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Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy

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Abstract

Hypertrophic cardiomyopathy (HCM) is a genetic disorder that is characterized by left ventricular hypertrophy unexplained by secondary causes, and a non-dilated left ventricle with preserved or increased ejection fraction. It is commonly asymmetric with the most severe hypertrophy involving the basal interventricular septum. Left ventricular outflow tract obstruction is present at rest in about one third of the patients, and can be provoked in another third. The histologic features of HCM include myocyte hypertrophy and disarray, as well as interstitial fibrosis. The hypertrophy is also frequently associated with left ventricular diastolic dysfunction.

In the majority of patients, HCM has a relatively benign course. However, HCM is also an important cause of sudden cardiac death, particularly in adolescents and young adults. Nonsustained ventricular tachycardia, syncope, a family history of sudden cardiac death, and severe cardiac hypertrophy are major risk factors for sudden cardiac death. This complication can usually be averted by implantation of a cardioverter-defibrillator in appropriate high-risk patients. Atrial fibrillation is also a common complication and is not well tolerated.

Mutations in over a dozen genes encoding sarcomere-associated proteins cause HCM. *MYH7* and *MYBPC3*, encoding β -myosin heavy chain and myosin binding protein C, respectively, are the two most common genes involved, together accounting for about 50% of the HCM families. In approximately 40% of HCM patients the causal genes remain to be identified. Mutations in genes responsible for storage diseases also cause a phenotype resembling HCM (genocopy or phenocopy). The routine applications of genetic testing and preclinical identification of family members represents an important advance. The genetic discoveries have enhanced understanding of the molecular pathogenesis of HCM and have stimulated efforts designed to identify new therapeutic agents.

SUBJECT TERMS

GENETICS; CARDIOMYOPATHY

Keywords

Cardiac Hypertrophy; Genetics; human; Mutation; Sudden Cardiac Death; Heart Failure; Myosin heavy chain; Pathogenesis; cardiomyopathy; hypertrophic cardiomyopathy

DEFINITION AND EPIDEMIOLOGY

Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes that is characterized by cardiac hypertrophy, unexplained by the loading conditions, a non-dilated left ventricle and a normal or increased ejection fraction. Cardiac hypertrophy is usually asymmetric with greatest involvement most commonly of the basal interventricular septum subjacent to the aortic valve. It is occasionally restricted to other myocardial regions, such as the apex, the mid-portion as well as the posterior wall of the left ventricle. At the cellular level, cardiac myocytes are hypertrophied, disorganized, and separated by areas of interstitial fibrosis.

HCM is a disorder without a distinct geographic, ethnic, or sex pattern of distribution. Prevalence of HCM has been estimated at 0.16% – 0.29% (~ 1:625 to 1:344 individuals) in the general adult population^{1–4}. In adults, HCM may be diagnosed by the presence of left ventricular end diastolic wall thickness > 13 mm on an echocardiogram or other imaging technique.¹ The European Society of Cardiology guidelines recommend using a left ventricular wall thickness of 15 mm in the diagnostic criteria.⁵ Estimating the prevalence of HCM based on detection of cardiac hypertrophy, while clinically valuable, has a number of limitations. Notable among them is the age-dependent expression of cardiac hypertrophy; the latter is present in approximately one half of patients with the underlying causal mutations by the third decade of life and in approximately three fourths by the sixth decade.^{6, 7} Given the age-dependent expression of HCM mutations, its prevalence is expected to be higher in older subjects. Indeed, HCM has been recognized in 0.29% (1:333) of 60-year old individuals undergoing echocardiography for cardiovascular evaluation in the U.S.² A similar prevalence has been reported in other parts of the world^{3, 4}. When more sensitive imaging methods are employed, when more family members are evaluated, and when genetic testing is more widely employed to them (see below), a much higher estimate of 0.6% (1:167) has been suggested^{8–10}.

Cardiac hypertrophy may be of late onset, and less than 13 mm, the diagnostic cut point for the diagnosis of HCM^{7, 11}. Hence, HCM may be under-diagnosed in such individuals. Conversely, cardiac hypertrophy could result from the phenocopy conditions (see below), which might account for 5 to 10% of the clinically diagnosed HCM cases in children^{12–14}. Moreover, the presence of concomitant conditions which may cause myocardial hypertrophy, such as arterial hypertension or aortic stenosis, may make the differentiation of primary (HCM) from secondary hypertrophy challenging. However, the asymmetric shape of the ventricle with greatest hypertrophy of the basal interventricular septum and genetic testing of the subjects and their families (see below) may be helpful in this population.

MOLECULAR GENETIC BASIS

HCM is an archetypical single gene disorder with an autosomal dominant pattern of inheritance¹⁵, whereby a single mutation is usually sufficient to cause the disease, albeit with variable penetrance and expression. The variability of the phenotype is due, at least in part, to the causal mutation acting in concert with a number of other genetic and of non-genetic influences. Approximately 60% of patients with HCM have a clearly recognizable familial disease. Autosomal recessive and X-linked modes of inheritance have been described but are rare^{16, 17}. An X-linked inheritance typically raises the possibility of a phenocopy condition, such as Fabry disease¹⁸. A phenocopy condition also occurs in syndromic conditions, such as the Noonan syndrome and in storage diseases, such as Anderson-Fabry disease.^{18–20} The phenocopy (genocopy) conditions are not discussed.

Pioneering studies by Christine and Jonathan Seidman have led to partial elucidation of the molecular genetic basis of HCM. The discovery of the p.Arg403Glu mutation in the *MYH7* gene, encoding sarcomere protein β -myosin heavy chain (MYH7) in the French-Canadian family described by Paré et al,²¹ paved the way for important subsequent discoveries.²² The identification of multiple separate mutations in the principal causal genes, all encoding sarcomere proteins, (Figure 1), established HCM as a genetically heterogeneous disease. Among the known causal genes, *MYH7* and myosin binding protein C (*MYBPC3*) are the two most common, together being responsible for approximately half of the patients with familial HCM^{23–26}. Mutations *TNNT2*, *TNNI3*, and *TPM1* are relatively uncommon causes of HCM and together are responsible for less than 10% of cases^{25–28}. Mutations in *ACTC1* (cardiac α -actin), *MYL2* (myosin light chain 2), *MYL3* (myosin light chain 3), and *CSRP3* (Cysteine and Glycine Rich Protein 3) are also established, albeit uncommon, causes of HCM,^{29–31}. Evidence for the causal role of the above nine genes in HCM is the strongest (Table 1).^{32, 33}

Mutations in *TTN* (titin), *TCAP* (telethonin), *MYOZ2* (myozenin 2), *TRIM63* (ubiquitin E3 ligase tripartite motif protein 63 or MuRF1) and *FHL1* (four and a half LIM domains 1) also have been implicated as causes of HCM, but occur typically in sporadic cases and small families^{34–41}. *FHL1* is located on the X chromosome and mutations might affect hemizygous males disproportionately. Finally, mutations in *TNNC1* (cardiac troponin C), *MYH6* (myosin heavy chain or α -myosin heavy chain), *PLN* (phospholamban), *CAV3* (caveolin 3), *ALPK3* (α kinase 3), and *JPH2* (junctophilin-2) have also been reported in patients with HCM^{42–47}, but their causal role in HCM is less certain and has not been established unambiguously (see below).

A subset of pathogenic variants that exert large phenotypic effects, exhibit high penetrance, and co-segregate with the phenotype in large HCM families are considered the causal mutations^{48–50}. Causality of such mutations is robustly established through co-segregation and linkage analysis. This is the case for the common HCM genes, such as *MYH7* and *MYBPC3*, whose causal role in HCM is unambiguous. Nevertheless, not all genetic variants in the established causal genes for HCM actually cause HCM⁵⁰. The ExAc database show that *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, and *TPM1* are highly constrained and not very tolerant to missense and loss-of-function (LoF) genetic variants (<http://>

exac.broadinstitute.org/). This means that missense and LoF variants in these genes are very rare in the general population but not totally absent. Therefore, not all missense and LoF variants in the above genes cause HCM. In contrast, *ACTC1* is exceedingly intolerant to missense and LoF variants, as no LoF variant in the *ACTC1* gene was observed in ~ 60,000 unrelated individuals (<http://exac.broadinstitute.org/>). Consequently, missense and LoF variants in the *ACTC1* gene typically cause HCM (or dilated cardiomyopathy).

Genetic variants with smaller phenotypic effects show incomplete penetrance. Penetrance and phenotypic effects of such variants depend on the presence of other genetic and environmental factors. Many low to moderate penetrance genetic variants are found in patients with sporadic HCM and in small families with HCM. Establishing the causal role of such variants in HCM is very challenging. Factors that contribute to difficulty in ascertaining causality include human genetic diversity, population-specific frequency of the variants, and the presence of several thousand pathogenic coding variants in each exome, which collectively make the distinction between a causal and incidental variant very difficult. ^{49–53}

HCM is caused by rare mutations. These mutations typically affect domains in genes that code for sarcomere and sarcomere-associated proteins. Accordingly, the prevalence of specific mutations in an HCM population is very low. Two notable exceptions are the p.Arg502Trp mutation in *MYBPC3*, which has been reported to occur in ~ 1.5 to 3% of HCM patients ^{54,55, 56} as well as the *MYBPC3* mutation p.Val762Asp, which has been identified in 3.9% of the Japanese population ⁵⁷. Almost all other mutations occur at a frequency of <1% in the HCM population and approximately half are found in a single proband or family. ⁵⁶ The high frequencies of these mutations might reflect “hot spots” for mutations or likely a founder effect. ⁵⁵ The high frequency is not a feature of mutations occurring in genetically independent HCM populations, and might be restricted to the reported study populations. Accordingly, with the possible exception of the above two mutations, there is no clear “hot spot” for mutation in any of the known genes, despite the initial reports ^{58–60}.

In general, there is no clear distinction between the location of the mutations in the domain of the encoded proteins and the HCM phenotype. However, mutations in the *MYH7* gene show a strong predilection toward the globular head and hinge region of the myosin heavy chain protein, albeit mutations causing changes in the rod domain have also been described ^{61–64}. Phenotypically, mutations in the converter domain and a flat surface area in the globular head of MYH7 have been associated with an earlier disease onset. ⁶⁴ Overall, *MYH7* and *MYBPC3* are not only the two most common causal genes in the usual form of HCM with involvement of the basal septum, but are also the two most common genes in apical HCM (see below) ^{65, 66}.

