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Molecular genetics and pathogenesis of hypertrophic cardiomyopathy

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Abstract

Advances in molecular genetics of hypertrophic cardiomyopathy (HCM) have led to identification of mutations in 11 genes coding for sarcomeric proteins. In addition, mutations in gene coding for the γ subunit of AMP-activated protein kinase and triplet-repeat syndromes, as well as in mitochondrial DNA have been identified in patients with HCM. Mutations in genes coding for the β-myosin heavy chain, myosin binding protein-C, and cardiac troponin T account for approximately 2/3 of all HCM cases. Accordingly, HCM is considered a disease of contractile sarcomeric proteins. Genotype-phenotype correlation studies show mutations and the genetic background affect the phenotypic expression of HCM. The final phenotype is the result of interactions between the causal genes, genetic background (modifier genes), and probably the environmental factors. The molecular pathogenesis of HCM is not completely understood. The initial defects caused by the mutant proteins are diverse. However, despite their diversity, they converge into common final pathway of impaired cardiac myocyte function. The latter leads to an increased myocyte stress and subsequent activation of stress-responsive signaling kinases and trophic factors, which activate the transcriptional machinery inducing cardiac hypertrophy, interstitial fibrosis and myocyte disarray, the pathological characteristics of HCM. Studies in transgenic animal models show that cardiac hypertrophy, interstitial fibrosis, and myocyte disarray are potentially reversible. These findings raise the possibility of reversal of evolving phenotype or prevention of phenotypes in human patients with HCM. Elucidation of the molecular genetic basis and the pathogenesis of HCM could provide the opportunity for genetic based diagnosis, risk stratification, and implementation of preventive and therapeutic measures in those who have inherited the causal mutations for HCM.

Keywords

Cardiomyopathy; hypertrophic; genetics - Genes - Mutation - Death; sudden; cardiac

Hypertrophic cardiomyopathy (HCM) is a primary disease of the myocardium caused by mutations in contractile sarcomeric proteins. It is clinically diagnosed by the presence of left ventricular hypertrophy (LVH) in the absence of an increased external load (unexplained LVH). Myocyte hypertrophy, disarray, and interstitial fibrosis are the commonly pathological features and myocyte disarray is considered the pathological hallmark.[1, 2] LV cavity is small and and LV global systolic function, as indicated by the ejection fraction, is preserved, but diastolic function is impaired. The latter commonly leads to an increased left ventricular end diastolic pressure and symptoms of heart failure.

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LVH is often asymmetric and interventricular septum is the predominant site of involvement. In apical HCM, which is more common in Japan, LVH is restricted to apex. Extent of LVH is variable and is, in part, determined by the underlying mutations, genetic background, age, gender, and possibly the environmental factors.[3] LVH frequently accelerates during adolescence and puberty.[4, 5] LVH, interstitial fibrosis, and myocyte disarray are the major determinants of mortality and morbidity in HCM.[6–9] Myocyte hypertrophy and disarray are more prominent in the interventricular septum, but scattered myocyte disarray is often present throughout the myocardium.[2] Myocyte disarray comprises <5% of the myocardium in the normal hearts and >20 to 30% of the myocardium in HCM.

The true prevalence of HCM is unknown. Its prevalence, detected by echocardiography, in 25–35 years old individuals is ~ 1:500.[10] It is expected to be higher in older subjects because the penetrance is age-dependent and many affected individuals do not exhibit the phenotype until later in life.[4, 11]

The clinical manifestations of HCM are also variable. The majority of patients with HCM are asymptomatic or mildly symptomatic. The main symptoms are dyspnea, chest pain, palpitations, and infrequently syncope. Cardiac arrhythmias, in particular atrial fibrillation and non-sustained ventricular tachycardia are relatively common and Wolff-Parkinson-White syndrome is present in approximately 5% of patients. Symptoms of heart failure are predominantly due to left ventricular diastolic dysfunction. Sudden cardiac death (SCD) is often the first manifestation of HCM in the young. Indeed, HCM is the most common cause of SCD in the competitive athletes.[12]

Physical findings are reflective of LVH and LV outflow tract obstruction. Physical examination may be completely normal or detect subtle abnormalities in subjects without significant LVH or outflow tract obstruction. The typical arterial pulse has two components of percussion and tidal waves. The jugular vein may show a prominent a wave reflective of poor right ventricular compliance. Apical impulse is strong and commonly bifid. A harsh, crescendo-decrescendo mid-systolic murmur in left sternal border is the most common and often the only finding on physical examination. The murmur rarely radiates to carotid arteries. Maneuvers that diminish left ventricular volume such as inhalation of amyl nitrate, or increases left ventricular contractility, such as infusion of inotropic agents, accentuate the murmur and those that increase ventricular volume, such as squatting diminish with intensity of the murmur. A loud S4 is commonly present.

HCM, the most common cause of SCD in the young athletes,[12] is a relatively benign disease in adult population. The estimated annual mortality rate of HCM is <0.7%.[13] Several potential risk factors for SCD have been identified and those with certain causal mutations, modifier genes, early age of onset, history of syncope, family history of SCD, exercise-induced hypotension, or malignant arrhythmias are considered at high risk for SCD (Table I).

