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Identifying Sarcomere Gene Mutations in HCM: A Personal History

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Abstract

This article provides an historical and personal perspective on the discovery of genetic causes for hypertrophic cardiomyopathy (HCM). Extraordinary insights of physicians who initially detailed remarkable and varied manifestations of the disorder, collaboration among multidisciplinary teams with skills in clinical diagnostics and molecular genetics, and hard work by scores of trainees, solved the etiologic riddle of HCM, and unexpectedly demonstrated mutations in sarcomere protein genes as the cause of disease. In addition to celebrating 20 years of genetic research in HCM, this article serves as an introductory overview to a thematic review series that will present contemporary advances in the field of hypertrophic heart disease. Through the continued application of advances in genetic methodologies, combined with biochemical and biophysical analyses of the consequences of human mutations, fundamental knowledge about HCM and sarcomere biology has emerged. Expanding research to elucidate the mechanisms by which subtle genetic variation in contractile proteins remodel the human heart remains an exciting opportunity, one with considerable promise to provide new strategies to limit or even prevent HCM pathogenesis.

Keywords

Hypertrophic cardiomyopathy; gene mutations; sarcomere

Late in the 1950's an enigmatic myocardial disease captured the attention of cardiologists, surgeons, and pathologists. Characterized as asymmetric septal hypertrophy,¹ functional aortic stenosis,^{2,3} hypertrophic obstructive cardiomyopathy,⁴ and idiopathic hypertrophic subaortic stenosis,⁵ early reports described dramatic clinical events associated with the disease: a healthy 14-year old succumbed while being "chased around the playground of his school"; a cyclist collapsed and died "during a thunderstorm without evidence of electric burns or serious injury resulting from the fall".¹ Post mortem examination of the hearts of sudden death victims showed striking cardiomegaly (Fig. 1a), with some heart weights > 500 gm, stunning asymmetry with disproportionate involvement of the interventricular septum, and bizarre histopathology with disordered muscle bundles, myocyte disarray and markedly increased myocardial fibrosis (Fig. 1b).

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None.

Sudden cardiac death due to unexplained ventricular hypertrophy had in fact been recognized for centuries⁶ and case reports from 1869 described distinctive cardiac murmurs⁷ and arrhythmias in patients who at autopsy had muscular obstruction of the left ventricular outflow tract obstruction and distortion of the anterior mitral valve leaflet.⁸

A plethora of manuscripts expanded upon the anatomic, histopathologic, and hemodynamic features found in affected patients. Authors of these studies appended scores of additional names to the disorder, which was emblematic of the clinical diversity exhibited by affected individuals and the lack of expert consensus on their significance. International task forces were formed, including several NHLBI-sponsored Clinical Bethesda Conferences,⁹ that established diagnostic criteria, defined the anatomic and hemodynamic underpinnings of obstruction and outflow tract gradients, assessed the natural history of disease, and proposed treatment strategies. The cause(s) of disease was widely debated. Potential etiologies that were put forward included benign tumors of the heart,¹ excessive catecholamine activation,¹⁰ developmental abnormalities of cardiac neural crest cells,¹⁰ and immune processes mediated by the B-12 HLA locus.¹¹ This last hypothesis was found to be predicated on fabricated data and was subsequently retracted.¹² Yet despite considerable confusion about the disease, two clinical features were universally recognized. First, left ventricular hypertrophy was idiopathic, and occurred in absence of common triggers such as aortic stenosis or hypertension. Second, cases were clustered in families, with first-degree relatives of patients at highest risk for being affected.

In the mid 1980s, two nascent technologies, human genetics and echocardiography, became sufficiently advanced to apply these to the study of hypertrophic cardiomyopathy (HCM). Until then, genetic researchers had limited biomarkers, for example ABO¹³ and HLA¹⁴ typing that could be used to discover the chromosome location of human disease genes. But in 1980 Botstein and colleagues¹⁵ theorized that DNA sequences that were scattered throughout the genome and encoded cleavage sites for restriction enzymes, could theoretically expand this potential. In combination with statistical methodologies to assess the likelihood of co-inheritance of traits while considering genomic recombination events,¹⁶ the field of linkage analyses was born. An early success was the mapping of the Huntington disease gene to chromosome 4 by Gusella and colleagues,¹⁷ an impressive achievement realized through the analyses of only 12 restriction fragment length polymorphisms (RFLPs) in one large affected kindred. Hundreds of novel RFLPs were soon characterized, and in 1987 the first genetic linkage map of the human genome was reported.¹⁸ This resource empowered a simple and elegant experimental design that provided a foothold, the chromosome location, for identification of gene mutations that were responsible for any inherited disease. Four steps were required: accurate ascertainment of affection status in families of sufficient size to define the pattern of inheritance; a renewable source of DNA, usually obtained from EBV-transformed lymphocytes; sequential Southern blot analyses to interrogate potentially hundreds of RFLPs located throughout the genome; statistical analyses that demonstrated significant co-segregation of RFLPs in affected family members.

