Published as: *Curr Opin Cardiol*. 2010 May ; 25(3): .

Genetics of Hypertrophic Cardiomyopathy

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Abstract

Purpose of review—Hypertrophic cardiomyopathy (HCM), the most common inherited cardiac disorder exhibits remarkable genetic and clinical heterogeneity. This manuscript reviews recent discoveries of disease-causing genes and their clinical consequences and provides an overview of research that aims to elucidate how HCM ensues from a single nucleotide mutation.

Recent findings—The spectrum of genes that are mutated in HCM has expanded. In combination with newly developed sequencing technologies, there are now robust strategies for gene-based diagnosis in HCM. Understanding the molecular pathophysiology of HCM has emerged from the study of genetically engineered animal models of disease, and new data indicate important roles for altered intracellular Ca2+ regulation and oxidative stress. Pharmacologic strategies to normalize these processes show promise in attenuating HCM in experimental models.

Summary—The current repertoire of HCM genes allows effective gene-based diagnosis, information that enables accurate assessment of disease risk in family members and provides some insight into clinical course. From mechanistic insights gleaned from fundamental investigations of experimental HCM models, novel therapeutic targets have surfaced that may provide new benefits for HCM patients.

Keywords

Hypertrophic Cardiomyopathy; sarcomere; gene mutation

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium characterized by increased ventricular wall thickness that is unexplained by underlying condition, myocyte enlargement and disarray, and increased myocardial fibrosis [1]. Clinical manifestations of HCM vary considerably among patients with symptoms ranging from mild exertional dyspnea to manifest heart failure. Arrhythmias, both atrial and ventricular, thromboembolic events and sudden cardiac death punctuate the clinical course of many patients and increase morbidity and mortality from HCM [2].

Two decades ago mutations in the beta-myosin heavy chain gene (MYH7) [3] were discovered to cause HCM and since then, hundreds of different disease-causing mutations have been identified in genes that encode proteins of the sarcomere [4]. These molecular etiologies account for the majority of familial disease [5] and a substantial subset of

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unexplained hypertrophy that occurs as a sporadic condition in adults and in children [6, 7]. Defining other genetic causes for unexplained left ventricular hypertrophy (LVH) that occurs as either a Mendelian disorder or common trait within the general population remains an important effort.

How HCM ensues from a single nucleotide change in a sarcomere protein remains a mystery. A further conundrum is why clinical expression of disease is delayed for many years, despite the expression of mutant protein at birth and throughout life. Fundamental insights into these processes have emerged from the development and study of experimental models that carry human HCM mutations. These models develop prototypic manifestations of human HCM including hypertrophy, myocyte disarray, and fibrosis with a timeline that mirrors human clinical courses: disease is absent in the young but with aging there is progressive expression of histopathology. Mechanistic understandings have emerged from these models, knowledge that predicts potential strategies to disrupt pathologic remodeling from HCM mutations. Translation of insights gleaned from HCM models into clinical trials in humans may provide new opportunities to improve clinical outcomes associated with this prevalent human pathology.

The Genetic basis of HCM: Mutations in Genes Encoding Sarcomere Protein

There is substantial diversity in the genetic causes of HCM. To date, nearly 900 different mutations have been reported in genes encoding 8 sarcomere proteins: beta-myosin heavy chain (MYH7), cardiac myosin-binding protein C (MYPBC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), cardiac actin (ACTC), alpha-tropomyosin (TPM1), essential myosin light chain (MYL3) and regulatory myosin light chain (MYL2) [7**]. Among these genes, mutations in MYH7 and MYPBC3 occur most often and account for approximately 50% of HCM cases, while mutations in TNNT2, TNNI3, ACTC, TPM1, MYL3 and MYL2 collectively account for less than 20% of HCM cases [8]. Evidence that mutations in these 8 genes cause HCM is compelling. Mutations within these genes segregate with affection status in HCM families and are universally absent from control populations. Mutations alter residues that are highly conserved throughout evolution, implying that change of each specific amino acid is deleterious – a model confirmed by animal models which have been engineered to carry sarcomere gene mutations. These experimental models develop cardiac remodeling that recapitulates human HCM. Unlike these HCM genes, mutations in other genes that have been reported to cause HCM are supported by less robust evidence for disease causality.

