Published in final edited form as:

Prog Pediatr Cardiol. 2011 May ; 31(2): 93–98. doi:10.1016/j.ppedcard.2011.02.005.

New Paradigms in Hypertrophic Cardiomyopathy: Insights from Genetics

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Abstract

Understanding the genetic basis of hypertrophic cardiomyopathy (HCM) provides a remarkable opportunity to predict and prevent disease. HCM is caused by mutations in sarcomere genes and is the most common monogenic cardiovascular disorder. Although unexplained left ventricular hypertrophy (LVH) is considered diagnostic, LVH is not always present. LV wall thickness is often normal until adolescence or later, even in individuals known to carry pathogenic sarcomere mutations. In contrast, genetic testing can identify both individuals who carry pathogenic sarcomere mutations and have a clinical diagnosis of HCM, as well as mutation carriers who have not yet manifest LVH but are at very likely to develop disease. Studying this important new patient subset, designated early or preclinical HCM, allows characterization of the initial consequences of sarcomere mutations, prior to the onset of overt hypertrophic remodeling. Such study has defined novel early phenotypes, including impaired left ventricular relaxation, myocardial energetic deficiencies, and altered collagen metabolism, in mutation carriers with apparently normal cardiac morphology. These results indicate that sarcomere mutations have substantial impact on myocardial function and biochemistry before the onset of frank hypertrophy. Furthermore, animal models of preclinical HCM have identified promising new treatment strategies that may diminish the emergence of overt disease. We can now begin to reshape the paradigm for treating genetic disorders. With improved mechanistic insight and the capability for early diagnosis, genetic advances can lead to new approaches for disease modification and prevention.

Keywords

Genetics; Cardiomyopathy; Hypertrophy

Introduction

The current clinical diagnosis of HCM is based on identifying unexplained LVH. However LVH alone cannot differentiate disease caused by sarcomere mutations from other types of cardiac hypertrophy that may have very different underlying biology and natural history. Moreover, LVH is binary. It only defines established disease and does not capture earlier disease phenotypes.(1, 2) The discovery of sarcomere mutations as the genetic basis of HCM provides remarkable opportunities to characterize pathogenesis at the molecular level, thereby fostering development of new ways to predict and prevent disease.(3, 4) Integrating

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basic science advances and clinical research has the potential to fundamentally transform the practice of medicine.

By incorporating genetic testing into clinical evaluation, we have learned that sarcomere mutations account for ~60% of isolated cardiac hypertrophy.(5) Over 1000 distinct mutations in genes encoding 11 different components of the sarcomere apparatus have been identified (Table). Mutations involving myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*) are most common, collectively accounting for ~75–80% of sarcomeric HCM. Through predictive genetic testing, we can now identify family members who have inherited the sarcomere mutation that causes HCM in their family (G+) and are therefore at high risk for developing HCM, but have not yet manifest diagnostic clinical features of HCM (LVH–). This important subset is denoted early or preclinical HCM (G+/LVH–). Using genetic testing to identify these individuals will help to substantially streamline family evaluation by allowing recommended longitudinal follow up(6) to be focused only on preclinical mutation carriers rather than all the first degree relatives of patients with HCM (Figure 1). From an academic perspective, systematic study of this intriguing preclinical cohort will advance understanding of disease pathogenesis, identify the early consequences of sarcomere mutations, characterize important intermediate phenotypes that predict disease development, and identify surrogate endpoints of treatment response for future clinical trials designed to attenuate and ultimately prevent the development of HCM.

Normal Cardiac Morphology in Sarcomere Mutation Carriers

In contrast to the typically striking morphologic features seen in overt HCM, conventional echocardiographic imaging cannot distinguish family members who have inherited sarcomere mutations from those who have not inherited mutations and bear no risk for disease. By definition, LV wall thickness is normal. Additionally, cavity dimensions, left atrial size, tricuspid regurgitation velocity, and standard Doppler mitral inflow parameters do not differ significantly from healthy controls that do not carry sarcomere mutations.(7, 8)

There is very limited experience using cardiac magnetic resonance imaging (CMR) in preclinical mutation carriers.(9, 10) The improved spatial resolution of CMR may help detect subtle and focal hypertrophy that is not well visualized by echocardiography, particularly at the lateral LV free wall, apex, or inferior base. As such, CMR imaging may facilitate the diagnosis of HCM by identifying approximately 16% of patients with LVH on CMR that was not appreciated by echocardiography.(9, 10) However, sarcomere mutation carriers with truly normal wall thickness have not been found to have other distinguishing changes, even with the use of gadolinium contrast (Figure 2). Late gadolinium enhancement is not a feature of preclinical HCM, although present in the majority of patients with overt HCM(11–13), suggesting that overt myocardial scar formation is typically not present prior to the development of LVH.

