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Review

Emerging Themes in Genetics of Hypertrophic Cardiomyopathy: Current Status and Clinical Application

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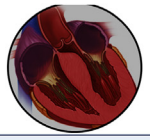
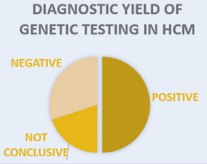
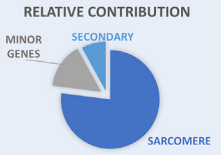


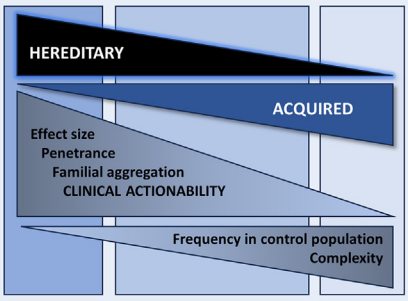
Genetics in hypertrophic cardiomyopathy
Current *status* and clinical application

BACKGROUND
- Unexplained LVH, 'HCM is a clinical phenotype in search of a diagnosis'
- HCM, prevalence in adults 1:350 - 1:500, is an important cause of unexpected sudden cardiac death (SCD) and refractory heart failure.
- The current diagnostic yield of genetic testing is 30 to 50%; HCM is mostly a disease of the sarcomere.





GENETIC ARCHITECTURE AND CLINICAL ACTIONABILITY IN HYPERTROPHIC CARDIOMYOPATHY



	SARCOMERIC	MINOR GENES	SECONDARY HCM
MAJOR GENES/ENTITIES	MYBPC3, MYH7, TNNT2, TNNI3, TPM1	FHOD3, ALPK3, TRIM63	RASopathies; Fabry disease, Amyloidosis; Glycogenosis, Mitochondrial
INHERITANCE PATTERN	AD	AD, AR	AD, AR, X-linked, Matrilineal
SYSTEMIC PHENOTYPE	N	Y	Y
SCD-RISK SCORE	Y	Y	N
EFFICACY OF MYOSIN INHIBITORS	Y	N	N
POTENTIAL FOR GENE THERAPY	IN EXPLORATION	UNKNOWN	IN EXPLORATION

** AD: Autosomal dominant; AR: Autosomal recessive; Y: yes; N: no*

ABSTRACT

Hypertrophic cardiomyopathy (HCM), defined clinically by the presence of unexplained left ventricular hypertrophy (LVH), with wall thickness ≥ 1.5 cm, is a phenotype in search of a diagnosis, which is most often a genetically determined, cardiac exclusive, or systemic disorder. Familial evaluation and genetic testing are required for definitive diagnosis. The role of genetic findings in predicting development of disease, outcomes, and increasingly to guide management is evolving

RÉSUMÉ

La cardiomyopathie hypertrophique (CMH), définie cliniquement par la présence d'une hypertrophie ventriculaire gauche (HVG) inexpliquée, avec une épaisseur de paroi ≥ 1,5 cm, est un phénotype en quête de diagnostic, qui est le plus souvent un trouble génétiquement déterminé, exclusivement cardiaque, ou systémique. Une évaluation familiale et des tests génétiques sont nécessaires pour établir un diagnostic définitif. Le rôle des résultats des tests génétiques dans la

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with access to larger data sets. The specific mutation and sex of the patient are important determinants that ultimately are likely to guide management. The genetic/familial evaluation is influenced by the accuracy of the clinical diagnosis and the extent/expertise of the genetic laboratory. Genetic testing in a patient with unexplained LVH without systemic manifestations will yield a definite/likely pathogenetic mutation in a sarcomere (30%-50%), regulatory/functional (10%-15%) or metabolic/syndromic (< 5%) gene associated with Mendelian inheritance. The importance of oligo- and polygenic determinants, usually in the absence of Mendelian inheritance, is under investigation with important implications, particularly related to familial evaluation and definition of risk of disease development in relatives of probands. The results of genetic testing are increasingly important in management strategies related to the use of the implantable cardioverter defibrillator for prevention of sudden death, use of myosin inhibitors for refractory symptoms in patients with and without outflow tract obstruction, and—on the immediate horizon—gene therapy. This review will focus on genetic and outcome data in sarcomeric HCM, and minor causative genes with robust evidence of their association will also be considered.

prédiction du développement de la maladie, des pronostics et, de plus en plus, dans l'orientation de la prise en charge, évolue avec l'accès à des ensembles de données plus grands. La présence d'une mutation spécifique et le sexe du patient sont des déterminants importants qui, en fin de compte, sont susceptibles d'orienter la prise en charge. L'évaluation génétique/familiale est influencée par la précision du diagnostic clinique et l'étendue/l'expertise du laboratoire de génétique. Les tests génétiques effectués chez un patient présentant une HVG inexpliquée sans manifestations systémiques révéleront une mutation pathogène certaine/probable dans un gène du sarcomère (30-50 %), régulateur/fonctionnel (10-15 %) ou métabolique/syndromique (< 5 %) associé à une hérédité mendélienne. L'importance des déterminants oligo- et polygéniques, généralement en l'absence d'hérédité mendélienne, fait l'objet de recherches qui ont des implications importantes, notamment en ce qui concerne l'évaluation familiale et la définition du risque de développement de la maladie chez les parents proches des probands. Les résultats des tests génétiques prennent de plus en plus d'importance dans les stratégies de prise en charge liées à l'utilisation du défibrillateur cardiaque implantable pour la prévention de la mort subite, à l'utilisation des inhibiteurs de la myosine pour les symptômes réfractaires chez les patients avec ou sans obstruction du tractus de sortie, et - à l'horizon immédiat - à la thérapie génique. Cette revue de littérature se concentrera sur les données génétiques et les pronostics de la CMH sarcomérique, et les gènes causaux mineurs avec des preuves solides de leur association seront également pris en compte.