The gene encoding cardiac troponin C (TNNC1) is notable as a sarcomere protein gene that has not been conclusively implicated in HCM [9]. From recent analyses of over 1000 HCM patients, 4 TNNC1 sequence variants, although genetic criteria for pathogenicity remain undetermined. Yet experimental analyses of some variants revealed increased Ca^{2+} sensitivity of force development and ATP-ase activation [9, 10], similar to biophysical changes found in established HCM disease genes.

HCM and Z-disc Protein Genes

Genes that encode molecules that interact with sarcomere proteins have also been interrogated for HCM mutations. Many of these analyses focus on proteins within the Z-disc, which connects sarcomere units to one another. Provocative variants have been identified in HCM patient in genes that encode titin (TTN) [11], muscle LIM protein (CSRP) [12, 13], telethonin (TCAP) [14] and myozenin 2 (MYOZ2) [15]. Sequence analyses have been limited to subsets of the 363 exons that encompass titin, a giant Z-disc molecule that spans half of the sarcomere from Z-disk to M-line, but mutational screens of other Z-disc proteins are more complete. In some instances functional studies of newly

identified sequence variants indicate that these alter protein-protein interactions. For example, altered residues titin that were identified in HCM patients show increased binding affinity for actinin [11, 16] or for the cardiac ankyrin repeat protein [17]. How these changes might produce the pathophysiology of HCM remain incompletely defined. Moreover, because sequence variants in Z-disc proteins have been identified in HCM families that are of insufficient size to provide statistically significant segregation analyses, the pathogenicity of some variants in HCM remains inconclusive.

Storage cardiomyopathies mimic HCM

Patients with unexplained LVH and atypical clinical manifestations from those usually observed with HCM, led to the identification of storage cardiomyopathies. The molecular etiologies for these disorders are distinct from HCM. Mutations in the gamma subunit of AMP-dependent protein kinase (PRKAG2) gene cause LVH that is inherited as a dominant trait like HCM, but cardiac histology shows marked accumulation of glycogen within myocytes and myocyte disarray is absent [18]. Unlike HCM, patients with PRKAG2 mutations also have electrophysiologic abnormalities and develop progressive conduction system demise. Mutations in the X-linked lysosome-associated membrane protein 2 (LAMP2) gene cause early and massive LVH in boys and young male adolescents, as well as profound ventricular arrhythmias and rapid progression to heart failure. The histopathology of LAMP2 mutations shows accumulation of autophagic vacuoles with undegraded cellular products [18]. Mutations in the alpha-galactosidase gene (GAA), which too is encoded on chromosome X, cause Fabry disease. Patients with GAA mutations usually exhibit cardiac hypertrophy with systemic manifestations, in some patients myocardial disease predominate [19] while renal, cutaneous, and neurologic findings are subclinical.

Analyses of these storage cardiomyopathies has strong evidence to support that each causes cardiac hypertrophy. However, given the histopathologic differences with HCM, distinct clinical phenotypes, and different functions of the molecules altered by mutations, these disorders are more aptly considered distinct from, rather than a variant of HCM.

Clinical Gene-based Diagnosis of HCM

An early clinical advance that ensued from discovery of genetics causes of HCM and other inherited forms of LVH is gene-based diagnosis. Given the overlapping clinical phenotype of unexplained LVH that occurs from different cardiomyopathies, and the lack of clinical findings to accurately predict involvement of a particular HCM gene, gene-based diagnostic platforms needed to comprehensively interrogate all sarcomere genes, sarcomere-related genes, and genes that cause storage cardiomyopathies. Until recently, this technically daunting task was extremely labor-intensive and expensive. With the development of next-generation sequencing, many obstacles to comprehensive gene-based diagnosis have diminished.