Despite the feasibility of these steps, analyses were not trivial and success never a guarantee. The early genomic assignments of many RFLPs were erroneous or fairly imprecise, which accounted for a 1985 report of linkage of the cystic fibrosis gene to RFLPs DOCR1-917 and PON,¹⁹ rather than to chromosome 7,²⁰ where these markers were eventually shown to reside. More vexing was the problem of inaccurate diagnoses, due to subclinical findings in otherwise healthy individuals or due to prevalent phenocopies of the disease under study. Undisclosed familial structures (e.g., nonpaternity, intrafamilial adoption) posed still more challenges.

Yet the value of knowing the chromosome location of a disease gene was considerable; this information immediately suggested candidates worthy of further study, based on their “guilt” by genomic location. By establishing expression of candidate genes in diseased tissue and identifying sequence variants in affected patients (but not unaffected relatives or controls) that were predicted to deleteriously impact the encoded protein’s structure or function, the definitive disease gene could be identified – even without a prior knowledge of its biologic function or potential mechanistic role in disease pathophysiology. For researchers studying myocardial diseases this strategy allowed triumph over many challenges faced by this discipline - the absence of myocardial cell lines, limited access to human cardiac tissues, and a paucity of robust models of heart disease.

Rapid clinical advances in cardiac imaging during this time also made hypertrophic cardiomyopathy ripe for human genetic analyses. Cardiac catheterization was the initial gold-standard approach for diagnosis,^{21, 22} but this invasive technique was impractical for defining the affection status of research subjects, in particular those who appeared unaffected based on symptoms and physical examination. Exclusion of subjects without a definitive diagnosis could overcome this issue, but would severely compromise the statistical power of modest sized families. The advent and rapid evolution of echocardiography solved this problem and enabled an accurate, low-risk, and low cost approach for family screening.^{23–25} The widespread adoption of echocardiography in clinical cardiology revealed the unanticipated finding that unexplained LVH, the diagnostic *sine quo non* of hypertrophic cardiomyopathy, occurs in 1 of 500 individuals.²⁶

Collaborating Clinicians, Families and Researchers

We approached Bill McKenna to join a collaboration aimed at discovering the genetic basis for hypertrophic cardiomyopathy in 1987. Trained by Goodwin, McKenna had established expertise in the diverse clinical and echocardiographic manifestations of hypertrophic cardiomyopathy.^{27, 28} We focused on a large family riddled by sudden cardiac death, deemed the “Coaticook curse” by the local community, reported in 1961 by Pare and colleagues,²⁹ as a hereditary cardiovascular dysplasia. Pare’s personal commitment to helping the family engendered such trust that they willingly agreed to participate, despite minimal understanding of genetic research. Over a hundred family members took part in weekend clinics where we performed physical examinations, EKGs, echocardiograms, and obtained blood samples. These studies complemented Pare’s earlier detailed clinical investigations and provided clear evidence for dominant inheritance of the cardiomyopathy and age-related disease expression, information that was critical for designing linkage studies.