The majority of the causal mutations in HCM are missense mutations with the exception of the mutations in *MYBPC3*, which exhibit a predilection to insertion/deletion and premature truncation mutations due to a frameshift ^{23, 25, 26}. The missense mutation may alter protein structure and function by changing the amino acid composition of the encoding protein. The insertion/deletion mutations, which induce a frame shift in the encoded protein, are commonly targeted for degradation by the nonsense mediated decay. Likewise, the

premature truncated proteins are subsequently degraded by the ubiquitin proteasome system (UPS), leading to haplo-insufficiency (see below). Rare deletion mutations in *MYH7*, *TNNT2*, and others also have been reported ^{61, 62}.

Missing causal genes

The difficulty in identifying the remaining causal genes, which are sometimes referred to as the missing causal genes, is typically relevant to HCM occurring in sporadic cases or in small families. The “missing causal gene” in HCM might be in part because of the difficulty in ascertaining the causality of the genetic variants, in an unambiguous manner, in the sporadic cases and small families ⁵⁰.

In general, genetic variants exert a gradient of effect sizes, ranging from large and causal to clinically negligible ^{48, 49, 67}. As described earlier, genetic variants which exert very large effect sizes are considered to be mutations responsible for autosomal dominant single gene disorders, including HCM, in large families. Such mutations have been mapped and identified through robust genetic approaches, such as co-segregation and linkage analyses. Examples include genetic variants in the *MYH7* and *MYBPC3* genes. On the other end of the spectrum of effect sizes are the genetic variants that have clinically small or indiscernible effects. Such variants, whenever functional, influence the phenotype, albeit modestly, but do not cause monogenic disorders. In the center of the spectrum is a subset of genetic variants that exert intermediary to large effect sizes and exhibit incomplete penetrance, i.e., their effects are influenced by other genetic and non-genetic factors. It is speculated that such variants cause HCM but with incomplete or low penetrance. In such situations, there is no clear co-segregation of the genetic variant with the phenotype and hence, linkage cannot be robustly established, particularly when the family size is small and obviously in the sporadic cases. The difficulty is in part because of the plethora of variants in each genome.

An approach to identify the missing causal genes is via large-scale association studies followed by analysis of rare variants. The demonstration of an association between a candidate gene and the HCM phenotype in a “discovery population” is considered provisional (i.e. hypothesis-generating) and requires testing for replication in an independent population.

Possible digenic/oligogenic etiology of HCM

A subset of HCM patients, approximately 5%, exhibits two (digenic) or more (oligogenic) causal mutations in the same gene or causal mutations in different genes ^{26, 56, 57, 68–74}. The severity of ventricular hypertrophy in subjects with such mutations appears to be more pronounced ^{57, 68–71}. Double mutations have been limited primarily to variants in well-known HCM genes identified in members of small families. Consequently, it has been difficult to show co-segregation and to establish unambiguously the causal role of each variant. Nevertheless, these observations raise the intriguing possibility that the “missing” causal genes may be explained, in part, because of the digenic or oligogenic nature in some patients with HCM. Thus, a subset of patients with HCM may not fit into the classic definition of a single gene disorder. In addition, these findings shift the focus from genetic causality of a single dominant mutation to identification of the pathogenic mutations in

sporadic HCM and HCM occurring in small families. There are inadequate data to determine differences in the phenotypic expression of HCM caused by two mutations on a single gene and one mutation on each of two causal genes.

PATHOGENESIS

A diverse array of mechanisms, mirroring the diversity of the causal genes and mutations, are implicated in the pathogenesis of HCM (Figure 2). The mechanistic events in HCM might be categorized into four sets of interlocking mechanisms. The primary defect is the mutation. Initial or proximal phenotypes are defined as those resulting from the direct effects of the mutations on the structure and function of the sarcomere proteins. The intermediary (or secondary) phenotypes include the molecular changes that occur in response to the changes in the sarcomere protein structure and function. Examples of the latter include altered gene expression and activation of the signaling pathways, such as the MAPK and TGF β 1 pathways. The tertiary effects are the ensuing histological and pathological phenotypes, which are the consequence of perturbation of a myriad of secondary molecular events in the myocardium, such as activation of the hypertrophic signaling pathways. These molecular and histological changes lead to the clinical phenotypes of HCM (quaternary). It is important to note that there is a mechanistic distinction between cases of HCM caused by sarcomere protein mutation and the phenocopy conditions, since ventricular hypertrophy in the latter may, at least in part, result from storage of material, such as glycogen and in part because of functional defects in myocytes, such as impaired contraction.

INITIAL (PROXIMAL) DEFECTS IN HCM

The initial defects in HCM, in accord with the diversity of HCM mutations, are also diverse. The mutations induce a set of initial changes, such as altered transcription rate and translation efficiency, changes in structure of the affected sarcomere protein, and sarcomere functions. These changes might be considered to be the inciting molecular events as they are the direct effects of the mutations.

Effects of mutations on transcription and translation—In autosomal dominant HCM, a small fraction of the HCM mutations result in premature truncation of the encoded proteins because of a gain of a stop codon (such as the p.Gln425X mutation in the *MYBPC3* gene¹¹) or because of a frame shift (such as the c.2864–2865delCT in the *MYBPC3* gene⁷⁵). A number of transcriptional surveillance and quality control mechanisms target the transcripts containing premature termination codon (PTC). Mechanisms such as the nonsense-mediated decay (NMD) pathway identify the PTC, releases the elongation factors (a set of proteins involved in adding amino acids during protein synthesis) from the template, and recruits the decay-inducing complex (a complex of proteins involved in mRNA degradation).^{76, 77} The net effect is degradation of such transcripts and reduced protein levels. In the case of transcripts lacking a naturally occurring stop codon, the mRNA surveillance mechanism referred to as “non-stop decay pathway” identifies and releases the transcripts from ribosomes to prevent their translation.^{78, 79} This is followed by degradation of the released transcripts by the exosome complex. Another mechanism is activation of the No-Go mRNA decay pathway, a mechanism that stalls progression of ribosomes during

translation and results in endonucleolytic cleavage of the mRNA transcript near the stalled site.⁷⁷ Collectively, these quality control mechanisms prevent synthesis of the truncated proteins.

Gain- or loss-of-stop codon mutations or frame shift mutations commonly abolish protein expression. In the heterozygous state, only the wild type allele is expressed. The net effect, therefore, is haplo-insufficiency, which is an uncommon mechanism in HCM, as the majority of the HCM mutations are missense mutations. Mutations in the *MYBPC3* gene, however, are predominantly stop-codon and frameshift mutations^{26, 80, 81}. Thus, compared to other HCM-causing genes, haplo-insufficiency is a more common mechanism in HCM caused by the *MYBPC3* mutations^{23, 25, 26, 75, 82–84}.

Transcripts containing PTC that escape the NMD are expected to be expressed as truncated proteins. However, premature truncated proteins are expressed at very low levels and are not commonly detectable by antibody-based techniques^{75, 83, 85}. This suggests that such proteins are likely to be unstable, misfolded, targeted by unfolded protein responses, and degraded by the ubiquitin-proteasome system. Experimental data in mouse models implicate this system in degradation of truncated MYBPC3 protein^{86, 87}.

In principle, both alleles of the causal gene carrying the heterozygous missense mutation are transcribed and translated into the corresponding wild type and mutant proteins. However, efficiency of transcription and translation of the wild type and mutant alleles may vary, generally being less for the mutant allele, due to suboptimal codon usage compared to the wild type allele^{88–90}. Such allelic imbalance is partially corrected by compensation from the wild type allele, presumably to maintain the fixed stoichiometry of the sarcomere proteins. However, allelic compensation is often less than complete. Therefore, the mutation might reduce expression level of the corresponding protein, and result in a mild deficiency of the involved protein^{88, 89}. Considerable myocyte-to-myocyte variability in the transcript levels of mutant alleles in HCM has been detected, which may explain variability in the myocyte function⁸⁹. Overall, variability in the transcription efficiency of the two alleles is in accord with the complexity of transcriptional regulation, which depends not only on the composition of the nucleotides but also on the sequence of adjacent regulatory elements.

Incorporation of the mutant protein into sarcomere—Missense mutations that impart structural changes in the encoded protein may reduce efficiency of sarcomere assembly⁹¹. Efficiency of incorporation of the mutant proteins containing missense mutations into sarcomeres has not been adequately determined. Analysis of the ratio of mutant to wild type MYBPC3 protein in the myofilament, as a surrogate for efficiency of incorporation, show considerable variability, with the fraction of mutant protein comprising 30 to 80% of the total MYBPC3 protein in the myofilaments⁹⁰. Variability in the expression levels and incorporation of the mutant proteins into sarcomeres and myofilaments is expected to exert variable functional defects, differing among various mutations as well as individual myocytes carrying the same genetic mutation. Such heterogeneity in the expression and incorporation of the mutant proteins at the myocyte level might in part explain the variable phenotypic expression of HCM.

Effects on myofilament function—Upon incorporation into sarcomeres, the mutant proteins exert a diverse array of functional effects. Mutations could affect various components of the acto-myosin cross-bridge cycling, ranging from Ca^{++} sensitivity of the troponin complex to the generation of power stroke. The latter is defined as bending of the myosin globular head at the hinge region and the ensuing displacement of the actin filament, which results in the force of contraction. Consequently, mutations could affect generation of force by a diverse array of functional defects, including altered Ca^{++} sensitivity and ATPase activity, which are inter-dependent.

Given the limitations of the *in vitro* studies to properly recapitulate the *in vivo* conditions, transgenic, knock out, and knock in mouse models have been generated to delineate the mechanism(s) involved in the pathogenesis of HCM^{92–99}. From the outset, it became clear that functional studies of HCM mutations in these models were compounded by the differences in sarcomere protein compositions between them and humans. As noted earlier, HCM mutations affect MYH7, which is the predominant myosin heavy chain isoform (>90%) in the human heart^{100–102}. This contrasts with the murine heart, in which the predominant myosin isoform is MYH6 or α -myosin heavy chain. Consequently, to study the human MYH7 mutation, it had to be transposed into MYH6 in the mouse models. The problem with this approach is the presence of major differences between MYH6 and MYH7 proteins in their ATPase activities and acto-myosin kinetics¹⁰³. The ATPase activity of the MYH6 protein and the velocity of actin displacement are several folds higher than those of MYH7 protein^{100, 104, 105}. The differences in these key biological aspects confound extrapolating the findings in model organisms that predominantly express MYH6 to human HCM.

