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The Molecular Genetic Basis for Hypertrophic Cardiomyopathy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM), the most common cause of sudden cardiac death (SCD) in the young ¹, is a relatively common disease ² with diverse clinical and pathological manifestations ³. HCM is diagnosed clinically by the presence of unexplained left ventricular hypertrophy (absence of hypertension, valvular disease, etc) and a small left ventricular cavity. The term asymmetric septal hypertrophy (ASH) is used to describe a subset of patients who exhibit hypertrophy predominantly in the interventricular septum. Left ventricular global systolic function, as indicated by the ejection fraction, is preserved. Left ventricular relaxation, however, is impaired. The latter commonly leads to an increased end diastolic pressure and symptoms of heart failure. Approximately 25% of patients with HCM exhibit left ventricular outflow tract obstruction and an intracavitary gradient, associated with mitral regurgitation.

The clinical manifestations of HCM vary from a benign asymptomatic course to that of severe heart failure and SCD ³. The latter is often the first manifestation of the disease in the young and the most common cause of SCD in competitive athletes ¹. Patients with HCM commonly exhibit symptoms of chest pain, dyspnea, palpitation, 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 HCM patients. Overall, HCM despite being the most common cause of SCD in the young, is a relatively benign disease in the adult population and has an estimated annual mortality rate of <0.7% ⁴. However, subgroups of patients with a high risk for SCD can be identified based on the mutation, modifier genes, early age of onset, history of syncope, family history of SCD, exercise-induced hypotension, or malignant arrhythmias.

Pathological features of HCM are also diverse and include myocyte hypertrophy and disarray, interstitial fibrosis, and thickening of the media of intramural coronary arteries ⁵. Cardiac hypertrophy and interstitial fibrosis are the major determinants of mortality and morbidity in HCM ^{6;7}. Myocyte hypertrophy and disarray are more prominent in the interventricular septum, but scattered myocyte disarray is often present throughout the myocardium. Myocyte disarray, comprising <5% of the myocardium, may be observed in normal hearts in areas where muscle bundles cross and at the junction of the interventricular septum with the ventricles. Generally, extent of myocyte disarray in patients with HCM is >5% of the myocardium and may involve the entire myocardium. Myocyte disarray, unlike cardiac hypertrophy, which is

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a common response of the heart to all forms of injury, is considered the pathological hallmark of HCM.

MOLECULAR 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. Approximately 2/3 of patients have a family history of HCM and thus have familial HCM. The remainder is sporadic, which is also due to mutations that arise de novo. Therefore, sporadic cases are also genetic and such patients are expected to transmit the mutation and thus the disease to their offspring. In general, the majority of mutations that cause HCM occur independently and there is no founder effect for a particular mutation.

Causal Genes and mutations

During the last decade genetic causes for many cardiovascular diseases including HCM have been identified⁸. More than 100 different mutations in 10 genes encoding contractile sarcomeric proteins (Table 1) have been identified in patients with HCM⁹. In addition, mutations in 2 genes coding for non-sarcomeric proteins and mitochondrial genome have been associated with HCM⁹. Furthermore, HCM is often present in patients with triplet repeat syndromes for which several causal mutations have been identified⁸. Collectively, these data suggest that HCM, defined as hypertrophy in the absence of an increased external load, can occur because of mutations in a variety of genes. In its pure form, i.e. in the absence of other cardiac and non-cardiac phenotypes, HCM is caused by mutations in contractile sarcomeric proteins. However, consistent with the notion that hypertrophy is a common response of the myocardium to all forms of stress and injury, HCM also could occur because of mutations in non-sarcomeric proteins. The latter is often present in conjunction with other cardiac and non-cardiac phenotypes.

Dr. Seidman and her group mapped the first responsible gene for HCM to the locus of β -MyHC on chromosome 14q1¹⁰. Subsequent screening of the β -MyHC gene led to identification of the R⁴⁰³Q missense mutation¹¹, which is the most commonly described mutation in HCM. The β -MyHC gene is comprised of 40 exons and codes for a 6 kb mRNA and a 220 kD protein¹². It is the predominant myosin isoform in the ventricle of large rodents and humans comprising >90% of the total myosin in the human ventricles¹³. Mutations in the β -MyHC are the most common cause of HCM and account for approximately 35–50% of all HCM cases¹⁴. Thus far over 60 different mutations have been described, the majority of which are missense mutations located within the globular head of the myosin molecule⁹. Codons 403 and 719 are considered hot spots for mutations^{15,16}. Two small (E930 17 and G10 18) and one large (exon 40 and 3' untranslated region) 19) deletion and one insertion/deletion (changing AA 395–404) 20 mutations in the β -MyHC gene have been described⁹. Mutations in the β -MyHC gene arise independently²¹, and therefore, the frequency of each particular mutation is relatively low.

The second most common gene responsible for human HCM is the myosin binding protein-C (MyBP-C) gene, which is located on chromosome 11q11²². Mutations in MyBP-C account for approximately 20% to 25% of all HCM cases²³. The MyBP-C gene has a complex structure comprised of 35 exons that span approximately 23 kb of DNA on chromosome 11²². The cardiac specific motif is comprised of 9 amino acids translated from exon 8 of the MyBP-C gene. Over 29 different mutations comprised of missense, deletion, and splice junction mutations have been identified^{22–25}. These mutations commonly affect the splice junctions and result in a frame-shift or are deletion mutations that affect the binding sites for MyHC and titin proteins.