Genetic basis of HCM

Clinical genetics

HCM is a genetic disease with an autosomal dominant mode of inheritance with the exception of those caused by mutations in the mitochondrial genome, which show a matrilinear transmission. Approximately 2/3 of patients have familial HCM and the remainder is sporadic, caused by de novo mutations. Sporadic cases transmit the mutation and thus the disease to their offspring. No founder effect is uncommon and the majority of mutations occur independently.[14–16]

Molecular genetics of HCM

Dr. Seidman and her group mapped the first locus to chromosome 14q1 and identified the R403Q missense mutation in the β-MyHC as the first causal mutation for HCM.[17, 18] Subsequently, mutations in cardiac troponin T (cTnT) and a-tropomyosin and other components of thin and thick filaments of sarcomere were identified, leading to the notion that HCM is a disease of contractile sarcomeric proteins.[19] Thus far, more than 100 different mutations in 11 genes encoding contractile sarcomeric proteins have bben identified. The list of the causal genes for HCM, shown in Table II, includes those encoding b-MyHC, cTnT, myosin binding protein-C (MyBP-C), cardiac troponin I (cTnI), cardiac troponin C (cTnC), titin, cardiac α-actin, and essential and regulatory light chains (ELC1 and ECL2). Mutations in non-sarcomeric genes are also known to cause a phenotype similar to HCM (Table III). Mutations in a gene coding for the AMP-activated γ2 non-catalytic subunit of protein kinase A, a regulator of cell bioenergetics, have been identified in families with Wolff-Parkinson-White syndrome and HCM.[20,21] Furthermore, mutations in mitochondrial genome have been associated with HCM and multi-organ disorders.[22] HCM is also often observed in patients with the triplet repeat syndromes.[23] Collectively, these data suggest that HCM, defined as hypertrophy in the absence of an increased external load, occurs primarily as a result of mutations in genes encoding the contractile sarcomeric proteins. However, HCM, often in conjunction with other cardiac and non-cardiac phenotypes, also occurs because of mutations in non-sarcomeric proteins, such as mitochondrial DNA.

Mutations in sarcomeric proteins

MYH7, MYBPC3, and TNNT2 are the three most common causal genes for HCM and collectively account for approximately three-fourths of all HCM cases. The β-MyHC gene (MYH7) is the most common gene responsible for HCM, accounting for approximately 35–50% of all HCM cases.[24] MYH7 is comprised of 40 exons and codes for a 6 kb mRNA and a 220 kD protein.[25] Over 60 different mutations in the β-MyHC have been identified and the majority are missense mutations. Codons 403 and 719 are considered hot spots for mutations.[26, 27] The majority of the mutations are located in the globular head of the myosin molecule.[22] Missense and deletion mutations[28–30] and an insertion/deletion mutation changing amino acids 395-404[31] in the rod and tail regions also have been described. The frequency of each particular MYH7 mutation is relatively low.

The second most common causal gene for human HCM is the MYBPC3 gene on chromosome.[11, 32] Mutations in MYBPC3 account for an approximately 20% to 25% of all HCM cases.[3, 4, 33] The MYBPC3 gene has a complex structure comprised of 35 exons spanning approximately 23 kb of DNA.[32] MyBP-C has a cardiac specific motif comprised of 9 amino acids translated from exon.[8] Over 40 different mutations in the MYBPC3 gene have been identified and the frequency of each mutation is low.[4, 32–35] Unlike mutations in the MYH7 gene, which are mostly missense mutations, the majority of mutations in the MYBPC3 are deletion/insertion or splice junction mutations.[33] Deletion/insertion mutations are expected to result in frame-shift or truncation of the MyBP-C proteins either leading to severe structural and functional defects in the protein or immediate degradation of the expressed protein.

More than 20 mutations in cardiac troponin T gene (TNNT2), located on chromosome 1q3, have been identified. Mutations in TNNT2, probably the third most common causal gene for HCM, account for approximately 20% of all HCM cases.[36] The majority of the mutations are missense mutations and codon 92 is considered a hot spot for mutations.[19, 37] Deletion mutations that involve the splice donor sites and lead to truncated proteins 19 also have been reported.

Mutations in two other components of the troponin-tropomyosin complex, namely troponin I,[38, 39] α-tropomyosin,[16, 19, 40, 41] troponin C,[42] have been identified in patients with HCM. Other relatively uncommon causal genes for HCM are ACTC, encoding cardiac α-actin;[43, 44] TTN, encoding titin;[45] MYL3, encoding MLC1,[46] and MYL2, coding for MLC2.[46, 47] Overall, mutations in the above components of thin and thick filaments are uncommon causes of HCM in humans.

HCM as a consequence of mutations in non-sarcomeric proteins

Cardiac hypertrophy is the common response of the heart to all forms of stress. Therefore, it is not surprisingly that HCM phenotype, *i.e.* hypertrophy in the absence of an increased external load, is also observed in a variety of conditions including triplet repeat syndromes, mitochondrial disorders, and metabolic disorders (Table III). Recently, mutations in PRKAG2 gene, encoding the γ2 regulatory subunit of AMP-activated protein kinase (AMPK), in families with HCM and Wolff-Parkinson-White syndrome were identified.[20, 21] The described phenotype varies from that of pre-excitation and conduction defects and minimal hypertrophy to that of severe and early onset hypertrophy with minority of patients showing pre-excitation.