In the laboratory scores of Southern blots were performed to assess RFLPs scattered across the genome, until definitive linkage was established with a chromosome 14q marker that yielded a LOD score = 9.3, indicating odds of 2,000,000,000:1 that the disease gene was nearby.³⁰ This finding immediately identified two attractive albeit unexpected candidate genes, *MYH6* and *MYH7*, that encode the α and β myosin heavy chains respectively. Both genes were robustly expressed in the heart, separated by only 3600 bp on chromosome 14,³¹ and the complete nucleotide sequence of *MYH7* was already published.^{32, 33} Despite these resources, it was technically impractical to directly sequence the 30 kb of both genes in samples from affected individuals. We elected to fine-structure map the locus with restriction enzymes. While this was ultimately a productive decision, this approach initially led to the identification of a polymorphic *MYH7* fragment in all samples from affected family members as well as in one unaffected individual. Several vexing possibilities might have accounted for this result - sample mix up, mistaken assignment of clinical status, false familial relationships, or a far more deflating concern, the potential that *MYH7* was linked

to, but was not the disease gene. As we tackled each possibility, our dilemma was resolved through the confidential disclosure of non-paternity, therein removing the sole piece of data that refuted *MYH7* as a disease gene. Divulging this personal secret was truly an heroic contribution that accelerate discovery of the cause of HCM.

Sequence analyses began immediately and revealed a missense variant in exon 13 of *MYH7* that substituted a highly conserved arginine residue (403) with glutamine (denoted Arg403Glu) in all affected, but no unaffected family members.³⁴ Concurrent restriction mapping of samples from other families revealed a rearrangement of the chromosome 14q locus characterized by a hybrid *MYH6-MYH7* gene as well as non-rearranged *MYH6* and *MYH7* genes.³⁵ Future studies³⁶ would reveal a missense variant (Arg453Cys) in the non-rearranged *MYH7* gene as the definitive cause of disease, a mutation that also arose independently in another HCM family without the locus rearrangement.

The identification of rare non-synonymous variants that segregated with HCM in unrelated families,³⁶⁻³⁸ which altered residues that were highly conserved during evolution and were absent from hundreds of control samples, provided compelling evidence that *MYH7* mutations caused HCM. But analyses of *MYH7* in many other HCM families were unrevealing of other mutations^{39, 40} and new linkage searches began to identify additional disease genes. HCM loci were mapped genes to chromosome 1q3⁴¹ and 15q2⁴². Identification of the HCM locus on 15q2 location was particularly fortuitous, despite a lack of candidates that were known to reside within that region of the human genome. The syntenic region of the mouse genome was known to encode α tropomyosin,⁴³ one of several thin filament sarcomere proteins that regulates actinomyosin interactions.⁴⁴ By harnessing information from the mouse gene, we cloned the human homologue, *TPM1*, mapped this to 15q2 and identified human mutations. Armed with the recognition that 2 HCM genes encoded contractile proteins, the disease gene encoded at 1q3 was soon recognized to be troponin T (*TNNT2*)⁴². An enigmatic myocardial disorder was no longer idiopathic, but a disease of the sarcomere.

Multiple research teams solidified the concept that sarcomere mutations caused HCM (Fig. 2). Schwartz and colleagues and our laboratory independently identified another HCM locus on chromosome 11,⁴⁵ where the thick filament myosin binding protein-C (*MYBPC3*) was mapped⁴⁶ and mutations identified.^{47, 48} Analyses of the myosin essential light chain (*MYL3*) and regulatory chain (*MYL2*) genes by Epstein and colleagues,⁴⁹ troponin I (*TNNI3*) by Sasazuki and colleagues,⁵⁰ and cardiac actin (*ACTC*) by Mogensen, Olson, Fanapazir and colleagues⁵¹ soon followed. After these teams reported variants that fulfilled criteria for pathogenic mutations, additional reports of mutations identified by other researchers in HCM families confirmed a definitive role for each of these genes in HCM.

Genes mutations in other sarcomere proteins (α myosin heavy chain,^{52, 53} titin⁵⁴ and troponin C⁵⁵), z disc-associated proteins (actinin,⁵⁶ ankyrin,⁵⁷ myozenin 2,⁵⁸ muscle LIM protein,⁵⁹ nexilin,^{60, 61} and telethonin^{61, 62}), and proteins involved in other myocyte functions (phospholamban⁶³ and vinculin⁶⁴) are also posited to cause HCM (Fig. 2). Among these, only the genes encoding myozenin-2⁵⁸ and actinin⁵⁶ were identified from unbiased genomic analyses, and novel variants in each were demonstrated to exhibit statistically significant segregation within HCM families. Identification of mutations in additional families will further support the causality of myozenin-2 and actinin in HCM. Whether the variants identified in other posited HCM genes are truly pathogenic remains less certain and warrants further confirmation, especially given the recent recognition that each human genome contains approximately 1000 rare non-synonymous variants, including premature stop signals.⁶⁵