Considering the above differences in the compositions of sarcomere proteins, studies performed in hearts that predominantly express MYH7 rather than MYH6, particularly the human cardiac muscle bundles, offer findings that are more relevant to the functional consequences of HCM mutations. These studies suggest that HCM mutations reduce sensitivity of the actin-myosin complex dissociation in response to ATP. Therefore, at any given moment, more myosin and actin molecules are in the bound than in the dissociated state. Experimental data show less maximal tension development per unit of ATP hydrolyzed, and hence, reduced efficiency of force generation^{106–109}. There is, however, considerable variability not only among mutations in different causal genes but also among mutations in the same gene^{106–111}. For example, mutations in *MYH7* and *MYBPC3* negatively affect force generation but those in *MYH7* reduce myofibrillar ATPase activity more than those in *MYBPC3*^{106, 107}. Accordingly, the energy cost of tension generation is significantly higher for *MYH7* than *MYBPC3* mutations¹⁰⁷. These functional alterations seem to be the direct effects of the mutations, as myocardial efficiency is also reduced in individuals who carry the causal mutations and do not show cardiac hypertrophy¹⁰⁷. Similarly, experimental data in transgenic rabbits, which predominantly express MYH7, as the human heart, show that expression of the mutant MYH7 p.Arg403Gln protein reduces Ca^{++} sensitivity of the myofibrillar ATPase activity, which occurs early and precedes the development of cardiac hypertrophy¹⁰⁹. At the clinical level, the increased cost of tension

generation correlates with reduced ratios of cardiac phosphocreatine to ATP in the heart in HCM ¹¹².

Findings in murine models also show reduced Ca^{++} activated myofibrillar force generation and increased cost of tension generation ^{94, 106, 110, 111, 113}. As observed in human cardiac tissues, studies in the murine models show significant variability in the functional defects ^{99, 109, 114}. The reduction of Ca^{++} sensitivity is not uniform and the magnitude of myofibrillar efficiency of force generation varies among causal genes and mutations. Single cell studies also point to the presence of considerable myocyte-to-myocyte variability not only at the level of the mutant transcripts but also in the Ca^{++} sensitivity, influencing maximal force generation. ⁸⁹ There is also considerable regional variability in gene expression and function, suggesting a mosaic molecular and functional phenotype in HCM ¹¹⁵.

Thin filament mutations: In contrast to HCM mutations in the thick filaments, mutations in the thin filaments enhance Ca^{++} sensitivity of myofibrillar ATPase activity, and hence of force generation ^{110, 111, 114, 116}. These changes appear to be the direct effects of the mutations, as they precede the development of cardiac hypertrophy, at least in the murine models ⁹⁸. Changes occurring after the development of cardiac hypertrophy, whether in the human or murine heart, are subject to secondary modifications of the sarcomere proteins, including phosphorylation of TNNI3 and MYBPC3, post-translational modifications that are known to affect sarcomere functions ^{116, 117}.

SECONDARY (INTERMEDIARY) MOLECULAR EVENTS

As discussed above, the initial defects, imparted by the various causal mutations on sarcomere structure and functions, instigate a cascade of secondary (intermediary) molecular events. These include activation of the Ca^{++} sensitive and stress-responsive molecular pathways that collectively mediate programming of cardiac hypertrophy and induce the morphological and histological (tertiary) phenotypes that are recognized as HCM. In general, the intermediary molecular events involve the pathways that are also activated in other forms of cardiac hypertrophic responses, such as pressure overload-induced cardiac hypertrophy. Accordingly, a multitude of pathways are perturbed, including expression and activation of trophic and mitotic factors, such as calcineurin, mitogen activated protein kinases, and transforming growth factor β pathways, as well as non-coding RNA and epigenetic factors ^{40, 118–125, 126, 127}. The characteristics of the molecular responses, while generally similar, vary according to the biological functions of genes carrying the causal mutations ^{125, 128, 129}. Nevertheless, cardiac hypertrophy, interstitial fibrosis, and myocyte disarray are considered to be consequences to activation of the intermediary molecules and pathways ^{130, 131}.

TERTIARY (HISTOLOGICAL) AND QUATERNARY (CLINICAL) PHENOTYPES

Histological and morphological phenotypes of HCM, including myocyte and cardiac hypertrophy, disarray, and interstitial fibrosis, among others, are the consequence of intermediary molecular changes in the heart. Histological and morphological phenotypes,

discussed under cardiac pathology, produce the clinical manifestations of HCM, including heart failure and cardiac arrhythmias, which are also discussed later.

DETERMINANTS OF THE HCM PHENOTYPES

The morphological, histological, and clinical phenotypes of HCM are the consequence of complex interactions among a large number of determinants, ranging from the causal genetic mutation to environmental factors. The causal mutation is the prerequisite and a major determinant of the phenotype. In addition, the histological and clinical phenotypes is also influenced by genetic backgrounds, which include the presence of additional pathogenic variants in pathways implicated in cardiac hypertrophy, epigenetic factors including non-coding RNAs, post-translational protein modifications, and environmental factors (Figure 3). Thus, the tertiary and quaternary phenotypes of HCM are complex traits, influenced by a large number of determinants, each exerting a small effect, with the causal mutations imparting the largest effects.

Initial genotype-phenotype correlation studies pointed to differences in severity and prognosis of patients with HCM caused by different mutations^{132–134}. Considering multiplicity of determinants variability in phenotypic expression of in HCM is to be expected. Such multiplicity also limits the impact of each determinant in accurately predicting the severity of the disease or clinical outcomes in a given individual. This variability is not restricted to phenotypic expression of HCM among patients with different causal mutations but it also extends to family members carrying the same mutation (Figure 4)^{134–136}. Overall, clinical phenotypes do not appear to differ significantly between the two most common HCM genes, i.e. *MYH7* and *MYBPC3*^{133, 135}. Compared to HCM caused by mutations in the protein components of the thick myofilaments, such as *MYH7* and *MYBPC3*, HCM caused by mutations in the thin myofilament proteins, such as *TNNT2*, exhibits a milder cardiac hypertrophy and an increased risk of systolic dysfunction.^{132, 137} However, the risk of serious cardiac arrhythmias and SCD does not seem to differ between the two groups.¹³⁷

The variability in phenotypic expression of HCM is in part due to the effects of modifier genetic variants and environmental factors. Each human nuclear genome contains an average of approximately 11,000 non-synonymous variants, 160 premature protein truncation variants, and 500,000 variants in the known regulatory regions^{52, 53}. Pathogenic variants in genes and pathways implicated in regulating cardiac hypertrophy and fibrosis could influence expression of the HCM phenotype and hence, function as modifier genetic variants. The modifier variants, unlike the causal mutations, are neither necessary nor sufficient to cause HCM. They simply influence expression of HCM, each exerting a modest effect. In accord with the diversity of the human genome, the modifier variants are also expected to differ among individuals and hence, in part, explain inter-individual variability in the phenotypic expression of HCM.

Although the majority of modifier genes and their variants in HCM are largely unknown, several modifier loci containing several candidate genes have been implicated in influencing expression of cardiac hypertrophy¹³⁸. For example, an insertion/deletion variant in the angiotensin-1 converting enzyme gene (*ACE*), which is associated with variation in the

plasma levels of ACE ¹³⁹, has been shown to modify, albeit modestly, expression of cardiac hypertrophy and the risk of sudden cardiac death in HCM ^{140–142}. Several other genes, identified primarily by the candidate gene approach, are also implicated as modifiers of HCM ^{142–144}. Likewise, experimental data in mouse models have implicated the *Fhl1* gene, encoding four-and-a-half LIM domain protein 1, as a possible modifier of cardiac hypertrophy and function ¹²⁸. Overall, data on the modifier genes in human HCM are preliminary.

Phenotypic variability due to multiple pathogenic variants in the causal genes

—A subset of patients with HCM carries two or more mutations in sarcomere proteins ^{68–70, 73, 74}. The data, albeit scant, suggest that the presence of multiple mutations is associated with more severe hypertrophy in HCM ^{68–70, 74}.

Phenotypic variability due to loading conditions—Considering that cardiac hypertrophy is a consequence of the initial defects caused by the mutations, changes in loading conditions, such as systemic arterial hypertension, would also be expected to enhance penetrance of the sarcomere protein mutations and severity of hypertrophy. In accord with the above notion, one might surmise that heavy physical activity, particularly isometric exercises to accelerate and exaggerate cardiac hypertrophy in the presence of mutations in genes encoding sarcomere proteins.

Pleiotropic (multiple) phenotypes of mutations—An intriguing aspect of sarcomere protein mutations is pleiotropy. Accordingly, mutations in the same gene could manifest as HCM, DCM, restrictive cardiomyopathy (RCM), and even left ventricular non-compaction syndrome ^{145–148}. The pleiotropic effects primarily apply to the effects of different mutations in a given genes, such as *TNNT2* or *MYH7*, causing the differing phenotypes of HCM and DCM ^{22, 149}. It may reflect location of the mutations in different domains of the protein, resulting in differential interactions of the mutant proteins with the other protein constituents of sarcomeres and activating different sets of intermediary molecular events ^{99, 110}. Likewise, differential effects of the causal mutations on Ca⁺⁺ sensitivity of ATPase activity and force generation could explain, in part, the ensuing pleiotropic phenotypes ^{99, 110, 150–154}. Accordingly, mutations in thin filament proteins, such as cardiac troponin T that cause HCM typically enhance Ca⁺⁺ sensitivity of myofibrillar force generation and ATPase activity, whereas those leading to DCM suppress these functional effects ^{99, 110, 150–155}. Moreover, differences in myofilament tension development between HCM- and DCM-causing mutations might explain the contrasting phenotypes resulting from sarcomere protein mutations ^{99, 110, 150–156}.

PHENOTYPIC CHARACTERISTICS

Patients with HCM exhibit a variable phenotype with ventricular hypertrophy being the cardinal manifestation, myocyte hypertrophy and disarray as well as interstitial fibrosis as key pathological hallmarks, and impaired ventricular filling and dynamic left ventricular outflow tract (LVOT) obstruction as important pathophysiologic features.