HCM also occurs in myotonic muscular dystrophy and Friedreich' ataxia, two triplet repeat syndromes due to expansion of trinucleotide repeat sequences in their respective genes (Table III). Myotonic muscular dystrophy, is an autosomal dominant disorder due to expansion of GCT trinucleotide repeats in in the 3′ untranslated region of dystrophia myotonica protein kinase (DMPK) gene from less than 40 in normal individuals to more than several hundreds and thousands.[48] Expansion of the repeats results in unstable DNA and decreased levels of mRNA and protein. It is the most common form of muscular dystrophy in adults and commonly manifests as progressive degeneration of muscles and myotonia, cardiomyopathy, male pattern baldness, infertility, premature cataracts, mental and endocrine abnormalities.[48] Cardiac involvement is common and often includes conduction defects, dilated cardiomyopathy and less often HCM.[49] The severity of the disease correlates with the number of the GCT repeats. Friedreich' ataxia is an autosomal recessive neuro-degenerative disease also caused by expansion of trinucleotide repeat sequences.[50] The mutation is expansion of the GAA trinucleotides located within intron 1 of FRDA, which codes for frataxin, a soluble mitochondrial protein with 210 amino acids.[50] Friedreich' ataxia involves both central and peripheral nervous system and cardiac involvement includes dilated and hypertrophic cardiomyopathy. The severity of clinical manifestations of Friedreich' ataxia also correlates with the size of the repeats.[51]

Mutations in mitochondrial DNA also have been found in patients with HCM.[52] Mutations in mitochondrial DNA often give rise to a complex phenotype involving multiple organs including the heart.[52] Mitochondrial DNA is a circular double-stranded genome of approximately 16.5 kilobases, which codes for 13 polypeptides of the respiratory chain complexes I, III, IV, and V subunits, 28 ribosomal RNAs, and 22 tRNAs. Each mitochondrion has multiple copies of its own DNA and each cells contains thousands of mitochondrial DNA. Therefore, mutations result in a significant degree of heteroplasmy (combination of wild type and mutant mitochondrial DNA), which makes establishing the causality of mitochondrial DNA mutations in HCM difficult. It is estimated >80 to 90% of mitochondrial DNA need to mutate before it causes a significant clinical phenotype.[53] An example of a disease caused by mitochondrial DNA mutation is the Kearns-Sayre syndrome (KSS), which is characterized by a triad of progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects.[54] Almost all patients with KSS exhibit sporadically occurring mutations in mitochondrial DNA.[54] While the classic cardiac abnormality in KSS is conduction defects, dilated and hypertrophic cardiomyopathies are also often observed but a lower frequency.

Thus, HCM, a genetic model of cardiac hypertrophy, is caused by a diverse array of mutations in a variety of genes, with the pure form (no other cardiac or non-cardiac phenotype) resulting from mutations in contractile sarcomeric proteins.

Genotype-phenotype correlation studies

Elucidation of the molecular genetic basis of HCM has led to a significant enthusiasm in identifying the genetic determinants of cardiac phenotypes in HCM, in particular the role of mutations in MYH7, TNNT2, and MYBPC3 in predicting the risk of SCD in HCM.[28, 33, 55–59] Unfortunately, the results of genotype-phenotype correlation studies are subjects to a large number of confounding factors. Potential confounders are the small size of the families, small number of families with identical mutations due to low frequency of each mutation, variability in the phenotypic expression in affected individuals within the same family or amongst families with identical mutations, influence of modifier genes, influence of non-genetic factors, and rarely homozygosity for causal mutations and compound mutations.[60, 61] Collective data indicate that mutations exhibit highly variable clinical, electrocardiographic, and echocardiographic manifestations and no particular phenotype is mutation-specific.[3] Keeping the limitations of the existing genotype-phenotype correlation studies, the data suggest mutations affect the phenotypic expression of HCM, in particular the magnitude of cardiac hypertrophy and the risk of SCD. In general, mutations in the β-MyHC are associated with an early onset of disease, more extensive hypertrophy, and a higher incidence of SCD than others.[4, 62] Inversely, mutations in the MyBP-C are associated with a relatively mild hypertrophy and late onset of clinical manifestations.[4, 33, 62] Mutations in cTnT are usually associated with a mild degree of LVH but a high incidence of SCD and more extensive disarray.[9, 58]

Mutations in MYBPC3 gene are often associated with a low penetrance, mild hypertrophy, and a low incidence of SCD.[4] The phenotype often develops late, which may coincide with the concomitant presence of hypertension. It has been suggested that hypertensive hypertrophic cardiomyopathy of the elderly may be a form of HCM caused by mutations in the MyBP-C and the concomitant hypertension.[4] Despite the overall benign nature of mutations in the MyBP-C, significant variability in the phenotypic expression of HCM also exists and the so-called “malignant” mutations also have been reported in the MYBPC3 genes.[33]

Mutations in α-tropomyosin are generally associated with a benign phenotype and mild left ventricular hypertrophy. Despite mild degree of LVH, a high incidence of SCD also has been described.[41] Mutations in essential and regulatory myosin light chains have been associated with mid-cavity obstruction in HCM and skeletal myopathy in some 46 but not in others.[47] Mutations in titin[45] and α-actin[43, 44] are uncommon and have been observed in a small number of families. With regard to HCM caused by mutations in PRKAG2, the phenotype is variable. In some families the predominant phenotype is pre-excitation and conduction abnormalities[20] and cardiac hypertrophy is present in the minority of the patients.[20] In others, early cardiac hypertrophy predominates and pre-excitation is present in a fraction of the cases.[21]

Mutations, regardless of the causal gene or mutation, exhibit an age-dependent penetrance. Therefore, a normal physical examination and clinical testing at an early age do not effectively exclude the possibility of developing HCM later in life.[11] This is particularly the case for HCM caused by mutations in MyBP-C, since the phenotype often develops in the fifth or sixth decades of life.[11] In general, mutations associated with milder hypertrophy, late onset of HCM, and a low penetrance are associated with a relatively benign prognosis.[63] In

contrast, those associated with more extensive hypertrophy, high penetrance, and an early age of onset of HCM carry a higher risk of SCD.

