCM

A: Normal parasternal long axis view demonstrating normal LV wall thickness, with both interventricular septum and posterior wall measuring 8 mm.

B. Parasternal long axis view from a patient with HCM demonstrating severe asymmetric septal hypertrophy. The interventricular septum measures 24 mm, the posterior wall measures 11 mm.

IVS= interventricular septum; PW= posterior wall; LV= left ventricle; LA= left atrium; Ao= aorta

Figure 3. Morphologic spectrum of HCM

Asymmetric septal hypertrophy is the most common morphologic pattern in HCM, however a myriad of different locations and extent of LVH have been described, as demonstrated in these still-frame images. No direct correlation between the distribution of LVH and clinical outcomes has been demonstrated. Courtesy of Dr. Barry J. Maron, Minneapolis Heart Institute Foundation, Minneapolis, MN.

A: Massive asymmetric septal hypertrophy with VS thickness >50 mm;

B: Septal hypertrophy with more prominent distal portion involvement;

C: Hypertrophy confined to the proximal septum, just below the aortic valve (arrows);

D: Apical HCM (asterisk);

E: Relatively mild hypertrophy in a concentric pattern showing similar thicknesses within each segment (paired arrows);

F: Inverted pattern with posterior free wall (PW) thicker (40 mm) than anterior VS. VS= ventricular septum; PW= posterior wall; AML= anterior mitral valve leaflet; LV= left ventricle. Calibration marks=1cm

Figure 4. HCM is caused by mutations in the sarcomere, the molecular motor of the heart
 The sarcomere is the fundamental unit of contraction in the cardiac myocyte. It is composed of interdigitating thick and thin filaments which generate force by cyclical cross-bridge formation between actin and myosin. Hypertrophic cardiomyopathy is a disease of the sarcomere, caused by dominantly inherited mutations in contractile genes, most commonly β -myosin heavy chain, myosin binding protein C, and cardiac troponins T and I. Adapted from Kamisago M, et al. *N Engl J Med* 2000;343:1688-96, with permission, © Massachusetts Medical Society.

Figure 5. Molecular structure of myosin heavy chain and location of mutations associated with HCM

This 3-dimensional molecular model is based on the x-ray crystallographic structure of chicken skeletal myosin heavy chain.⁵⁹ The residues shown correspond to human residues Asp3 through Lys841. The actin binding domain is shown in green; the ATP binding site in yellow. The myosin regulatory and essential light chains are overlaid in violet and orange, respectively. Mutations which cause HCM are shown in blue, superimposed onto the molecular structure. Light chain mutations are shown in light blue.

Courtesy of Steven DePalma, PhD, Department of Genetics, Harvard Medical School, Boston, MA.

Figure 6. The penetrance of left ventricular hypertrophy in HCM is dependent on age and influenced by the underlying sarcomere mutation

HCM caused by mutations in β -myosin heavy chain is typically associated with demonstrable LVH early in life, with near universal expression by the age 20 years. In contrast, HCM due to mutations in the myosin binding protein C gene may not show clinically evident LVH until middle age or later.

Adapted with permission from Niimura H, et al New Engl J Med 1998; **338**:1248-1257, © Massachusetts Medical Society.

Figure 7. Diastolic abnormalities are present prior to the development of LVH

A. Invasive hemodynamic studies on isolated hearts and intact 6 week old $\alpha\text{MHC}^{403/+}$ mice have shown decreased minimal peak $-\text{dP}/\text{dt}$, decreased rates of LV pressure decline, increased tau (the time constant of isovolumic relaxation), and increased time to peak filling. Gross and histologic LVH, myocyte disarray, and fibrosis are not consistently present until 20–25 weeks of age.

B. Echocardiographic studies on genotyped human populations with HCM also demonstrate impaired relaxation prior to the development of LVH in otherwise healthy family members who carry pathogenic sarcomere mutations. Reduced early myocardial relaxation velocity (E' velocity) on tissue Doppler interrogation indicates impaired relaxation. E' velocity is normal and brisk in the genotype-negative control relative (left panel) but mildly reduced in a relative who carries a gene mutation but has not yet developed clinical disease (G+/LVH–; center panel). With development of overt disease, there is a marked reduction in E' velocity (G+/LVH+, right panel).

