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MINI-REVIEW

Pediatric Hypertrophic Cardiomyopathy: Exploring the Genotype-Phenotype Association

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ABSTRACT: Pediatric hypertrophic cardiomyopathy (HCM) is the most common form of cardiomyopathy in children and a leading cause of sudden cardiac death. Yet, the association between genotype variation, phenotype expression, and adverse events in pediatric HCM has not been fully elucidated. Although the literature on this topic is evolving in adult HCM, the evidence in children is lacking. Solidifying our understanding of this relationship could improve risk stratification as well as improve our comprehension of the underlying pathophysiological characteristics of pediatric HCM. In this state-of-the-art review, we examine the current literature on genetic variations in HCM and their association with outcomes in children, discuss the current approaches to identifying cardiovascular phenotypes in pediatric HCM, and explore possible avenues that could improve sudden cardiac death risk assessment.

Key Words: cardiomyopathy ■ congenital heart disease ■ genetics ■ hypertrophy ■ imaging

Hypertrophic cardiomyopathy (HCM) is the most common form of cardiomyopathy, affecting at least 1 in 500 individuals, and is a leading cause of sudden cardiac death (SCD) in adolescents and young adults.[1] When presenting during childhood and adolescence, the disease is associated with significant morbidity and mortality.[2] Genetic variations have been identified with strong causal evidence of association with ventricular hypertrophy typical of HCM and are often mutations in sarcomere genes or mutation in sarcomere-related proteins.[3] Despite this evidence, the biomolecular mechanisms leading to the HCM phenotype are not completely elucidated. Certain variations in genotype increase the risk of SCD in pediatric HCM (PHCM), yet the relationship between genotype and degree of ventricular hypertrophy is not strong enough to adequately predict SCD risk in children.[1,4,5] Finally, the classic sarcomeric genetic variants attributed to HCM do not exclusively induce myocardial

hypertrophy but can be associated with a multitude of other phenotypic parameters, such as fibrosis, abnormal myocardial perfusion, electrocardiographic findings, and increased myocardial stiffness (Figure 1).[1,6-8]

Understanding the relationship between genotype and phenotype may improve current risk prediction models that use parameters from the clinical history and physical examination along with conventional diagnostic testing (eg, echocardiogram, ECG, ambulatory rhythm monitoring, cardiac magnetic resonance imaging (CMR), cardiopulmonary exercise testing, and genetic testing).[5,9] Although the body of evidence that characterizes these genotypes and phenotypes is evolving in the adult literature, the pediatric literature is more limited.[10] The objective of this article is to review the current literature on genetic variations in PHCM and their association with outcomes, discuss the current approaches to identifying cardiovascular phenotypes in PHCM, and explore genotype-phenotype

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Nonstandard Abbreviations and Acronyms

CMD	coronary microvascular dysfunction
DD	diastolic dysfunction
HCM	hypertrophic cardiomyopathy
LGE	late gadolinium enhancement
PHCM	pediatric hypertrophic cardiomyopathy
SCD	sudden cardiac death

driven approaches that could improve SCD risk assessment.

PART I: EMERGING KNOWLEDGE OF THE GENETICS OF HCM

Definition of Pathogenic or Likely Pathogenic Variants

The genetic classifications for HCM are identical for children and adults. The clinical diagnosis of HCM is characterized by left ventricular hypertrophy (LVH) in the absence of another cardiac, systemic, or metabolic disease capable of producing that magnitude of hypertrophy.[1] Genetic variations are classified as pathogenic if there is strong causal evidence to support its association with ventricular hypertrophy typical of HCM,[3] and likely pathogenic is used when there is moderate to strong causal evidence of HCM. Among patients with HCM, 30% to 60% have an identifiable pathogenic or likely pathogenic variant.[1] In addition, the terms benign or likely benign are used if there is evidence that the

mutation is unlikely to cause a phenotype consistent with HCM. Finally, variants of unknown significance indicate variants with conflicting evidence for pathogenicity and should be periodically revisited to assess if the variant should be moved to a pathogenic or benign classification based on new evidence. The classification of genetic variation has strong clinical implications as guideline-directed management recommends cascade genetic screening in phenotype-negative family members only if probands have pathogenic or likely pathogenic variants.[11]