Early Consequences of Sarcomere Mutations

We postulate that LVH is a late feature of disease and that sarcomere mutations cause abnormalities of myocardial biochemistry and function well before overt cardiac hypertrophy develops. These key early phenotypes can be detected with the use more sensitive imaging techniques and assessment of informative biomarkers. Identification and characterization of the early consequences of sarcomere mutations will advance our understanding of disease pathogenesis—information critical to the development of novel treatment strategies to modify and ultimately prevent HCM.

Subtle Abnormalities of Diastolic Function are Present in Early HCM

To facilitate understanding of how sarcomere mutations cause disease, animal models of HCM have been developed by introducing sarcomere mutations that cause human disease into the mouse genome.(14) As with human HCM, mouse models show age-dependent penetrance of key morphologic features. LVH and histopathological myocyte disarray and fibrosis are not the earliest or primary manifestations of sarcomere mutations. These prototypic changes appear to develop concurrently and relatively late in life. They are not consistently present until the mice reach adulthood, at 20–25 weeks of age. (14) By following these animals over time, phenotypic evolution can be better defined. The primary effects of sarcomere mutations can be distinguished from secondary changes to the heart that may result from, but not cause, overt disease development.

Early manifestations of sarcomere mutations have been identified. Changes in cardiac function and biochemistry can be seen well before changes in cardiac morphology are observed. Invasive hemodynamic studies have demonstrated that diastolic abnormalities precede the onset of LVH. In both isolated heart preparations and *in vivo* studies in 6 week-old animals, mutation (+) mice showed impaired diastolic function (manifest as increased tau, time to peak filling, and end diastolic elastance; decreased $-dp/dt_{min}$) as compared to age-matched wild type controls.(14, 15) The molecular mechanisms underlying diastolic abnormalities have not been fully elucidated, but there is evidence of slowed actin-myosin dissociation kinetics with decreased rates of crossbridge detachment.(16) Decreased rates of reuptake of calcium into the sarcoplasmic reticulum have also been described(17–19)-- a biochemical finding that may account for impaired relaxation.

A number of different model systems have been used to evaluate systolic function, however results have been somewhat variable and the impact of sarcomere mutations on systole is less well characterized.(20) Studies on mutant myosin heavy chain protein and myofilaments have suggested that the predominant biophysical impact of mutations, in isolation, is enhanced active force generation.(21) Increased actin sliding velocity, maximal force generation, and ATPase turnover rate have been described. An important caveat is that these studies were performed on purified mutant protein in the absence of the normal regulatory milieu and myocardial architecture. As such, these models may provide insight into the primary biophysical effects of sarcomere mutations, but may not reflect complex composite result at the level of the intact organism.

More contemporary echocardiographic techniques such as tissue Doppler imaging (TDI) and echocardiographic strain analysis have allowed more precise characterization of the pathophysiology of human HCM. TDI measures myocardial velocities in systole (S'), early diastole (E'), and with atrial contraction (A'). By measuring TDI velocities in a genotyped patient population, impaired relaxation, as manifest by reduced E' velocities, have been demonstrated prior to the onset of LVH in sarcomere mutation carriers. Individuals with preclinical HCM have a significant 13–20% decrease in E' velocity compared with normal controls without sarcomere mutations (Figure 3).(7, 22) Patients with overt disease have an even more profound decrease in diastolic function.

These data indicate that diastolic abnormalities are an early, potentially direct, manifestation of the underlying sarcomere mutation, not merely a secondary consequence of LVH, disarray, or fibrosis. However, despite the biological significance of this finding, the diagnostic sensitivity of a reduced E' velocity is low, limiting its use in clinical practice. For example, statistical models using E' velocities in family members without LVH were constructed to determine if E' could differentiate at-risk preclinical mutation carriers from non-carriers. A global E' velocity (reflecting the average E' of the septal, lateral, anterior, and inferior walls) ≤ 12 cm/sec in an individual ≤ 25 years old had a positive predictive value

of 86% and negative predictive value of 22% in differentiating relatives with mutations from those without mutations.(23) Therefore, the presence of a normal E' velocity does not exclude the possibility that an apparently unaffected (i.e., LVH (-)) member of a family with HCM actually carries a sarcomere mutation. Genetic testing is required for definitive determination of risk.