The early recognition and understanding of patients with hypertrophic cardiomyopathy (HCM) were primarily focused on clinical and hemodynamic features of left ventricular outflow tract obstruction. The terms used to describe the condition—such as idiopathic hypertrophic subaortic stenosis, muscular subaortic stenosis, and hypertrophic obstructive cardiomyopathy—reflected initial perceptions of the disease. The advent of imaging with M-mode echocardiography shifted the focus toward morphologic abnormalities, particularly left ventricular hypertrophy (LVH).

M-mode echocardiography enabled the visualization of the thickest and thinnest basal segments of the left ventricle: that is, the basal septum and posterior wall, leading to the proposal of asymmetric septal hypertrophy (ASH) as a genetically determined diagnostic feature. According to the proposed diagnostic criteria, a wall thickness in adults $\geq$ 1.5 cm was considered indicative of HCM. Despite advances in imaging and recognition that segment thickness varies from base to apex and on body size, these diagnostic criteria, proposed more than 50 years ago, continue to be used in clinical diagnosis.[1] Recent literature on diagnosis of HCM has highlighted the variations in segment thickness between the base and apex of the heart as well as among individuals of different sizes, genders, and genetic backgrounds.[2] The extent to which these diagnostic issues contribute to observed differences in the demographics of patient cohorts and proportions with a positive genetic test remains to be determined.

The familial basis of HCM was recognized early on, exemplified by a large French Canadian family and published in 1961.[3] This family ultimately provided the clinical foundation for identifying the first disease-causing gene approximately 30 years later, a missense variant in the gene encoding beta-myosin heavy chain.[4,5] Subsequently, other disease-causing mutations were identified in genes coding for sarcomeric contractile proteins, with mutations found in approximately 30% to 50% of patients who met diagnostic criteria. Notably, there are discrepancies in HCM cohorts regarding age, left ventricular wall thickness, outcomes, and the proportion of patients with potential disease-causing genes. Again, some of these discrepancies may be attributed to the accuracy of diagnosis and extent of genetic testing.

The advances and evolution in the recognition, understanding and management of HCM are closely tied to technological progress. We have transitioned from using the stethoscope, electrocardiogram, and cardiac catheter to employing advanced imaging techniques, such as M-mode and 2-dimensional echocardiography complemented by cardiac magnetic resonance. Therapeutic approaches, initially focused on pharmacologic and surgical interventions for relief of symptoms, have now expanded to include risk stratification and treatment/prevention of potentially life-threatening arrhythmias. Although the application of genetic knowledge into clinical practice is not yet fully realized, the development of myosin inhibitors and early gene therapy studies provide a promising foundation for novel therapies and improvements in managing HCM.

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See page 751 for disclosure information.

The prevalence of HCM is considered to be approximately 1 in 500 adults in different populations from around the world. The prevalence is highest in men and American Blacks. The majority of studies use a diagnostic criterion of unexplained left ventricular hypertrophy $\geq$ 1.5 cm. Most studies do not systematically exclude other nonsarcomere inherited conditions (eg, Noonan syndrome, Fabry disease, Danon disease), although the combined prevalence of these conditions in adults is low when the cardiac phenotype is predominant, and the correct diagnosis not apparent. These conditions are unlikely to contribute significantly to the estimated prevalence of 1 in 500 adults. Most prevalence studies, however, do exclude patients with systemic hypertension; if individuals who have a left ventricular wall thickness of $\geq$ 1.5 cm who also have systemic hypertension are included, the prevalence figure is closer to 1 in 350 adults. Both HCM and systemic hypertension are relatively common and may well coexist, although it is unclear to what extent hypertension may trigger or influence the severity of genetically determined HCM. These data, although not generated by a structured epidemiologic case-control study, are nonetheless consistent across numerous populations and are sufficiently robust to support the view that HCM is the most common form of inherited cardiac disorder, with a prevalence of at least 1 in 500 adults.

Extrapolation of prevalence data of 1 in 500 to the recognized number of patients with HCM in different countries suggests that the majority of patients with HCM do not receive correct diagnoses. A population-based cohort study in the United Kingdom linked general practice, hospital, and national outcomes databases; the study of 3,290,455 individuals revealed a diagnosis of HCM in 1160 (prevalence 1 in 2500).[6] The average age was 57 years, and 41% were female. Cardiovascular outcomes were significantly worse in the HCM cohort compared with control populations, consistent with a possible selection bias of more severely affected HCM patients. These data, however, suggest that approximately 80% of adults in the United Kingdom who would fulfil diagnostic criteria for HCM are not diagnosed. Analogous epidemiologic data from North America and other European countries are not available, but there is nothing to suggest that the United Kingdom is an outlier in relation to disease recognition and diagnosis of HCM.

Current Status of Genetic Testing in HCM

An analogous issue to under diagnosis is the underuse of genetic testing in HCM for managing patients and their families. Familial evaluation, genetic counselling, and the overall skills and expertise required to perform genetic testing is generally a challenge beyond the capacities of the normal cardiology clinical practice, with the ideal setting being a dedicated inherited cardiac disease unit/team. The logistics to establish such teams differ from country to country. In France, there is a national network of 4 reference centres (Centres de Reference Maladies Rares [CRMR]) and 13 university affiliated hospitals with expertise in diagnosis, management, and the genetics of cardiomyopathy, to which patients with HCM are referred to undergo familial evaluation with mutation analysis to complement detailed clinical diagnostic and outcomes evaluation. In contrast, other countries (eg, Germany) with comparable resources dedicated to health care have no structured national system, and although there are isolated groups with expertise, the majority of patients with HCM do not undergo detailed familial evaluation or genetic testing. This is similar to the situation in the United States. Other countries, including the United Kingdom, Canada, Italy, and Spain have inherited cardiovascular disease clinics with HCM expertise, but budgets to enable genetic testing of HCM probands—and, where appropriate, their families—are limited, and anecdotal experience indicates that the majority of patients with HCM in the United Kingdom do not undergo mutation analysis. The relative simplicity of noninvasive cardiac tests to evaluate family members, and the lack of clear actionability of specific genetic diagnoses to treatment, have undermined application of North American and European guidelines for HCM, which have considered comprehensive mutation analysis of probands and potential cascade screening of relatives as a Class 1 recommendation. This is despite data to suggest that 1-time genetic testing is cost and time effective when compared with serial cardiovascular valuations in family members.[7]

