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Mutation Type is Not Clinically Useful in Predicting Prognosis in Hypertrophic Cardiomyopathy

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Overview

Hypertrophic cardiomyopathy (HCM), or clinically unexplained hypertrophy of the heart, is a common genetic cardiovascular disorder marked by genetic and phenotypic heterogeneity. As the genetic mutations underlying the pathogenesis of this disease have been identified, investigators have attempted to link mutations to clearly defined alterations in survival in hopes of identifying prognostically relevant biomarkers of disease. While initial studies labeling particular *MYH7*-encoded beta myosin heavy chain and *TNNT2*-encoded cardiac troponin T mutations as "malignant" or "benign" raised hopes for mutation-specific risk stratification in HCM, a series of subsequent investigations identified mutations in families with contradictory disease phenotypes. Furthermore, subsequent proband-based cohort studies indicated that the clinical prognostic relevance of individual mutations labeled as "malignant" or "benign" in large referral centers is negligible. Herein, we seek to summarize the controversy and dispute the notion that mutation-specific risk stratification in HCM is possible at the present time. We provide evidence for clinicians and basic scientists alike to move beyond simple mutation descriptors to a more nuanced understanding of HCM mutations that fully captures the multi-factorial nature of HCM disease expression.

Introduction

Over the last two decades, the genetic underpinnings of heritable cardiovascular disease have begun to be unveiled, starting with the first discovery of rare pathogenic mutations that cause cardiomyopathies and cardiac channelopathies. The simple paradigm of Mendelian inheritance, while helpful in certain monogenic disease processes, is fundamentally incapable of explaining the entirety of how complex diseases express in the context of complex human physiology under the influence of a myriad of intrinsic and extrinsic variables. Our understanding of the intricate interplay between one such intrinsic variable, the genome, and manifestation of disease was advanced significantly in the decoding of a handful of human's genomes in February of 2001[1,2]. Despite the decade of research these

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DISCLOSURES

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discoveries have initiated, clinicians and scientists alike are only beginning to appreciate the impact of this revolution on our understanding of health and disease. One disease, hypertrophic cardiomyopathy (HCM), typifies this struggle, as we seek to integrate the role of genetic alterations into the variation we see in this sudden death-predisposing disease.

Defined by clinically unexplained hypertrophy of the ventricular walls and/or septum, HCM affects approximately 1 in 500 persons and is the most common inherited cardiovascular disease[3]. HCM is the most common cause of sudden cardiac death (SCD) in young athletes and a significant cause of sudden death in the young in general[4,5]. A heterogeneous disease, HCM demonstrates phenotypic variation in the degree of hypertrophy (none to extreme), fibrosis and myocyte disarray (none to extreme), left ventricular (LV) outflow tract obstruction (none to severe), morphological subtype (reverse curve, sigmoidal, and apical-HCM for example), associated symptoms (none to debilitating symptoms refractory to pharmacotherapy), and sudden death susceptibility (normal longevity to premature sudden death). The clinical progression is variable as well, with some patients remaining asymptomatic over their lifetime while others present during infancy with profound cardiac hypertrophy.

The Genetic Basis of Hypertrophic Cardiomyopathy

The sentinel discovery of a genetic locus responsible for familial HCM was identified in 1989 by Jarcho and colleagues[6]. Jarcho utilized linkage analysis of a large, multi-generational family to identify a portion of the long arm of chromosome 14 which co-segregated with incidence of disease. The following year, Geisterfer-Lowrance and investigators identified the first HCM-causative mutation in the *MYH7*-encoded beta myosin heavy chain[7]. Over the past 20 years, HCM has been appreciated as principally an autosomal dominant disease with variable expressivity and penetrance, and hundreds of mutations found in dozens of genes encoding various sarcomeric/myofilament, Z-disc, and calcium (Ca^{2+})-handling proteins have been identified. These HCM-susceptibility genes are summarized in Table 1. In addition, the genetic basis of myocardial disease which can masquerade as HCM, so-called HCM phenocopies, have also been elucidated (Table 2).

The majority of HCM is due to mutations in genes encoding the components of the cardiac sarcomere responsible for generating molecular force of myocyte contraction. This sarcomeric basis of HCM is comprised of proteins of the thick myofilament (*MYH7*, *MYL2*-encoded regulatory myosin light chain, and *MYL3*-encoded essential myosin light chain[8,9]), the intermediate myofilament (*MYPBC3*-encoded cardiac myosin binding protein C[10]), and the thin myofilament (*ACTC*-encoded actin[11], *TPM1*-encoded alpha-tropomyosin[12], *TNNT2*-encoded cardiac troponin T[12], *TNNI3*-encoded cardiac troponin I[13], and *TNNC1*-encoded cardiac troponin C[14]). Finally, while a complete coding region interrogation through a large cohort of HCM probands has yet to be performed, a small number of mutations have been identified in the giant filament, *TTN*-encoded titin. In this exceptionally large protein, which extends throughout half of the cardiac sarcomere, TTN-R740L has been identified in a single individual[15]. In an independent study Arimura and colleagues identified two additional mutations, TTN-R8500H and R8604Q, in a cohort of 384 HCM probands[16].