Genetic Heterogeneity and Founding Mutations in HCM

Over 1000 distinct sarcomere protein gene mutations have been identified to cause HCM, with the vast majority of these found in one or only a few families.⁶⁶ Moreover haplotype analyses of unrelated patients who share a common HCM mutation typically indicate that these defects arose from independent mutational events.⁶⁷ Two theories may account for the considerable genetic heterogeneity observed in HCM. Although HCM is not usually thought to have substantial impact on reproductive health, sudden cardiac death in the young and early-onset of significant co-morbidities such as thromboembolism, stroke, and heart failure,⁶⁸ and increasingly personal choice, promote the gradual loss of HCM mutations from populations. In addition, because mutational events are presumed to occur randomly in the genome, larger genes are more likely to acquire these defects. Protein-encoding sequences for the 8 sarcomere protein genes that definitively cause HCM encompass approximately 23 kb, therein providing an ample target for new mutational events.

Recent genetic studies also indicate that some HCM reflects ancient, founding mutations. In addition to sharing an identical HCM mutation, the extended haplotypes flanking these HCM genes are shared among mutation carriers. Reported in the Netherlands,⁶⁹ Finland,⁷⁰ South Africa,⁷¹ Italy,⁷² India,⁷³ Japan,⁷⁴ and the U.S.,⁷⁵ founding HCM mutations might be expected in populations that are relatively genetically homogenous due to geographic or social isolationism, that experienced a population bottleneck, or when there is little selective disadvantage from the mutation. That founding mutations almost universally occur in *MYBPC3* and typically encode a truncated protein, is remarkable, and implies that these defects have far less deleterious consequences than other HCM mutations. As such, founding mutations provide evidence that distinct clinical outcomes arise from particular HCM mutations. Based upon genetic epidemiologic analyses, the 25-basepair deletion in *MYBPC3* found in 4% of individuals with Southeast Indian ancestry, arose approximately 33 ± 23 thousand years ago.⁷³ Maintenance of this genomic defect is best explained by neutral selection throughout human evolution, which would occur if this HCM mutation had minimal impact on survival. Indeed, only with improved human health and increased life expectancy has the medical significance of this *MYBPC3* mutation become evident: a 7-fold increased risk for heart failure late in life.

The contrast of genetic heterogeneity and founding mutations in HCM provides a new approach for assessing the relationship of genotype and clinical phenotype. Using an evolutionary perspective, founding mutations are expected to have less adverse impact on cardiac physiology and be associated with better prognosis than other HCM mutations. A corollary of this model is that when a new HCM mutation arises in a genome that carries or lacks a founder mutation, particularly severe consequence may ensue. Comparison of outcomes in patients with one *MYBPC3* founding mutation that occurs alone or combination with another HCM defect⁷⁵ illustrates how clinical course can diverge due to different genotypes. Consideration of these issues is important for clinical application of HCM genotypes and for designing cost-effective gene-based diagnostic platforms.⁷⁶

Harnessing Mutations to Probe Mechanism

With the possible exception of truncating *MYPC3* mutations,^{77, 78} other pathogenic HCM mutations⁷⁹ encode the insertion of a single erroneous amino acid into one contractile protein – a change that is unlikely to have egregious effects on stability or prevent incorporation of the mutant peptide into the sarcomere. Moreover because mutations are dominant, HCM sarcomeres contain an admixture of normal and mutant proteins. These factors imply that the consequences of HCM mutations will be significant but subtle, which may account for the slow emergence of clinical disease in mutation carriers.

Early studies of the biochemical and biophysical consequences of HCM mutations capitalized on recombinant technologies that enabled heterologous expression of some sarcomere proteins in bacteria⁸⁰ and cells.⁸¹ Mutant myosin heavy chain fragments were produced and shown to bind ATP normally^{81, 82}, but to have reduced ATPase activity and in vitro actin-sliding motility in comparison to wildtype fragments⁸¹. Ex vivo analyses of myosins isolated from skeletal muscles of HCM patients⁸³ similarly showed abnormal actin-myosin interactions. As such, *MYH7* mutations appeared to reduce force production by the sarcomere, a result that implied that hypertrophic remodeling was a compensatory response to diminished cardiac performance.