Figure 8. Intracellular calcium homeostasis is altered in HCM

A. Normal excitation-contraction coupling is initiated when membrane depolarization by the action potential opens voltage-gated L-type calcium channels on the cardiac myocyte membrane. The resultant influx of Ca^{2+} leads to calcium-induced calcium release (CICR) from stores in the sarcoplasmic reticulum (SR) and a more marked increase in intracellular Ca^{2+} concentration. Ca^{2+} binds to the sarcomere, allowing actin-myosin crossbridge formation and generation of the power stroke. Calcium is then taken back up into the SR via the SERCA pump (SR calcium ATPase).

B. In HCM, normal calcium cycling may be disrupted, possibly due to "trapping" of calcium in the mutated sarcomere (mutations indicated by *). This may lead to altered intracellular calcium homeostasis with a relative excess of calcium in the sarcomere and relative depletion in the sarcoplasmic reticulum.

Adapted from Semsarian et al J. Clin. Invest. 2002 109:1013

Figure 9.

The histopathology of metabolic cardiomyopathies caused by mutations in *PRKAG2* (panels A–C) and *LAMP2* (panel D) is distinct from HCM and characterized by glycogen-filled vacuoles without significant disarray, fibrosis, or myocyte hypertrophy.

Fig 10.

Table 1

Risk predictors for sudden death in HCM.

	Criteria	Comments
History	Exertional or recurrent Syncope	Risk is greatest in children
	Family history of sudden death or known malignant genotype	Risk is related to family size and number of family members with SCD
Diagnostic Evaluation	Severe LVH (Maximal wall thickness ≥ 30 mm)	Risk increases as wall thickness increases
	Nonsustained Ventricular Tachycardia (ambulatory Holter monitoring)	Higher predictive value in children and patients with history of syncope
	Abnormal hemodynamic response to exercise (failure to augment SBP by at least 20 mmHg)	Less applicable to patients >40 y/o

Table 2

Sarcomere mutations in hypertrophic cardiomyopathy

Protein	Gene	Chromosome	Prevalence	Function	Comments
Cardiac β -Myosin Heavy Chain *	<i>MYH7</i>	14q1	~40%	Thick Filament-Force generation	Younger onset is typical
Cardiac Myosin Binding Protein C *	<i>MYBPC3</i>	11q1	~40%	?Structural support	Association with later onset LVH
Cardiac Troponin T *	<i>TNNI2</i>	1q3	~5%	Thin Filament-Regulation	Increased SCD risk in some
Cardiac Troponin I *	<i>TNNI3</i>	19p1	~5%	Thin Filament-Regulation	
α -Tropomyosin *	<i>TPM1</i>	15q2	~2%	Thin Filament-Regulation	
Myosin Essential * and Regulatory * Light Chains	<i>MYL2, MYL3</i>	3p, 12q	~1%	Thick Filament	
Actin *	<i>ACTC</i>	11q	~1%	Thin Filament-Force generation	
Titin	<i>TTN</i>	2q3	Rare		
Myozenin	<i>MYOZ2</i>	4q26	Rare	Z-disk	
α -Myosin Heavy Chain	<i>MYH6</i>	14q1	Rare	Thick Filament-Force generation	

* = Clinical genetic testing available

Table 3

Mutations in genes which produce phenocopies of hypertrophic cardiomyopathy.

Protein	Gene	Chromosome	Associated Disease	Comments
Metabolic Cardiomyopathies γ -Subunit, AMP Kinase	<i>PRKAG2</i>	7q3		Pre-excitation and conduction disease
Lysosome associated membrane protein	<i>LAMP2</i>	Xq2	Danon Disease	Cardiomyopathy, skeletal myopathy, and mental retardation; Pre-excitation on EKG; Rapid progression in adolescence, particularly males
α -Galactosidase	<i>GLA</i>	X	Fabry Syndrome	Assess plasma or lymphocyte α -Gal activity (males); Consider enzyme replacement