Based on the replication and wide-spread acceptance of the role of these genes in the pathogenesis of HCM, this panel of genes, with the exception of *TTN*, has moved from the realm of research investigation to commercially/clinically available genetic tests for HCM. Depending on the cohort analyzed, the overall yield of HCM genetic testing, or its research equivalent, varies from 24% to 63% (24% Swedish[17], 34% German/Turkish[18], 38% United States[19], and 63% European[20] cohorts, respectively, among others). In comparison, the yield for the commercially available genetic test is purported to be 50–70% depending on the company. While the frequency of mutations in these nine genes depends on the cohort studied, mutations in *MYBPC3* and *MYH7* comprise the majority of mutations among myofilament genes. Depending on the cohort, the prevalence of MYBPC- and MYH7-HCM mutations varies among mutation-positive HCM probands, yet these two genes represent the most common genetic subtypes of HCM[17,18,20].

While the clinically available genetic test represents a significant advance in the understanding of HCM pathogenesis, a significant proportion of the HCM population remains genotype-negative with no biomarker for, or mechanistic explanation of, their disease process. One possible explanation for the incomplete yield of mutation-positive HCM may be due to limitations in the mutation detection methodology. As most genetic analysis utilizes direct DNA sequencing of coding exons, possibly including a denaturing high-performance liquid chromatography intermediate platform, large genetic deletions or duplications as well as intronic or promoter variations are missed[21]. Another potential explanation, which is certainly not mutually exclusive with the first, is that the disease causative pathogenic substrate lies elsewhere in the genome, thereby fostering the possibility for subsequent investigation into the causes of genotype-negative HCM to identify not only disease biomarkers but also novel cardiac physiology and disease pathophysiology.

The search for novel HCM genes moved away from principle myofilaments of the cardiac sarcomere to the genes that encode proteins comprising the adjacent cardiac Z-disc. Serving as mechanical integration site of the myofilaments, the network of Z-disc proteins anchor the thin filaments from adjacent cardiac sarcomeres and allow for transduction of sarcomere force generation. Further, rather than being passive molecular tethers within the cardiocyte, Z-disc proteins serve as molecular platforms for signal transduction and initiation of several intracellular signaling cascades, particularly those responding to cardiac stretch[22]. The first Z-disc mutations associated with HCM were described in *CSRP*-encoded muscle LIM protein[23] and *TCAP*-encoded telethonin[24,25]. Subsequently, *LDB3*-encoded LIM domain binding 3, *ACTN2*-encoded alpha actinin 2[26], *VCL*-encoded vinculin/metavinculin[27,28], *MYOZ2*-encoded myozenin 2[29], and *ANLRD1*-encoded cardiac ankyrin repeat protein[16] have been identified as rare causes of HCM.

Apart from sarcomeric- and Z-disc-HCM, independent studies have identified rare genetic mutations in genes encoding Ca^{2+}-handling or Ca^{2+}-regulatory proteins, including *JPH2*-encoded junctophilin 2[30], *CALR3*-encoded calreticulin[31], and the previously mentioned Ca^{2+}-sensitive *TNNC1*[14], in individuals with myofilament negative-HCM. All told, mutations in these genes explain only a small percentage of HCM, yet may expand understanding of the role of Ca^{2+} in the pathogenesis of HCM.

The Genesis of "Benign" and "Malignant" Mutations

The first studies exploring the possibility of mutations holding prognostic importance came on the heels of the identification of the first HCM mutation. Just two years after the first mutation was discovered, Watkins and investigators identified four families with mutations in *MYH7* associated with a marked reduction in survival upon Kaplan-Meier analysis[32]. Family members hosting either the MYH7-R403Q or R453C missense mutation had increased disease-related deaths and sudden deaths compared to those hosting a V606M mutation. The R403Q and R453C were designated "malignant" mutations, while the V606M was considered "benign." At the time, it was postulated that these initial malignant *MYH7* mutations might cluster around a "hot spot" on myosin, a loop that forms part of the binding cleft for actin, imparting a more dramatic functional impact on the protein than mutations seen elsewhere[33]. Anan et al identified a MYH7-F513C "benign" mutation as well as "malignant" MYH7-G716R and R719W[34]. In particular, the R719W mutation was associated with decreased survival when compared to a family hosting the "benign" F513C mutation.

Watkins and colleagues went on to identify mutations in additional genes, including four in *TNNT2* in seven families which was associated with decreased life expectancy and a high incidence of SCD despite minimal cardiac hypertrophy[35]. Specifically, TNNT2-I79N, R92Q, a deletion of Q160 (delQ160), and a G to A transition in the 5' splice donor site of intron 15 (intervening sequence, IVS15 +1 G>A) were found to have reduced survival compared to the "benign" MYH7-V606M yet similar to the previously described "malignant" MYH7-R403Q. Moolman and colleagues identified a TNNT2-R92W by linkage analysis in two pedigrees of familial HCM[36]. Among the 18 clinically-examined individuals hosting this mutation, only six demonstrated LV wall thickness ≥ 13mm by echocardiographic evaluation. Despite this mild HCM phenotype, the authors show increased mortality, particularly in young males, with TNNT2-R92W positive individuals.