Echocardiographic strain analysis can quantify global and regional systolic function in the major components of myocardial motion: longitudinal, radial, and circumferential.(24–27) Systolic strain reflects myocardial deformation, expressed as the percent change in length of a myocardial segment, relative to end-diastolic length.(28) Systolic strain rate (SSR) is an early systolic index which reflects the rate of myocardial deformation. SSR correlates with end-systolic elastance and peak dP/dt, and therefore may be an accurate noninvasive metric of myocardial contractility.(29) In contrast to diastolic function, systolic strain and SSR were preserved in preclinical HCM, not significantly different compared to healthy genotype-negative family members serving as normal controls (Figure 4). In subjects with overt HCM, systolic strain and strain rate are reduced, despite the presence of preserved LV ejection fraction (EF).(23)

In aggregate, these findings lead us to postulate that diastolic abnormalities may be a primary consequence of the sarcomere mutation. Subtle systolic abnormalities are seen in overt disease and may result not only from the mutation, but also from the prototypic changes in myocardial architecture that develop later in life in conjunction with LVH, namely myocyte disarray and fibrosis. As seen in other disorders such as cardiac amyloidosis,(30, 31) these findings also demonstrate that left ventricular ejection fraction may be insensitive to subtle contractile abnormalities. Impaired longitudinal systolic strain and strain rate were detected in overt HCM despite normal LV EF. From a clinical perspective, these results suggest that future strategies aimed at diminishing the development of myocyte fibrosis and hypertrophy, starting before LVH develops, may help to offset the loss of systolic function and impede progression to symptomatic heart failure in HCM.

Biochemical Abnormalities in Early HCM

The study of animal and human prehypertrophic sarcomere mutation carriers has provided fundamental insights regarding the role of myocardial energetics, biochemistry, and fibrogenesis in disease pathogenesis. For example, impaired myocardial energetic has been proposed as a unifying mechanism by which sarcomere mutations may result in both cardiac hypertrophy and heart failure.(17, 32, 33) Using ³¹P magnetic resonance spectroscopy (MRS), a significantly decreased ratio of phosphocreatine to ATP (P_{Cr}/ATP) has been demonstrated in the early, prehypertrophic stage, as well as in patients with clinically overt HCM.(32) These data indicate that sarcomere mutations give rise to an early compromise in the energetic state of the myocardium and lend further support to the primary role energy deficiency in the pathogenesis of HCM.(32)

Myocardial fibrosis is a hallmark feature of HCM and has been postulated as an important contributor to sudden cardiac death, ventricular tachyarrhythmias, LV dysfunction, and heart failure.(34–38) However, the factors driving development of fibrosis are unknown. Cardiac expression profiling studies in young, prehypertrophic HCM mice demonstrate activation of pathways involved in fibrosis and collagen deposition early in life when cardiac morphology and histology are normal.(39) Recent studies in humans corroborate the suggestion that fibrotic pathways are activated early in response to sarcomere mutations. Analysis of serum biomarkers of collagen metabolism demonstrated evidence of increased collagen synthesis in sarcomere mutation carriers before the development of LVH. Elevated levels of C-terminal propeptide of type I procollagen (PICP) indicate that a pro-fibrotic milieu is present

early in human HCM (Figure 5) in the absence of cardiac hypertrophy or visible focal fibrosis on cardiac magnetic resonance imaging.(40)

Collectively, these studies expand our understanding of the early phenotypes of sarcomere mutations and demonstrate that these mutations have considerable adverse impact on the heart before HCM can be clinically diagnosed. These findings stand in contrast to traditional models of HCM where disease consequences have been assumed to stem from the development of cardiac hypertrophy and attendant deleterious effects on myocardial compliance and perfusion. Rather, diastolic dysfunction, impaired myocardial energetics, and increased collagen synthesis appear to be much more intrinsic consequences of the underlying sarcomere mutation. Identifying new phenotypes may lead to the discovery of key pathogenic pathways that may be targeted therapeutically to modify or prevent the development of disease. The presence of such early phenotypes may help to identify individuals at risk for arrhythmias, sudden death, or heart failure. Finally, novel, early, and quantitative traits such as E' velocity, P_{Cr}/ATP ratio, and serum biomarkers may serve not only as markers of disease development, but also as key surrogate endpoints to monitor treatment effect in novel disease modifying strategies.