Modifier genes

The phenotype of single gene disorders, particularly autosomal dominant disorders, is also affected by genetic factors other than the causal mutation. Genetic background, often referred to as the modifier genes is known to affect phenotypic expression of single-gene disorders, such as HCM. It should be noted that the modifier genes do not cause the disease but simply affect the severity of its phenotypic expression. Despite the significance of modifier genes in HCM, they remain unknown but several candidates have emerged.[64–66] Association studies suggest that functional variants of angiotensin-1 converting enzyme-1 (ACE-1) gene, which are associated with an increased risk of SCD[64] and the magnitude of left ventricular hypertrophy,[65] endothelin-1, and tumor necrosis factor-α,[67, 68] are potential modifier genes for HCM. The results of association studies should be considered preliminary and large-scale studies are needed to identify the potential modifier genes.

Functional studies of mutant sarcomeric proteins

Elucidation of the molecular genetic basis of HCM has led to a variety of *in vitro* and *in vivo* structure-function studies that collectively provide significant insight into the pathogenesis of HCM. The results are summarized here.

Effects of mutations on sarcomere and myofibril formation

Mutant sarcomeric proteins, when expressed *in vitro,* incorporate into myofilaments and sarcomeres. However, when expressed at high levels, they also could induce sarcomere dysgenesis[69] and myofibrillar disarray.[70] The efficiency of incorporation of mutant protein into sarcomere also is reduced for mutations such as a truncated MyBP-C protein in transgenic mice.[70] Overall, the majority of the mutant sarcomeric proteins assemble into myofilaments and sarcomere and do not cause immediate sarcomere dysgenesis or myofibrillar degeneration.[71, 72]

Effects of mutations on interaction of actin and myosin

Mutations impact the interaction of actin filaments with myosin and the net outcome varies for different mutations and experimental conditions, such as Ca^{+2} concentration.[73–80] The majority of the studies show mutant MyHC proteins reduce the ability of the myosin molecules to dislocate the thin actin filaments. Reduced velocity of actin dislocation is partly because of the reduced affinity of the mutant myosin for the actin filaments as evidenced by an increased dissociation rate. Similarly, the cross-bridging kinetics between the thin and thick filaments and the excitation-contraction coupling of myocytes carrying the mutant MyHC are also impaired.[81, 82] The degree of impairment of acto-myosin interaction is associated with the prognostic significance of the causal mutations. Those associated with a poor prognosis exert a more pronounced effect than those associated with a benign prognosis.[73–75]

Mutant cTnT and α-tropomyosin also impair acto-myosin interactions and the results vary for different mutations and experimental conditions. CTnT mutations could increase the rate of actin displacement, without affecting the affinity of the troponin complex for tropomyosin, or that of troponin/tropomyosin complex for actin, or the affinity of the thin filaments for myosin.[78, 80] Mutations in α-tropomyosin show a Ca^{+2}-dependent effect on sliding velocity of actin filaments by myosin[77] and increase the displacement rate under activating conditions (pCa5).

Effects of mutations on myosin ATPase activity

Mutations in the β-MyHC could affect the ATP binding site in the globular head of β-MyHC and thus, the rate of ATP hydrolysis.[76, 83, 84] Reduced affinity of the mutant myosin for thin actin filaments could reduce actin-activated ATPase activity, but not the intrinsic ATPase activity of the MyHC molecule.[76] In contrast to the previous findings, a recent study showed single myosin molecules isolated from the heart of α-MyHC-403 homozygous mice had a 2.3 fold increase in the actin-activated ATPase activity, while the unitary forces and displacement were unchanged.[84]

Effects of mutations on Ca^{+2} sensitivity of myofibrils and myocytes

Ca^{+2} modulates the cyclic interaction of the Myosin and actin. Ca^{+2} also activates a variety of Ca^{+2}-sensitive signaling molecules. A variety of studies have explored the effects of mutations on Ca^{+2} sensitivity of the acto-myosin interaction 85–91. Overall, the effects of mutations on Ca^{+2} sensitivity of the myofibrils and myocytes vary for different mutations and according to the experimental conditions. The effect is mutation-specific and the majority enhance Ca^{+2} sensitivity of contractile apparatus in muscle cells.[61, 86, 91, 92]

Effects of mutations on contraction of cardiac and non-cardiac myocytes

Muscle fibers isolated from the slow skeletal muscles, expressing mutant β-MyHC, show reduced mechanical performance, which correlates with the severity of the cardiac phenotype.[93, 94] Similarly, cardiac myocytes isolated from α-MyHC-403 heterozygote mice exhibit impaired contraction and relaxation.[95] In contrast, studies of single myosin molecules isolated from mice homozygous for the α-MyHC-mutation show a 1.6-fold faster actin filament sliding in *in vitro* motility assay and a 2.2-fold greater average force generation.[84] The dichotomy may reflect the potential limitations of single myosin molecules not duplicating the *in vivo* heterozygous state in HCM.

Expression of mutant cTnT and α-tropomyosin proteins in cardiac myocytes[72, 96, 97] and in myotubes[98, 99] led to impairment of mechanical performance. The net effect varies according to the loading conditions and Ca^{+2} concentration. Collectively, these data suggest power output of cardiac myocytes expressing the mutant sarcomeric proteins is reduced.