Together, these initial studies nucleated an archetype whereby an individual mutation type could, by itself, be considered a poor prognostic biomarker associated with increased risk of sudden death (MYH7-R403Q, R453C, G716R, and R719W; TNNT2-I79N, R92Q, R92W, delQ160, and IVS15 +1 G>A) or a reassuring indicator of reduced mortality risk (MYH7-F513C, V606M)[37]. Investigators quickly extended these studies beyond individual mutations and attempted to link the entire gene, independent of the specific type of mutation, to a particular genotype-specific clinical HCM manifestation. The following genotype-specific pronouncements emerged: MYH7-HCM and early onset with increased hypertrophy and susceptibility to SCD, MYBPC3-HCM and later onset of diagnosis with lower risk, TNNT2-HCM and youthful disease presentation, particularly among males, SCD-predisposition, and minimal hypertrophy, ACTC-HCM and benign prognosis and apical LV hypertrophy morphology[38–40].

Non-Replication, Contradictions, and Confusion

Just as quickly as the field of prognostically relevant mutations expanded, a series of studies directly contradicted, or at least failed to replicate, many of these initial observations. In a family with the "malignant" MYH7-R403Q mutation, Fananapazir and Epstein found no

SCD or disease-related deaths among six MYH7-R403Q positive/HCM phenotype positive individuals, yielding a 100% survival at 50 years of age[41] compared to 9/44 SCD and 21/44 disease-related deaths previously observed[32]. In addition to contradicting the "malignant" label of this mutation, investigators went on to contradict the "benign" nature of the MYH7-V606M mutation in a multigenerational family with HCM and prevalent SCD. Among eight MYH7-V606M positive/HCM phenotype positive individuals, four succumbed to SCD between the ages of 15 and 27 years, yielding a 71% cumulative cardiac event rate at 50 years of age. In this way, Fananapazir and Epstein began to challenge the notion that clinical analysis of a single large pedigree was sufficient to designate a discrete mutation as intrinsically "malignant" or "benign."

A second, independent group led by Havnrup et al, also noted the "benign" MYH7-V606M in a family with HCM and a high incidence of SCD[42]. In this multigenerational family demonstrating complete disease penetrance, three individuals, including a son of the index case, suffered youthful SCD with pronounced septal hypertrophy. Among the surviving four MYH7-V606M positive/HCM phenotype positive individuals, all were diagnosed before 18 years of age and three demonstrated either non-sustained ventricular tachycardia or atrial fibrillation.

These contradictions were not limited to just MYH7-HCM. The "malignant" TNNT2-I79N mutation, which was first associated with the SCD of 4/9 mutation-positive individuals in the sentinel pedigree[35], was identified by Menon et al in a family with a mixed cardiomyopathic phenotype[43]. The mutation was identified in each of the nine affected family members who held diagnoses of restrictive cardiomyopathy (N=2), dilated cardiomyopathy (N=2), HCM (N=4), and a mixed cardiomyopathy (N=1). Further, while there was a high incidence of atrial tachyarrhythmias, there was no incidence of SCD. Taken together with previous studies, these results began to call into question the associations between individual mutations and patient survival. In addition to survival, contradictory reports began to emerge about the role of specific mutations influencing other aspects of HCM disease manifestation, such as the septal hypertrophy morphology.

In the sentinel study implicating *TNNI3* as an HMC-associated gene, Kimura et al. identified a proband hosting a deletion of lysine 183 (TNNI3-delK183) which demonstrated apical-type HCM while his son, hosting the same mutation, had "typical" HCM[13]. A later study by Kokado et al. identified an identical finding in a seemingly independent group of 25 individuals from seven families, associated with a highly variable clinical expression of the deletion[44]. Indeed, among the 15 individuals demonstrating hypertrophy, only one had apical disease while seven did not exhibit the apical morphology. Similarly, Brito and investigators identified two independent families with an identical novel MYH7-I263T mutation[45]. Despite hosting an identical mutation, family A (N = 20 members) had increased LV hypertrophy when compared to family B (N = 18 members, mean 23.4mm vs. 16mm, respectively). Conversely, family B demonstrated reduced disease penetrance (100% vs. 33%, respectively) with an increased propensity for SCD (0/20 vs. 2/18, respectively) when compared to family A.

Taken together, these kindred studies illustrated the multi-factorial nature of HCM in that the distinct mutation cannot be the sole factor which dictates clinical phenotype. Accordingly, one must be extremely cautious in assigning prognostic value to a specific mutation. Indeed, even in families carrying so-called "malignant" mutations, such as TNNT2-I79N and R92Q there was significantly reduced disease penetrance with 3/9 (33%) and 7/32 (22%) mutation-positive individuals failing to show any clinical signs of HCM, respectively[46]. A major limitation of each of these studies is the small number of individuals available for analysis in even the largest, multi-generational family. Further, confounding inherited factors that would be retained within a family, independent of the specific HCM-causative mutation, might greatly influence the ultimate expression of disease. What was not appreciated at the time, and may not be fully appreciated now, is the role of genomic and epigenetic influences on disease expression. Approaching the pathogenesis of HCM as a classical monogenic disease process, such as cystic fibrosis, does not fully capture the influence of other disease-modifying genetic variation outside the "gene of interest," or biologically relevant factors inherited apart from the genome in an epigenetic fashion. These confounding factors might be one explanation for contradictory findings in families hosting identical disease-associated mutations. Lastly, these studies do little to capture the epidemiologic relevance of these "malignant" or "benign" mutations, and one is left wondering what the overall clinical impact of these mutations might be, if any, among the HCM population.