PATHOLOGY

Cardiac hypertrophy is the keystone to clinical diagnosis, which is typically based on detection by cardiac imaging¹⁵⁷ (Figure 5). The hypertrophy is frequently asymmetric, and predominantly involves the basal interventricular septum, just below the aortic valve but usually involves the free wall of the left ventricle as well.¹⁵⁸ In “asymmetric septal hypertrophy” (an earlier name for HCM¹⁵⁹), the ratio of the thickness of the septum to the free wall of the ventricle = 1.3/1.0; this applies to many but not all patients, and it is not specific. The cardiac apex is occasionally the predominant site of involvement, and this subset is referred to as “apical HCM.” Rarely, the posterior or lateral walls are the sites of predominant hypertrophy.

Other frequent pathologic features include elongation of the anterior or both leaflets of the mitral valve, as well as abnormal insertion of the associated papillary muscle.¹⁶⁰ The right ventricle is infrequently involved by hypertrophy and only rarely manifests outflow tract obstruction^{158, 161}.

Microscopic Anatomy—The cardiac myocytes are enlarged with bizarre shapes and pleiotropic nuclei. They are in disarray, with loss of normal parallel alignment due to haphazard orientation of hypertrophic myocytes which give a swirling appearance to the myocardial architecture (Figure 6).^{162,163} This disarray typically involves >10% of the myocardium in HCM, is widely distributed, with a predilection for the hypertrophied interventricular septum^{163, 164}. Extensive, severe myocyte disarray has been observed at autopsy in patients in whom sudden cardiac death (SCD) has occurred¹⁶⁵. Non-invasive assessment of myocyte disarray is challenging but might be accomplished using diffusion tensor imaging, which assesses myofibrillar orientation¹⁶⁶.

Increased interstitial fibrosis is a common feature of HCM^{167–169}. Cardiac magnetic resonance imaging (CMRI) has emerged as a useful tool for providing precise measurements of cardiac structure and to quantify late gadolinium enhancement (LGE), a marker of interstitial fibrosis. (157) LGE is frequently detectable in patients with HCM and its extent is associated with adverse clinical outcomes, including heart failure SCD as well as nonfatal cardiac arrhythmias^{168–171}. The small, intramural coronary arteries exhibit wall thickening and narrow lumina.¹⁷² These vessels are imbedded in the interstitial fibrous tissue and can contribute to myocardial ischemia. Cleavage products of collagen synthesis and degradation have been used as biomarkers for interstitial fibrosis^{173–175}. Likewise, elevated levels of cytokines, cardiac troponin T, and markers of myocardial inflammation have been associated with and reflect myocardial necrosis and fibrosis in patients with HCM^{176–178}. Moreover, circulating levels of several microRNAs (especially miR29a) are elevated in HCM and may serve as markers for cardiac hypertrophy and interstitial fibrosis^{179–181}. However, the clinical utilities of plasma levels of these markers in evaluation of cardiac hypertrophy and myocardial fibrosis in HCM remain to be established.

HEMODYNAMICS

The left ventricle in HCM usually has a normal end-diastolic volume, a high-normal (65–70%) or elevated (>70%) ejection fraction and a reduced end-systolic volume. The LVOT is

encroached upon by the hypertrophied septum. In the presence of hyperdynamic ejection, there is systolic anterior motion (SAM) of the anterior leaflet of the mitral valve, which abuts the hypertrophied interventricular system during systole, causing obstruction to outflow, reflected in a systolic pressure gradient between the left ventricular cavity and the aorta that is present at rest in approximately one third of patients with HCM (Figure 5).^{158, 182–184} The obstruction is dynamic in nature, a unique feature of HCM. The severity of the LVOT obstruction is influenced by the ventricular volume, which in turn is a function of the interactions between myocardial contractility, ventricular preload and afterload. Increases in contractility, reductions in preload and afterload reduce ventricular volume and cause or intensify obstruction; the opposite occurs with reductions in contractility and increases in preload and afterload.^{185–188} Thus, muscular exercise, infusion of isoproterenol, inhalation of amyl nitrite, sublingual nitroglycerin, and the strain phase of the Valsalva maneuver can provoke LVOT obstruction in HCM patients without a resting gradient.

Diastolic dysfunction is frequent in HCM.¹⁸⁹ It is caused by the increased interstitial fibrosis as well as the slowed relaxation and increased stiffness of the thickened ventricular wall. Left atrial volume, an indirect indicator of left ventricular diastolic pressure, is often increased in patients with HCM and is a predictor of the development of atrial fibrillation and heart failure¹⁹⁰. Regional systolic myocardial function is also commonly impaired, as detected by pulsed and tissue Doppler imaging, 3-dimensional speckle tracking echocardiography, and magnetic resonance imaging^{191–193}. In about 5% of patients with HCM, usually elderly patients with extensive, longstanding LVOT obstruction and severe interstitial fibrosis, systolic function declines, the left ventricular wall thins, the cavity enlarges, and heart failure with reduced ejection fraction, sometimes referred to as “burnt out HCM”, develops.

CLINICAL MANIFESTATIONS

Despite the presence of cardiac hypertrophy, patients with HCM are commonly asymptomatic or minimally symptomatic. The most frequent symptoms result from four major pathophysiologic conditions: diastolic ventricular dysfunction, obstruction to left ventricular outflow, imbalance between myocardial oxygen supply and demand, and cardiac arrhythmias.

Diastolic Dysfunction—As a consequence of this common pathophysiologic manifestation in HCM (see above)¹⁸⁹, the left ventricular end diastolic pressure is elevated¹⁹⁴, which in turn raises left atrial, pulmonary venous, and pulmonary capillary pressures¹⁹⁵. The left ventricular diastolic pressure increases markedly on exertion, causing exertional dyspnea, exercise intolerance, orthopnea, peripheral edema, and HFpEF.

LVOT Obstruction—Approximately one-third of patients with HCM have LVOT at rest, which is intensified with exercise. One third have provokable obstruction (see below) and the remaining third have left ventricular hypertrophy without obstruction at rest and is not provokable.^{196–198} Patients with severe obstruction usually have elevated ventricular diastolic pressure and exertional dyspnea; some develop frank heart failure. Exertional or

immediately post exertional syncope may be due to severe obstruction, with or without ventricular arrhythmia.

Chest pain—Patients with HCM often experience ischemic chest pain, which may or may not have the typical features of angina pectoris. This symptom occurs because of imbalance between myocardial oxygen supply and demand. There is myocardial hypoperfusion secondary to reduced blood flow through the aforementioned thick walled, intramural coronary arteries with luminal narrowing and the increased oxygen demand of the hypertrophied myocardium¹⁷².

Arrhythmias—Palpitations, pre-syncope, and syncope, often due to recurrent non-sustained ventricular tachycardia, are among the cardinal clinical manifestations. Supra-ventricular and ventricular ectopic beats are quite common and non-sustained ventricular tachycardia (NSVT) is detected in 20 to 30% of patients^{199, 200}. NSVT is a major risk factor for SCD, as such episodes may lead to ventricular fibrillation, the usual cause of SCD.^{199, 201, 202} Syncope may also be caused by severe LVOT obstruction^{201–204}. The underlying mechanisms of ventricular arrhythmias in HCM are largely unknown. Potential mechanisms include ventricular remodeling that is associated with cardiac hypertrophy, interstitial fibrosis, myocardial ischemia and myocyte disarray.

Atrial fibrillation occurs in about a quarter of patients with HCM and LVOT obstruction and has an annual incidence of ~ 2 to 3 %^{205–208}. This arrhythmia is poorly tolerated since the combination of the loss of the atrial contribution to ventricular filling and the rapid ventricular rate results in further elevations of left ventricular diastolic pressure and symptoms of heart failure.^{205, 208, 209} It is also a major risk factor for thromboembolic stroke.^{205, 207, 208} Left atrial size and function as well as LVOT obstruction are major risk factor for atrial fibrillation²⁰⁷. The underpinning mechanism(s) of atrial fibrillation in HCM has not been delineated. Potential mechanisms include atrial enlargement and stretch due to diastolic dysfunction, atrial fibrosis, expression of the mutant protein, and altered gene expression.

Physical Examination—On palpation, the precordial impulse is usually forceful and displaced leftward and the peripheral arterial pulses are brisk. In patients with marked ventricular hypertrophy, atrial contraction is often especially vigorous, reflected in a prominent atrial contraction (a) wave in the jugular venous pulse, a presystolic apical lift and, importantly, a prominent fourth heart sound (S4).¹⁵⁸

In patients with LVOT obstruction, a harsh, mid-systolic, Grade 3–4/6 murmur loudest between the apex and the left sternal border is usually audible. This murmur typically varies with interventions that alter ventricular loading and contractility (see above). Thus, the murmur increases in intensity when left ventricular volume declines during the strain of the Valsalva maneuver, when assuming the erect position, as well as during and immediately after exercise. In contrast, it diminishes during squatting, isometric handgrip, and immediately after release of the Valsalva maneuver. Mitral regurgitation, which is frequently present, is usually accompanied by a prominent, high pitched blowing holosystolic murmur loudest at the apex.¹⁵⁸

Electrocardiogram—The ECG is abnormal in most patients with HCM, including those with no or only mild LVOT obstruction. The most common abnormalities are voltage changes of left ventricular hypertrophy, ST-T wave changes, and deep Q waves probably caused by depolarization of a hypertrophied interventricular septum. ECG evidence of left atrial enlargement may also be evident. About 2 to 5% of patients with HCM exhibit ECG findings of pre-excitation and may present with AV nodal supraventricular reciprocating arrhythmias, the Wolff-Parkinson-White syndrome.

DIAGNOSIS

The clinical diagnosis of HCM is based on the presence of left ventricular hypertrophy, typically defined by an end diastolic ventricular septal thickness in adults ≥ 13 mm, occurring in the absence of abnormal loading conditions or other secondary causes, such as hypertension, aortic stenosis, the physiologic hypertrophy of athletes (see below), or phenocopied conditions. The cut point of 13 mm in adults offers high sensitivity in detecting HCM but has the risk of over-diagnosis, particularly in the presence of concomitant diseases. A cut point of 15 mm has been recommended by the European Society of Cardiology working group⁵. It offers a greater diagnostic specificity for HCM but a lower sensitivity. Expression of cardiac hypertrophy in HCM is age-dependent. It is infrequent in childhood and most commonly develops during adolescence and seldom after the fifth decade⁶. In children, a Z-score, reflecting deviation from an age- and sex-matched population, is often used to define cardiac hypertrophy.²¹⁰ Also of value in diagnosis are genetic testing (see below), electrocardiography, and CMRI.