Genetic Cause of HCM

Gene variants that affect the proteins of the sarcomere are the leading genetic cause of HCM.[1] The sarcomere is the contractile subunit of the cardiac myocyte and consists of myosin thick filaments, myosin binding proteins, and actin thin filaments. Most pathogenic gene mutations (*b-myosin*, *a-tropomyosin*, *cardiac troponin T*, *MYBPC*, *MYL2*, *MYL3*, *TNNI3*, and *cardiac a-actin*) code for proteins for one of these filaments. PHCM tends to have a higher incidence of pathogenic variations than adult HCM.[12] However, nonthick and thin filament genes are emerging as causative agents of HCM (Figure 2).[13] Furthermore, noncoding variants that help regulate protein-coding cardiomyopathy genes could contribute to the genetic expression of cardiomyopathies (Figure 2). Noncoding variants include genes that do not directly provide the genetic code for a protein and instead are involved in DNA regulation, such as binding sites for the proteins that perform DNA transcription (promoters) and binding sites for proteins that aid in DNA transcription (enhancers). A whole
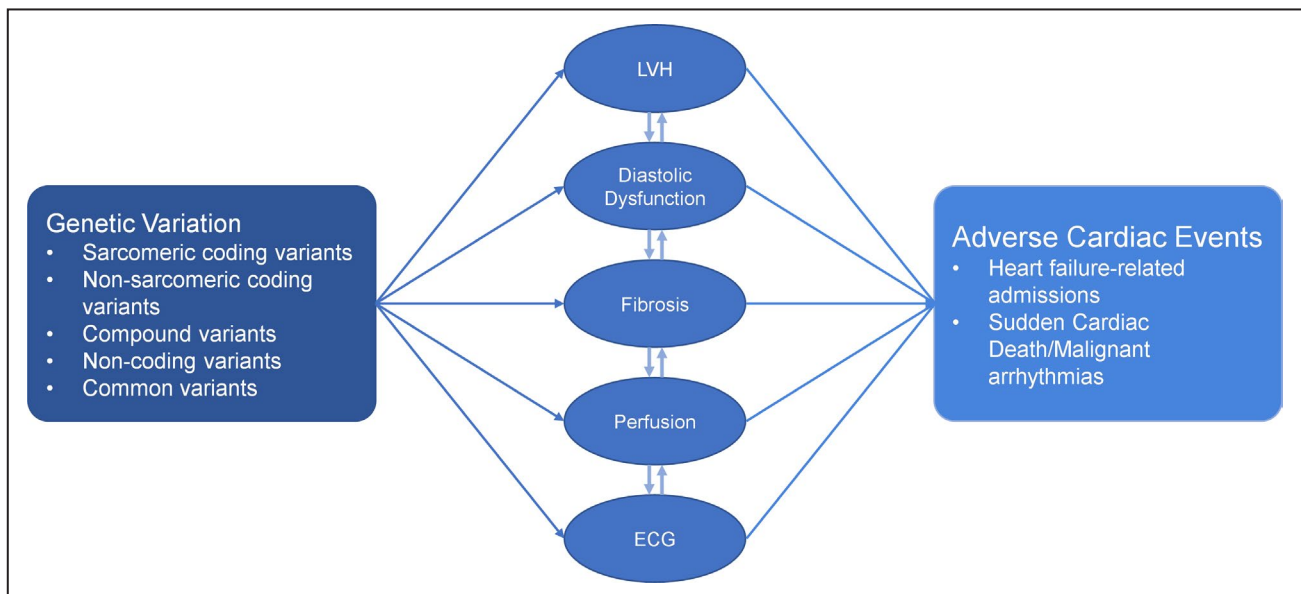