A Proband-Based Cohort-Approach to Validation

In an attempt to move beyond kindred-based investigations of HCM mutation prognostic relevance and to identify "benign" and "malignant" mutations outside of the confounding influences of the genetic milieu of the family, a proband-based cohort approach was undertaken. Van Driest and colleagues identified five probands (1.7%), out of a cohort of nearly 300 consecutive index HCM cases, which hosted one of two "benign" HCM mutations: MYH7-R719Q or L908V[47]. Initial investigations by Consevage et al described the R719Q mutation in a large Hispanic family with no history of arrhythmia or SCD among 64 "at risk" family members[48]. Further, Epstein et al initially identified the L908V mutation in a family with mild HCM with only 2 (4%) out of 46 individuals <55 years of age experiencing SCD and only 5 (26%) out of 19 individuals ≤ 30 years of age with a maximal LV thickness >12mm[49]. In contrast, each of the "benign" mutation probands identified by Van Driest et al demonstrated significant clinical disease with an average age at diagnosis <30 years and LV outflow tract obstruction requiring surgical myectomy, with four necessitating beta- and calcium channel-blockade post myectomy. Three of the individuals had a positive family history of SCD, while one required cardiac transplant in the second decade of life due to end-stage HCM. In each of these cases, genetic counseling pertaining to the identification of each patient's "benign" mutation would have been sorely amiss.

A follow-up study by Ackerman et al sought to determine the prevalence of purported "malignant" mutations in this cohort of clinically robust HCM probands[50]. Despite the large size of the cohort, only three probands (1%) of the 293 hosted the "malignant" MYH7-R453C, G716R, and TNNT2-R92W, leaving 98% of the 95 patients within the cohort with a positive family history of HCM, 99% of the 69 patients with family history of SCD, 92% of the 25 patients treated with an implantable cardioverter-defibrillator (ICD), and 89% of the

patient with extreme (>30mm) hypertrophy without a known “malignant” mutation. Further, the TNNT2-R92W mutation proband was identified in a 24 year old female who had no family history of SCD despite a mutation-positive family. While limited by an incomplete picture of all possible “malignant” mutations, this study suggests that even if all “malignant” mutations identified in the literature were indeed deleterious to survival, presence of one of these mutations accounts for a minute fraction of those patients with phenotypically severe HCM.

Since these initial studies, we have grown the proband-based cohort to a cohort of 1064 cases (~60% male) diagnosed with HCM at 44.4 ± 18.6 (standard deviation) years with a mean ventricular septal thickness of 20.9 ± 5.9mm, and a mean resting left ventricular outflow tract gradient of 43.7 ± 43.5mmHg. A search of the literature to identify additional “prognostically relevant” HCM mutations not otherwise mentioned in earlier studies listed herein, identified the “malignant” MYH7-V406M[51], -R723G[52], MYL2- R58Q[20,53,54], -D166V[20,54], TNNT2-R94L[55], -A104L[56], homozygous -S179F[57] and the “benign” MYH7-R663H[51], MYL2-E22K[53], and heterozygous TNNT2-S179F[57]. Within this expanded cohort, the 16 previously annotated “malignant” mutations were identified in 8/1064 (0.75%) patients while those 10 mutations previously annotated as “benign” were seen in 28 patients (2.63%). As seen among the initial cohort of unrelated patients, many of the owners of a so-called “benign” mutation manifested a severe HCM phenotype and were part of families with SCD-predisposition (Figure 1).

One newly identified host of the “benign” MYH7-V606M mutation was diagnosed with HCM after an aborted SCD attempt and was found to be in ventricular fibrillation prior to resuscitation. A second proband hosting MYH7-V606M suffered the loss of his father from an HCM-related SCD at the age of 40 years as well as the SCD of a first cousin at the age of 10 years. A newly identified proband hosting MYH7-R719Q reported a significant family history of SCD-predisposition with SCD of a nephew at age 10 years, four first degree relatives requiring ICD therapy, and a brother requiring cardiac transplant. In the context of previous studies which cast doubt on the prognostic relevance of individual mutations, this study further supports the conclusion that other factors which play into the heterogeneous expression of HCM easily overshadow the effects of specific mutation type or the gene that is mutated. These findings, as well as a summary of all studies directly contradicting the traditional label of “malignant” and “benign” are summarized in Table 3.