The identification of mutations in genes encoding proteins of the cardiac sarcomere spawned early genotype phenotype studies in patients with HCM. Initial reports in highly selected cohorts supported phenotype and outcome differences in patients with myosin heavy chain and troponin-T mutations. The subsequent experience of larger data sets in less selected patients, however, revealed that the important determinants of phenotype and outcome related to the specific mutation (eg, *MYH7* Arg403Glu; alleles encoding amino acids 92-95 in *TNNT2*), which are associated with adverse outcomes in comparison with other *MYH7* and *TNNT2* mutations. The naysayers who highlight the challenges in implementing therapeutic regimens in response to the information provided by genetic testing are further supported by the recognition that intermediate variants are potential influencers of phenotype and outcomes: a finding that is particularly relevant to patients with HCM and loss of function mutations in *MYBPC3*, which are associated with disease in 15% to 20% of patients with HCM. These challenges, particularly related to the performance and interpretation of genetic sequence data, are being met by the drive to implement genetically based therapies such as myosin inhibitors and gene therapy.

The current diagnostic yield of genetic testing in HCM is variable, ranging from 30% to 50%, depending on many factors, including the clinical characteristics of the cohort such as severity of disease, age of onset, familial aggregation, and concomitant clinical features.[8] Laboratory expertise is also vital, with consideration of the latest evidence regarding new genes including genes associated with phenocopies, specific regions such as deep intronic ones in specific genes (such as *MYBPC3*), detection of copy number variations, and development and application of good data management for variant classification according to American College of Medical Genetics (ACMG) guidelines.[9]

Sarcomere Mutations

Mutations in genes encoding sarcomeric proteins are the most frequent finding in patients with HCM and have led early guidelines to consider HCM as a disease of the

sarcomere. Most sarcomere disease exhibits autosomal dominant inheritance, with variable penetrance and age of onset.[10]

Mutations in sarcomeric genes are associated with different clinical phenotypes (genetic pleiotropy), including other cardiomyopathies (dilated, restrictive, noncompaction), and uncommonly with skeletal myopathies and congenital heart disease (eg, septal defects or Ebstein anomaly).[11]

Early reviews emphasized HCM as a disease of young men and older women. Contemporary studies of sarcomere mutations and disease highlight earlier age at presentation and high penetrance in men, but more severe disease particularly related to heart failure and its complications in women, mostly in the middle and later decades, and often refractory to therapy.[12,13] Sarcomeric HCM is usually expressed earlier and more severely when other genetics (second genetic modifier, epigenetic factors) or environmental modifiers (such as abnormal loading conditions) are present. More severe disease is also associated with complex genotypes (compound or double heterozygosis disease-causing mutations), which occur in 5% to 10% of cases.[14]

The evolution to end-stage/burnt-out HCM is approximately 8% in studies from large cohorts. The **S**arcomeric **H**uman C**ar**diomyopathy **Re**gistry (SHaRe) registry of 1316 patients identified a sarcomeric disease-causing mutation as an independent risk factor for the development of left ventricular systolic dysfunction, especially when complex genotypes encompassing sarcomere mutations were involved.[15]

The genes most frequently implicated in the development of HCM are *MYBPC3* and *MYH7*, which encode 2 proteins belonging to the thick filaments of the sarcomere: myosin-binding protein C and beta-myosin heavy chain, respectively. Mutations in these 2 genes account for approximately 35% of HCM cases (20% and 15%, respectively). Mutations in genes encoding the troponin complex (*TNNT2*, *TNNI3*, *TNNC1*) are identified in approximately 10% of HCM cases. Mutations in *ACTC1*, and the myosin light chains *MYL2* and *MYL3*, respectively, are established—but less common—putative genes in HCM, responsible for less than 5% to 10% of cases.[16]

MYBPC3

Mutations in *MYBPC3* are the single most common cause of HCM. These are most often null variants (nonsense, frameshift, splice-site, start-loss, structural), associated with haploinsufficiency (causing disease through allelic loss of function). Nonsynonymous variants (missense) are less common and mainly affect key residues involved in the structural integrity or function of the protein.[17] Results obtained from the SHaRe registry suggest that no significant differences in terms of structural disease expression and prognosis exist between pathogenic missense and null variants in *MYBPC3*.[18]

Historically, *MYBPC3* mutations have been considered more benign than those occurring in other sarcomeric genes, with later expression and better prognosis. However, there are also cases with early clinical expression, severe hypertrophy, and high risk of sudden death; an additional genetic modifier was identified in some of the cases with adverse outcomes. This variability, also observed within families with null-type variants (considered a molecularly homogeneous genetic substrate), suggests that the involvement of genetic and nongenetic modifiers play an important role in the expression of *MYBPC3* disease.[18,19]

Current risk models for sudden death prediction do not include sex or genetic findings. Patients with mutations in *MYBPC3* and *MYH7*, the most common mutations in HCM, are likely to be over-represented in the model compared with the other recognized genetic causes. Although disease expression is variable, events most often occur in patients with mutations in *MYBPC3* and *MYH7* who have severe structural, functional, or arrhythmic features. Patients with mutations in other sarcomere genes in which disease expression may apparently be milder—but individuals nonetheless at risk—will be less well served by the risk model, highlighting the importance of incorporating both sex and the specific mutation into future models.