The third most common gene responsible for human HCM is the cardiac troponin T (cTnT), which is estimated to account for approximately one-fifth of all HCM cases¹⁴. It is located on chromosome 1q3 and through alternative splicing, encodes several isoforms in the heart²⁶. The most abundant cTnT mRNA isoform in the human heart is 1.1 kb in size that encodes an approximately 35 kD protein. More than 20 mutations in the cTnT gene have been identified and codon 92 is considered a hot spot for mutation^{27,28}. The majority of the mutations in cTnT are missense and deletion mutations that involve the splice donor sites and lead to truncated proteins²⁷. Overall, mutations in the three most common genes responsible for HCM, namely the β -MyHC, MyBP-C and cTnT, account for approximately three-fourths of all HCM cases.

Identification of mutations in the contractile sarcomeric proteins led to the notion that HCM is a disease of contractile sarcomeric proteins. Systematic screening of HCM cases for mutations in genes encoding for other sarcomeric proteins led to identification of mutations in α tropomyosin²⁷, cardiac troponin I (cTnI)²⁹, essential and regulatory light chains³⁰, α -cardiac actin³¹, and titin³². Overall, the frequencies of these mutations are relatively low and each of the above genes account for <5% of all HCM cases.

In addition to mutations in contractile sarcomeric proteins, mutations in two genes encoding for non-sarcomeric proteins also have been identified in patients with HCM. Recently, a deletion mutation in a potassium voltage gated channel, KCNQ4 located on chromosome 1p34, in a family with congenital deafness and HCM was described (<http://archive.uwcm.ac.uk/uwcm/mg/ns/4/kcnq4.html>). More recently, a point mutation in the AMP-activated gamma 2 non-catalytic subunit of protein kinase A (PARAG2) located on chromosome 7q22–q23 was described in two families with HCM and Wolff-Parkinson-White syndrome {Gollub M and Roberts R., Unpublished data}. Furthermore, mutations in mitochondrial genes encoding for tRNA isoleucine and tRNA glycine also have been associated with HCM³³. Thus, HCM is a genetic model of cardiac hypertrophy 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

In an attempt to determine the impact of causal genes and mutations on the phenotypic expression of HCM, genotype-phenotype correlation studies have been performed for a limited number of mutations in the β -MyHC, cTnT, and MyBP-C genes^{17,34–38}. Several confounding factors, such as small size of the families, small number of families with identical mutations, variability in the phenotypic expression in affected individuals within the same family or amongst families with identical mutations, low frequency of each mutation, and Influence of modifier genes and non-genetic factors on the phenotypic expression of HCM limit the utility and conclusions of genotype-phenotype correlation studies. In general, it is clear that no particular clinical phenotype is mutation-specific and mutations exhibit highly variable clinical, electrocardiographic, and echocardiographic manifestations. Despite the limitations of existing genotype-phenotype correlation studies, it is generally agreed that mutations affect the phenotypic expression of HCM, in particular the magnitude of cardiac hypertrophy and the risk of SCD. It appears that HCM caused by mutations in the β -MyHC manifests at a younger age and is associated with more extensive hypertrophy and a higher incidence of SCD compared to HCM arising from mutations in the MyBP-C or α -tropomyosin genes^{23,39}. Studies in a small group of families have shown that the prognostic significance of mutations in the β -MyHC gene is a function of their influence on the magnitude of hypertrophy⁴⁰. Mutations that are associated with a high incidence of SCD and premature death often exhibit high penetrance and an early age of onset. In contrast, those associated with a benign prognosis often exhibit low penetrance, late onset of disease, and milder left ventricular hypertrophy. This general

notion does not apply to mutations in the cTnT gene, since they exhibit less hypertrophy but a high incidence of SCD, particularly in young adult males³⁷. Homozygosity for causal mutations and compound mutations have been described that lead to a more severe morphological phenotype and a higher incidence of SCD^{41;42}.

Mutations in the α -tropomyosin and MyBP-C genes are often associated with low penetrance, mild hypertrophy, and a low incidence of SCD²³. However, significant variability exists and the so-called malignant mutations in the α -tropomyosin and MyBP-C genes have been observed. It has been proposed that hypertensive hypertrophic cardiomyopathy of the elderly is also a form of HCM often caused by mutations in the MyBP-C gene²³. Mutations in essential and regulatory myosin light chains have been reported in patients with HCM who exhibit mid-cavity obstruction and skeletal myopathy³⁰. Mutations in titin³² and α -actin³¹ are uncommon and have been observed in a small number of families. We emphasize that the number of families with each specific mutation is relatively small to make strong conclusions regarding the results of genotype-phenotype correlation studies. Thus, the described phenotypes may be unique to the particular families described and not generally applicable. Table 2 lists mutations that are associated with a high, intermediary and low risk of SCD in patients with HCM.