Van Driest and colleagues further challenged the notion that mutations in certain genes, by the nature of their genetic location, might be associated with a particular clinical phenotype[58]. Investigators dissected a proband-based cohort of nearly 400 consecutive individuals with HCM based on genotype, and were unable to discern a clearly different clinical phenotype among unrelated patients with thick filament (*MYH7*, *MYL2*, and *MYL3*), intermediate filament (*MYBPC3*), and thin filament (*ACTC*, *TPM1*, *TNNT2*, and *TNNI3*) HCM mutations. Indeed, between these three myofilament-based subtypes, there was no statistical difference in age at diagnosis, the number presenting with cardiac symptoms, family history of HCM or SCD, LV wall thickness, proportion with severe hypertrophy ≥30mm, LV outflow tract gradient, and the proportion receiving myectomy, pacemaker, or ICD implantation.

For example, while MYBPC-HCM has been correlated with benign disease diagnosed late in life compared to MYH7-HCM which was associated with extensive hypertrophy, Van Driest identified no statistical difference in age at diagnosis (MYH7, 33.0±17 years vs. MYBPC, 37.6±15) or LV wall thickness (23.5±7mm vs. 22.5±5mm, respectively, Figure 2). In addition to being unable to replicate many of the genotype-phenotype correlations which had been identified from multigenerational families, this study also highlighted that the two most common genetic subtypes of HCM, MYBPC- and MYH7-HCM, were clinically similar.

A Rose by Any Other Name

While it appears clear that a particular HCM-causative mutation is not inherently "malignant" or "benign", there is still a clear diagnostic role for HCM genetic testing in identifying occult disease. Identification of a disease-associated mutation in a proband with HCM provides the genetic biomarker for the systematic genetic evaluation of his/her offspring, siblings, parents, and more distant relatives that do not demonstrate clinically apparent disease. Further, a positive genetic test, independent of prognostic value of the discrete mutation, allows for risk stratification of family members based on the presence of this biomarker including: i) close surveillance of the genotype-positive, pre-clinical individual and ii) casual observation or dismissal of the genotype-negative/phenotype-negative relative and his/her future progeny[59]. In this way, identification of a "benign" mutation in a family with HCM should not exclude close follow-up of all mutation-positive individuals, nor should identification of a "benign" mutation solely dictate clinical management of a patient with HCM. Indeed, just as Juliet pondered "What's in a name? That which we call a rose by any other name would smell as sweet," in William Shakespeare's *Romeo and Juliet*, HCM mutations should be regarded as such without consideration for old descriptors.

Recent Advances in the Prognostic Role of Genotyping

While significant controversy surrounds the notion of mutation-specific and genotype-specific risk stratification, recent evidence has emerged revealing that unrelated patients with a positive HCM genetic test have a distinctively more severe phenotype than patients with a negative HCM genetic test. In the Mayo Clinic study, compared to patients with a negative genetic test, patients with a positive genetic test were younger at diagnosis, demonstrated greater hypertrophy, were more likely to have a positive family history of HCM, and were more likely to receive an ICD from their HCM specialist even though the cardiologists were blinded to the patient's genetic status[19]. Further, a positive genetic test conferred a hazard ration of 4.3 (1.5–12.5 95% confidence interval) which was greater than that of age, degree of outflow tract obstruction, and presence atrial fibrillation. Subsequently, these same distinguishing features between patients with a positive genetic test and those with a negative genetic test were seen in an independent cohort of patients with HCM from Italy. In this study, Olivotto and colleagues demonstrated a marked difference in outcome among those with a positive myofilament genetic test (Figure 3)[60]. In this collection of 203 index cases, the 126 patients (62%) with a positive HCM genetic test had an increased combined risk of cardiovascular death, nonfatal stroke, or progression to New York Heart Association class III or IV symptoms compared to those with a negative genetic test. Further,

myofilament-positive individuals demonstrated a greater probability of severe LV systolic (ejection fraction <50%) and diastolic (restrictive filling pattern) dysfunction. These studies represent the first time a “positive genetic test” might be associated with adverse outcome in patients with HCM.

Thus, while mutation-specific risk stratification is not possible, genetic test-based risk stratification appears clinically informative. Still, the translation of this observation into a clinically meaningful and “actionable” biomarker for the patient with already clinically manifest HCM is unclear. Knowing the difference in natural history and the increased likelihood towards disease progression, should patients with a positive genetic test be seen more frequently, intervened upon sooner, and if so, with what interventions? Perhaps, the greatest contribution of the HCM genetic test for the phenotypically positive host will be for the clinician to “relax” somewhat for the patient with a negative HCM genetic test knowing that collectively, such HCM gene test negative-individuals exhibit a milder disease phenotype and are far less likely to progress. Perhaps, such HCM patients with a negative HCM genetic test will require less frequent evaluations and cardiologic tests.