Genetically engineered animal models of HCM

To elucidate the pathogenesis of human HCM, several transgenic and knock out/knock-in mouse models, a rat model, and a rabbit model have been generated (Table V). The genetically engineered animal models provide the opportunity to delineate the pathogenesis of HCM and explore new therapeutic targets for treatment and reversal of cardiac phenotypes in HCM. The α-MyHC-$Q403^{+/-}$ and $MyBPC^{-/+}$ mouse models mimic the genotype of human HCM, while transgenic models offer the opportunity for dose-titration studies (effects of various levels of expression of the mutant proteins on cardiac structure and function). The α-MyHC-$Q403^{+/-}$ and $MyBPC^{-/+}$, cTnT-Q-92,[100, 101] α-tropomyosin,[102] and truncated MyBP-C[70] mouse models exhibit a variety of cardiac phenotypes, including myocyte disarray, interstitial fibrosis, and systolic and diastolic dysfunction. However, the existing mouse models do not show significant cardiac hypertrophy, the phenotypic hallmark of HCM in humans, or show only mild hypertrophy that develops late and varies according to the genetic background. In contrast, cardiac hypertrophy develops in mice homozygous for the mutant sarcomeric proteins,[103, 104] a transgenic rat model expressing a truncated cTnT and only after exercise,[105] and in a transgenic rabbit model expressing mutant β-MyHC-Q403.[106] Premature death is also relatively uncommon in the transgenic animal models. Global systolic function in adult life is often impaired in transgenic mouse models, but preserved or increased function in the very young mice (5-

week-old).[103, 107] Transgenic rabbits expressing β-MyHC-Q403 show reduced tissue Doppler systolic and diastolic velocities, cardiac hypertrophy, disarray, interstitial fibrosis.[106] A variety of cellular and biochemical abnormalities, such as reduced crossbridge kinetics 81, altered calcium sensitivity of myocytes and myofibrils,[70, 108, 109] reduced myocyte contractility,[95] myocyte atrophy,[108] altered energetics,[110] impaired excitation-contraction coupling[82] and electrophysiological abnormalities[111, 112] in transgenic mouse models and reduced tissue Doppler velocities in a transgenic rabbit model[113] also have been described. Altogether, data in transgenic animal models point to the diversity of the molecular and cellular mechanisms involved in the pathogenesis of final phenotypes of HCM, which are summarized in Table V.

Limitations and utility of genetically engineered animal models

A concern with the mouse models of human HCM, is the presence of major differences in the composition of sarcomeric proteins between humans and mice, which could limit the utility of the transgenic mouse models in deciphering the pathogenesis of human HCM. In contrast to mouse hearts, in which α-MyHC predominates, the β-MyHC is the predominant MyHC isoform in human and rabbit hearts.[114] It comprises >90% of the total myosin pool in the human heart.[114] Therefore, the concern regarding the utility of mouse model to decipher the pathogenesis of HCM is particularly relevant to HCM caused by mutations in the β-MyHC, since β-MyHC is expressed only at a very low level in the adult mouse heart and α-MyHC predominates.[114] The presence of major differences in the rate of Mg-ATPase activity and acto-myosin kinetics between α (fast) and the β (slow) MyHC isoforms could affect the phenotypic response of the heart to mutant sarcomeric proteins. The lack of significant or mild cardiac hypertrophy, the clinical hallmark of HCM, in transgenic mouse models[100, 101, 109, 115] and in some cases the presence of cardiac and myocyte atrophy,[101] further underscores this concern. Differences in calcium handling of myofibrils, implicated in the pathogenesis of HCM,[116] between rabbits and mice also favor the use of transgenic rabbits to elucidate the pathogenesis of human HCM.[117]

The β-MyHC-Q^{403} transgenic rabbit model for human HCM fully recapitulates the phenotype of human HCM and exhibit cardiac hypertrophy (50% increase in wall thickness), interstitial fibrosis (2–3-fold increase), myocyte disarray (10–20% of the myocardium), premature death particularly during the first 3 months of life, and diastolic dysfunction.[106] Myocardial contraction and relaxation velocities are reduced in all mutant transgenic rabbits, including those without detectable hypertrophy.[118] Thus, β-MyHC-Q^{403} transgenic rabbits fully recapitulate the phenotype of HCM in human patients caused by the β-MyHC-Q^{403} mutation.

Pathogenesis of HCM

The results of *in vitro* and *in vivo* studies suggest that mutations cause a diverse array of initial defects in the structure and function of sarcomeric proteins. Type of the mutations (missense, frame shift, deletion, etc.), their topography, and the function of the affected protein account for the diversity of the initial defects. However, despite the diversity of the initial defects, the final phenotype is cardiac hypertrophy, fibrosis, and disarray. The intermediary pathways that connect the initial defects to the final phenotype of hypertrophy, disarray, and fibrosis at the present time are largely unknown. Overall, it appears that the initial phenotypes are mostly functional, followed by the molecular phenotype, which are likely the intermediary phenotypes, and subsequent structural phenotypes.