Figure 1. A potential link between genetic variation, phenotypic expression, and adverse events.
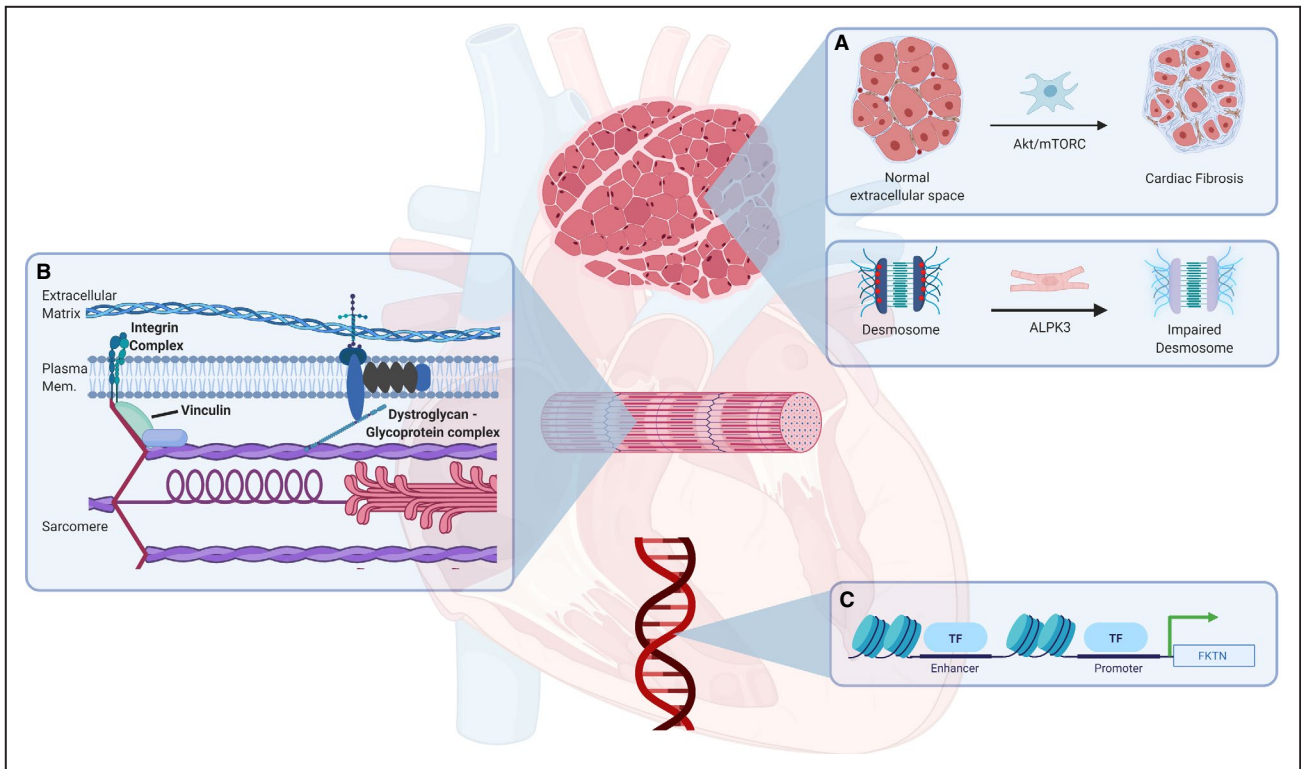LVH indicates left ventricular hypertrophy.