Modifier genes

A characteristic feature of human HCM, like many other autosomal dominant diseases, is the presence of significant variability in the phenotypic expression of phenotypes. It is now well established that genetic factors other than the causal mutations, referred to as the modifier genes, affect the phenotypic expression of a monogenic disorder such as HCM. Modifier genes are neither necessary nor sufficient to cause HCM, but they affect the severity of the disease significantly. In the case of HCM, mutations in contractile sarcomeric proteins are necessary to cause HCM, however, the contribution of causal mutations to the magnitude of left ventricular hypertrophy is relatively modest and the modifier genes (genetic background) play a significant role. This concept, although not new and could be deduced from the observations on the variability of phenotypes in monogenic disorders, has not been systematically explored. Thus far, studies to identify the potential modifier genes for HCM have been limited to allelic association studies, whereby the possible association of variants of candidate genes with cardiac phenotypes has been explored⁴³⁻⁴⁵. In this regard, we and others have shown that functional variants of angiotensin-1 converting enzyme (ACE-1) gene are potential modifiers of HCM phenotype, since they are associated with the risk of SCD⁴³ and the magnitude of left ventricular hypertrophy⁴⁴. Patients with the DD genotype, exhibit higher tissue and plasma levels of ACE-1⁴⁶, a higher incidence of SCD, and more extensive hypertrophy than those with the II genotype. We have also explored association of functional variants of several trophic factors and have shown that variants of endothelin-1 and tumor necrosis factor- α are also potential modulators of cardiac phenotypes in HCM^{47;48}. In view of limitations of association studies and the allelic and non-allelic heterogeneity of HCM, large-scale studies are needed to identify potential modifier genes for cardiac phenotypes in HCM.

MOLECULAR PATHOGENESIS

An overview of the molecular basis for the phenotype of familial HCM

The evidence is accumulating from in vitro and in vivo studies that the causal mutation imparts an inherent defect that leads to impaired cardiac myocyte contractile performance. The phenotype of sarcomeric disarray, hypertrophy and increased fibrosis are secondary to the primary defect of impaired contractile performance. To compensate for the impaired contractility, stress-responsive growth factors are released, which stimulate myocyte hypertrophy and fibroblast proliferation. The evidence supporting the molecular basis for this temporal sequence of events is discussed subsequently.

Sarcomere as the contractile unit of striated muscles

All of the causal genes for the pure form of human HCM code for contractile sarcomeric proteins and hence HCM is considered a disease of contractile sarcomeric proteins²⁷. Sarcomeres are the contractile units of striated muscles, comprised of thick and thin filaments. Each sarcomere unit is approximately 2.2 μ in length and is attached to its neighboring sarcomeres through the Z disks. The thick filaments are formed through the assembly of several hundred MyHC molecules in conjunction with MyBP-C and myosin light chain (MLC) -1 and MLC-2 proteins. Thin filaments are comprised of actin, the troponin complex (troponin T, I, C), and α -tropomyosin in a 7:1:1 molar ratio. Another important sarcomeric protein is titin that spans half of the sarcomere length with one end attached to the M line and the other to the Z disk. Titin provides elasticity to the contractile units and is involved in generation and transmission of force. Complex interactions between sarcomeric proteins, regulated by calcium via the troponin-tropomyosin complex, leads to displacement of the thin filaments by the globular head of the MyHC molecule, resulting in sarcomere shortening and muscle contraction.

The β -MyHC protein comprises approximately 1/3 of the total myofibrillar protein and is the motor unit of the sarcomere. It has a globular head that contains actin and ATP binding domains. The globular head of the myosin molecule is attached to a hinge region, which flexes during each cardiac cycle. The rod portion of the MyHC is comprised of α -helices and mediates tail-to-tail interbinding of myosin molecules. Myosin exists as a hexameric molecule comprised of two MyHC, with the two α helices coiled around each other in the rod region, and two essential and two regulatory light chain proteins. Several hundred myosin molecules assemble to form the thick filaments of the sarcomere. Each individual myosin molecule is capable of generating a force of 7 to 11 piconewtons that shortens the sarcomere by 10 to 12 nm⁴⁹.

MyBP-C is a member of the intracellular immunoglobulin superfamily that binds to myosin in the A band region of sarcomere. It has 10 distinct domains comprised of seven immunoglobulin I-set and three fibronectin-III domains^{50;51}. The myosin-binding region of MyBP-C is located in the last 102 C-terminal amino acids in the C10 domain. The titin-binding region comprises amino acids located in the C8 to C10 domain. Binding of MyBP-C to myosin and titin provides further stability to structure of the sarcomere⁵². Cardiac MyBP-C possess a unique N-terminal motif located between the C1 and C2 domains that serves as a phosphorylation site for cAMP-dependent - as well as calcium/calmodulin-dependent protein kinases⁵⁰. Phosphorylation of the cardiac specific motif modulates cardiac contractility⁵³.

Thin filaments, comprised of actin and troponin-tropomyosin complex, are involved not only in the generation force, but also in transmission of the force to cell boundaries. Cardiac troponin T, α -tropomyosin, and troponin I, each comprises < 5% of the total myofibrillar protein. cTnT attaches the troponin complex (C, I, and T) to tropomyosin and the latter, a rod shaped coiled α -helix protein, places the entire complex on actin⁵⁴. The troponin complex plays a major role in the Ca²⁺ regulation of cardiac contraction and relaxation⁵⁵. The α -tropomyosin protein forms a homodimer by coiling around another tropomyosin (coiled-coil) and each homodimer binds to seven actin monomers. Cardiac troponin I is a cardiac specific protein that functions as the inhibitory component of the troponin-tropomyosin complex, modulating calcium-stimulated actomyosin interaction of ATPase activity⁵⁴. Cardiac α -actin is a 38 kD protein that is involved in the generation of force of contraction through its interaction with MyHC and transmission of the generated force from sarcomeres to anchoring cytoskeleton through interaction with actinin and dystrophin. Titin is a giant sarcomeric protein that extends from the M line to Z disk, thus spanning the entire half of the sarcomere length. Titin plays a major role in sarcomere assembly and contains several coils that maintain the resting tension of myocytes. Titin interacts with MyHC and MyBP-C in the A band region and with α -actin and α -actinin at the Z disk.