The majority of mutation in HCM are missense mutations and do not appear to interfere with initial assembly and the proper alignment of myofilaments and sarcomeres. Therefore, proteins with missense mutations are likely to function as “poison-peptides” exerting a

dominant-negative effect on myocyte function following incorporation into myofibrils.[17] Deletion or truncation mutations that abolish the stop codon or the polyadenylation site or encode truncated proteins that are likely to degrade immediately after translation,[30, 119] could alter stoichiometry of the sarcomeric proteins. Such mutation could function as a "null-allele" and exert an effect through "haplo-insufficiency". Gene targeting experiment in mice suggest that "haplo-insufficiency" may be gene-specific, since ablation of one copy of the murine α-MyHC gene[120] led to alteration in sarcomeric structure and myocardial dysfunction, in contrast, ablation of one copy of α-tropomyosin did not induce a detectable morphological or functional abnormalities.[121, 122]

Functional defects precede cardiac hypertrophy

Experimental and clinical data suggest cardiac hypertrophy, the clinical hallmark of HCM, is a compensatory phenotype. LVH often occurs late and is absent in a significant number of patients who have inherited the causal mutation for HCM. Structure-function studies in adult cardiac myocytes and in intact hearts suggest that functional abnormalities precede cardiac hypertrophy in human subjects with HCM.[96–98, 113] A recent study showed that tissue Doppler velocities of myocardial contraction and relaxation were reduced in human subjects with the mutations even in the absence of detectable cardiac hypertrophy.[123] Similarly, myocardial contraction and relaxation velocities are reduced in the β-MyHC-Q^{403} transgenic rabbits prior to development of cardiac hypertrophy or interstitial fibrosis.[113] Furthermore, gene-transfer studies in adult cardiac myocytes show that their function is impaired prior to the development of discernible sarcomere or myofibrillar disarray.[96, 97] Moreover, skeletal myotubes and muscle fibers, isolated from the skeletal muscles of patients with HCM, show reduced force generation in the absence of structural abnormality.[93, 94] Finally, myocytes isolated from the hearts of transgenic mice expressing a mutant α-MyHC protein[95] show impaired mechanical performance. Collectively these results suggest the functional impairment precedes the structural changes in HCM.

Evidence for compensatory nature of LVH

Cardiac hypertrophy, the ubiquitous response of the myocardium to all forms of stress, commonly develops late in humans with HCM. Several lines of evidence suggest that LVH is a compensatory process due to yet to be defined impetus provided by the mutant sarcomeric proteins (Table VI). As discussed earlier, the primary defect induced by the mutant proteins are diverse and the link between the primary defects and subsequent evolution of LVH remain unknown.

Current hypothesis—We and others have proposed that mutant sarcomeric proteins cause a diverse array of initial defects that converge into a common phenotype of impaired cardiac myocyte function and subsequent development of compensatory hypertrophy, fibrosis, and disarray (Fig. 1). Accordingly, the common defect in HCM, regardless of the diversity of the causal mutations and the initial defects, is impaired cardiac myocyte mechanical function,[124] which increases myocyte stress and leads to activation of stress-responsive intracellular signaling kinases and trophic factors. Collectively stress-responsive signaling kinases and trophic factors activate the transcription machinery leading to cardiac hypertrophy, interstitial fibrosis and other histological and clinical phenotypes of HCM.[124] Stimuli are also provided by altered Ca^{+2} sensitivity of myofibrils, reduced ATPase activity, and sarcomere dysgenesis. Accordingly, myocyte hypertrophy and disarray, interstitial fibrosis, and thickening of the media of intra-mural coronary arteries are "secondary" phenotypes and potentially reversible. Other cellular mechanisms, such as cardiac myocyte atrophy and myocyte "drop-out" possibly due to apoptosis also have been implicated in animal models. However, their significance in human HCM remains to be established.

Pharmacological interventions in genetically engineered animal models could provide new therapeutic opportunities for human patients with HCM—Despite recognition of HCM as a major cause of mortality and morbidity, current pharmacological interventions for treatment of human patients with HCM are empiric and not proven to regress cardiac hypertrophy, fibrosis or disarray. Genetically engineered animal models of HCM provide the opportunity to test the effects of pharmacological interventions that are targeted to specific pathways involved in the pathogenesis of HCM. Such studies provide the opportunity to determine reversibility of the evolving phenotypes or the ability to prevent their development.

Reversal of interstitial fibrosis in the cTnT-Q^{92} transgenic mice—Interstitial fibrosis is considered as a major risk factor for SCD in human patients with HCM and ventricular arrhythmias.[6, 125] In a recent randomized study we tested the effects of blockade of angiotensin II receptor 1 on cardiac phenotype in the cTnT-Q^{92} transgenic mouse model.[126] It is noted that despite the well-established role of blockade of renin-angiotensin-aldosterone system in reversal of cardiac fibrosis in a variety of cardiovascular pathology, they are not currently used in treatment of human patients with HCM. The concern arises from the possible worsening of outflow gradient because of afterload reduction with these agents. In the cTnT-Q^{92} mice, treatment with losartan reduced interstitial collagen volume by 49% and expression of collagen α1 (I) mRNA and TGF-β1, a known mediator of profibrotic effects of angiotensin II by ~50%. Losartan had no significant effect on the extent of myocyte disarray. Because the cTnT-Q^{92} mice, unlike the β-MyHC-Q^{403} rabbits, do not exhibit cardiac hypertrophy,[100] the effects of losartan on cardiac hypertrophy could not be assessed.

