Is genotype clinically useful in predicting prognosis in hypertrophic cardiomyopathy?

**Genetics and Clinical Destiny: Improving Care in Hypertrophic Cardiomyopathy**

Carolyn Y. Ho, MD

The greatest opportunity afforded by discovering the genetic basis of human heart disease is accurate prediction and prevention of illness. Hypertrophic cardiomyopathy (HCM) provides a paradigm to fulfill this opportunity. Human genetics research has identified many gene mutations that result in cardiac hypertrophy, of which HCM is the most common and well-characterized. Sarcomere gene mutations in HCM result in left ventricular hypertrophy (LVH), myocardial fibrosis and disarray, diastolic dysfunction, and increased risk for arrhythmias, sudden death, and heart failure. Making the clinical diagnosis of HCM currently hinges on identifying unexplained hypertrophy, but LVH is a sign of established disease only. This finding cannot identify at-risk mutation carriers and cannot discriminate HCM from other forms of cardiac hypertrophy, either genetic or acquired.

In contrast, gene-based diagnosis is not constrained in this manner. Defining the mutation that causes LVH in an individual provides an accurate diagnosis for that patient and, therefore, considerable information about their prognosis. Moreover, unlike clinical diagnosis which only identifies overt disease, genetic diagnosis can also identify patients at risk for developing disease. There are certainly many challenges to realizing the full potential of genetics, but such information provides unprecedented promise. Continued efforts to refine and clinically implement genetic testing in HCM will bring important payoffs in the future, and will serve as a model for other genetic cardiovascular diseases. By identifying at-risk individuals prior to clinical diagnosis, characterizing disease pathogenesis, and fostering development of novel therapies to delay or prevent phenotypic expression, genetic discoveries will improve the lives of our patients with HCM.

**Genetics of HCM**

The familial, autosomal-dominant nature of HCM has long been recognized, but the precise genetic etiology was discovered through genome-wide linkage studies in the 1980s. This seminal work identified pathogenic mutations in genes encoding contractile proteins and established the paradigm that HCM is a disease of the sarcomere.1,2 Over the past 20 years, more than 900 individual mutations have been identified, the majority (≈75% to 80%) involving cardiac β-myosin heavy chain (MYH7) and cardiac myosin binding protein C (MYBPC3). Other sarcomere genes, including cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), α-tropomyosin (TPM1), the myosin light chains (MYL2, MYL3) and actin (ACTC) have also been established as causing HCM.

Current testing is based on a candidate-gene approach, typically analyzing the 8 sarcomere genes most commonly implicated in HCM, listed above, and a small number of genes associated with metabolic/storage cardiomyopathies that may mimic HCM, including PRKAG2, LAMP2, and GLA, as discussed below. Information regarding
clinical genetic testing can be obtained at http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests. Sarcomere mutations are found in approximately 65% of adult and pediatric patients with familial HCM and approximately 40% of patients with unexplained LVH but no family history of disease.3–7

In addition to these well-established sarcomere genes, mutations in other sarcomere-associated genes have been reported in association with HCM, including cardiac troponin C (TNNC1), z-disc components telethonin (TCAP), and muscle LIM protein (CRP3).8–10 Mutations in these genes are extremely rare—identified in only a small number of isolated probands. Due to the lack of rigorous genetic support, they have not yet been definitively demonstrated to be disease-causing. Clinical genetic testing is not available.