MYH7

The beta-myosin heavy chain, encoded by the *MYH7* gene, is the major component of the thick filaments of the sarcomere. Cardiac beta-myosin is a relatively large and pleomorphic protein, comprising functionally well-characterized domains. More than 200 mutations, mainly missense, have been reported as disease causing. The relative contribution of different functional regions differs; the motor domain within the head of the protein contains the most putative mutations.[20] In recognition of this, ACMG/Association for Molecular Pathology (AMP) considered this particular region, 181 to 937 residues, as a hotspot in which a novel variant is more likely to be disease causing in contrast to a variant outside the region.[21]

MYH7 disease-causing mutations in HCM are generally associated with typical disease expression, with moderate to severe ASH manifesting in adolescence or young adults. Mutations in *MYH7* less frequently may cause dilated cardiomyopathy (DCM) and noncompaction in isolation or overlapping/developing in patients with an HCM phenotype. Less frequently, some specific variants have been also associated with Ebstein anomaly and skeletal myopathy.[22]

Some studies have suggested that overall prognosis of beta-myosin associated HCM is worse than *MYBPC3*, especially in terms of heart failure endpoints. In a subanalysis from the SHaRe investigators, *MYH7* mutation carriers had a significantly higher risk of the overall composite endpoint of atrial fibrillation and advanced heart failure (defined as New York Heart Association [NYHA] III/IV) or need for left ventricular assist device or heart transplant.[23]

There is a large variation in clinical expression and related prognosis among different nonsynonymous mutations, which depends largely on the type of change and the region affected. Variants affecting the head domain with which the allosteric interactions with other sarcomere genes are associated have worse prognoses.[20] However, even within this region, there are important differences in severity and prognosis associated with different mutations. Mutations in the converter region involved in the transmission of the mechanical impulse are associated with a more adverse prognosis than mutations in other areas, but even in this region the severity of clinical expression varies with some mutations that affect certain amino acids (Fig. 1).[24]

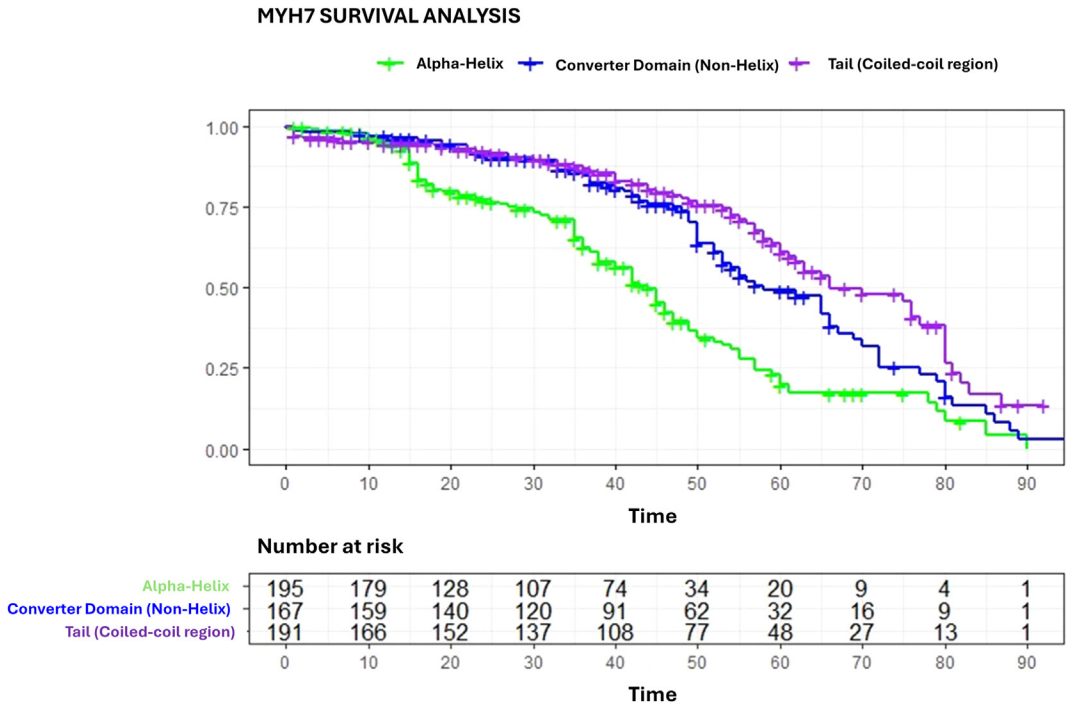

Figure 1. A Kaplan-Meier cardiovascular death-free survival curve (appropriate defibrillator discharge/resuscitated cardiac arrest, heart transplantation, and sudden or heart failure death) in carriers of pathogenic nonsynonymous variants in 1 particular region, the helix-localized converter region (residues 715-722; **green**), in the *MYH7* converter region, excluding that particular region (residues 709-715; 723-777, **blue**), and in the coiled-coil tail region (1217-1935 residues, **purple**). A significant difference in terms of cardiovascular death is observed among the 3 regions: helix region vs converter log-rank test $P < 0.0001$, converter vs tail $P = 0.034$, and then helix vs tail $P < 0.00001$, with a median cardiovascular death-free of 44, 56, and 68 years in each of the groups, respectively. Adapted and extended analysis from García-Giustiniani et al.[24] Articles containing clinically relevant information for depicting the graph are listed in Supplemental Appendix S1.

TNNT2

Cardiac troponin T, encoded by the *TNNT2* gene, promotes the assembly of the troponin-tropomyosin complex into actin filaments. Pathogenic variants in this gene are also mostly missense, and HCM is the most prevalent phenotype (approximately 80%) followed by DCM.

This gene, along with other genes from the troponin complex, is another example where disease-causing variants are heterogeneously distributed along the protein. A study examining the location of different mutations in relation to disease expression and outcomes, revealed that there are clusters in which mutations are more frequently associated with HCM (90-129 and 200-288, the former being associated with higher arrhythmic risk), and an additional cluster (131-179), associated with the development of systolic impairment and a phenotype resembling DCM.[25]

In carriers of disease-causing mutations in *TNNT2* the hypertrophy can be mild, but a mismatch between ventricular thickness and severity of myocyte disorganization may be observed, with an associated risk of malignant arrhythmias.[26,27] This fact could lead current risk models to underestimate risk of sudden death in patients with high-risk *TNNT2* mutations in which left ventricular wall thickness, a variable used as an independent predictor, is mild (Fig. 2).[28]

TNNI3

The *TNNI3* gene encoding cardiac troponin I is known as the inhibitory subunit of the troponin complex because it prevents myosin binding to actin in diastole. Although the majority (~80%) of mutations in *TNNI3* cause typical HCM, an important subset can cause a primary restrictive or HCM/restrictive cardiomyopathy (RCM) overlapping phenotype. Less commonly (5%), mutations may cause a DCM phenotype.[29-31]