Further insights came from the study of HCM mutations that were engineered into mice.^{84, 85} Our lab produced mice with 3 different myosin mutations, Arg403Gln,⁸⁶ Arg719Gln,⁸⁷ or Arg453Cys.⁸⁸ Equivalent to disease in human patients, the clinical expression of HCM in mice (ventricular hypertrophy, myocyte disarray and increased myocardial fibrosis) is delayed until early in adulthood.⁸⁶ Isolation of mutant myosins from young pre-hypertrophic mice allowed assessment of single molecule mechanics (reviewed by Leinwand, Spudich and colleagues⁸⁹) of myosins carrying HCM mutations. Surprisingly, mutant myosin heavy chains exhibited enhanced contractile properties, including increased force generation, ATP hydrolysis and action-myosin sliding velocities, indicating that HCM mutations produce a gain in function.⁹⁰ Similar conclusions were reached from analyses of human HCM mutations introduced into troponin T.⁹¹ In HCM hearts, the admixture of mutant and wildtype sarcomere proteins might have an additional consequence, of uncoordinated activity.

Based upon these findings, we hypothesized that mutant sarcomeres activate signaling pathways to initiate hypertrophic remodeling. To identify these, myocytes from young pre-hypertrophic mice were studied using biochemical analyses and impairment of calcium homeostasis was found.⁹² Recent investigations appear to link the early-onset of calcium abnormalities in mutant myocytes with later events in HCM hearts. Abnormal calcium signals can lead to Mef2 activation in HCM hearts through calcium/calmodulin dependent protein kinase II (CaMKII) phosphorylation.⁹³ We observed heterogeneous Mef2 activation in HCM hearts, which was localized in myocytes juxtaposed to foci of necrosis and replacement fibrosis. By studying mice bred to carry homozygous HCM mutations, Mef2 activation was substantially increased and evident shortly before rampant myocyte death that occurs in this model. Together these studies implicate calcium-dependent Mef-2 activation as a signal that defines profoundly stressed and pre-morbid mutant myocytes, and predestines sites of focal myocardial scarring in HCM hearts.

Transcriptional profiling of ventricular tissues⁹⁴ and isolated cells⁸⁷ from pre-hypertrophic HCM has also been informative of pathways activated by sarcomere mutations. Expression of Tgf β (transforming growth factor- β), connective tissue growth factor and periostin are increased in the ventricles of young mutant mice, implying that these potent regulators of fibrosis and collagen deposition contribute to impaired cardiac relaxation and the characteristic histopathology of HCM. Our recent studies identified the source of these molecules to be non-myocyte cells,⁸⁷ presumably cardiac fibroblasts, and demonstrated that continual inhibition of Tgf β , initiated in the pre-hypertrophic phase of disease, reduced the emergence of fibrosis and limited hypertrophy remodeling that emerged in untreated mutant mice.

By combining knowledge of the genetic basis for HCM, with insights gleaned from biochemical, biophysical and transcriptional analyses in HCM models, an integrated understanding of the pathophysiology of disease has begun to emerge. HCM mutations disrupt normal biophysical properties of sarcomere and cause mechanical and calcium-

induced biochemical signals that activate gene transcription, including increased Tgf β expression. Tgf β may stimulate expression of pro-fibrotic molecules and fibroblast proliferation, which expands the interstitium and may promote development of diastolic dysfunction, a clinical hallmark of HCM. Persistent activation of this pathway is predicted to impose stress on mutant myocytes (evidenced by Mef2 activation), leading to premature death with focal myocardial scarring.

Future Opportunities

The considerable diversity of HCM mutations has provided an unparalleled set of molecular reagents for exploring sarcomere biology. Continued elucidation of the impact of mutations on myocyte contraction, relaxation, and signaling is expected to expand knowledge of cardiac biology in health and disease. Articles that will follow this perspective will explore these concepts in depth.

From a human genetics perspective, there is still more to learn about HCM. Understanding the cause in 25–35% of HCM patients without a pathogenic mutation remains an important challenge. Defining the biochemical, morphologic and functional changes in large genotyped cohorts, from the pre-clinical phase of disease to overt HCM, may provide inform the discovery of molecules and mechanisms that limit clinical expression in young mutation carriers or that account for the emergence of HCM in adolescence and beyond. Developing new cellular models through induced pluripotent stem cells should enable high-throughput investigation of myocyte responses to many more sarcomere gene mutations. Application of whole genome sequencing technologies in patients with atypical clinical presentations may uncover the roles of modifying genetic factors in HCM. Pursuit of these and other research opportunities in HCM⁹⁵ hold the promise for better ways to diagnose, treat and prevent this extraordinary disease.