Transforming Care of HCM through Genetics

Improved understanding of the pathogenesis of HCM at the molecular level can help to transform the clinical management of our patients. Such knowledge will allow development of therapies to slow or prevent disease development, rather than merely palliating symptoms. Indeed, disease-modifying studies are in active development in animal models of HCM. For example, abnormalities in intracellular calcium homeostasis are present at ~4 weeks of age in mouse models of HCM and may be one of the earliest manifestations of sarcomere mutations. Myofibrillar preparations from mice carrying the Arg403Gln missense mutation in *MYH7* are activated at lower Ca^{2+} concentrations than wild type controls. Levels of sarcoplasmic reticulum (SR) Ca^{2+} binding proteins are also decreased in HCM mice. Furthermore, these HCM mice demonstrate a blunted release of calcium from the SR after caffeine stimulation, suggesting decreased SR stores of Ca^{2+} .(18, 19) These abnormalities are present far in advance of diastolic abnormalities (~age 6 weeks), and visible LVH, fibrosis and disarray (~age 20–25 weeks). Early treatment with the L-type calcium channel blocker, diltiazem, appeared to mitigate development of hypertrophy and fibrosis if started while cardiac morphology was still normal. If started after hypertrophy was allowed to develop, diltiazem was unable to reverse established LVH.(19) These studies have several intriguing clinical implications. They suggest a mechanistic link between calcium dysregulation and the development of LVH. Moreover, they provide some of the first evidence that mechanism-based pharmacological therapy may be effective in influencing the development of HCM. There may be phenotypic plasticity in the early, prehypertrophic stage of disease such that interventions started at this time may be able to impact the natural history of HCM. To test the feasibility of this strategy, a pilot human randomized control trial is ongoing, comparing diltiazem to placebo in sarcomere mutation carriers who have not yet developed LVH (<http://clinicaltrials.gov/ct2/show/NCT00319982>).

More recently, early treatment with the angiotensin II receptor blocker (ARB), losartan, in prehypertrophic mice with an Arg719Trp *MYH7* mutation has also shown promise in mitigating the development of fibrosis and LVH. This effect may be mediated through its inhibition of TGF- β -mediated pathways.(41) In these studies, losartan was unable to reverse established hypertrophy, again emphasizing the potential importance of early treatment and preventive strategies.

Other medications have been studied in animal models to attempt to reverse the effects of established disease. Losartan,(42) HMG-CoA reductase inhibitors (simvastatin),(43) aldosterone antagonists (spironolactone),(44) and the antioxidant, N-acetylcysteine(45) have shown encouraging results in animals in decreasing myocardial fibrosis and collagen content. A pilot study investigating the use of spironolactone in established HCM in a non-genotyped population is ongoing (<http://clinicaltrials.gov/ct2/show/NCT00879060>).

Pilot human studies using ARBs and simvastatin have been reported, with mixed results. (46–49) The small sample sizes, variable study designs, and heterogeneous populations limit interpretation of these studies. For example, only one study specifically targeted sarcomere mutation carriers.(49) This may be a critical issue because all of the animal trials were performed on models with specific genetic substrate and may only be applicable to patients with sarcomere mutations, not other forms of cardiac hypertrophy.

Summary

Studying early HCM in animal models and preclinical human mutation carriers provides unique opportunities to characterize fundamental mechanisms of disease. This knowledge will help expand understanding not only of the full range of phenotypes associated with sarcomere mutations, but may also identify key pathways involved in the development of hypertrophy, fibrosis, and heart failure in more common acquired forms of heart disease. Furthermore, genetics allows us to identify susceptible individuals early in life prior to clinical diagnosis. Sarcomere mutations cause changes in the heart's biochemistry and function before HCM can be diagnosed clinically. Impaired relaxation, increased collagen synthesis, energetic deficiencies, and altered myocyte calcium homeostasis are all present in advance of overt cardiac remodeling. Leveraging these discoveries will promote new paradigms of disease modification and prevention, rather than palliation. In this manner, characterizing the genetic basis of HCM will help to transform medicine and improve the lives of our patients and families.