As with troponin T, some HCM disease-causing mutations cluster in specific regions (residues 131-176, a region interacting with TnC in the calcium-bound state).[25] Also, there may be a significant dissociation between the risk of complications (in particular, sudden death) and the degree of ventricular hypertrophy.[29]

ACTC1

Cardiac alpha-actin is encoded by the *ACTC1* gene, the major component of thin sarcomere filament. This gene is associated with isolated HCM (1%), but specific mutations can present an overlapping phenotype of HCM, noncompaction cardiomyopathy (NCCM), familial septal defects, and early-onset atrial arrhythmias.[32] *ACTC1* has a highly conserved sequence with low variability tolerance; a novel undescribed variant therefore has a high probability of causing disease.[33]

TPM1

Alpha-tropomyosin encoded by *TPM1* is a sarcomere protein linked to actin-myosin interactions in response to intracellular Ca2+ concentration. Disease-causing variants in

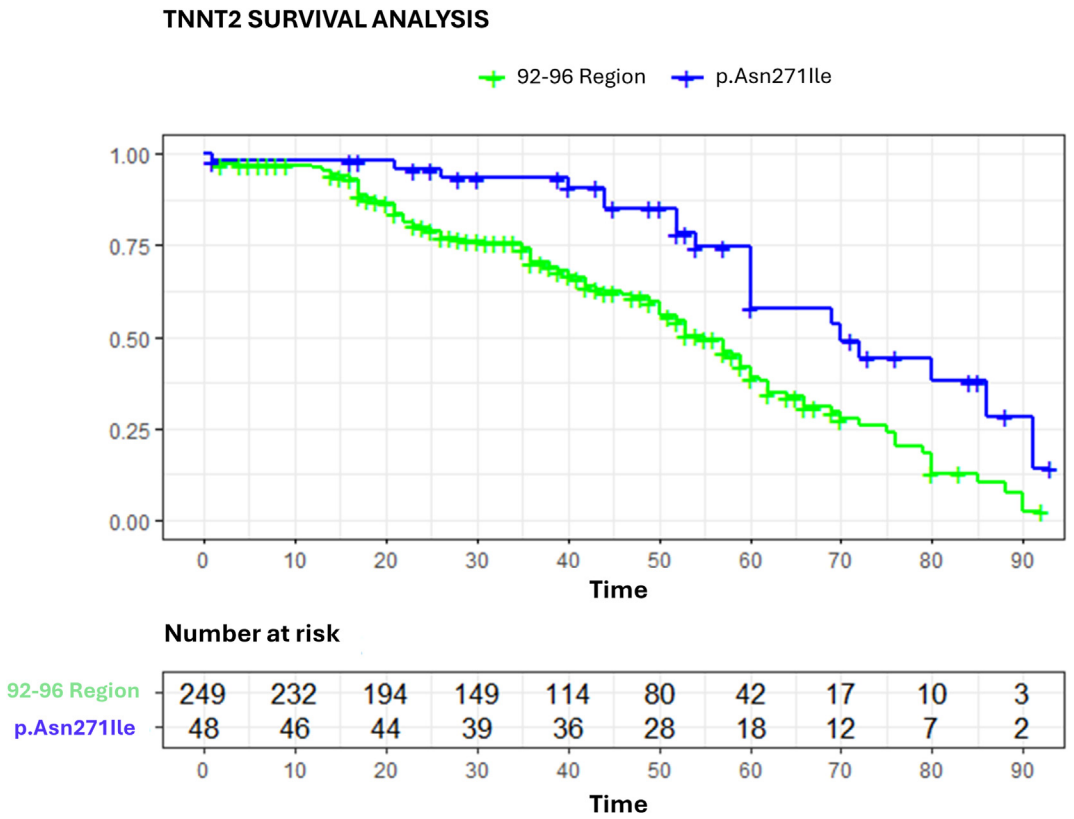

Figure 2. A Kaplan-Meier cardiovascular death-free survival curve (outcome events as per Figure 1) in carriers of pathogenic variants in the *TNNT2* gene, considering 2 groups: variants affecting the residues 92 to 96 and the variant p.Asn271Ile, a Galician founder mutation, with a known relatively good prognosis. A significant difference in terms of this endpoint is observed between the 2 regions ($P < 0.001$), with a median cardiovascular death-free of 50 and 70 years in each of the groups, respectively. Articles containing clinically relevant information for depicting the graph are listed in Supplemental Appendix S2.

TPM1 are thought to account for a small proportion of sporadic and familial HCM (1%-5%).[34] This gene represents one of the clearest extreme examples of intra- and interfamilial variability among subjects carrying the same variant.[35]

Less Prevalent Regulatory and Structural Genes With Established Association With HCM

To perform its function properly, the cardiac sarcomere cannot be an isolated entity within the myocyte; it is part of a complex, interrelated network that links it to the other sarcomeres and to the cell membrane. Essential to its function are the Z-disk proteins, other structural proteins, and the intermediate filaments, which link the Z-disk to the cell membrane via the costameres. Some genes in this network have additional roles in transcriptional regulation, calcium-handling, and constitutive sarcomeric protein turnover. Many genes involved in this complex network have been explored and proposed as candidates in the study of HCM. Relatively few genes have a proven association with the phenotype (Fig. 3).

This section presents those genes with sufficient evidence to consider them causal for HCM, such as robust variant familial segregation, de novo presentation, clear enrichment through well-designed case-control studies, significant number of serial cases with biallelic involvement in the case of recessive genes, and enough functional evidence according to ACMG guidelines. This evidence, along with the role of each gene and the related phenotypes, are synthesized in Table 1.

Mutations in sarcomeric genes account for approximately 85% to 90% of genetically confirmed HCM. The global contribution of nonsarcomeric genes, described here, has not been established, but their prevalence has been estimated at 5% to 10%.[36]

ALPK3

This gene encodes alpha-protein kinase 3, a nuclear protein with transferase and protein kinase activity, and with a particular ubiquitous expression. It is considered to play an essential role in the early differentiation of cardiomyocytes.