Figure 2. Sources of genetic variation.
Nonsarcomeric genetic variations can lead to the ventricular hypertrophy phenotype and outcomes associated with hypertrophic cardiomyopathy (HCM). **A**, Mutations in genetic pathways that are not directly linked to sarcomeric gene mutations, such as those essential in fibrosis or cardiomyocyte differentiation, can lead to pathologic hypertrophy. **B**, Mutations in proteins that are associated with the sarcomeric unit, especially those that attach the sarcomere to the extracellular membrane, have been linked to HCM. **C**, Noncoding mutations, such as in the enhancer or promoter regions of DNA transcription of cardiomyopathy genes, have also been implicated in HCM. Created with BioRender.com. Akt indicates protein kinase B; ALPK3, α-protein kinase 3; FKTN gene (or FCMD): provides instructions for making a protein called fukutin. Mem., membrane; mTORC, mammalian target of rapamycin complex; and TF, transcription factor.

exome sequencing study on patients with childhood-onset cardiomyopathy identified noncoding variants involved with α-dystroglycan glycosylation and desmosomal signaling.[13] These variants were then validated on zebrafish knockout models that exhibited small left ventricular (LV) end-diastolic volumes in the setting of preserved ejection fraction.[13]

Role of Nonsarcomeric Signaling Pathways in the Pathogenesis of HCM

It is well known that nonsarcomeric genetic variants can lead to systemic manifestations along with ventricular hypertrophy similar to HCM (ie, HCM "mimics"), such as Fabry disease and Danon disease, or the pathologic hypertrophy histologically indistinguishable from sarcomeric disease associated with Noonan syndrome.[14] Recent proteomics studies have revealed the upregulation of proteins in the Ras–mitogen-activated protein kinase (a major signaling pathway implicated in Noonan syndrome), fibrosis, and inflammatory pathways in patients with HCM compared with those with adaptive LVH

attributable to hypertension.[15,16] Of note, less than one third of the patients with HCM had a pathogenic/likely pathogenic variant, and HCM mimics were screened in this cohort by genetic testing and advanced imaging. Although the implications of proteomics are not completely understood, this study provides evidence that the upregulation of nonsarcomeric genes synergizes with sarcomeric variants and leads to the pathogenesis and disease severity in HCM. However, the fact that most patients did not have a pathogenic variant for HCM raises the possibility that genetic variants in signaling pathways, such as Ras–mitogen-activated protein kinase, can lead to a "true" HCM phenotype (ie, ventricular hypertrophy, fibrosis, diastolic dysfunction [DD], or perfusion deficits) in the absence of sarcomeric genetic variations and systemic disease manifestations typically attributed to those pathways.[17] In summary, we speculate that there are signaling pathways in multiple disease processes that lead to a cardiac phenotype similar to HCM (ie, secondary or systemic HCM), and it is possible for a genetic variation in one of these pathways to lead to the HCM phenotype without the other systemic/secondary manifestations.

Other nonsarcomeric genetic variants that could be considered include other signaling pathways that are upregulated in HCM, such as protein kinase B and mammalian target of rapamycin complex 1, which both promote cell growth and lead to ventricular hypertrophy and heart failure when overexpressed in the heart[15,18] (Figure 2). Infants with pathologic hypertrophy are often associated with inborn errors of metabolism, which confers a significantly increased risk of death.[19] It could be possible that variants in pathways associated with metabolic disorders could be another example. In addition, genetic variants of α-protein kinase 3 have been implicated as a pediatric cardiomyopathy gene. It is thought to play a large role in regulating transcription factors responsible for cardiomyocyte differentiation, with loss-of-function mutations in murine models leading to dysfunctional intercalated discs likely attributable to impaired desmosome formation.[20] Clinical studies in children with α-protein kinase 3 variants were notable for progressive dilated cardiomyopathy that transitioned into ventricular hypertrophy with histopathological characteristics yielding focal cardiomyocyte hypertrophy and subendocardial fibroelastosis.[21]