Hypertension or valvular aortic stenosis can develop in patients with HCM and it can be challenging to clarify the coexistence of these conditions. Features characteristic of HCM such as the distribution pattern of cardiac hypertrophy, its severity, a hyperdynamic left ventricle with a small cavity and the presence of LVOT obstruction, and genetic testing all can aid in the recognition of HCM in the presence of secondary hypertrophy.

Adolescents and adults who are active in competitive sports often exhibit significant physiologic cardiac hypertrophy with left ventricular wall thickness between 13 and 18 mm²¹¹. Given that HCM is the most common cause of SCD in young athletes, distinction between physiological hypertrophy of athletes and pathological hypertrophy of HCM is of considerable importance^{212, 213}. An important distinguishing feature is the size of the left ventricular cavity, which is not enlarged in HCM but is typically enlarged in the physiologic hypertrophy of the athlete's heart^{211, 214}. In addition, the distribution pattern of cardiac hypertrophy with asymmetric septal hypertrophy strongly favors HCM.^{211, 214–216} Electrocardiographic findings of abnormal Q waves, left atrial enlargement, and prominent repolarization abnormalities are features of HCM and are uncommon in physiological cardiac hypertrophy^{214, 217}. Genetic testing (see below) could also be helpful.²¹⁸

Myocardial hypertrophy may also occur in patients with so-called phenocopy conditions which may mimic HCM. These include Fabry disease, the glycogen storage diseases, lysosomal storage diseases, mitochondrial diseases, triplet repeat syndromes, and others (Table 2). The possibility of a phenocopy condition may be suspected in patients with exceptionally severe ventricular hypertrophy with very high voltage QRS complexes and a

delta wave on a 12-lead ECG, and the presence of concomitant non-cardiac phenotypes, such as skeletal myopathy. Genetic testing (see below), when positive, is helpful in the distinction between HCM and a phenocopy condition. Endomyocardial biopsy and specific histological examination may identify a phenocopy condition, while the presence of myocyte disarray supports the diagnosis of HCM.

Prognosis

HCM is the most common cause of SCD in adolescents and young adults, particularly in competitive athletes^{212, 213, 219, 202, 203}. The risk factors for SCD are shown in Table 3 and discussed below.

Despite the occurrence of SCD and heart failure in a minority of patients, as Maron has pointed out,^{220, 221} HCM is a relatively benign disease, with approximately two-thirds of patients with HCM experiencing a normal life span without significant morbidity^{209, 220–222}. This is particularly the case for patients with HCM without significant LVOT obstruction who may be totally asymptomatic or experience mild or moderate exertional dyspnea secondary to diastolic dysfunction.^{196–198, 209} Although the prognosis is guarded in patients deemed to be at high risk of SCD and in those with heart failure secondary to severe LVOT obstruction; fortunately, therapies for both of these major complications are now available (see below).

GENETIC TESTING

The combination of an increased understanding of the molecular-genetic basis of HCM and a variety of technical innovations for detecting mutations in causal genes, has ushered in the era of genetic testing. Patients in whom the diagnosis of HCM has been established, or appears likely, should undergo such testing which is now available in both academic and certified commercial laboratories.^{56, 223} Currently available techniques, primarily based on whole exome sequencing followed by analysis of a panel of approximately 100 candidate genes implicated in cardiomyopathies, will identify such causal variants in approximately 30% to 50% of probands with HCM.^{222–224} The main challenge is in interpretation of the findings, particularly in a single affected individual. This is because of the plethora of the genetic variants in each gene in the human genome and the uncertain evidence of causality for a number of genes implicated in HCM^{32, 33}. Consequently, unambiguous ascertainment of causality in a single case or small families is almost impossible. To avoid over-interpretation of the genetic testing findings, some have recommended restricting the testing to the well-established causal gene in HCM³³.

Genetic testing, if positive, will support the diagnosis in a proband, but if it is negative will not exclude it. If a proband with a positive test is identified, cascade screening, i.e. testing for the presence of the variant in family members should be undertaken. A positive screen, i.e. mutation carrier relative of a patient with HCM, should lead to a detailed examination for the presence of the HCM phenotype. If the phenotype is expressed, the relative may be considered to have HCM and should be managed as described below. Relatives who are mutation carriers but phenotype negative should be followed with clinical evaluation (history, physical examination, electrocardiogram and echocardiogram) at yearly intervals,

or more frequently if symptoms develop. Detailed examination of the mutation carriers might detect clinical and laboratory abnormalities, such as reduced tissue Doppler velocities, and elevated serum biomarkers.^{191, 225, 226} Given the age-related penetrance of the mutation, a number of mutation carriers/phenotype negative relatives, especially those below the age of 25–30 years will eventually express the phenotype. However, as such individuals age, the likelihood of their conversion to phenotype positivity diminishes progressively, and longer intervals between follow-up examinations (e.g. every three to five years) are appropriate. Due to incomplete penetrance, some mutation carriers remain free of the clinical phenotype for their entire lives, but they should be informed that they can pass the gene on to their offspring. Family members who do not carry the causal mutation are very unlikely to develop HCM and should be counseled appropriately; they may, of course, participate in competitive sports.

An important contribution of genetic testing is that it allows distinction between HCM and the phenocopy conditions. (Table 2) Genetic testing for HCM detects pathogenic variants in genes known to cause phenocopy conditions in approximately 3% of the tested individuals.⁵⁶ Identification of the latter has important implications, since their natural history and treatment differ from HCM and from one another. For example, specific enzyme replacement therapy has become available for selected phenocopy conditions, such as Fabry disease.²²³

A shortcoming of current genetic testing for HCM is its failure to identify approximately 50% to 60% of patients with HCM.²²⁴ This is primarily because of the so-called “missing causal genes” (see above). In large families in which the causal gene and its pathogenic mutation have not been identified, linkage analysis may be useful. In small families or sporadic cases, either whole exome sequencing or the candidate gene approach may be required. Another limitation of genetic testing results from the great genetic heterogeneity of HCM (more than 1500 individual mutations have been described), which has prevented the genetic analysis from predicting the severity of hypertrophy or the risk of complications including SCD and heart failure. However, as already mentioned, the rare detection of multiple mutations (compound heterozygosity) by genetic testing has been associated with particularly severe hypertrophy.^{57, 68–71}

MANAGEMENT

CLINICAL ASSESSMENT

Evaluation of patients with HCM includes a detailed personal and family history for HCM, SCD, or heart failure, physical examination, 12-lead ECG, and complete echocardiographic assessment. Cardiac rhythm monitoring, cardiac magnetic resonance imaging, and cardiopulmonary exercise testing are optional, the latter being useful in patients suspected of having reduced exercise tolerance. Periodic re-evaluation is recommended, including in asymptomatic patients. Since the majority of patients with HCM are asymptomatic or minimally symptomatic, they do not require pharmacologic treatment. However, all should be counseled to the genetic nature of the disease, the risk of passing it on to offspring, and the need to avoid participation in competitive sports or intensive exercise. However, most patients with HCM may participate in low-intensity sports such as golf or bowling.

Pharmacotherapy—Beta adrenergic receptor blockers, without intrinsic sympathetic activity, were first used in the treatment of HCM in the 1960s^{227–229}, and have, since then, remained the cornerstone of pharmacological treatment of symptomatic patients. They are effective in the relief of ischemic chest discomfort and may attenuate exercise-induced LVOT obstruction and resulting dyspnea as well²³⁰. Disopyramide, a negative inotropic agent, when added to a beta blocker may reduce symptoms further in patients with LVOT obstruction²³¹. L-type calcium channel blockers, such as verapamil or diltiazem, may be beneficial in patients who do not tolerate or respond to beta blockers.²³² Diuretics may be used in patients with HCM, pulmonary congestion, and frank heart failure, but minimal effective doses and careful observation are required to avoid hypovolemia, hypotension, and intensification or provocation of LVOT obstruction. New onset atrial fibrillation is best treated with cardioversion. Since persistent and paroxysmal atrial fibrillation are risk factors for thromboembolism, long-term anti-coagulation is necessary.²⁰⁸

Management of patients at risk of SCD—The risk of SCD ranges from 0.5% to 2% per year in adults with HCM, which is the most common cause of SCD in adolescents. Competitive athletes are at particular risk.^{201, 233, 234} The major cause is ventricular fibrillation, which cannot be prevented reliably by pharmacological intervention. However, in most instances it can be treated effectively with an implanted cardioverter/defibrillator (ICD), which as Maron et al have pointed out^{235–238}, is recommended in patients at a high risk of SCD. At highest risk are patients who have survived a cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia, in whom implantation of an ICD is strongly indicated for secondary prevention.^{201, 233, 234} For primary prevention, high risk features include unexplained syncope, an abnormal blood pressure response to exercise (hypotension), massive (> 30 mm) thickness of the interventricular septum or ventricular wall, a family history of HCM with SCD, multiple episodes of documented NSVT, which may be identified by an extended (30-day) period of cardiac rhythm monitoring, as well as extensive (> 15% of the left ventricular mass) late gadolinium enhancement determined by CMRI. ICD implantation is typically considered in patients who have one (or more) of these primary risk factors. (Table 3) The rate of appropriate ICD discharge in HCM patient ranges from 3% to 15% per year depending on the specific indications, and it is higher in those with a prior arrhythmic event and in children^{235–238}. The rate of ICD complications is less than 5% per year^{236, 238}.