Contemporary sequencing strategies have the capacity to interrogate millions of nucleotides – which exceeds the current compendium of all HCM and LVH genes - at reasonable cost. An additional advantage is that these platforms define gene sequence and also gene dosage. Recent discoveries indicate that mutations that alter the copy number of genes can cause human disease including congenital heart disease, neuro-cognitive disorders, and malignancies [20, 21]. Whether some HCM occurs from an abnormal number of gene copies (that increase or decrease gene dosage) remains unexplored. Mutations that alter gene dosage in HCM might accounts for the absence of a defined mutation in some HCM patients, as these escape detection by traditional sequencing strategies. The model that HCM could be caused by altered gene dosage of sarcomere protein genes is particularly appealing,

since some HCM mutations in the MYPBC3 gene have been demonstrated to cause disease by reducing protein levels [*22, *23]. Mutations that altered the dosage of the MYPBC3 gene and perhaps other sarcomere protein genes, would be expected to substantially impact protein levels and might similarly cause HCM.

Genotype-phenotype correlations in HCM

One of the many opportunities that may ensue from broad-based genetic testing in HCM and other causes of unexplained LVH is better assessment of the relevance of genotype in phenotype. The value of genetic testing in HCM, while widely recognized to accurately predict disease development in at-risk relatives, is often criticized as unable to predict the clinical course for each patient. While this observation may be true, we suggest that the numbers of genotyped HCM patients remains too few to explore meaningful correlations, particularly given genetic heterogeneity and the influence that modifiers, such as background genotypes [24], gender [25], and environment [26] have on disease expression. Despite these complexities, clinical course is recognized to be more adverse in HCM patients with an identified mutation than patients in whom no mutation is found [27]. Outcomes may also be influenced by specific mutations. The incidence of sudden cardiac death is higher in specific MYH7 mutations (R403Q, R453C, G716R and R719W) [28] and progression to heart failure is more commonly observed from mutations in MYH7 (R719W), TNNI3 (Lys183 deletion), and MYPBC3 (intron 32 deletion), than from other HCM mutations [29, 30**]. Knowledge of full spectrum of HCM genes combined with molecular analyses of well-characterized patient cohorts may help to expand these correlations and improve understanding of the clinical heterogeneity of HCM.

Mechanisms of cardiac hypertrophy in HCM: Altered Sarcomere function

Several models have been proposed to account for the mechanisms by which sarcomere gene mutations produce HCM. As was previously discussed, experimental models and recent analyses of human heart specimens demonstrate that normal levels of myosin binding protein-C protein are diminished in hearts with MYBPC3 missense amino acid residues and truncation mutations [22, 23]. These data suggest that haploinsufficiency of MYBPC3, or a reduction in the amount of functional protein due to a dominant gene mutation that inactivates one allele, is one pathologic mechanism for HCM. In contrast, studies of most other sarcomere mutations indicate these impact that protein levels are normal but that function is perturbed. Biophysical properties of sarcomeres that carry MYH7 mutations indicate a gain of function. Myosins that contain HCM mutations have enhanced myosin ATPase activity, increased generated force, and accelerates actin filament sliding [31]. Analyses of human TNNT2 mutations parallel these abnormalities and exhibit increased force development [32] and ATPase activation [33].

The consequences of altered biophysical properties of contractile proteins could broadly impact sarcomere performance, myocyte cell biology, and myocardial energetics. Due to the presence of both mutant and normal proteins within sarcomeres, regulated contraction would become discoordinated, as has been recently demonstrated with HCM mutations in myosin: HCM mutation MYH7 R403Q attachds to actin at highly variable angles compared to normal myosin [34]. Biophysical changes in mutant sarcomeres are also expected to altered calcium cycling and contribute to increase susceptibility to arrhythmias in experimental and human HCM [35]. Increased ATP-ase activity by sarcomere mutations may also incur greater myocardial energy consumption, which if unmet could accelerate myocyte death and contribute to focal scarring in HCM [36*].