Genotype, Ventricular Hypertrophy, and Outcomes

Recent literature on the PHCM population shows that variations in genotype not only cause the classic HCM phenotype (ie, myocardial hypertrophy) but may influence severity of ventricular hypertrophy and SCD risk. In a single-center prospective cohort study in patients with childhood-onset HCM, Mathew et al found that myosin heavy chain 7 (MYH7) had a higher association with ventricular hypertrophy and adverse events compared with other pathogenic gene mutations.[4] A similar effect was also seen in patients with multiple genetic variations, and with confirmed de novo variants.[4] In a literature review assessing the frequency of multiple variants, the occurrence of multiple pathogenic/likely pathogenic mutations was rare but when present, conferred a severe phenotype (eg, homozygous myosin binding protein C (cardiac MyBP-C) [MYBPC3] variants).[22] Building on this body of knowledge, Miron et al developed a predictive model via a large multicenter study of PHCM with a larger sample size and a method that assesses for predictive accuracy using discovery and replication cohorts. They found that having a pathogenic/likely pathogenic MYBPC3 variant instead confers a modest increase in risk of SCD compared with the other known mutations.[5] Finally, the impact of multiple gene mutations was derived and validated against LV traits characterized by CMR from the UK Biobank.[23] They found that a higher polygenic risk score, a predictive model derived from genome-wide association surveys of patients with HCM that considers and weights

multiple gene variants, was associated with greater severity of LV dimensions and LV systolic function.

In summary, the discovery of the synergistic nature of multiple genetic variants, along with the fact that noncoding variants influence phenotypic expression, improves our understanding on how genetic variations may explain the degree of ventricular hypertrophy and explain genetic associations with outcomes. These discoveries could help explain the pleiotropy and variable penetrance of sarcomeric gene mutations on LVH and SCD.

PART II: EMERGING KNOWLEDGE OF PHENOTYPES IN PHCM

Definition of Phenotype in PHCM

The classic phenotype in PHCM is the manifestation of LVH in the absence of systemic or secondary disease that can lead to hypertrophy of pathologic magnitude.[1] According to the recent American College of Cardiology/American Heart Association guidelines on PHCM, hypertrophy consistent with PHCM is defined as a maximal end-diastolic wall thickness that meets "a threshold of z-score >2.5 may be appropriate to identify early HCM in asymptomatic children with no family history, whereas for children with a definitive family history or a positive genetic test, a threshold of $z>2$ may suffice for early diagnosis."[1] There is an explicit lack of a z-score model (eg, Pediatric Heart Network, Boston, or Detroit) specified in this guideline as there have not been studies comparing z-score models of LV thickness to specific outcomes within PHCM. However, choosing which model to derive z-scores in clinical practice is a major consideration as each model has systematic differences that affect which patients qualify for the diagnosis of hypertrophy consistent with PHCM, in particular at the extremes of body surface area.[24] Ultimately, the echocardiography laboratory and heart function team at each heart center must decide what criteria to use based on the context of their patient population and clinical practice. In addition, genotype may independently contribute to other phenotype parameters not included in this definition. Further delineating these additional phenotypes could aid in increasing the sensitivity of the diagnosis of PHCM, especially in cases where pathologic hypertrophy is not readily apparent on initial evaluation. The phenotypes explored herein (eg, diastolic function, fibrosis, perfusion, and ECG phenotype) impact each other. It is difficult to assess the degree of causality a genetic variant has on each individual parameter without studies that comprehensively assess these phenotypes with genetic variation. Nevertheless, these parameters could impact the prognosis of a patient with PHCM (Figure 1).

Diastolic Function

DD, abnormalities in delayed relaxation and compliance of the ventricles, is well known to be associated with PHCM, although its relationship with genotype and SCD needs further evaluation. Genotype alone appears to have a direct impact on delayed relaxation, a key component in diastolic function, and can do so by impacting myocardial function at the biomolecular level. Impaired relaxation in certain genetic variations in HCM (MYH7 variants with pathogenic, likely pathogenic, and variant of unknown significance classifications) leads to inefficient ATP hydrolysis, which alters cardiomyocyte contraction, leads to delayed relaxation, and results in subsequent energy loss.[6,25] Morphologic remodeling in HCM is also associated with DD by primarily impacting chamber compliance of the ventricles. Children with HCM tend to have increasing levels of diffuse interstitial fibrosis and can also manifest fiber disarray,[8,26] both of which increase stiffness at the level of the myocardium. Cardiac myocyte stiffness and abnormal thickening of the ventricular myocardium reduces chamber compliance, which is a major component of diastolic function.[27] Therefore, DD assessment may be a sensitive tool to assess the phenotypic impact of a gene mutation. Indeed, studies have correlated DD parameters in HCM to brain natriuretic peptide levels, a parameter that increases with stretch of the LV cardiac myocytes and thus decreasing compliance of the LV cavity.[28]