Other sarcomeric proteins involved in HCM are essential and regulatory myosin light chains, referred to as MLC-1 and MLC-2, respectively³⁰. Myosin light chain proteins are 18–28 kD proteins that bind to the α -helices of MyHC proteins and are involved in the regulation of cardiac muscle contraction⁵⁶. Removal of MLC proteins from the MyHC impairs actomyosin interaction⁵⁷. Phosphorylation of MLC-2 modulates increases in force production during actomyosin interaction, and conversely mutations in the phosphorylation sites of MLC-2 reduce the power output of the striated muscles⁵⁸. Five different isoforms of MLC proteins are expressed in the human heart and their expression is regulated during development as well as in response to altered stress⁵⁹. Switch in expression of MLC isoforms also impairs cardiac function⁶⁰.

Effects of mutant sarcomeric proteins on sarcomere and myofibril formation

Sarcomere and myofibril formations are tightly regulated and coordinated processes that could be affected by the structural changes induced by the mutations. Results of several studies have shown that the majority of the mutant sarcomeric proteins incorporate into myofibrils and sarcomeres^{61;62} and do not impede normal sarcomere assembly. However, the efficiency of incorporation of mutant sarcomeric proteins into sarcomere varies according to the mutation and is reduced for a truncated mutation in the MyBP-C⁶³. In addition, when incorporated at high levels, they could induce sarcomere dysgenesis⁶⁴ and myofibrillar disarray⁶³. Sarcomere and myofibrillar disarray are often observed in human patients with HCM, but their pathogenesis remain unknown. Whether these phenotypes are the direct consequences of misincorporation of the mutant proteins into sarcomere or are secondary to perturbation of regulators of sarcomere assembly remains to be explored.

Effects of mutant sarcomeric proteins on ATPase activity

The globular head region of β -MyHC contains a catalytic site for ATP hydrolysis and an actin-binding domain. Muscle contraction is the result of interaction of the β -MyHC protein with actin filament, coupled to hydrolysis of ATP to ADP and inorganic phosphate. Mutations in MyHC and other sarcomeric proteins reduce the actin-activated ATPase activity, but not the intrinsic ATPase activity of the MyHC molecule⁶⁵. In the case of β -MyHC the reduced ATPase activity reflects the reduced affinity of the mutant protein for thin actin filaments and varies according to topography of the mutations⁶⁵. In contrast, single myosin molecules isolated from the α -MyHC⁴⁰³ homozygous mice exhibit a 2.3 fold higher actin-activated ATPase activity without a significant change in unitary forces and displacement⁶⁶. Since in human patients with HCM, mutant MyHC co-exists with the wild type MyHC, the results of studies of isolated single mutant myosin molecule may not model human HCM.

Effects of mutant sarcomeric proteins on Ca^{+2} sensitivity

Cyclic interaction of MyHC and actin is mediated by binding and release of Ca^{+2} to a single regulatory site at the N-terminus of cardiac troponin C (cTnC)⁵⁵. Binding of Ca^{+2} to cTnC strengthens the binding of the cTnC to cTnI and weakens the affinity of cTnI with actin. The latter initiates the actomyosin interaction leading to muscle contraction. Removal of Ca^{+2} from cTnC reverses the process and leads to muscle relaxation. Therefore, mutations in sarcomere proteins could affect Ca^{+2} sensitivity and thus the actomyosin interaction during cardiac cycles. While the majority of the existing data show an enhanced Ca^{+2} sensitivity imparted by the mutant sarcomeric proteins, the results remain controversial and vary according to the experimental conditions. Isolated rat cardiac myocytes that express mutant cTnT-Q⁹² protein exhibit significant desensitization of the contractile apparatus to activation by calcium⁶⁷, while generation of maximum calcium-activated force remain unchanged. In contrast, permeabilized rabbit cardiac muscle fibers expressing the cTnT-Q⁹² protein exhibit heightened Ca^{+2} sensitivity without alterations in tension-generating capability⁶⁸. Mutations

in cTnT also increase Ca^{+2} sensitive ATPase activity of rabbit cardiac myofibrils and increase the maximum level of myofibrillar ATPase activity⁶⁹. In addition, skeletal muscle fibers carrying the mutant α -tropomyosin-N¹⁷⁵ also exhibit an increased Ca^{+2} sensitivity⁷⁰, but the maximum force and maximum shortening velocities remain unchanged. Furthermore, expression of mutant α -tropomyosin-T⁷⁰, -N¹⁷⁵, and -G¹⁸⁰, via adenoviral-mediated gene transfer into adult cardiac myocytes, results in increased Ca^{+2} sensitivity and force output at submaximal Ca^{+2} concentration⁶². Overall, these data suggest a mutation-specific increase in Ca^{+2} sensitivity of contractile apparatus in muscle cells, which could play a major role in induction of cardiac phenotypes in HCM.