Conclusion

It is clear that HCM is a truly complex disease which can present at any age with variable hypertrophy and outflow tract obstruction, and it can progress in an innocuous fashion, or predispose individuals to arrhythmia and SCD. This clinical heterogeneity is matched by the genotypic heterogeneity associated with the pathogenesis of this disease. While the mutated genes which serve as the molecular substrate for this disease are becoming increasingly understood, the mechanistic link between a HCM-susceptibility mutation and disease pathogenesis and expressivity remains a significant challenge to elucidate. In large part, this is due to the multiplicity of factors which can modulate disease phenotype beyond the discrete HCM-causative pathogenic substrate. These additional patient-specific factors, whether intrinsic or extrinsic to the myocardium, can cause the same genetic misspelling to ultimately lead to dramatically different phenotypic variations of HCM in different individuals. Until these factors are more clearly understood, and the explanation for the contradiction and non-replication of many of the studies trying to link specific HCM mutations to a particular phenotype is understood, there is no prognostic utility of a specific mutation in isolation.

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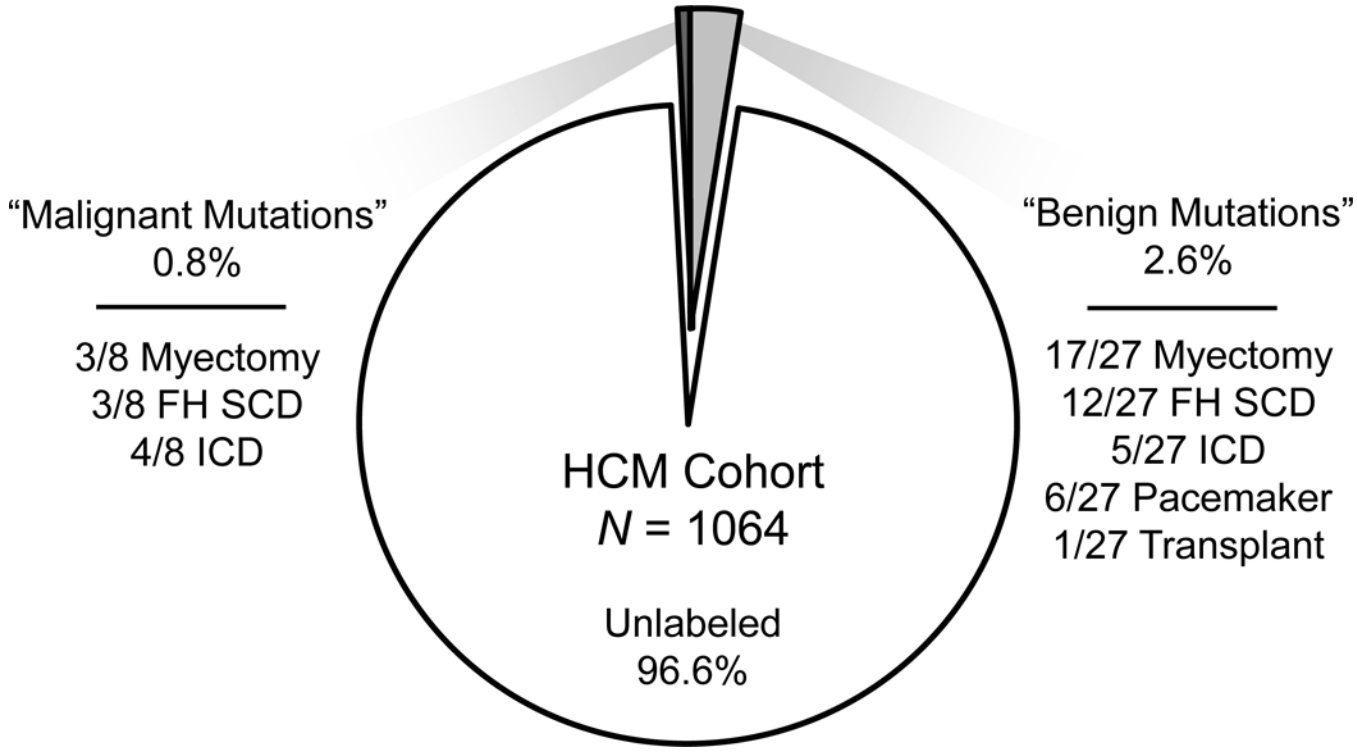

Figure 1:
Pie chart of the proportion of our 1064-proband HCM cohort that hosted literature-described "malignant" and "benign" mutations. Clinical characteristics of these patients, such as whether the proband underwent myectomy, are noted. FH, family history; SCD, sudden cardiac death; ICD, implantable cardioverter-defibrillator.