Table 1. Benefits and Limitations of Genetic Testing in HCM

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Examples and Consequences</th>
<th>Future Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm diagnosis in ambiguous situations</td>
<td>An athlete with LVH and a pathogenic sarcomere mutation is advised to stop competitive sports due to sudden death risk</td>
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<tr>
<td>...</td>
<td>A patient with mild LVH, hypertension, syncope, and a family history of sudden death is found to have a pathogenic sarcomere mutation, triggering family screening and ICD placement</td>
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</tr>
<tr>
<td>Definitive identification of at-risk family members</td>
<td>Longitudinal clinical screening is focused only on mutation carriers, reducing health care costs and unnecessary restrictions in mutation (-) relatives</td>
<td>Studying young mutation carriers without LVH will identify early phenotypes of sarcomere mutations and improve understanding of disease mechanisms</td>
</tr>
<tr>
<td>...</td>
<td>A patient with a severe mutation (early SCD and transplant in relatives) has reproductive choices, including preimplantation genetic diagnosis</td>
<td>Mutation carriers without LVH will be targeted for treatment trials to prevent disease development</td>
</tr>
<tr>
<td>Accurate identification of disease phenocopies</td>
<td>Genetic testing reveals Fabry disease and the patient is referred for multi-system care and potential enzyme replacement therapy</td>
<td>...</td>
</tr>
<tr>
<td>...</td>
<td>A LAMP2 mutation is identified and evaluation for cardiac transplantation is initiated early, just before precipitous clinical deterioration</td>
<td>...</td>
</tr>
<tr>
<td>Definition of disease etiology</td>
<td>Reassurance for genotype-negative family members, including older relatives who may have LVH due to HTN</td>
<td>Improve understanding of disease pathogenesis</td>
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<tr>
<td>...</td>
<td>...</td>
<td>Support development of new treatment strategies based on mechanistic insights</td>
</tr>
<tr>
<td>Limitations</td>
<td>Genotype-phenotype correlations are still emerging</td>
<td>More comprehensive and longitudinal studies of mutation carriers will identify more precise phenotypes</td>
</tr>
<tr>
<td>Incomplete knowledge of all genes associated with LVH</td>
<td>Results currently may not change management</td>
<td>Next generation sequencing will allow a larger no. of genes to be analyzed simultaneously and will detect a greater variety of mutations, including copy no. variants</td>
</tr>
<tr>
<td>Pathogenicity of DNA variants can be ambiguous</td>
<td>Negative genetic testing results are not informative</td>
<td>Improved assays to determine pathogenicity are in development</td>
</tr>
<tr>
<td>...</td>
<td>Genetic test results may currently be difficult to interpret</td>
<td>Increasing numbers of genotyped patients will improve assignment of pathogenicity</td>
</tr>
<tr>
<td>...</td>
<td>If variant pathogenicity is uncertain, genotype cannot be used for clinical decision-making</td>
<td>Next generation sequencing will substantially reduce costs</td>
</tr>
<tr>
<td>Genetic testing is expensive</td>
<td>Genetic testing may not currently be feasible for all patients</td>
<td></td>
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</tbody>
</table>

Genotype Provides Insights Into HCM Diagnosis, Prognosis, and Treatment

Cardiac hypertrophy is a sign of disease rather than a specific diagnosis. Disease processes other than HCM can lead to the common finding of LVH, but have different prognoses. The underlying pathological process cannot be determined on the basis of LV morphology alone. In contrast, the identification of a pathogenic sarcomere gene mutation establishes a definitive diagnosis of HCM and the exact genetic etiology of disease. This information provides both key insight into the patient’s prognosis and guidance in the management of their family. Furthermore, leveraging genetic insights will teach us about the fundamental biology of HCM and drive development of im-
proved treatment strategies. Table 1 describes the benefits and limitations of genetic testing.

Current Applications of Genetic Testing

Genetic Testing Identifies Individuals at Risk for Developing Disease

In medicine, we are rarely able to identify individuals who will develop disease years before typical clinical manifestations appear. Genetic testing in HCM provides extraordinary opportunities in this regard. It is particularly fruitful in the context of familial disease, since a sarcomere mutation can be identified in ∼60% of probands, and half of their first degree relatives are predicted to carry the mutation. Genotype determination provides substantial prognostic insight through its ability to definitively and precisely identify relatives at risk for developing disease at an early stage, independently of other clinical features. Simply put, if the family’s pathogenic mutation is not inherited, there is no risk of HCM, either in that relative or their offspring. If a mutation is present, HCM is very likely to develop. Longitudinal clinical follow up can then be focused on pathogenic mutation carriers, as only they are at risk (Figure 1). Family members who have not inherited a pathogenic mutation can be reassured that neither they nor their offspring are at risk for disease development and do not require serial clinical evaluation or lifestyle restrictions. Figure 2 presents a general framework for incorporating genetic testing in HCM patients and families. Predictive testing in HCM families with a known pathogenic sarcomere mutation can also be used for reproductive planning through preimplantation genetic diagnosis to attempt to achieve a pregnancy with an embryo that does not carry the mutation.