Effects of mutations on acto-myosin motility

The ability of the mutant MyHC proteins to translocate actin filaments has been assessed using an in-vitro motility assay, in which the MyHC molecules are fixed to a membrane^{65;71–73}. Mutations in the β -MyHC mutation impair the ability of the mutant protein to displace thin actin filaments. Mutations that are associated with a poor prognosis exert a more pronounced effect than those associated with a benign prognosis^{71–73}. The impaired ability of the mutant myosin to displace actin filaments in part reflects its reduced binding affinity for the actin filaments as evidenced by an increased dissociation rate⁶⁵. Similarly, the cross-bridging kinetics between the thin and thick filaments and excitation-contraction coupling of myocytes carrying the mutant MyHC are also impaired^{74;75}. In contrast, a mutant cTnT, namely I^{91N}, has been shown to increase the rate of actin displacement without affecting the affinity of the troponin complex for tropomyosin, or troponin/tropomyosin complex for actin, or the thin filaments for myosin⁷⁶. In addition, the impact of two mutations in the α -tropomyosin gene on acto-myosin interaction has been determined and was found to be dependent on the concentration of Ca^{+2} ⁷⁷. While, α -tropomyosin mutations had no effect on the acto-myosin interaction under relaxing conditions (pCa9), they increased displacement rate of actin filament under activating conditions (pCa5). Thus, these data suggest the effects of the mutant sarcomeric proteins on acto-myosin interaction are diverse and in part are determined by the mutation itself and perhaps in part by the experimental conditions.

Effects of mutant sarcomeric proteins on muscle and non-muscle cell mechanics

Slow skeletal muscle fibers also express the mutant β -MyHC proteins in patients with HCM caused by mutations in the β -MyHC gene. Muscle fibers isolated from the slow skeletal muscles of such patients exhibit impaired contractile performance^{78;79}. The extent of reduced mechanical performance is variable and correlates with the severity of the cardiac phenotype. Similarly, myocytes isolated from the hearts of α -MyHC⁴⁰³ heterozygote mice exhibit impaired contraction and relaxation⁸⁰. In contrast, studies of single myosin molecules isolated from mice homozygous for the α -MyHC⁴⁰³ mutation show 1.6 fold faster actin filament sliding in *in vitro* motility assay, 2.3 fold higher actin-activated ATPase activities, and 2.2 fold greater average force generation⁶⁶. The latter results, unlike the results of previous studies, suggest that the α -MyHC⁴⁰³ mutation is a gain of function mutation. Differences may be due in part to experimental conditions and differences in the mechanical properties of α and β isoforms of myosin protein.

Impacts of mutant cTnT proteins on cardiac myocyte^{67;81} and myotubes^{82;83} also have been explored. Expression of the mutant cTnT-Q⁹², known to cause HCM in man, in adult feline cardiac myocytes leads to decreased peak and the rate of cell shortening⁸¹. Similarly, expression of mutant cTnT-Q⁹² protein imparted a contractile deficit in rat cardiac myocytes⁶⁷, which was a dominant-negative effect and preceded structural changes in the myocytes. Furthermore, expression of a truncated cTnT protein in cultured quail myotubes impaired their contractile performance⁸². While the unloaded shortening velocity of myotubes expressing mutant cTnT-Q⁹² protein was increased by two-fold⁸³. With regard to α -tropomyosin,

expression of mutant human proteins in cultured adult rat myocytes resulted in an increased force output at submaximal Ca^{+2} concentration⁶². Collectively, these data suggest an abnormal power output of cardiac myocytes imparted by the mutant sarcomeric proteins.

TRANSGENIC AND KNOCK-IN ANIMALS MODELS

To elucidate the pathogenesis of human HCM, a number of transgenic and knock-in animal have been generated that express a variety of mutant sarcomeric proteins in the heart. Table 3 shows list of animal models generated for human HCM through genetic manipulation. The best-characterized model is the α -MyHC-Q⁴⁰³ knock in model, in which one allele of mouse α -MyHC was replaced by the mutant α -MyHC-Q⁴⁰³ allele, mimicking the genotype of human patients with HCM⁸⁴. Studies in the α -MyHC-Q⁴⁰³ knock-in model have shown a variety of cardiac phenotypes, including myocyte disarray and interstitial fibrosis. However, cardiac hypertrophy, the phenotypic hallmark of HCM in humans, is mild or absent. The phenotype observed in the transgenic mouse models, such as cTnT-Q⁹²^{85;86} α -tropomyosin⁸⁷ and truncated MyBP-C⁶³ are to some extent similar to those observed in human HCM. Myocyte disarray, interstitial fibrosis and diastolic dysfunction are common, however, unlike human HCM, significant cardiac hypertrophy is commonly absent. Cardiac hypertrophy has been observed in mouse models that are homozygous for the mutant sarcomeric proteins^{88;89}, in a transgenic rat model expressing a truncated cTnT, only after exercise⁹⁰, and in a transgenic rabbit model expressing mutant β -MyHC-Q⁴⁰³⁹¹. Premature death is also relatively uncommon in the transgenic animal models. Transgenic mice expressing mutant sarcomeric proteins often exhibit impaired global systolic function in adult life, but preserved or increased function in the very young age (5-week-old)^{88;92}. A variety of cellular and biochemical abnormalities, such as reduced crossbridge kinetics⁷⁴, altered calcium sensitivity of myocytes and myofibrils^{63;93;94}, reduced myocyte contractility⁸⁰, myocyte atrophy⁹³, altered energetics⁹⁵, impaired excitation-contraction coupling⁷⁵ and electrophysiological abnormalities^{96;97} in transgenic mouse models and reduced tissue Doppler velocities in a transgenic rabbit model⁹⁸ also have been described. Altogether they point to the diversity of the molecular and cellular mechanisms involved in the pathogenesis of final phenotypes of HCM.