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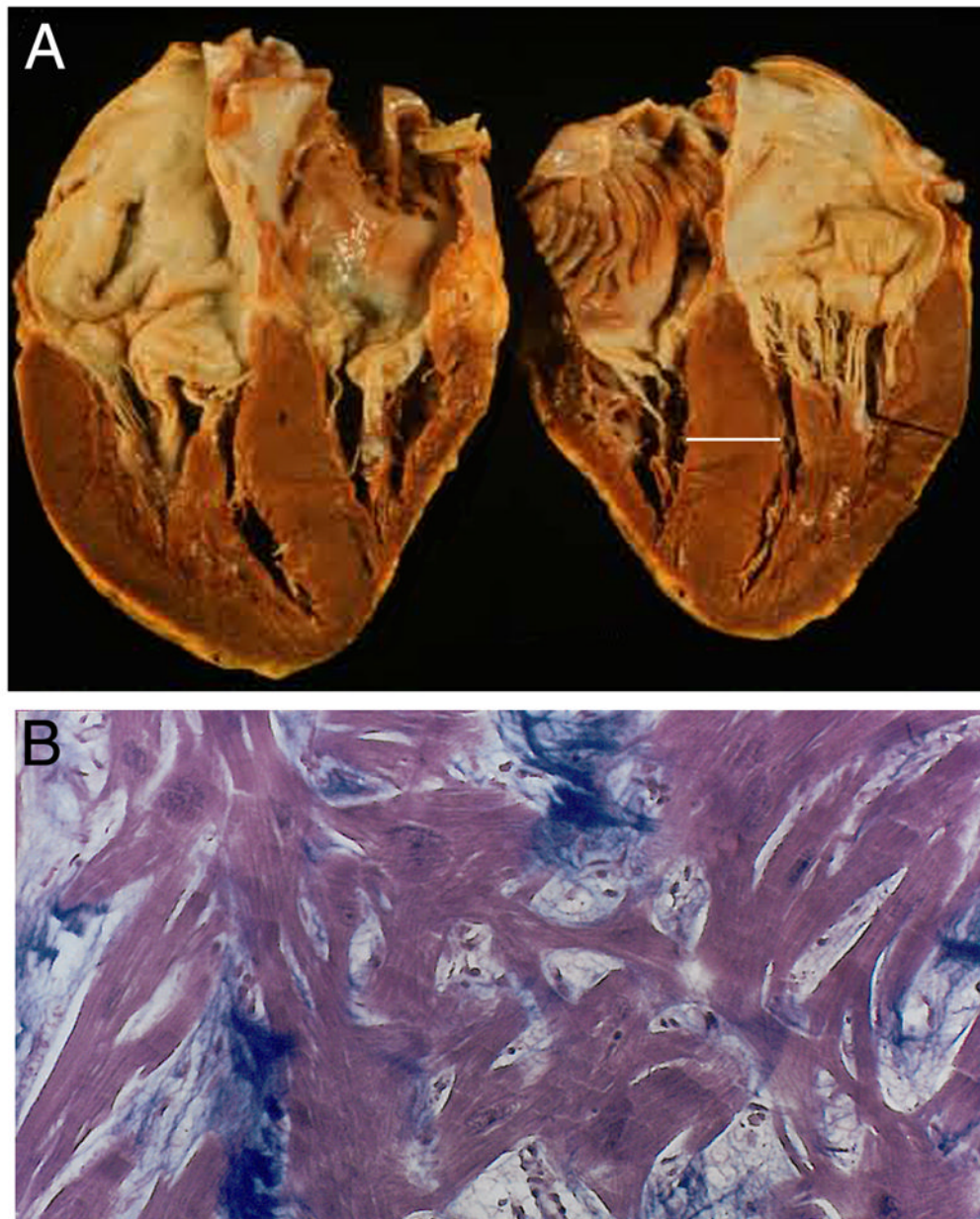


Figure 1. The anatomic and histopathologic findings of HCM. A. Gross anatomy of an HCM heart shows marked hypertrophy with involvement of the interventricular septum, left ventricular free wall, and papillary muscle. Wall thickness (bar) = 20 mm (normal = 12 mm). Left atrial enlargement is also evident. B. Mason trichrome stained ventricular tissue reveals markedly disorganized, enlarged myocytes (magenta) with prominent nuclei. The interstitium (blue) is expanded in HCM due to increased numbers of fibroblasts and extracellular matrix material.