Such gene-based diagnostic strategies in families have economic as well as medical benefits. Because HCM follows autosomal dominant inheritance and the penetrance of LVH is age-dependent, serial clinical screening of first degree relatives is recommended, including physical examination, 12-lead EKG, and echocardiography. Cardiac magnetic resonance imaging, Holter monitoring, and exercise testing may also be pursued. This translates into roughly $1000 for each family member for each visit. Over time, this will cost ≈$6000 to follow the child of an HCM patient through puberty when the frequency of screening is highest, and ≈$20,000 over their lifetime. Compared with these longitudinal expenses, genetic testing is a relative bargain. It currently costs ≈$3000 to identify a mutation in a family through genetic testing of a single affected individual. Predictive genetic testing for the rest of the family to determine whether or not the mutation has been inherited costs ≈$400 per relative. Since only mutation carriers are at risk for developing HCM, genetic testing results will reduce the number of family members who require serial follow up, as illustrated in Figure 1. This will lead to substantial healthcare cost-savings, especially as the price of genetic testing falls in the future. An important caveat to this strategy is that there must be a high degree of confidence that the family’s mutation is pathogenic. If there is uncertainty as to whether
an identified DNA sequence variant can cause disease, it should not be used to drive management.

**Genetic Testing Clarifies Ambiguous Diagnoses**

Clinicians may be confronted with patients who have mild LVH and confounding features such as mild to moderate hypertension or intensive athletic training. In these situations, there may be ambiguity as to whether the degree of hypertrophic remodeling can be explained by coexisting pressure load or physical conditioning, or whether a primary cardiomyopathy is present. Since HCM is a genetic condition associated with increased risk for arrhythmias and sudden death, clarifying the underlying etiology is of major importance to the patient and their family. Distinguishing HCM from hypertensive heart disease or athlete’s heart may be straightforward, for example, by documenting regression of LVH after controlling blood pressure or stopping athletic training. However, the diagnosis may remain unclear despite comprehensive clinical evaluation. Identifying a pathogenic sarcomere mutation in this setting would confirm the diagnosis of HCM and trigger appropriate management of the patient and their family, including cessation of competitive athletics, assessment of sudden death risk, and screening relatives.

**Not All Cardiac Hypertrophy Is HCM: Genetic Testing Identifies Phenocopies**

Cardiac hypertrophy is a relatively nonspecific phenotype that may reflect the final common pathway for a number of different disease processes. It does not indicate etiology or reveal underlying pathophysiology. In contrast, genetic testing affords a level of discrimination not attainable by cardiac imaging or even histological evaluation. Gene-based diagnosis can identify the precise disease process underlying a patient’s hypertrophy at the molecular level. As a result of broader application of genotyping, phenocopies of HCM have been identified where cardiac hypertrophy is caused by mutations in genes distinct from those which encode sarcomere proteins (Table 2). For example, a separate category of metabolic cardiomyopathies has been described in families and sporadic patients with unexplained LVH who commonly also have concomitant conduction abnormalities (progressive atrioventricular block, atrial fibrillation, ventricular preexcitation). In these individuals, cardiac hypertrophy is caused by mutations in PRKAG2, encoding the γ2 regulatory subunit of adenosine monophosphate-activated protein kinase, and in LAMP2, encoding the X-linked lysosome associated membrane protein. Mutations in these genes are rare but may be present in roughly 2% to 12% of individuals with a clinical
Table 2. Mutations in Genes Associated With Phenocopies of HCM, Resulting in Metabolic or Storage Cardiomyopathy

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Associated Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-Subunit, AMP kinase</td>
<td>PRKAG2</td>
<td>7q36</td>
<td></td>
<td>Preexcitation and conduction disease</td>
</tr>
<tr>
<td>Lysosome associated membrane protein</td>
<td>LAMP2</td>
<td>Xq24</td>
<td>Danon disease</td>
<td>Cardiomyopathy, skeletal myopathy, and neurologic involvement may be present; preexcitation on EKG; rapid progression to end stage heart failure in adolescence, particularly males; high risk of sudden death</td>
</tr>
<tr>
<td>α-Galactosidase</td>
<td>GLA</td>
<td>Xq22</td>
<td>Fabry syndrome</td>
<td>Assess plasma or lymphocyte α-Gal activity (males); consider enzyme replacement</td>
</tr>
</tbody>
</table>