In view of the concerns regarding the utility of the transgenic mouse models to fully recapitulate human phenotype, we generated transgenic rabbits that express the β -MyHC-Q⁴⁰³⁹¹, known to cause HCM in humans. The β -MyHC is the predominant myosin isoform in the human and rabbit hearts, in contrast to the mouse hearts in which α predominates¹³. The β -MyHC-Q⁴⁰³ transgenic rabbits fully recapitulate the phenotype of human HCM and exhibit significant cardiac hypertrophy, interstitial fibrosis, diastolic dysfunction, preserved global systolic function, and increased incidence of premature death⁹¹. In addition, myocardial contraction and relaxation velocities were reduced consistently in all β -MyHC-Q⁴⁰³ transgenic rabbits, prior to the development of cardiac hypertrophy⁹⁸. Thus, the transgenic rabbit model, which has a sarcomeric protein composition similar to that in human hearts, exhibits a phenotype virtually identical to human HCM. Studies are under way to elucidate the pathogenesis of HCM phenotypes.

Molecular Pathogenesis of HCM

Molecular genetic studies in conjunction with *in vitro* and *in vivo* functional studies have shed significant light onto the pathogenesis of human HCM. Identification of mutations in contractile sarcomeric proteins provided the first clue by suggesting that HCM is a disease of contractile sarcomeric proteins. Thus, the primary defect, which remains to be elucidated and could be diverse or mutation-specific, is expected to affect the structure and function of the sarcomere. Overall, experimental data suggests that mutant sarcomeric proteins become incorporated into sarcomere and impart a variety of structural, biochemical and mechanical

defects that lead to impaired myocyte function and ultimately perpetuate the hypertrophic response in the heart. While the initial defects are divergent, they converge into common final pathways that lead to myocyte hypertrophy, disarray, interstitial fibrosis, and other phenotypes.

Functional abnormalities precede histological and morphological abnormalities in HCM

While cardiac hypertrophy in the absence of increased external load defines HCM, it is often a late manifestation of the disease and absent in a significant number of patients who inherit the causal mutation. *In vitro* and *in vivo* structure-function studies following gene transfer into adult cardiac myocytes or in the intact hearts suggest that functional abnormalities precede the development of cardiac hypertrophy and myocyte disarray in human HCM^{67;81;82;98}. We and others have shown that expression of mutant contractile sarcomeric proteins in adult cardiac myocytes impairs their contractile performance prior to the development of discernible sarcomere or myofibrillar disarray^{67;81}. Similarly, studies performed in skeletal myotubes and in muscle fibers isolated from the skeletal muscles of patients with HCM show reduced force generation in the absence of structural abnormality^{78;79}. In addition, tissue Doppler studies in the β -MyHC-Q⁴⁰³ transgenic rabbits consistently show reduced myocardial contraction velocities prior to development of cardiac hypertrophy⁹⁸. These results are also in accord with the results of *in vitro* motility studies of mutant myosin that show an impaired acto-myosin interaction^{71–73}. Further evidence is provided by the results of studies of myocytes isolated from the hearts of transgenic mice expressing a mutant α -MyHC protein⁸⁰ showing impaired mechanical performance. Finally, *in vivo* studies in cTnT-Q⁹² transgenic mice indicate that left ventricular global function is impaired prior to myocyte disarray and increased interstitial collagen content⁹⁹. Collectively these results suggest the functional impairment precedes the structural changes in HCM.

Hypertrophy as a “secondary” or compensatory phenotype

Cardiac hypertrophy is the ubiquitous response of the myocardium to all forms of stress and injury. Current hypothesis suggests that hypertrophy in HCM is compensatory triggered by the stimulus provided by the mutant contractile sarcomeric proteins¹⁰⁰. The primary stimulus that provides the impetus for compensatory cardiac hypertrophy remains to be proven. However, experimental data evoke impaired cardiac myocyte function and/or altered Ca^{+2} sensitivity as the impetus for the development of cardiac hypertrophy in HCM. The primary stimulus (or the stimuli) imparted by the mutant contractile sarcomeric proteins activates the genetic program in the heart in a manner that is common to all forms of cardiac hypertrophy. In addition, non-genetic factors also modulate the magnitude of cardiac phenotypes in HCM. Therefore, the final hypertrophic phenotype is determined not only by the primary genetic defect, but also by the genetic background of the individual (modifier genes) and non-genetic (environmental) factors. The potential influence of non-genetic factors, such as increased pressure or volume on the manifestations of HCM is supported by the observation that HCM is predominantly restricted to the left ventricle, despite expression of the mutant sarcomeric proteins in equal abundance in both ventricles. The virtual exclusive manifestation of the disease in the left ventricle may reflect the greater chamber pressure in the left ventricle. Evidence corroborating the compensatory nature of hypertrophy in HCM is summarized in Table 4.

Current Hypotheses

Identification of missense mutations in contractile proteins in patients with HCM led to the “poison peptide” hypothesis, which proposes that mutant sarcomeric proteins incorporate into myofibrils and act as dominant negative proteins¹¹. Since the majority of the mutations in contractile sarcomeric proteins are point mutations, “poison peptide” hypothesis is the predominant hypothesis in the pathogenesis of HCM. An alternative hypothesis is the “haplo-insufficiency” or “null-allele” hypothesis, which suggests that HCM phenotypes result from insufficient amount of the sarcomeric protein. Identification of deletion mutations in β -MyHC and MyBP-C that lead to premature truncation of the protein or deletion

of the stop codon and polyadenylation signal support this notion^{19;101}, since such proteins are not expected to be expressed or even if expressed, are not expected to incorporate into myofibrils. These observations suggest that altered stoichiometry of sarcomeric proteins is a possible mechanism for HCM. The results of a recent gene targeting experiment in mice, whereby one copy of the murine α -MyHC gene is ablated, provides more credence for the haplo-insufficiency hypothesis¹⁰². In these experiments, ablation of one copy of the α -MyHC gene led to alteration in sarcomeric structure and myocardial dysfunction. However, ablation of α -tropomyosin, a gene responsible for HCM does not lead to detectable morphological or functional abnormalities in mouse^{103;104}. Thus, it appears that the null mutations may lead to HCM, only when compensatory mechanisms fail to overcome the haplo-insufficiency.