Pathogenic variants affecting both alleles of the gene are associated with the development of pediatric-onset cardiomyopathy (HCM and DCM), with Noonan-like syndromic traits (eg, musculoskeletal and dysmorphologic) in > 80% of the cases, and with prolonged QT interval in more than 50%. Most of the autosomal recessive cases harboured a null *ALPK3* variant, but missense variants are described (compound heterozygosis with a loss of function or in homozygosis).[37,38]

There is emerging evidence on the pathogenicity of variants in simple heterozygosity (all null type) and the development of HCM. There is enrichment with cosegregation in 2 independent cohorts with incomplete penetrance throughout

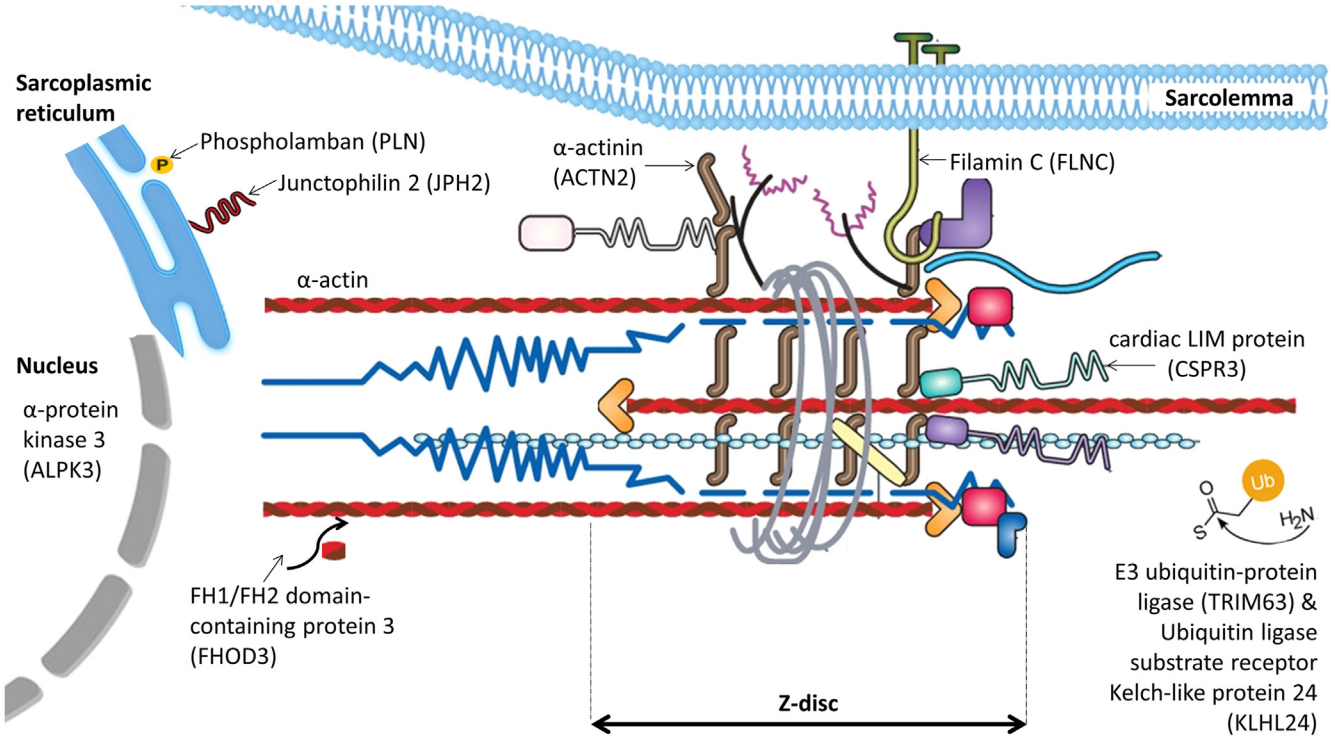

Figure 3. Schematic representation of the less prevalent regulatory and structural genes and their association with the sarcomere.

life. Atypical forms of HCM (apical, concentric) predominate in more than 50% of cases.[39,40]

FHOD3

FH1/FH2 domain-containing protein 3, encoded by *FHOD3*, acts by regulating actin polymerization. Its association with HCM has been demonstrated through a robust enrichment analysis and segregation studies.

Disease-causing variants in this gene, all of them missense, cluster in 2 regions of the gene (coiled-coil domain, residues 622-655, and the residues p.Ser527, p.Tyr528). Penetrance is relatively late and incomplete (particularly for some rare or nonfamilial variants), with disease developing after age 40 in men and 55 in women. Ventricular hypertrabeculation was detected in some of the described families. The inheritance pattern is autosomal dominant. This gene contributes to approximately 1% to 2% of HCM cases.[41] The role of truncation variants is uncertain.

ACTN2

This gene encodes alpha-actinin 2, a major Z-disc structural protein, essential for anchoring the contractile apparatus, transmitting force, and sensing mechanical traction and sarcomeric distension. To date, the evidence associating *ACTN2* with the development of HCM comes from a discrete number of missense variants, with strong evidence on familial segregation with autosomal dominant inheritance.[42] Functional studies performed in human-induced pluripotent stem cell-derived cardiomyocytes revealed typical HCM findings, with myofibrillar disorganization, myocyte hypertrophy, increased myofilament calcium sensitivity, hypercontractility, and prolonged relaxation.[43]

The genotype-phenotype correlations are inconclusive to date, with variable patterns of hypertrophy, obstructive and nonobstructive disease, left ventricular (LV) dilatation, atrial and ventricular arrhythmias, and conduction disease, even among members of the same family.