Prognostic insight can be gained comparing individuals with and without sarcomere mutations. In addition to the HCM phenocopies discussed above, sarcomere mutations are not currently identified in ≈30% to 60% of individuals with a clinical diagnosis of HCM. The molecular basis of unexplained LVH in the absence of a sarcomere mutation is unknown and may represent complex rather than Mendelian genetics. Sarcomere-negative subjects cannot be reliably differentiated on the basis of cardiac imaging or clinical features alone. However, making the distinction may be important from a diagnostic and prognostic standpoint, as the outcome of patients with sarcomere mutations appears to be worse than that of those without. In one of the few longitudinal studies of a genotyped HCM cohort, investigators demonstrated an increased risk of cardiovascular death, nonfatal stroke, or progression to New York Heart Association III/IV functional class in HCM patients with sarcomere mutations as compared to those with negative genetic testing. As shown in Figure 4, mutation-positive HCM patients were significantly more likely to achieve the composite end point, and to develop systolic and severe diastolic dysfunction as compared to mutation-negative patients. Multivariate analysis showed that the presence of a sarcomere mutation was the strongest independent predictor of an adverse outcome with a hazard ratio of 4.27 (95% confidence interval 1.43, 12.48; \( P = 0.008 \)). Genotype outperformed clinical variables such as age, the presence of LV outflow tract obstruction, and atrial fibrillation.

Gene dosage likely also influences prognosis in HCM. Approximately 3% to 5% of probands with HCM have more than one sarcomere mutation (compound or double heterozygosity). Individuals with more genetic “hits” tend to have more severe disease expression, even if the variant results in relatively mild disease in isolation. Disease can be particularly severe in rare cases of triple mutations and homozygosity. At the level of the individual gene, prognostic insights have been derived by comparing MYH7 and MYBPC3 mutations, as well as by assessing mutation type and the functional domain affected. MYBPC3 mutations have been associated with delayed, even elderly-onset disease, and may have a higher rate of incomplete penetrance than MYH7 mutations. In children, MYBPC3 missense mutations (resulting in an amino acid substitution) were more common, whereas trun-
cation mutations predominate in adults. In *MYH7* mutations, amino acid substitutions resulting in a change of charge in the ATP hydrolysis active site or in the head–rod junction may be associated with a higher risk of heart failure and reduced survival. At the level of the *individual nucleotide*, a small number of specific point mutations have been associated with more predictable severe phenotypes in unrelated HCM families. For example, the clinical course of *MYH7* missense mutations in which arginine is replaced by glutamine at amino acid residue 403 (Arg403Gln) and Arg719Trp have shown a markedly increased risk of sudden death or near-universal development of end-stage heart failure requiring cardiac transplantation, respectively. Certain *TNNT2* mutations (Arg92Trp, Arg92Gln, Ile79Asn) have also been associated with an increased risk of sudden death in certain families. However, these mutations are rare, accounting for 0.2 to 0.6% of probands referred for genetic testing (personal communication, Dr. H. Rehm, Director, Laboratory for Molecular Medicine) so a strategy of screening only for previously characterized mutations will not have appreciable clinical yield. Furthermore caution is needed in generalizing these observations to individual patients, as exceptions have been well documented and mutations are not uniformly malignant or benign. Nonetheless, identifying both potential trends and exceptions helps to further the understanding of myocardial biology and disease pathogenesis.

**Future Applications of Genetics: Changing Clinical Destiny**

Our current approach to diagnosing and managing HCM is unsatisfying as it is largely reactive and palliative. Patients are diagnosed when unexplained LVH is identified and treated to alleviate symptoms. To truly transform medicine, we need more precise information regarding pathogenesis and therapies that prevent disease. This can be achieved by...
integrating basic science discovery with patient management in HCM. A combined genetic and clinical approach allows identification of individuals at risk for developing disease independently of clinical findings, better characterization of the full spectrum of phenotypes caused by sarcomere mutations, and development of rational new strategies to change the natural history of disease, based on mechanistic insights.

**Gene-Based Diagnosis: Redefining Phenotype**

Genetic testing can identify individuals who carry pathogenic sarcomere mutations, and are therefore at high risk for developing disease, before a clinical diagnosis of HCM can be made. As such, this population provides a remarkable window into the future, casting new light on the earliest cellular responses to sarcomere gene mutations and teaching us about the biology of disease. Moreover, preclinical mutation carriers are a key target of future trials designed to prevent development or progression of HCM.

Using this approach, novel early phenotypes have been identified in prehypertrophic sarcomere mutation carriers, providing key information about the development of myocardial function, energetics, biochemistry, and fibrogenesis in disease pathogenesis (Figure 5). At the functional level, mutation carriers have been found to have diastolic dysfunction before LVH develops, as reflected by reduced early myocardial relaxation velocities (E’ velocity) on tissue Doppler interrogation (Figure 5A). At the biophysical level, impaired myocardial energetics has been proposed as a unifying mechanism by which sarcomere mutations give rise to cardiac hypertrophy and heart failure.  