Activation of Ca^{2+}-dependent signals in HCM

Dysregulation of intracellular Ca^{2+}, a critical modulator of myocyte contraction and relaxation, can activate hypertrophy and failure in the stressed myocardium [37]. Experimental models of HCM myocytes exhibit abnormal intracellular Ca^{2+}, including decreased levels in the sarcoplasmic reticulum and increased diastolic Ca^{2+} levels [32, 38]. Ca^{2+} abnormalities precede hypertrophic remodeling in HCM models, and longitudinal studies indicate that early pharmacologic interventions that normalized Ca^{2+} dysregulation attenuated the development of hypertrophy [38]. An inherent question raised by these biochemical findings is what hypertrophic pathways are activated by Ca^{2+} dysregulation in HCM myocytes?

In experimental models of pressure-overload hypertrophy, intracellular Ca^{2+} activates calmodulin and its downstream phosphatase, calcineurin with subsequent dephosphorylation and activation of the nuclear factor of activated T cell (NFAT) transcriptional factor, a molecule known to participate in some hypertrophic remodeling [39]. Over-expression of calcineurin in hearts causes hypertrophy that is prevented by calcineurin inhibitors such as cyclosporine and FK506 [40]. However, cyclosporine given to HCM mice have the opposite effect: accelerated pathologic remodeling and heart failure [41]. While the mechanism by which calcineurin exaggerated HCM is unknown, these studies evidenced a crucial role for Ca^{2+} dependent signaling in the pathogenesis of HCM. These observations promoted preventative studies aimed at normalizing Ca^{2+} dysregulation in HCM models. Young HCM mice (myosin R403Q) without evidence of hypertrophy were treated with the L-type Ca^{2+} channel inhibitor, diltiazem. Intracellular Ca^{2+} was normalized the development of cardiac hypertrophy was significantly inhibited [38], findings which suggest that targeting key intracellular events in development of HCM pathology might prevent disease development.

HCM Increases Myocyte Stress

Altered biophysical forces and intracellular Ca^{2+} in HCM myocytes as well as increased energy demands impose increased stress on HCM myocytes. Additionally, microvascular dysfunction, which has been demonstrated by positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) in patients with HCM [42, 43], can cause ischemia in HCM. Morevover, factors that increase myocyte stress are presumed to promote myocyte death and result in myocardial scarring in HCM [44].

Molecular analyses also support increased myocyte stress in HCM. Fetal cardiac genes, which are normally repressed after embryonic development but re-expressed with myocyte stress, are found in HCM models [45] and human HCM hearts [46]. Levels of lipid peroxides, which indicated oxidative stress, are also increased in HCM models [47]. Analyses of pathways involved in oxidative stress in HCM hearts implicated thio-sensitive pathways, an observation that prompted study of N-acetylcysteine in HCM models. High levels of this agent reduced biohemical markers of oxidative stress and remarkably showed reversal of fibrosis in HCM models [36*]. The potential benefit of anti-oxidant agents in human HCM may merit investigation.

Summary

Discovery of human mutations that cause HCM has enabled accurate diagnosis and provided opportunities to understand the molecular pathophysiology of this disorder. From the e study of HCM experimental models, insights have emerged that bridge the gap from mutation to cardiac phenotype. Harnessing this knowledge has great potential to attenuate and even prevent disease in patients with HCM mutations.

Acknowledgments

This work was supported in part by grants from the Banyu International Foundation for Cardiovascular Research (T.K.), the National Institutes of Health (S.C., J.G.S.), Howard Hughes Medical Institute (CES), and the Leducq Foundation (J.G.S., C.E.S).

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