Patients with LVOT obstruction and/or heart failure—Patients with obstruction (systolic pressure gradient > 50 mmHg at rest or with provocation) who are symptomatic despite pharmacologic treatment should be considered for septal reduction therapy, either surgical septal myectomy or alcoholic septal ablation.²³⁹ Advanced stages of heart failure with preserved or reduced ejection fraction who have failed pharmacotherapy and, when indicated, septal reduction therapy, may require implantation of a left ventricular device or cardiac transplantation.¹⁴⁵

EXPERIMENTAL THERAPIES

Current pharmacological or interventional treatment of patients with HCM, while often effective in relieving or preventing symptoms, do not target either the underlying genetic

defect or the key intermediary pathways involved in the pathogenesis of the phenotype. Hence, they are not effective in prevention or induction of regression of cardiac hypertrophy and fibrosis. Elucidation of the molecular genetics and pathogenesis of HCM is stimulating development and testing of a number of pharmacological interventions. (Table 4)

Preliminary studies in animal models of HCM suggested possible benefits of angiotensin II receptor blockers, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), mineralocorticoid receptor blockers, and anti-oxidant N-acetylcysteine^{122–124, 240–242}. Despite the beneficial effects of some of these approaches in the models, preliminary studies in humans have been largely disappointing.^{243, 244}

Delivery of *Mybpc-3* by means of adeno-associated virus (AAV) encoding cardiac myosin-binding protein C prevented development of HCM in a mouse model.²⁴⁵ HCM-mutant mRNA encoding myosin-binding protein C has also been repaired by 5′-trans splicing, which prevented development of HCM in neonatal mice with frame-shift mutations.²⁴⁶ Gedicke-Hornung et al produced a modified mRNA and protein encoded by the *Mybpc-3* gene which reduced a lethal mutation in a neonatal mouse and prevented the development of HCM.²⁴⁷ An RNAi approach delivered by an AAV that selectively targets the mutant *Mhy6* allele that encodes β myosin heavy chain has also been shown to delay expression of cardiac hypertrophy and fibrosis in this model.²⁴⁸

The calcium channel blocker diltiazem has been shown to prevent the development of HCM in a mouse model as well as in a small randomized human pilot trial in *MYBP-3* carriers.²⁴⁹ The VANISH trial has randomized 150 patients who are sarcomere mutation carriers with no or minimal symptoms to the angiotensin receptor blocker valsartan or placebo [NCT01912534]. Results are expected in 2019.²¹⁰

MYK-461 is an orally administered small molecule that allosterically inhibits myosin ATPase activity, diminishes myocyte force production and has been shown to suppress development of cardiac hypertrophy, myocyte disarray, and fibrosis in a mouse model of HCM²⁵⁰. After successful completion of three Phase I clinical trials with this compound, it is now being evaluated in a Phase 2 trial in patients with HCM and LVOT obstruction. [NCT02842242]

A partial list of ongoing clinical trials in human patients with HCM is provided in Table 4.

FUTURE DIRECTIONS

Since its modern characterization more than a half century ago, progress in the diagnosis and management of patients with HCM has paralleled technological advances in genetic testing, cardiac imaging, prevention of serious arrhythmias, cardiac surgery and interventional cardiology. Enhanced annotation of the human genetic variants and their variable relation to clinical expression is likely to facilitate identification of persons who carry the pathogenic variants. It will provide much needed information on the prognosis of the growing number of such persons, many of whom are relatives of patients with HCM and who harbor the same mutation but have no observable manifestations of HCM. Such individuals might, in the future, become subjects for treatments designed to slow or prevent conversion to phenotypic

positivity. These may include pharmacological treatments and other interventions, now still in the experimental stage. Also, much more needs to be learned about non-mutation carriers who are phenotype positive, including sporadic cases of HCM, to identify their “missing” causal genes (if any) and their natural history.

It is anticipated that in the future the field will shift from targeting phenotypes such as myocyte hypertrophy, fibrosis, arrhythmias and LVOT obstruction, toward correcting the underlying genetic disorders. It is hoped that the focus will shift from population- to individual-based approaches, using genetic and phenotypic characterization of each patient or potential patient. This was elegantly expressed a century ago by Sir William Osler: “The good physician treats the disease; the great physician treats the patient who has the disease.” (<http://www.osler.org.uk/osleriana-2/oslers-aphorisms/>, accessed 3/9/2017)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Nonstandard Abbreviations and Acronyms

ACE	Angiotensin converting enzyme
ACTC1	Cardiac alpha actin
ALPK3	α kinase 3
CAV3	Caveolin 3
CMRI	Cardiac magnetic resonance imaging
CSRP3	Cysteine and Glycine Rich Protein 3
DCM	Dilated cardiomyopathy
FHL1	Four and a half LIM domains 1
HCM	Hypertrophic cardiomyopathy
HFpEF	Heart failure with preserved ejection fraction
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
ICD	implanted cardioverter/defibrillator
JPH2	Junctophilin-2
LGE	Late gadolinium enhancement
LoF	Loss of function
LVOT	Left ventricular outflow tract obstruction
MYBPC3	Myosin binding protein C3

MYH6	Myosin heavy chain 6 or alpha
MYH7	Myosin heavy chain 7 or beta
MYL2	Myosin light chain 2
MYL3	Myosin light chain 3
MYOZ2	Myozenin 2
NMD	Nonsense-mediated decay
NSVT	Non-sustained ventricular tachycardia
PLN	Phospholamban
PTC	Premature termination mutation
RCM	Restrictive cardiomyopathy
SAM	Systolic anterior motion
SCD	Sudden cardiac death
TCAP	Telethonin
TNNC1	Cardiac troponin C
TNNI3	Cardiac troponin I
TNNT2	Cardiac troponin T
TPM1	alpha tropomyosin
TRIM63	Ubiquitin E3 ligase tripartite motif protein 63 or MuRF1
TTN	Titin
UPS	Ubiquitin proteasome system

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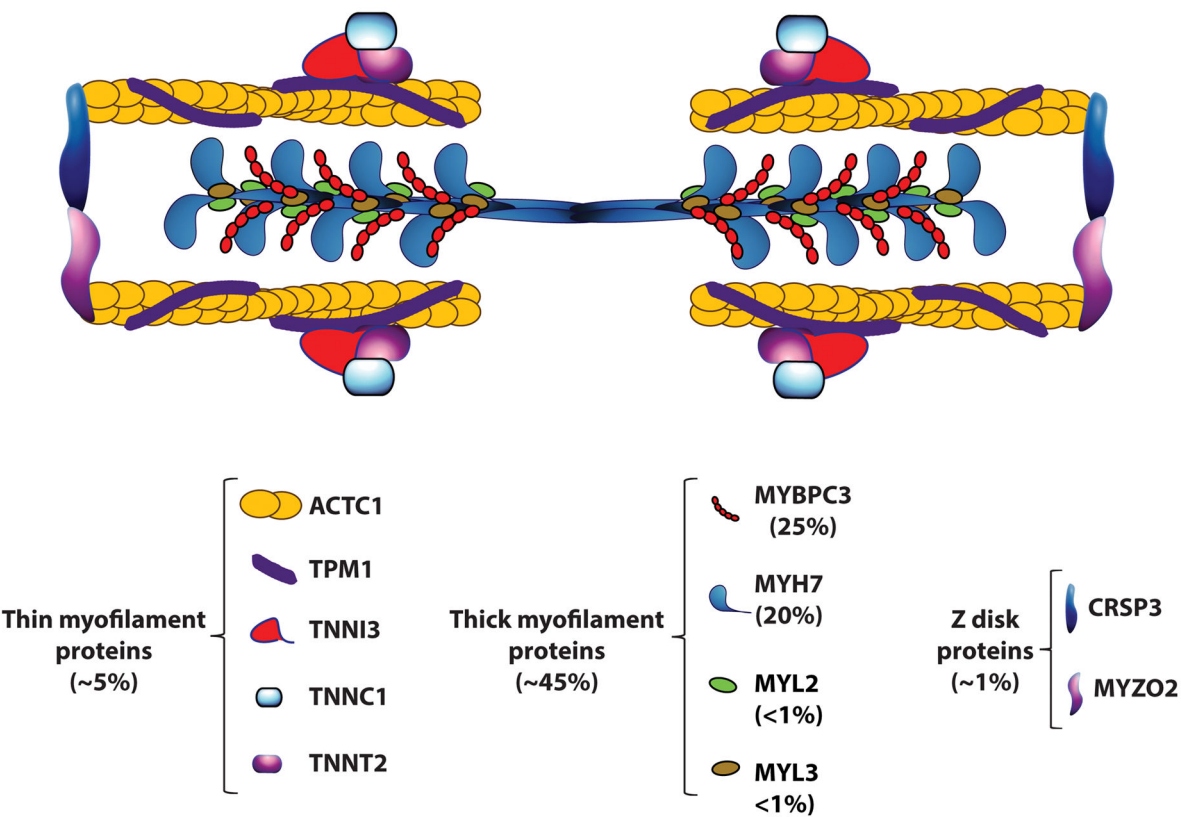


Figure 1. HCM as a disease of sarcomere proteins
A schematic structure of a sarcomere composed of thick and thin filaments and Z discs is depicted along with its protein constituents involved in HCM. Established causal genes for HCM and their population frequencies are listed.