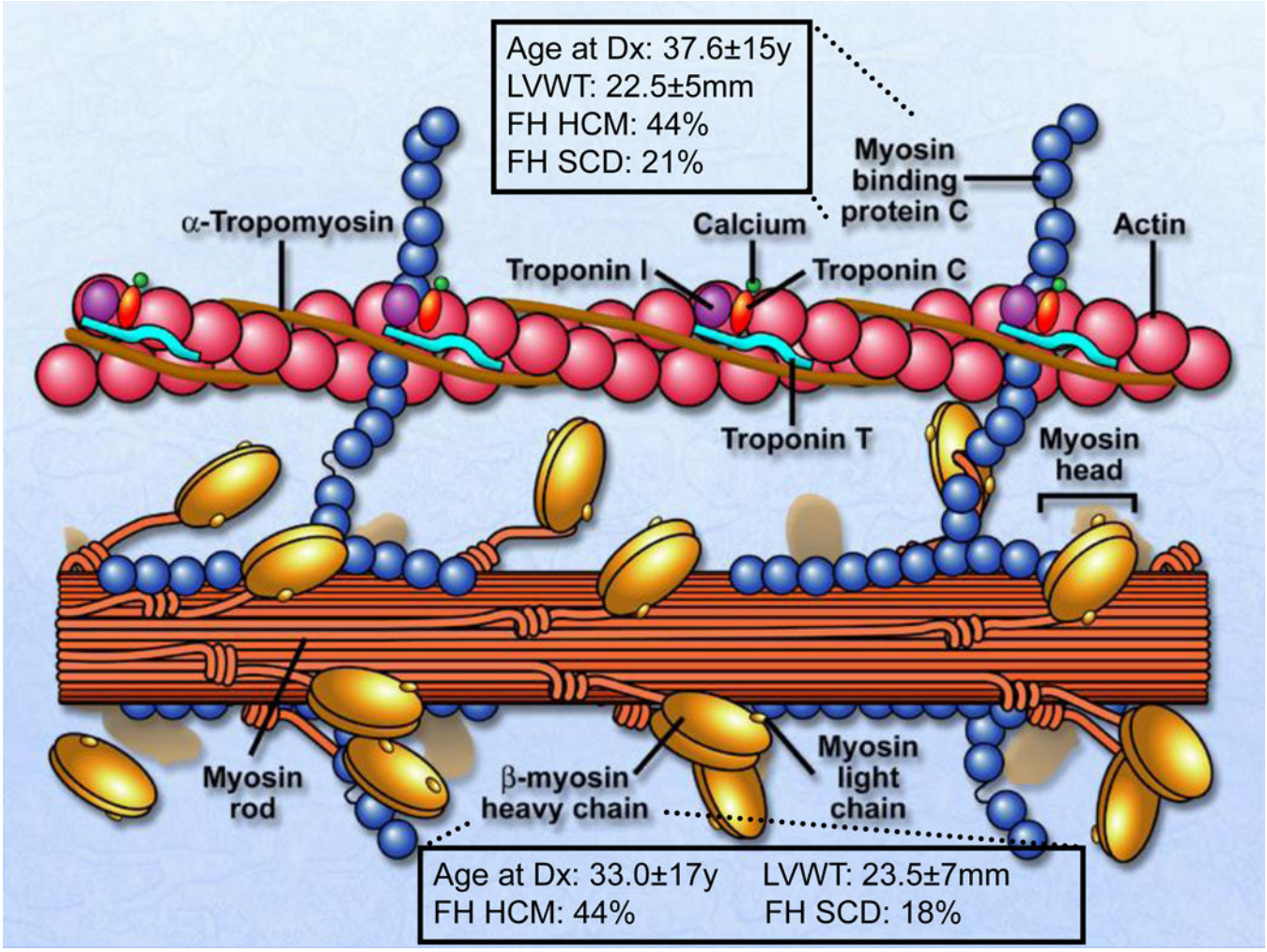

Figure 2:

Drawing of the proteins which comprise the cardiac myofilaments include *MYPBC3*-encoded myosin binding protein C and *MYH7* encoded β-myosin heavy chain. Clinical characteristics for patients hosting *MYBPC3* and *MYH7* mutations are given and adapted from Van Driest et al[58]. Drawing adapted from Spirito et al[37]. Dx, age at diagnosis in years; LVWT, left ventricular wall thickness; FH, family history; SCD, sudden cardiac death.

A

Characteristic	Positive	Negative	P-Value
Age at Dx (yr)	36±17	45±19	<0.001
MLVWT (mm)	23±7	21±6	0.002
FH of HCM	68%	59%	<0.001
ICD	25%	10%	<0.001

Characteristic	HR	95% CI	P-Value
Positive Test	4.3	1.5-12.5	0.008
Age (per yr)	1.03	1.01-1.06	0.017
LVOTO (≥30mmHg)	1.33	0.7-2.7	0.43
Atrial Fibrillation	1.67	0.7-3.8	0.22

B

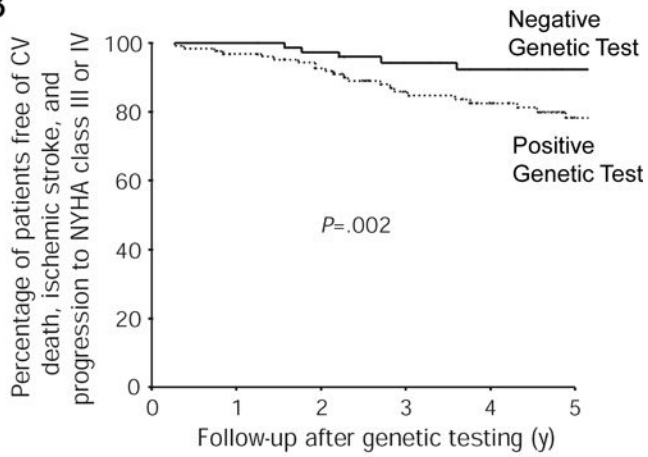

Figure 3:

A) Top, table of the associations between clinical characteristics and a positive and negative HCM genetic test. Variance measured as standard deviation. Dx, diagnosis; MLVWT, maximal left ventricular wall thickness; FH, family history; ICD, implantable cardioverter-defibrillator. Bottom, table of the hazard ratio and 95% confidence interval of a positive HCM genetic test compared with age, left ventricular outflow tract obstruction, and atrial fibrillation. Adapted from Van Driest et al[19]. **B)** Kaplan-Meier analysis of the probability of cardiovascular (CV) death, nonfatal ischemic stroke, or progression to heart failure with a negative and positive HCM genetic test.