Reversal of cardiac hypertrophy, interstitial fibrosis and improvement in cardiac function in the β-MyHC-Q^{403} rabbits: Recent data raises the possibility that HMG-CoA reductase inhibitors could be used to inhibit signaling kinases involved in the pathogenesis of cardiac hypertrophy and thus could potentially attenuate cardiac hypertrophy and fibrosis in pathological state.[127–129] We performed a randomized study and determined the effects of simvastatin, a pleiotropic HMG-CoA reductase inhibitor, on cardiac structure and function in the β-MyHC-Q^{403} transgenic rabbits. Treatment with simvastatin reduced mean left ventricular mass was reduced by 37%, septal and posterior wall thickness by approximately 20%, and collagen volume fraction by ~50%. Indices of left ventricular filling pressure were improved significantly. At mechanistic level, expression of active ERK1/2 was reduced in the treatment group, but levels of other active signaling kinases were unchanged. Thus, simvastatin and probably other HMG-CoA reductase inhibitors are potential candidates for reversal of cardiac hypertrophy and fibrosis, major predictors of mortality and SCD, in human patients with HCM.[6, 7]

Worsening of cardiac phenotype in α-MyHC-$Q^{403+/-}$ mice following treatment with calcineurin inhibitors: There has been significant controversy regarding the utility of calcineurin inhibitors in treatment and prevention of cardiac hypertrophy in a variety of conditions.[130] With regard to HCM, a recent study showed that treatment of α-MyHC-$Q^{403+/-}$ mice with FK506 or cyclosporin A increased cardiac hypertrophy, worsened myocyte hypertrophy, disarray and interstitial fibrosis, increased mortality, and impaired Ca^{+2} flux 116. Pre-treatment with diltiazem, an L-type Ca^{+2} channel blocker, prevented the exaggerated cardiac hypertrophic response to inhibitors of calcineurin.

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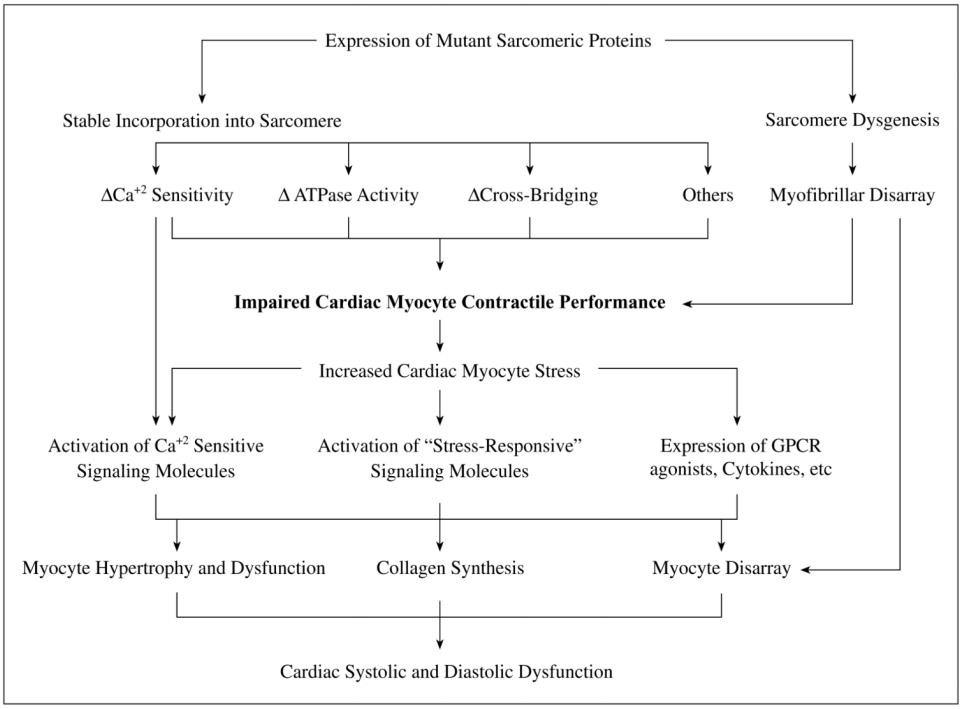

Fig. 1.
Pathogenesis of HCM.

Table I

Potential risk factors for sudden cardiac death in hypertrophic cardiomyopathy.

History of SCD
Family history of premature death
Causal mutations
Modifier genes
History of syncope
Magnitude of left ventricular hypertrophy
Extent of myocyte disarray
Extent of interstitial fibrosis
Early onset of the disease
Myocardial ischemia on perfusion tomography
Abnormal blood pressure response to exercise
Presence of non-sustained VT on Holter

Table II

Causal genes for HCM: genes coding for sarcomeric proteins.

Gene	Symbol	Locus	Frequency	Mutations
β-myosin heavy chain	MYH7	14q12	~35%	>70, predominantly missense mutations
Myosin binding protein-C	MYBPC3	11p11.2	~20%	>40, Predominantly splice junction and insertion/deletion mutations
Cardiac troponin T	TNNT2	1q32	~20%	> 15, Mostly missense
α-tropomyosin	TPM1	15q22.1	~5%	> 5 missense mutations
Cardiac troponin I	TNNI3	19p13.2	~5%	3 missense and 1 deletion mutations
Essential myosin light chain	MYL3	3p21.3	<5%	2 missense mutations
Regulatory myosin light chain	MYL2	12q23-24.3	<5%	7 missense and 1 truncation mutations
Cardiac α-actin	ACTC	15q11	<5%	2 missense mutations
Titin	TTN	2q24.1	<5%	1 missense mutation
α-myosin heavy chain	MYH6	14q1	Rare	1 missense and 1 rearrangement mutations
Cardiac troponin C	TNNC1	3p21.3-3p14.3	Rare	1 missense mutations in a patient with HCM

Table III

Causal genes for HCM: genes coding for non-sarcomeric proteins.