At the histological level, myocardial fibrosis is a hallmark of HCM and postulated to be the substrate underlying sudden cardiac death, ventricular tachyarrhythmias, LV dysfunction, and heart failure. The trigger for increased myocardial fibrosis in HCM is unknown. Cardiac gene expression studies performed on young, prehypertrophic HCM mice showed early activation of pathways involved in fibrosis and collagen deposition even when cardiac histology is normal. Recent studies in humans also show evidence of increased collagen synthesis in sarcomere mutation carriers before the development of LVH. Increased levels of C-terminal propeptide of type I procollagen indicate that a profibrotic milieu is present early in human HCM (Figure 5C) in the absence of cardiac hypertrophy or visible fibrosis on cardiac magnetic resonance imaging.

These studies indicate that sarcomere mutations have considerable adverse impact on the heart before the development of clinically recognized disease. Diastolic dysfunction, impaired myocardial energetics, and increased collagen synthesis appear to be early phenotypes that are intrinsic manifestations of the underlying sarcomere mutation, rather than a secondary reaction to the abnormalities in myocardial structure and function that accompany clinically overt disease. The presence of such early phenotypes may identify individuals at risk for arrhythmias, sudden death, or heart failure. Furthermore, identification of new phenotypes may highlight previously unrecognized pathways that contribute to disease development that may be targeted therapeutically. Finally, quantitative traits such as E’ velocity, PCr/ATP ratio, and serum biomarkers may serve as surrogate endpoints to monitor treatment effect, thereby fostering development of novel treatment strategies to change the natural history of HCM.

**Translating Genetic Discoveries: Preventing Disease**

Greater understanding of the molecular pathogenesis of HCM provides the necessary rationale to develop new therapies designed to slow or prevent disease development and improve outcomes in HCM. Disease-modifying studies are in active development in animal models of HCM. These genet-
ically modified animals carry sarcomere mutations that cause human disease and replicate the HCM phenotype. For example, in mice carrying the Arg403Gln missense mutation in MYH7, abnormalities in intracellular Ca\(^{2+}\) homeostasis (present at 4 weeks of age) are one of the earliest detectable manifestations of sarcomere mutations, preceding the development of diastolic abnormalities (\(\approx\) age 6 weeks), and visible LVH, fibrosis and disarray (\(\approx\) age 20 weeks). Early treatment with the L-type calcium channel blocker diltiazem appeared to mitigate development of hypertrophy and fibrosis if started prior to development of LVH. More recently, early treatment with losartan in mice with an Arg719Trp MYH7 mutation has shown promising results in mitigating the development of fibrosis, potentially by inhibiting TGF-\(\beta\)-mediated pathways. A pilot human randomized control trial comparing diltiazem to placebo in sarcomere mutation carriers who have not yet developed LVH is ongoing (http://clinicaltrials.gov/ct2/show/NCT00319982). A collaborative, NIH-sponsored multicenter effort has recently been established to facilitate clinical translational research in early HCM and to support future trials of disease prevention. Other strategies have been trialed in animal models to reverse the effects of established disease by targeting myocardial fibrosis. Administration of angiotensin II receptor blockers (losartan), HMG-CoA reductase inhibitors (simvastatin), aldosterone antagonists (spironolactone), and the antioxidant N-acetylcysteine have shown encouraging results in decreasing myocardial fibrosis and collagen content. Notably, all of these trials were performed on animal models with specific genetic substrate and may only be applicable to patients with sarcomere mutations and not other forms of cardiac hypertrophy. As such, genotype may profoundly influence disease management and prognosis in the future. Limitations of Genetic Testing When the genetic underpinnings of HCM were first described, there was great optimism and perhaps unrealistic expectations that this knowledge would quickly revolutionize the prognosis and management of disease. However, as is typically the case with complex biological systems, practical application of these scientific breakthroughs has not been immediate or straightforward. Significant obstacles are created by the marked heterogeneity of HCM and by difficulties in determining whether novel DNA sequence variants are pathogenic and capable of causing disease. Therefore, the utility of incorporating genotype data into clinical management has been appropriately criticized. As indicated in Table 1, it is important to recognize the advantages, limitations, implications, and applications of genetic testing both now and in the future.