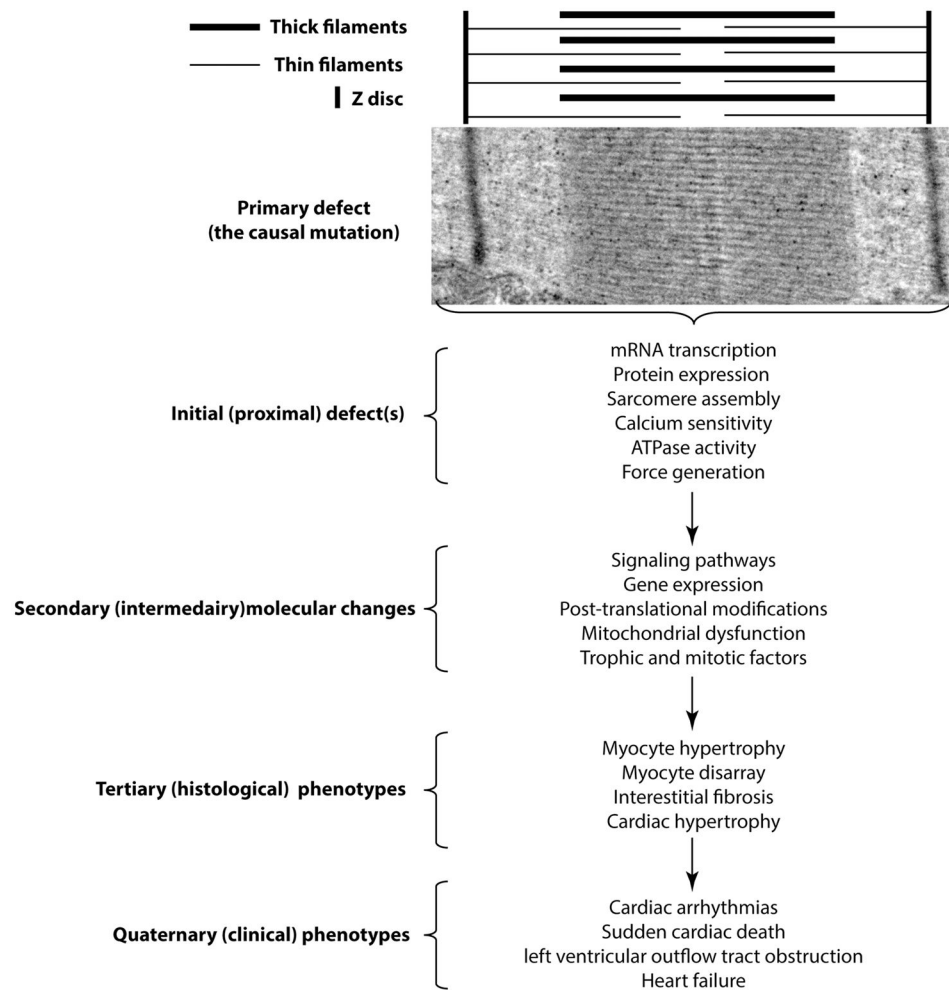


Figure 2. Pathogenesis of HCM

The primary defect is the mutation in the sarcomere, composed of thick and thin filaments and the Z disks. A change in the amino acid sequence in the sarcomere protein or the deficiency of a sarcomere protein (the primary defect) instigates a series of initial (or proximal) defects, such as altered levels of the sarcomere protein, calcium sensitivity, or ATPase activity. These initial defects activate expression of a series of intermediary molecular or secondary changes, such as altered transcriptomics or signaling pathways. The latter set of the molecular changes induce histological and morphological changes in the myocardium, such as myocyte hypertrophy and fibrosis, which could be considered tertiary phenotypes. These molecular and histological changes lead to the clinical or quaternary phenotypes of HCM, such as cardiac arrhythmias and heart failure.

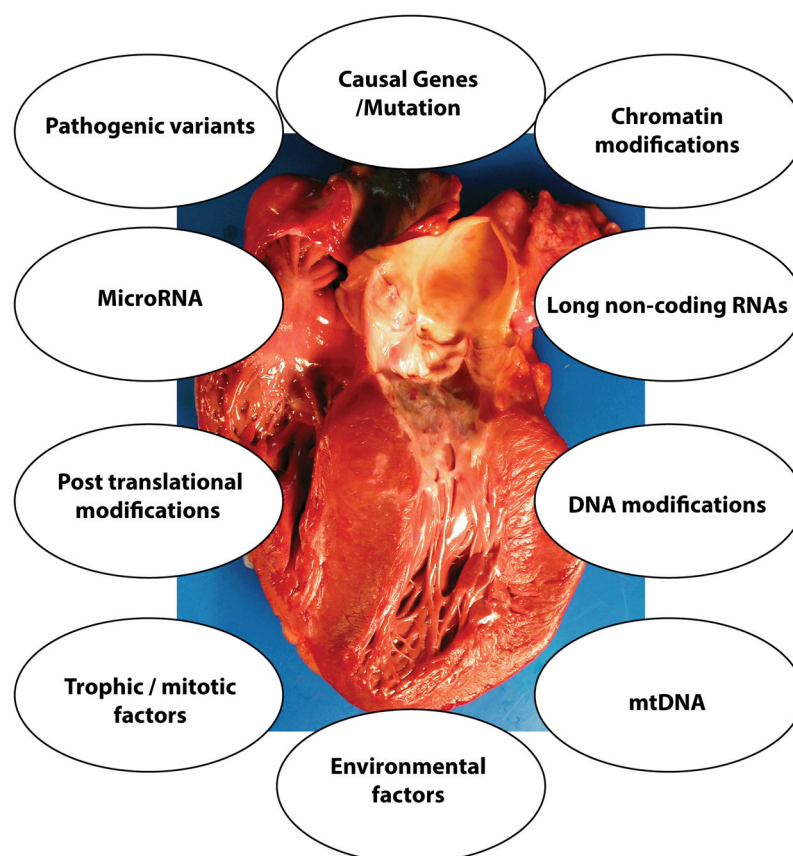


Figure 3. Determinants of phenotype in HCM

Selected factors contributing to expression of cardiac phenotype in HCM are shown. The causal mutation imparts the main effect and several others, such as other pathogenic genetic variants (modifiers), genomics (such as non-coding RNAs), proteomics (such as post-translational modifications), and environmental factors (such as isometric exercises) contributing to expression of the phenotype.

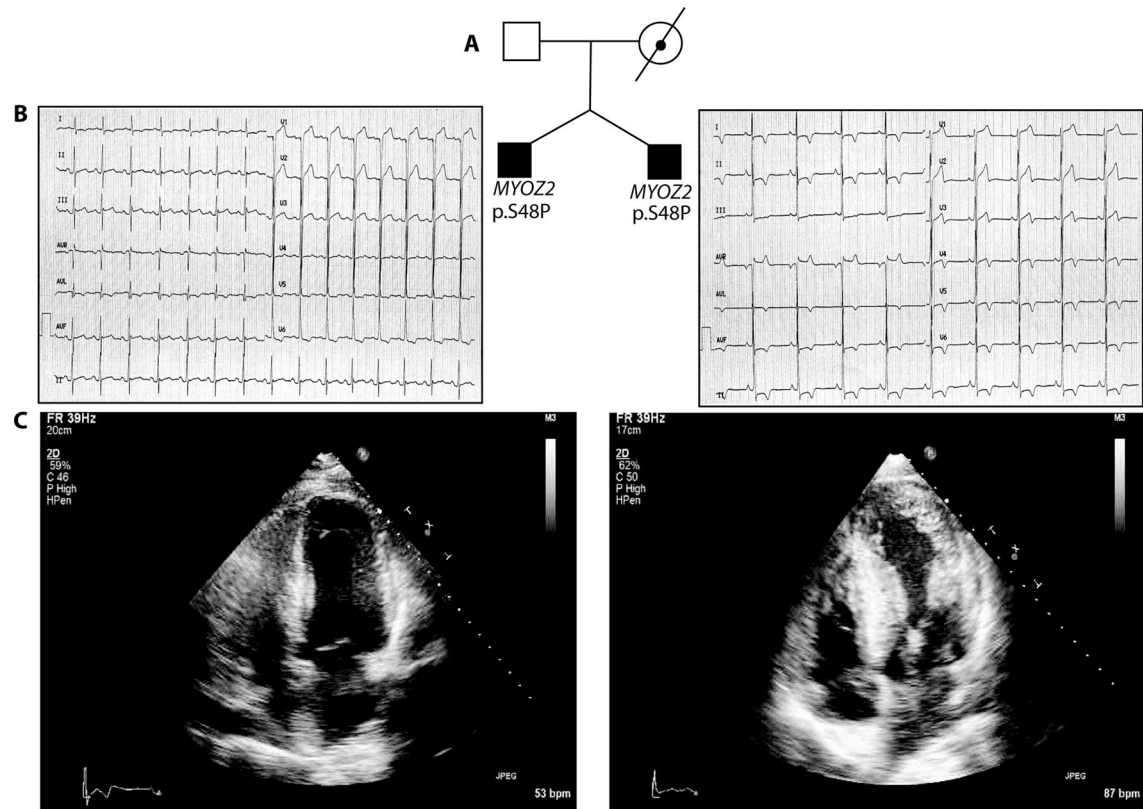


Figure 4. Variability in the phenotypic expression of HCM

A. A truncated pedigree depicting dizygotic twins with HCM caused by the p.Ser48Pro mutation in the *MYOZ2* gene. Despite sharing the same causal mutation, one expresses mild and the other severe cardiac hypertrophy, as reflected in the electrocardiograms (**B**) and echocardiographic images (**C**).

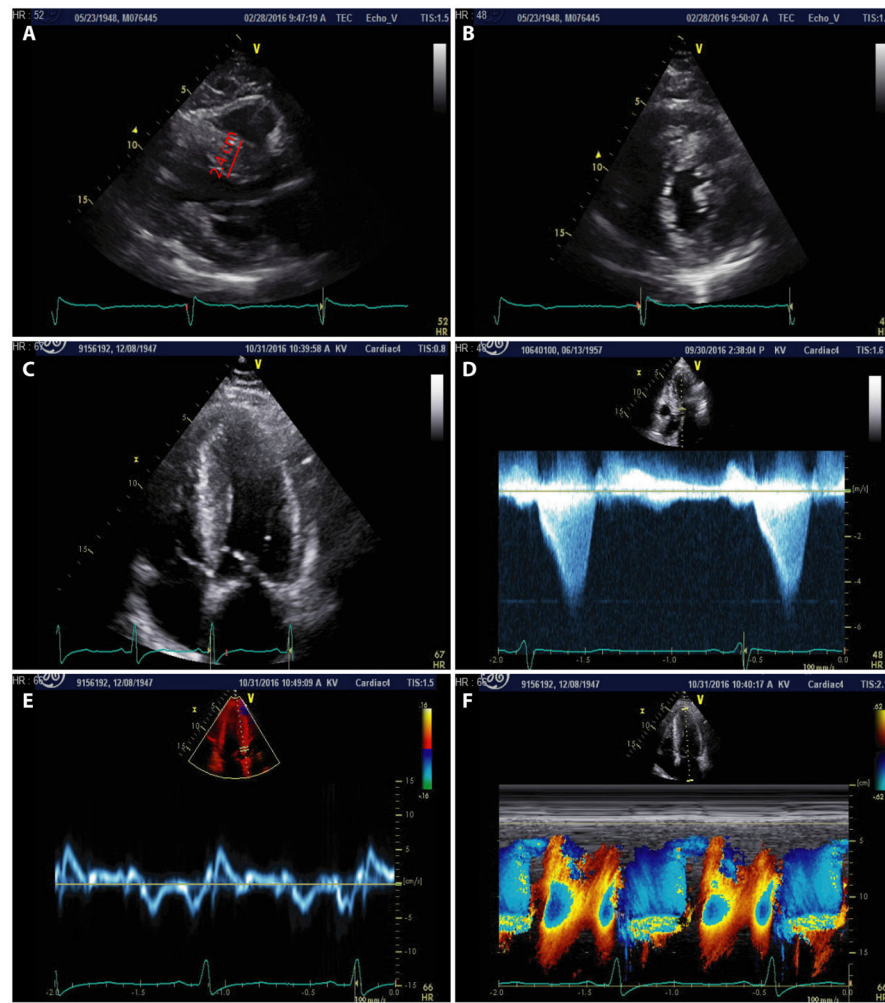


Figure 5. Echocardiographic phenotypes of HCM

A. A parasternal view of the ventricles showing septal hypertrophy; **B.** A parasternal short axis view showing concentric cardiac hypertrophy; **C.** Systolic anterior motion (SAM) of mitral leaflets, contributing to left ventricular outflow tract obstruction; **D.** Doppler velocities recorded at the left ventricular outflow tract showing about 100 mmHg gradient; **E.** Tissue Doppler recording of the interventricular septum showing reduced velocities; **F.** Color Doppler M mode imaging of the left ventricle showing velocity of flow progression in the left ventricle during a cardiac cycle, which is used, along with other indices, to assess diastolic function.