The fundamental question concerns the mechanism(s) by which a point or a deletion mutation leads to cardiac hypertrophy, myocyte disarray, interstitial fibrosis and other histological and morphological phenotypes in HCM. Based on the results of in vitro and in vivo functional studies, we have proposed that the crucial link between the mutant contractile proteins and final phenotypes is impaired cardiac myocyte mechanical performance¹⁰⁰. Accordingly, impaired cardiac myocyte mechanical performance leads to an increased myocyte stress, which provides the impetus for activation of stress-responsive mitotic and trophic factors, such as angiotensin II, transforming growth factor β 1, insulin-like growth factor-1, and endothelin-1 and signaling kinases in the myocardium. Activation of trophic factors and signaling kinases provokes the transcriptional machinery leading to cardiac hypertrophy, interstitial fibrosis and other cardiac phenotypes. Additional stimuli are provided by altered Ca^{+2} sensitivity of myofibrils, reduced ATPase activity, and structural deterioration of the sarcomere (dysgenesis). Thus, 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.

In support of the proposed hypothesis, we note that markers of compensatory cardiac hypertrophy are also upregulated in the myocardium of patients with HCM^{105–108}. These findings suggest involvement of common molecular pathways in modulating cardiac hypertrophy, regardless of whether the stimulus is a genetic defect or induced pressure overload. Furthermore, results of recent studies in the cTnT-Q⁹² transgenic mouse model of HCM, show that interstitial fibrosis could be reversed by blockade of angiotensin II receptor 1, a finding that lends further support to the “secondary” nature of histological and morphological phenotypes in HCM {unpublished data}. Additional evidence that support the above hypothesis are listed in Table 5.

In summary, mutations in contractile sarcomeric proteins, 2 non-sarcomeric proteins, and mitochondrial DNA cause HCM. The results of the in vitro and in vivo functional studies suggest that despite the diversity of the mutations and the initial defects (summarized in Table 5), the fundamental abnormality in HCM is abnormal cardiac myocyte function. The latter leads to increased myocyte stress and activation of stress-responsive trophic and mitotic factors and signaling kinases in the heart, which provokes the transcriptional machinery leading to cardiac myocyte hypertrophy, disarray, increased collagen synthesis and others.

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TABLE 1

Genes and Mutations Responsible for Human HCM, their loci and estimated frequencies

Gene	Symbol	Locus	Frequency	Mutations
β -Myosin heavy chain	<i>MYH7</i>	14q12	~30%	67, mostly missense, a few non-sense, and 3 deletion mutations
Myosin binding protein-C	<i>MYBPC3</i>	11p11.2	~ 20%	29; 11 missense/nonsense, 10 splice, 8 deletion/insertion mutations
Cardiac troponin T	<i>TNNT2</i>	1q32	~ 20%	14: 12 missense, 1 splice, and 1 deletion mutations
α -tropomyosin	<i>TPM1</i>	15q22.1	~5%	4 missense mutations
Cardiac troponin I	<i>TNNI3</i>	19p13.2	~5%	7 missense and 1 deletion mutations
Myosin light chain, essential	<i>MYL3</i>	3p21.3-p21.2	<5%	2 missense mutations
Myosin light chain regulatory	<i>MYL2</i>	12q23.q24.3	<5%	7 missense and 1 truncation mutations
Cardiac α -actin	<i>ACTC</i>	11q	<5%	2 missense mutations
K voltage gated channel	<i>KCNQ4</i>	1p34	Rare	1 deletion mutation in conjunction with deafness
Titin	<i>TTN</i>	2q24.1	<5%	1 missense mutation
Protein Kinase A, β subunit	<i>PRKAR2B</i>	7q22-q31.1	?	1 point mutation in conjunction with WPW
α -Myosin heavy chain	<i>MYH6</i>	14q	Rare	1 missense and 1 rearrangement mutations
Mitochondrial DNA	<i>MTTI</i>	Mitochondrial	Rare	tRNA Isoleucine and tRNA glycine

TABLE 2**Mutations and Prognosis in HCM**

Gene	Good	Intermediary	Poor
β -MyHC	G ²⁵⁶ E	R ²⁴⁹ Q	R ⁴⁰³ Q
	L ⁹⁰⁸ V	E ⁹³⁰ K	R ⁷¹⁹ W
	V ⁶⁰⁶ M*	V ⁶⁰⁶ M*	R ⁴⁵³ C
	F ⁵¹³ C		R ⁷²³ G
	N ²³² S		
CTnT	S ¹⁷⁹ F	F ¹¹⁰ I	R ⁹² Q
			R ⁹² W
			Intron 15 G1>A
			Ile ⁷⁹ Asn
			Δ E ¹⁶⁰
			S ¹⁷⁹ F (homozygous)
MyBP-C	All unless listed	SASint20	
α -Tropomyosin	D ¹⁷⁵ N		
MLC	Insufficient data		

* Varies according to genetic background.