Gene	Symbol	Locus	Frequency	Mutations
AMP-activated protein kinase, γ2 regulatory subunit	PRKAG2	7q35-q36	<5%	3 point and 1 insertion mutations
Mitochondrial DNA	MTTI	Mitochondrial	Rare	tRNA Isoleucine and tRNA glycine
Frataxin (Friedreich' ataxia)	FRDA	9q13		>200 GAA in intron 1
Myotonin protein kinase (Myotonic dystrophy)	DMPK	19q13	Uncommon	>50 CTG in 3′-UTR

Table IV

Initial defects conferred by mutant contractile sarcomeric proteins.

Mechanical defect
Impaired acto-myosin interaction
Impaired cardiac myocyte, skeletal myoblasts and myofibril contractile performance
Biochemical defects
Impaired Ca+2 affinity, force and myofibril sensitivity
Bioenergetics
Impaired ATPase activity
Structural defects
Impaired sarcomere assembly
Impaired subcellular localization of sarcomeric proteins
Altered stoichiometry

Table V

Genetically engineered animal models of HCM

	Phenotype
Knock out/in models	
α–MyHC-Q403 mice	Myocyte disarray, interstitial fibrosis, hypertrophy mild and late, enlarged left atrium, premature death, neonatal dilated cardiomyopathy in homozygous mice 131, systolic and diastolic dysfunction,[95, 115] increased contractile performance in very early life,[107] heterogeneous ventricular conduction, inducible ventricular tachycardia [111, 112, 132], reduced crossbridge kinetics, increased force generation of single myosin molecules and [Ca+2]I sensitivity,[81, 82, 84, 116] reduced [PCr], and increased [Pi] 110, increased actin-activated ATPase activity.
α–MyHC knock out mice	Embryonic lethality in −/−, +/− show fibrosis, sarcomere disarray, impaired contractility and relaxation[120]
α–Tropomyosin knock-out	Embryonic lethality in homozygotes, no phenotype in heteozygotes, normal cardiac function[121, 122]
Transgenic mice	
α–MyHC-Q403/ΔAA468-527	Myocyte disarray, interstitial fibrosis, ventricular hypertrophy in female and dilatation in male mice, Increased ANF[133, 134]
α–MyHC-Δ LCBD	Myocyte disarray, hypertrophy (only in homozygote), valvular thickening, decreased Ca^{+2} sensitivity and diastolic dysfunction[103]
cTnT-ΔC-terminus	Myocyte disarray, interstitial fibrosis, myocyte atrophy and drop out, cardiac atrophy, premature death, systolic and diastolic dysfunction[108]
cTnT-Q92	Myocyte disarray, interstitial fibrosis, myocyte drop out, cardiac atrophy, systolic and diastolic dysfunction[100, 101, 108]
cTnT-N179	Normal, normal survival, no hypertrophy, increased Ca^{+2} sensitivity of ATPase activity and force generation, increased rate of contraction and relaxation, lower maximum force/cross section area and ATPase[135]
MyBP-C-ΔC-terminus	Myocyte disarray, sarcomere dysgenesis, interstitial fibrosis, no cardiac hypertrophy[109]
Truncated MyBP-C	Neonatal dilated cardiomyopathy in homozygous mice expressing <10% of the truncated protein, disarray, minimal or mild hypertrophy, decreased contractility and diastolic dysfunction[136]
ELC-V149 (human gene)	Papillary muscle hypertrophy, altered stretch-activation response[104]
ELC-V149 (mouse cDNA)	Normal, no hypertrophy, increased Ca^{+2} sensitivity and impaired relaxation[137]
α–Tropomyosin-N175	Myocyte disarray and hypertrophy, impaired contractility and relaxation, Increased Ca^{+2} sensitivity and decreased relaxation[102, 135]
cTnI-G146	Myocyte disarray, interstitial fibrosis, premature death. Increased Ca^{+2} sensitivity, hypercontractility, and diastolic dysfunction[138]
Transgenic rat	
cTnT-ΔExon 16	Normal, no cardiac hypertrophy, systolic and diastolic dysfunction. After 6 months of exercise hypertrophy, myofibrillar disarray[105]
Transgenic rabbit	
β-MyHC-Q403	Cardiac hypertrophy, myocyte disarray, interstitial fibrosis, increased mortality and SCD, systolic and diastolic dysfunction, preserved global systolic function, reduced myocardial contraction and relaxation velocities[106, 118]

$[Ca^{+2}]$I: Intracellular Ca^{+2} concentration; [PCr]: phosphocreatinine; ↑[Pi]: Inorganic phosphate; −/−: null (homozygous for the deletion); +/−: heterozygous, LCBD: Light chain binding domain, MyHC: myosin heavy chain; cTnT: Cardiac troponin T: cTnI: Cardiac troponin I; MyBP-C: Myosin binding protein C, ELC: Essential light chain.

Table VI

Evidence in support of compensatory hypertrophy in HCM.

1	Impaired myocyte mechanical performance following expression of mutant sarcomeric proteins in the absence of structural abnormalities.
2	Upregulation of expression of the molecular markers of compensatory hypertrophy, such as atrial and brain natriuretic peptides, endothelin-1, transforming growth factor (TGF) β1 and insuling like growth factor-1 (IGF-1).
3	Predominant presence of hypertrophy in the left ventricle (high pressure chamber) despite expression of mutant MyHC protein in the right (low pressure chamber) as well.
4	LVH is affected by the genetic background and the environmental factors.
5	Remodeling of LVH in humans following septal ablation and alleviation of outflow tract gradient.
6	Reversal of cardiac hypertrophy and interstitial fibrosis in transgenic animal models of HCM by blockade of angiotensin II, receptor 1, or with simvastatin.