The global prevalence of this gene in HCM is estimated to be low (< 1%). There is no global enrichment of rare variants in this gene in large HCM case-control studies, suggesting that only specific variants are associated with disease.[16]

TRIM63

E3 ubiquitin-protein ligase *TRIM63* encoded by *TRIM63* is also linked to the constitutive turnover of sarcomeric and intermediated filament proteins. Biallelic pathogenic missense or null variants in this gene have been definitely associated to HCM, probably the most common recessive genetic substrate in this disease. They are associated with a particular phenotype of concentric hypertrophy with a high incidence of progression to systolic dysfunction (> 20%).[44]

PLN

Phospholamban, encoded by *PLN*, is a protein that regulates calcium reuptake by the sarcoplasmic reticulum. Mutations have been associated with a form of arrhythmogenic/dilated cardiomyopathy and rarely with null-type variants in simple heterozygosis and incomplete penetrance to HCM.[45]

The mechanism of *PLN*-induced cardiomyopathy is attributed to SERCA2 dysfunction and inappropriate Ca2+−

Table 1. Less prevalent regulatory and structural genes with established association to HCM

Gene / protein	Role	HCM contribution	Other related phenotypes	Inherited pattern	Variant types
ALPK3 / α-protein kinase 3	Nuclear-TF	1%-2%	DCM, Noonan-like phenotype, LQTS (AR)	AD AR	LoF (AD and AR) Missense (AR)
FHOD3 / FH1 / FH2 domain-containing protein 3	Sarcomeric regulation	1%-2%	DCM?	AD	Missense
ACTN2 / α-actinin 2	Z-disc	Low (< 1%)	LVNC	AD	Missense
TRIM63 / E3 ubiquitin-protein ligase TRIM63	Sarcomere and IF regulation	< 1%	DCM (evolutionary form)	AR	LoF and missense
PLN / phospholam-ban	Sarco/endoplasmic reticulum Ca 2+	Low (< 1%)	DCM	AD	LoF
CSPR3 / cysteine-rich cardiac LIM protein	Z-disc	1%	Mild skeletal muscle disease? DCM?	AD	Missense
FLNC? / filamin C	IF	NE	RCM Myofibrillar myopathy	AD	Missense
JPH2 / junctophilin 2	Sarcoplas-mic reticulum Ca 2+	NE	DCM (evolutionary form) Conduction disorders	AD	Missense
KLHL24 / ubiquitin ligase substrate receptor Kelch-like protein 24	IF regulation	NE	Neuromuscular	AR	LoF

AD, autosomal dominant; AR, autosomal recessive; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; IF, intermediate filaments; LoF, loss of function; LQTS, long QT syndrome; LVNC, left ventricular noncompaction; NE, not established; SE, significant enrichment.

handling, which significantly alters the contraction and relaxation of the heart.[46]

PLN is a very small gene (with a single coding exon), so few variants have been identified, and its expected contribution to HCM is low (< 1%).

CSRP3

The gene *CSRP3* encodes the cysteine-rich cardiac LIM protein, an important structural component of the Z-disc. Variants in this gene, mostly missense, have been consistently associated with HCM with familial segregation, enrichment, and functional evidence.[47]

Some specific variants have been well characterized in relation to the associated phenotype, such as p.(Cys150Tyr), which is associated with a late-onset disease, incomplete penetrance, and a mild phenotype, both in terms of degree of hypertrophy and adverse outcomes.[48] Previous reports suggest similar clinical phenotypes are seen with other disease-causing missense variants. The association of this gene with DCM and skeletal myopathy has been suggested but remains unproved.

FLNC

FLNC encodes filamin-C (or gamma filamin), which is a muscle-specific cytoplasmic protein involved in the reorganization of the actin cytoskeleton in response to signalling events.

Pathogenic variants in this gene were initially associated with LV arrhythmogenic cardiomyopathy (loss-of-function variants), skeletal myopathy, and restrictive cardiomyopathy (specific missense variants).

There has been speculation regarding the connection between nontruncating variants in the *FLNC* gene and the development of HCM. However, the majority of studies do not provide convincing evidence of cosegregation.[49]

There is a putative association between certain *FLNC* nontruncating variants (most of them located in the ROD2 domain) and HCM, although this association likely pertains to mild and late-onset phenotypes in the majority of cases. Because of its substantial size, identifying *FLNC* variants in high-throughput sequencing studies is commonplace. In most instances, these variants lack clinical relevance, making it challenging to identify causal variants. The presence of restrictive physiology may offer supportive evidence, but—in most of the cases—determining the pathogenicity of a novel nontruncating variant in a patient with HCM is challenging.[50]

JPH2

This gene encodes junctophilin 2, a protein involved in the interaction of L-type calcium channels on the plasma membrane and ryanodine receptor type 2 in the sarcoplasmic reticulum.

To date, a few variants, mostly missense, have been associated with autosomal dominant HCM, based on segregation, de novo presentation, or functional studies. Most of the reported variants are in membrane occupation and recognition nexus (MORN) motifs, which are functionally important. One of the best-characterized variants is associated with moderate hypertrophy, systolic and diastolic dysfunction, and

GENETIC ARCHITECTURE OF HYPERTROPHIC CARDIOMYOPATHY

	MONOGENIC	OLIGOGENIC	POLYGENIC
MAF* CONTROL POPULATION	<0.001%	<1%	>1%
INHERITANCE PATTERN	MENDELIAN	NEAR-MENDELIAN	NON-MENDELIAN
FAMILIAL AGGREGATION	HIGH (Segregation)	INTERMEDIATE	LOW
EFFECT SIZE	HIGH	INTERMEDIATE	LOW/NOT-ESTABLISHED
ENRICHMENT	CLEAR		COMPLEX-COMBINED
CLINICAL IMPACT	CAUSAL	POTENTIALLY CAUSAL	INCREASE SUSCEPTIBILITY
GLOBAL HCM CONTRIBUTION	HIGH (≈50%)	NOT-ESTABLISHED	

** MAF: Minor allele frequency (%)*

Figure 4. Genetic architecture of hypertrophic cardiomyopathy.

the development of atrial fibrillation and conduction disturbances.[51]

KLHL24

KLHL24 encodes for the protein ubiquitin ligase substrate receptor Kelch-like protein 24, which is involved in the maintenance of intermediate filament stability. Pathogenic variants in this gene (null variants) are associated with a recessive form of HCM, characterized by early-onset disease and high rate of arrhythmic events and, additionally, with neuromuscular involvement, apparently mediated by glycogen accumulation or desmin abduction.[52]

The Role of Non-Mendelian Genetic Variation in the Development of HCM: Intermediate Effect Variants and Polygenic Inheritance

The current performance of genetic testing in identifying a monogenic genetic variant for fully explaining the phenotype does not reach 50% for most of the published HCM cohorts. Genetic-negative HCM is generally associated with a better prognosis in terms of cardiovascular events, and the presence of classical cardiovascular risk factors (diabetes, obesity, and hypertension) is more frequent. The familial aggregation in patients with genetic-negative HCM is variable and lower than in genetic-positive, suggesting a complex non-Mendelian etiology.[53]

There is an increasing interest in deciphering the genetic architecture underlying the phenotypic variability characteristic of HCM. In addition, there is emerging evidence on non-Mendelian genetic factors for increasing diagnostic yield in familial and nonfamilial disease.