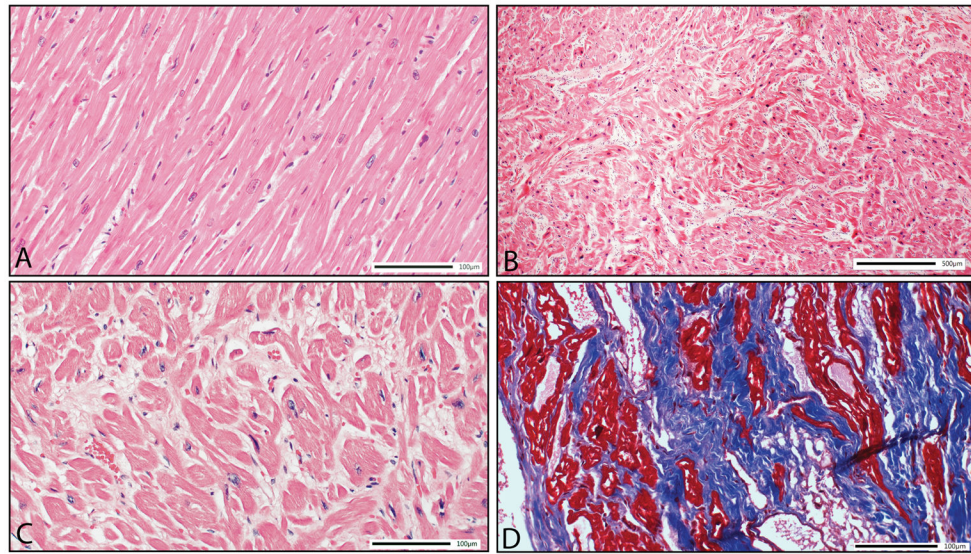


Figure 6. Histological phenotypes

A. A normal thin myocardial section stained with H&E. **B.** A low magnification ($\times 4$) H&E stained thin myocardial section from a patient heart with HCM showing disorganized myocardial architecture. **C.** A higher magnification ($\times 20$) H&E stained myocardial section showing myocyte disarray ($\times 20$). **D.** A thin myocardial section ($\times 20$) stained with Masson trichrome in blue showing areas of interstitial fibrosis.

TABLE 1

A. Established Causal Gene HCM (Large families)				
Gene	Protein	Function	Tolerance to variation	
			Missense (Z score)	LoF (pLI)
<i>MYH7</i>	β -Myosin heavy chain	ATPase activity, Force generation	6.54	0.00
<i>MYBPC3</i>	Myosin binding protein-C	Cardiac contraction	0.69	0.00
<i>TNNT2</i>	Cardiac troponin T	Regulator of acto-myosin interaction	1.54	0.01
<i>TNNI3</i>	Cardiac troponin I	Inhibitor of acto-myosin interaction	1.88	0.17
<i>TPM1</i>	α -tropomyosin	Places the troponin complex on cardiac actin	3.42	0.80
<i>ACTC1</i>	Cardiac α -actin	Acto-myosin interaction	5.25	0.95
<i>MYL2</i>	Regulatory myosin light chain	Myosin heavy chain 7 binding protein	0.86	0.02
<i>MYL3</i>	Essential myosin light chain	Myosin heavy chain 7 binding protein	0.75	0.89
<i>CSRP3</i>	Cysteine and glycine-rich protein 3	Muscle LIM protein (MLP), a Z disk protein	-0.66	0.00

B. Likely causal genes for HCM (small families)				
Gene	Protein	Function	Tolerance to variation	
			Missense (Z score)	LoF (pLI)
<i>FHL1</i>	Four-and-a-half LIM domains 1	Muscle development and hypertrophy	1.29	0.92
<i>MYOZ2</i>	Myozenin 2 (calsarcin 1)	Z disk protein	0.03	0.02
<i>PLN</i>	Phospholamban	Regulator of sarcoplasmic reticulum calcium	0.57	0.11
<i>TCAP</i>	Tcap (Telethonin)	Titin capping protein	0.45	0.08
<i>TRIM63</i>	Muscle ring finger protein 1	E3 ligase of proteasome ubiquitin system	0.02	0.00
<i>TTN</i>	Titin	Sarcomere function	-5.48	0.00

C. Genes associated with HCM				
Gene	Protein	Function	Tolerance to variation	
			Missense (Z score)	LoF (pLI)
<i>ACTN2</i>	Actinin, alpha 2	Z disk protein	1.76	1.0
<i>ANKRD1</i>	Ankyrin repeat domain 1	A negative regulator of cardiac genes	-0.01	0.00
<i>CASQ2</i>	Calsequestrin 2	Calcium binding protein	-1.08	0.00
<i>CAV3</i>	Caveolin 3	A caveolae protein	1.19	0.34
<i>JPH2</i>	Junctophilin2	Intracellular calcium signaling	3.93	0.01
<i>LDB3</i>	Lim domain binding 3	Z disk protein	0.32	0.00
<i>MYH6</i>	Myosin heavy chain alpha	Sarcomere protein expressed at low levels in the adult human heart	2.87	0.00
<i>MYLK2</i>	Myosin light chain kinase 2	Phosphorylate myosin light chain 2	0.73	0.22
<i>NEXN</i>	Nexilin	Z disc protein	-1.32	0.00
<i>TNNC1</i>	Cardiac troponin C	Calcium sensitive regulator of myofilament function	2.22	0.51
<i>VCL</i>	Vinculin	Z disk protein	3.11	0.99

The Z score for each gene reflects deviation of the observed variants in the ExAC database from the expected number. A higher positive Z score indicates that the gene is intolerant to variation. Likewise, pLI indicates probability of intolerance to Loss-of-Function (LoF) variants with 1 indicating total intolerance.

TABLE 2

Phenocopy Conditions for Hypertrophic Cardiomyopathy

Phenotype	Gene	Protein	Phenotypic clue
AMPK mediated Glycogen storage	<i>PRKAG2</i>	Protein Kinase A, γ subunit	Normal or reduced left ventricular systolic function, pre-excitation pattern
Pompe disease	<i>GAA</i>	α -1,4-glucosidase (acid maltase)	Autosomal recessive, multi-organ disease, Pre-excitation pattern
Anderson-Fabry disease	<i>GLA</i>	α -galactosidase A	X-linked, multi-system also involving skin, kidney and peripheral nerves
Danon disease	<i>LAMP2</i>	Lysosome-associated membrane protein 2	X-linked dominant, Proximal muscle weakness, intellectual disability, short PR on ECG, elevated CK levels
Amyloidosis	<i>TTR</i>	Transthyretin	Low QRS voltage, other organ involvement, Subendothelial LGE
Kearns-Sayre syndrome	<i>mtDNA</i>	Mitochondrial protein	Multi-system disease
Friedreich ataxia	<i>FRDA</i>	Frataxin	Autosomal recessive, neurodegeneration
Myotonic dystrophy	<i>DMPK</i>	Myotonin Protein kinase	Myotonia, muscular dystrophy, cataract, frontal baldness
	<i>ZNF9</i>	Zinc Finger Factor 9	
Noonan/LEOPARD syndromes (Rasopathies)	<i>PTPN11</i>	Protein tyrosine phosphatase, nonreceptor type 11	Congenital heart defects, Lentigines, Café-au-lait spots
	<i>SOS1,SOS2</i>	Son of Sevenless	
	<i>RAF1</i>	Murine leukemia viral oncogene homolog 1	
	<i>KRAS</i>	Kirsten rat sarcoma virus homolog	
	Others (<i>A2ML1, BRAF, CBL, MAP2K1, MAP2K2, NRAS, RIT1, RRAS, SHOC2</i>)		
Neimann-Pick disease	<i>NPC1</i>	Neimann-Pick	Autosomal recessive neuro-degenerative disease
Refsum disease	<i>PAHX (PHYH)</i>	Phytanoyl-CoA hydroxylase	Retinitis pigmentosa, peripheral neuropathy, and ataxia
Deafness	<i>MYO6</i>	Unconventional myosin 6	Autosomal dominant deafness

Abbreviations: ECG: Electrocardiogram; CK: Creatine kinase; LGE: late gadolinium enhancement

TABLE 3**Risk Factors for Sudden Cardiac Death in Patients with HCM****Major risk factors**

- Prior episode of cardiac arrest (aborted SCD)
- Family history of SCD (more than one family member)
 - Reflective of the causal mutations, including double mutations, and the modifier genes
- History of recurrent syncope (due to arrhythmias)
- Sustained and repetitive non-sustained ventricular tachycardia

Intermediary Risk factors

- Severe cardiac hypertrophy
- Extensive late gadolinium enhancement on cardiac MRI

Questionable Risk Factors

- Severe left ventricular outflow tract obstruction (LVOT gradient > 80 mmHg)
- Abnormal blood pressure response to exercise
- Severe myocyte disarray
- Early onset of clinical manifestations (young age)
- Presence of myocardial ischemia

Abbreviations: SCD: Sudden cardiac death; MRI: Magnetic Resonance Imaging; LVOT: Left ventricular outflow tract gradient;

TABLE 4

Selected Ongoing Trials in HCM

Study	Medication	Sample size	Primary end point
HALT-HCM	NAC	42	Feasibility/LVM
LIBERTY-HCM	GS-6615	160	VO2 Max
INHERIT	Losartan	130	LVM
NCT01150461	Losartan	20	LVM
NCT00319982	Diltiazem	39	Diastolic function
METAL-HCM	Perhexiline	44	VO2 Max
NCT00011076	Pirfenidone	50	Diastolic function
RHYME	Ranolazine	14	Safety
NCT00001534	Enalapril	112	Symptoms
NCT00001965	Cyclosporine	32	Safety
VANISH	Valsartan	150	Combined end point
NCT01696370	Trimetazidine	90	VO2 Max
Light-CARMIDO	BX1514M	40	6 MWT