TABLE 3

Transgenic and knock in animal models of human HCM

Gene	Mutation	Phenotype
α -MyHC	Q ⁴⁰³ (knock-in) 84	Myocyte disarray, interstitial fibrosis, systolic and diastolic dysfunction, $\uparrow$ left atrium, heterogeneous ventricular conduction, $\uparrow$ SNRT, inducible VE, $\downarrow$ crossbridge kinetics, $\uparrow$ [Ca ⁺²] _i , $\downarrow$ [PCr], $\uparrow$ [Pi] and premature death. $\uparrow$ actin-activated ATPase activity and force generation of single myosin molecules. Neonatal dilated cardiomyopathy in homozygous mice
	Q ⁴⁰³ & Δ AA ⁴⁶⁸⁻⁵²⁷ 109	Myocyte disarray, interstitial fibrosis, ventricular hypertrophy in female and dilatation in male mice, $\uparrow$ ANF
	Δ LCBD 88	Myocyte disarray, hypertrophy (only in homozygote), valvular thickening, $\downarrow$ Ca ⁺² sensitivity, and diastolic dysfunction
	Knock-out 102	Embryonic lethality in $-/-$, $+/-$ show fibrosis, sarcomere disarray, impaired contractility and relaxation
CTnT	Δ C-terminus 93	Myocyte disarray, interstitial fibrosis, cardiac diastolic dysfunction, and myocyte atrophy and reduced number of myocytes, premature death
	Q ^{9285;86}	Myocyte disarray, interstitial fibrosis, systolic and diastolic dysfunction
	N ¹⁷⁹ 110	Normal survival, no hypertrophy, $\uparrow$ in Ca ⁺² sensitivity of ATPase activity and force, $\uparrow$ in rate of contraction and relaxation, lower maximum force/cross section area and ATPase activity
	Δ Exon 16 (Rat model) 90	No cardiac hypertrophy but systolic and diastolic dysfunction. After 6 months of exercise hypertrophy, myofibrillar disarray, sudden death, and ventricular fibrillation.
MyBP-C	Δ C-terminus 94	Myocyte disarray, sarcomere dysgenesis, interstitial fibrosis, no cardiac hypertrophy
	Truncated MyBP-C 111	Neonatal dilated cardiomyopathy in homozygous mice expressing $<10\%$ of the truncated protein
ELC	V ¹⁴⁹ (human genomic) 89	Papillary muscle hypertrophy and altered stretch-activation response
ELC	V ¹⁴⁹ (mouse cDNA) 112	No hypertrophy, $\uparrow$ Ca ⁺² sensitivity and impaired relaxation
α -Tm	N ¹⁷⁵ 87	Myocyte disarray and hypertrophy, impaired contractility and relaxation, $\uparrow$ Ca ⁺² sensitivity
	Knock-out 104	Embryonic lethality in homozygotes, no phenotype in heterozygotes
CTnI	Gly ¹⁴⁶ 113	Myocyte disarray, interstitial fibrosis, premature death, $\uparrow$ Ca ⁺² sensitivity, hypercontractility, and diastolic dysfunction
β -MyHC	Q ⁴⁰³ (Rabbit Model) 91	β -MyHC-Q ⁴⁰³ transgenic rabbits exhibit cardiac hypertrophy, myocyte disarray, interstitial fibrosis, diastolic dysfunction, reduced myocardial systolic and diastolic mechanical function, but preserved global systolic function and increased incidence of premature death.

$\uparrow$: increased; $\downarrow$: decreased; SNRT: sinus node recovery time; VE: ventricular ectopies; [Ca⁺²]_i: Intracellular Ca⁺² concentration; [PCr]: phosphocreatinine; $\uparrow$ [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 4**Evidence that hypertrophy in HCM is compensatory**

1	In-vitro cell culture studies showing impaired myocyte mechanical performance following expression of mutant sarcomeric proteins.
2	Re-expression of the molecular markers of “secondary” or compensatory hypertrophy in HCM, such as nuclear proto-oncogenes <i>c-fos</i> , <i>c-jun</i> , and <i>c-myc</i> , atrial and brain natriuretic peptides, endothelin-1, transforming growth factor (TGF) β 1 and insulin like growth factor-1 (IGF-1)
3	Predominant presence of hypertrophy in the left ventricle despite expression of mutant MyHC protein in the right (low pressure chamber) and left (high pressure chamber) ventricles
4	Absence of significant clinical abnormality in the skeletal muscles of patients with HCM, despite expression of the mutant MyHC
5	Genetic background and environmental factors affecting the magnitude of hypertrophy
6	Increase in hypertrophic expression during growth spurts in young adults
7	Remodeling of left ventricular hypertrophy in human following septal ablation and alleviation of outflow tract gradient
8	Reversal of interstitial fibrosis in a transgenic mouse model of HCM by blockade of angiotensin II, receptor 1.

TABLE 5

Diversity of the Initial defects induced by mutant contractile sarcomeric proteins

Mechanical defects
Reduced crossbridge kinetics of thin and thick filaments
Reduced acto-myosin interaction
Reduced cardiac myocyte mechanical performance
Reduced maximum power output of muscle fibers
Biochemical defects
Reduced ATPase activity
Altered Ca^{+2} sensitivity
Structural defects
Sarcomere dysgenesis
Altered stoichiometry of the sarcomeric proteins