The etiology of genetic-based heart diseases can be represented as a continuum, in which at one extreme are classic Mendelian variants (very rare in controls, familial aggregation, and high penetrance) and, at the other extreme, common variants in control populations (single nucleotide polymorphisms [SNPs] with 1% to 5% of minor allele frequency [MAF]), found in genome-wide association studies (GWAS), with a global small effect size, which jointly could increase the likelihood of developing HCM traits (maximum LV wall thickness, LV mass) in polygenic risk scores.[24,54,55]

In the middle of the spectrum are intermediate-effect variants, seen in controls (MAF $<$ 1%), with higher statistical indices (strength of association and etiologic fractions), which, in isolation (or in combination with other factors), could increase the diagnostic yield. The clinical actionability in terms of familial evaluation and prognosis is likely to depend on the behaviour of such intermediate variants and needs to be elucidated. These variants have been neglected to date because they are not included in GWAS studies (they are too rare) and most of the time are not reported in genetic studies (they are too common). These variants could potentially be found in any of the sarcomeric or regulatory genes previously described. Two examples of these variants previously described are the p.Arg278Cys in *TNNT2*, and p.Glu441Lys in *MYBPC3* (Fig. 4).[24]

The ultimate importance of oligo- and polygenic inheritance in HCM remains to be fully established. If preliminary findings are substantiated, they will be increasingly important in the management and diagnosis of HCM. Other putative genes, including desmosomal variants, have been considered but remain to be established as causal in HCM.[56,57]

Syndromic and Metabolic Forms of HCM

Several systemic conditions manifest with unexplained LVH. This heterogeneous group of diseases are generally referred to as "genocopies" and may account for up to 10% of patients with HCM. Different nonsarcomeric pathways may be involved: metabolic disorders (lysosomal and glycogen storage conditions), RAS-Map kinases (RASopathies), myocardial infiltration/inflammation (cardiac amyloidosis and myocarditis), mitochondrial disorders, neuromuscular syndromes (Friedreich ataxia, desminopathies). Usually, these syndromes present with inheritance patterns other than autosomal dominant (eg, recessive, matrilineal, X-linked). Differential diagnosis with sarcomeric HCM is sometimes challenging, and genetic testing is valuable. In this regard, a correct diagnosis is crucial, as clinical prognosis varies and disease-specific treatments are increasingly available; in addition, the risk calculator for prediction of sudden death does not apply. Detailed descriptions of the syndromic and metabolic disease associated with HCM are presented in a separate article.

Familial and Genetic Evaluation

Familial and genetic evaluation of probands with HCM is variable, largely dependent on local capacities. The importance of a dedicated inherited cardiac disease clinic cannot be overemphasized. Clinical expertise in electrocardiography, imaging, and management of arrhythmia and heart failure in the context of HCM are required. The skills of a geneticist or genetic counsellor to enable a 3-generation pedigree and provide the necessary counselling and support interpretation of genetic findings with links to a reliable genetics laboratory are also fundamental. Ideally, the clinic would also have capacity to evaluate children and adolescents, either directly or with links to an analogous pediatric team. Current international guidelines recommend familial evaluation with a 3-generation pedigree and genetic testing of probands who fulfill diagnostic criteria for HCM. Guidelines also recommend cascade screening of first-degree relatives when a definite or probable disease-causing mutation is identified in the proband. This enables identification of relatives who are at risk of developing disease to enable closer surveillance as well as identification of relatives who are not at risk and can be reassured without further surveillance.

The utility of mutation analysis in predicting outcomes and guiding management is less well established, and, hence, international guidelines vary in their recommendations. Data support the view that the specific mutation and sex of the patient are important determinants of disease expression and outcome. It is 35 years since the first disease-causing mutation was identified in a HCM family, and adequate data are now emerging to indicate that specific mutations provide actionable information. A young carrier of a troponin-T mutation involving residues 92 to 95 warrants serious consideration for a cardioverter defibrillator, even in the absence of a severe phenotype or risk factors for sudden death; data indicate a 40% risk of sudden death by age 50 (Fig. 2). In contrast, by the same age, a carrier the p.Asn271Ile variant in troponin T or a missense mutation in the tail of the myosin heavy chain may require annual surveillance only and is unlikely to develop heart failure complications or lethal arrhythmias.

Such examples of mutation analysis provide potentially actionable information to guide management and, in addition, provide a stimulus to obtain the necessary data from comprehensive genetic testing of probands and their families to enable multicentre registries and public databases. At present, it is unclear to what extent genetic information will guide management, but there is sufficient and growing experience that knowledge of the specific mutation or the presence of second variants will help guide management in the future.

Conclusions

HCM is a phenotype characterized by electrocardiographic and imaging evidence of LVH. When found in isolation, the most common cause is a mutation in a gene encoding sarcomere proteins. A genetic diagnosis is important because different mutations are associated with different phenotypes and outcomes, and this knowledge may influence management. Increasingly, the importance of oligo- and polygenic genetic determinants is being recognized. When HCM is associated with other phenotypes, nonsarcomere genes are more important, and these are equally important to recognize, as these genetic diseases are increasingly amenable to specific targeted therapies.

Ethics Statement

The research reported in this paper adhered to the appropriate local Ethics Guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this review article, which does not analyze individual identifiable data.

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Supplementary Material

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