The daunting clinical and genetic variability of HCM limit robust genotype-phenotype correlations. In considering sarcomere genes only, mutations can occur in tens of thousands of base pairs of DNA and only \(\approx 1000\) have been identified so far, often only in a single proband. Given the great variability in the genetic cause of HCM, it is not surprising that clinical...
outcome cannot be accurately predicted from identifying single mutations. Moreover, although mutations trigger development of disease, they are not the sole determinant of the final phenotype, as genetic modifiers, environmental influences, and comorbid illnesses exert important influences that are currently not well understood. Mutations initially characterized as “benign” or “malignant” in the context of studying large families have not always result in a consistent phenotype in unrelated probands.34,59 These unavoidable complexities diminish direct application of genotyping for rigorous prediction of risk. Identifying the exact sequence variant responsible for causing HCM typically will not directly impact prognosis or management decisions for the individual patient, such as the need for an implantable cardioverter-defibrillator, indications for surgery, exercise recommendations, or initiation of medical therapy.

Additionally, sarcomere mutations are not universally identified in all patients with a clinical diagnosis of HCM. Depending on other characteristics such as family history, over 50% of patients may have negative, and therefore noninformative, genetic testing from analysis of sarcomere genes. This statistic again highlights that LVH is a crude and nonspecific tool for diagnosing disease. However, the imperfect yield of HCM genetic testing also reflects incomplete knowledge of all genes that cause LVH. Ongoing gene discovery efforts will identify new genes associated with HCM, but this process takes many years.

Other technical issues that limit the yield of genetic testing will be solved more quickly. Next-generation sequencing platforms, and ultimately whole exome strategies, will soon be able to interrogate millions of bases of DNA faster and cheaper than current strategies.60 In addition to improving the availability of genetic testing because of lowered costs, this technology will allow two major advances. First, many more genes can be interrogated simultaneously—an improvement from the existing strategy of examining a fixed subset of genes (sarcomere) for specific diseases (HCM). More comprehensive sequencing will identify potential interactions between different genetic pathways, beyond the sarcomere. For example, variants in genes implicated in other cardiomyopathies, inherited arrhythmias, calcium regulation, and myocardial metabolism may interact to shape disease phenotype. Secondly, new sequencing strategies will also be able to determine if variation in the number of copies of sarcomere genes cause HCM. Copy number variants have been implicated in congenital heart disease, neurological disease, and malignancy, and may indeed be relevant in HCM but undetected by traditional sequencing strategies.

**Conclusions**

Genotype analysis offers unique information regarding prognosis in HCM that is relevant both now and in the future. Genetic testing provides definitive diagnosis of disease, preclinical recognition of at-risk individuals, and a powerful means to dissect disease pathogenesis. Identifying the genetic basis of disease is a critical first step in the long journey that will allow us to advance and transform medicine based on mechanistic insight, early diagnosis, and disease prevention.

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None.

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Response to Ho

Andrew P. Landstrom, BS; Michael J. Ackerman, MD, PhD

Traditionally considered a monogenic disease whereby mutations in sarcomeric protein-encoding genes result in left ventricular hypertrophy, we are beginning to understand the numerous factors influencing the phenotypic variability seen in hypertrophic cardiomyopathy (HCM). Although advances have been made, we are still unable to precisely predict the penetrance and expressivity of even the most robustly investigated HCM-associated mutations. As such, mutation type is not yet prognostically useful.

Despite the findings of early studies that specific HCM-associated mutations could be “benign” or “malignant” in nature, numerous subsequent studies have called these early conclusions into question. As acknowledged by Ho, this lack of replication argues against the notion of a prognostically relevant HCM-associated mutation. Also acknowledged by Ho, “benign”- or “malignant”-labeled mutations make up an almost negligible proportion of all genotype-positive individuals, which minimizes the epidemiological significance of these descriptors. At the level of the gene, there is a similar degree of controversy surrounding genotype-specific clinical associations. Despite early studies suggesting genotype-phenotype correlations among patients hosting HCM-associated mutations in MYH7, MYBPC3, or TNNT2, we and others have been unable to replicate these associations in large cohorts of unrelated patients with HCM.

Ultimately, as Ho also concedes, the true prognostic role of HCM genetic testing may not lie with the type or location of a particular mutation, but rather whether the test is positive. Should the current studies be validated, a positive HCM genetic test, regardless of genotype, location, or the discrete mutation identified, may host the greatest prognostic value.
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