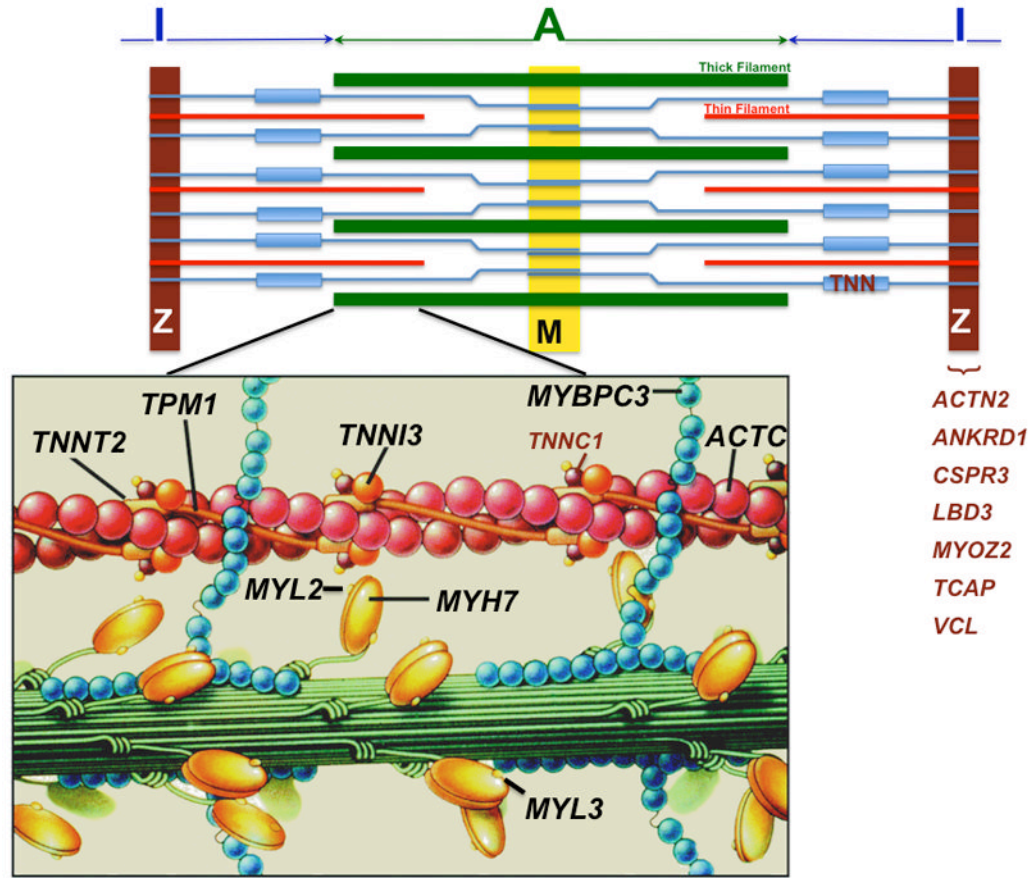


Figure 2. Definitive and posited HCM genes. A schematic representation of a sarcomere (the unit of contraction that spans two neighboring Z-bands) is shown with the locations of thin and thick filaments in relationship to I, A and H bands. The detailed representation of the A band, highlights definitive HCM genes (black) that encode β myosin heavy chain (*MYH7*), myosin binding protein C (*MYBPC3*), troponin T (*TNNT2*), α tropomyosin (*TPM1*), myosin regulatory light chain (*MYL2*), myosin essential light chain (*MYL3*) and (*ACTC*). More than 50% of human mutations occur in β myosin heavy chain and myosin binding protein C. Additional genes that have been implicated in HCM (brown) encode Z-disc proteins, troponin C (*TNNT1*), titin (*TNT*), α myosin heavy chain (*MYH6*, not depicted) and phospholamban (*PLN*, not depicted).