Table 1:

Summary of Hypertrophic Cardiomyopathy-Associated Genes

Gene	Locus	Protein	Frequency
Myofilament/Sarcomeric HCM			
Giant Filament			
TTN	2q31	Titin	Rare
Thick Filament			
MYH7	14q11.2-q12	β-Myosin heavy chain	25–40%
MYH6	14q11.2-q12	α-Myosin heavy chain	Rare
MYL2	12q23-q24.3	Regulatory myosin light chain	Rare
MYL3	3p21.2-p21.3	Essential myosin light chain	Rare
Intermediate Filament			
MYBPC3	11p11.2	Cardiac myosin-binding protein C	25–40%
Thin Filament			
TNNT2	1q32	Cardiac troponin T	3–5%
TNNI3	19p13.4	Cardiac troponin I	1–5%
TPM1	15q22.1	α-Tropomyosin	1–5%
ACTC	15q14	α-Cardiac actin	Rare
TNNC1	3p21.1	Cardiac troponin C	Rare
Z-Disc HCM			
CSRP3	11p15.1	Muscle LIM protein	Rare
TCAP	17q12-q21.1	Telethonin	Rare
LBD3	10q22.2-q23.3	LIM binding domain 3	Rare
ACTN2	1q42-q43	α-Actinin 2	Rare
VCL	10q22.1-q23	Vinculin/metavinculin	Rare
MYOZ2	4q26-q27	Myozenin 2	Rare
ANKRD1	10q23.31	Cardiac ankyrin repeat protein	Rare
Calcium-Handling HCM			
PLN	6q22.1	Phospholamban	Rare
CALR3	19p13.11	Calreticulin 3	Rare
CASQ2	1p13.3-p11	Calsequestrin	Rare
RYR2	1q42.1-q43	Ryanodine receptor 2	Rare

Table 2:

Summary of HCM Phenocopy Genes

Syndrome	Gene	Locus	Protein
Barth syndrome/LVNC	*DTNA*	18q12	α-dystrobrevin
Barth syndrome/LVNC	*TAZ*	Xq28	Tafazzin (G4.5)
Danon's syndrome/WPW	*LAMP2*	Xq24	Lysosome-associated membrane protein 2
Fabry's disease	*GLA*	Xq22	α -galactosidase A
Forbes disease	*AGL*	1p21	Amylo-1,6-glucosidase
Friedrich's ataxia	*FXN*	9q13	Frataxin
Noonan's syndrome	*KRAS*	12p12.1	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
Noonan's syndrome	*SOS1*	2p22-p21	Son of sevenless homolog 1
Noonan's syndrome, LEOPARD syndrome	*PTPN11*	12q24.1	Protein tyrosine phosphatase, non-receptor type 11, SHP-2
Noonan's syndrome, LEOPARD syndrome	*RAF1*	3p25	V-RAF-1 murine leukemia viral oncogene homolog 1
Pompe's disease	*GAA*	17q25.2-q25.3	α−1,4-glucosidase deficiency
WPW	*PRKAG2*	7q35- q36.36	AMP-activated protein kinase

LVNC, left ventricular non-compaction; WPW, Wolff-Parkinson-White syndrome

Table 3:

Summary of Contradictory Follow-Up Studies

"Malignant"			
MYH7	**Family/Cohort**	**Phenotype**	**Ref**
R403Q	Family	No sudden death in 6/6 individuals	[41]
TNNT2			
I79N	Family	No sudden death in 9/9 individuals	[43]
R92W	Cohort	No family hx of SCD	[50]
"Benign"			
MYH7			
V606M	Family	SCD <30 years of age in 4/8 individuals	[41]
V606M	Family	Youthful SCD in three individuals	[42]
V606M	Cohort	Aborted SCD, family hx of SCD	Mayo
R663H	Cohort	Aborted SCD, family hx of SCD	Mayo
R719Q	Cohort	Family hx of SCD, transplant	[47]
R719Q	Cohort	Family hx of SCD, family hx of transplant	Mayo
L908V	Cohort	Family hx of SCD	[47]
L908V	Cohort	Family hx of SCD	Mayo

Family/cohort, the type of follow-up study conducted; phenotype, pertinent clinical characteristics of kindred within the family or probands within the cohort studied; hx, history; SCD, sudden cardiac death/arrest. Mayo, results from analysis of the unpublished 1064 Mayo Clinic HCM probands.