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A. Clinical Diagnosis

B. Genetic Diagnosis

Figure 1.

Genetic testing in families can identify individuals who are definitively at risk for developing disease despite the presence of normal LV wall thickness. Consensus guidelines recommend that longitudinal clinical screening be performed on first degree relatives of patients with HCM to identify affected individuals with left ventricular hypertrophy. However, this longitudinal clinical follow-up can be focused only on mutation carriers, as relatives who have not inherited the family's mutation are not at risk for developing HCM.

- A. Pedigree of a family with HCM: In this example, clinical screening was performed on the surviving siblings of an individual (circled) who suffered sudden death and was diagnosed with HCM at the time of autopsy. Two siblings (darkened symbols) were found to have clinical HCM, previously unrecognized. There are 17 other family members (arrows) who did not have LVH but are at risk for developing HCM and require longitudinal clinical evaluation. Genotype was initially unknown (?).
- B. With genetic testing, longitudinal clinical screening can be focused on mutation carriers. In this family, a pathogenic *MYH7* mutation was identified. Only the 4 mutation carriers without clinical HCM (arrows) would require prospective serial follow up to monitor for the onset of disease.

Circles, females; squares males; solid symbols, clinical diagnosis of HCM; slash, deceased; ?, genotype unknown; +, mutation present; -, mutation absent

Figure 2.

Cardiac morphology is normal in preclinical HCM, even with the use of gadolinium-contrast cardiac MRI (Gd-CMR). Below are images from 2 subjects with a myosin heavy chain missense mutation. As illustrated, sarcomere mutation carriers without LVH do not typically demonstrate late gadolinium enhancement (LGE), indicating that gross myocardial scar is not a prominent feature of the preclinical stage. In contrast, the majority of patients with overt HCM have demonstrable LGE.

A, C, E- Preclinical HCM: Gd-CMR revealed no morphological abnormalities suggestive of HCM. Note the absence of LVH or late gadolinium enhancement.

B, D, F- Overt HCM: Gd-CMR demonstrated typical findings of HCM, including a markedly thickened septum (panel B; arrow) associated with areas of heterogeneous epicardial LGE, affecting over 50% of total LV mass and involving the anteroseptum (panel D; arrow) and the inferoseptum (panels D and F; arrows).

RV=right ventricle; LV= left ventricle; RA=left atrium; LA=left atrium; LGE= late gadolinium enhancement.

Figure 3.

Impaired relaxation can be detected in sarcomere mutation carriers without LVH. Subjects with preclinical HCM have consistently demonstrated evidence of abnormal diastolic function, manifested by a 13–20% reduction E' velocity, relative to normal controls. There is a further decrease in E' velocity in subjects with overt HCM.

Figure 4.

Systolic function is relatively preserved in sarcomere mutation carriers without LVH, but decreased in overt HCM.

- A.** Global longitudinal strain is not significantly different in G+/LVH- preclinical subjects compared to genotype-negative healthy controls, however subjects with overt HCM (G+/LVH+) demonstrate a significant 27% reduction in peak longitudinal systolic strain.
- B.** Similar results are seen for global longitudinal systolic strain rate. There is no significant difference between the G+/LVH- and control cohorts. A significant 14% reduction in systolic strain rate is seen in the G+/LVH+ cohort.

Figure 5.

Myocardial type I collagen synthesis is increased in sarcomere mutation carriers, irrespective of LVH. Levels of PICP were comparably and significantly increased in preclinical (G+/LVH-) and overt (G+/LVH+) subjects relative to normal controls. Compared to controls, PICP levels are 31% higher in preclinical HCM and 69% higher in overt HCM. The threshold for statistical significance is $p < 0.017$.

Table 1

Sarcomere genes associated with HCM.

Protein	Gene Symbol	Chromosome	Prevalence
Cardiac β -Myosin Heavy Chain	<i>MYH7</i>	14q1	~40%
Cardiac Myosin Binding Protein C	<i>MYBPC3</i>	11q1	~40%
Cardiac Troponin T	<i>TNNT2</i>	1q3	~5%
Cardiac Troponin I	<i>TNNI3</i>	19p1	~5%
α -Tropomyosin	<i>TPM1</i>	15q2	~2%
Myosin Essential and Regulatory Light Chains	<i>MYL2</i> <i>MYL3</i>	3p 12q	~1%
Actin	<i>ACTC</i>	11q	~1%