The noninvasive clinical assessment of diastolic function is primarily assessed by spectral Doppler, tissue Doppler imaging, and left atrial/ventricular strain/volume parameters. Jhaveri et al studied the relationship between diastolic function parameters in 3 distinct groups of children: children with clinically diagnosed HCM with ventricular hypertrophy, genotype-positive but phenotype-negative patients, and healthy volunteers.[7] They found that left atrial reservoir strain in the 2-chamber view was significantly different between patients with HCM with ventricular hypertrophy, genotype-positive patients without ventricular hypertrophy, and healthy volunteers (mean strain % [SD]: phenotype positive, 30±11; genotype positive phenotype negative, 41±9; control, 51±9). The ability to distinguish between these 3 groups was also found to be possible in adult HCM studies using echo DD parameters.[29,30] Indeed, the link between genetics and echocardiographic function can even be detected between variations in risk alleles (such as variations in the VEGF1 allele) in PHCM.[31]

With respect to outcomes, McMahon et al studied 80 consecutive patients with PHCM and assessed the correlation between echocardiographic and exercise stress test findings to adverse events.[32] They demonstrated an inverse relationship with septal early diastolic mitral annular tissue velocity (E)/peak mitral annular velocity during early filling ratio and maximum oxygen consumption ($r=-0.74$; $P<0.001$). Furthermore, the only predictor of SCD on multivariable analysis was septal E/peak mitral annular velocity during early filling ratio ($R^2=0.37$; $P<0.001$). Villemain et al observed a similar correlation between myocardial stiffness, which is also a key parameter for diastolic function, and maximum oxygen consumption.[26] Unfortunately, these outcome-based DD studies in children did not study genotype in the context of diastolic function and outcomes. Thus, there is potentially a strong link between genotype, diastolic function, and outcomes in PHCM, but more research needs to be done to elucidate this relationship.

Despite these associations, diastolic function is difficult to assess by ultrasound, especially in PHCM.[33] The reason is multifactorial, but thought to be related to the fact that (1) echocardiographic measurements do not directly assess ventricular filling pressures (ie, ventricular end-diastolic pressures) as this cannot be directly visualized by echocardiography; and (2) each of these echocardiographic measurements is instead used to estimate components that affect diastolic function (eg, myocardial relaxation and loading conditions), which have their own complex nonlinear interactions.[33] Furthermore, accounting for changes in growth of a child adds significant variability and tends to make the range of normal broad.[34] For example, the peak mitral annular velocity during early filling in children has been shown to not predictably decrease in diseased myocardium unlike in adults, where it is a key parameter in the adult echocardiographic DD diagnostic algorithm.[33,35] Therefore, better means of assessing diastolic function are needed to improve our understanding of the PHCM phenotype. To this end, novel echocardiographic technologies are being explored to assess major quantitative components of diastolic function. For example, myocardial stiffness can be assessed accurately using ultrafast ultrasound sound-derived shear wave elastography of the myocardium.[36] Myocardial stiffness assessment could thus provide a better phenotypic diastolic parameter that is related to outcomes.

Myocardial Perfusion

Coronary microvascular dysfunction (CMD) is a clinical diagnosis where inadequate myocardial perfusion occurs in the absence of obstruction of the larger (>500-μm) epicardial vessels in the coronary system. It is well documented that patients with HCM have smooth muscle hypertrophy, collagen deposition, and intimal thickening at the level of the coronary arterioles (<100 μm), which contributes to CMD.[37] Furthermore, positron emission tomography and CMR studies on coronary blood flow of the myocardium in patients with

HCM have identified that dysregulation of the coronary microvasculature could play a role in development of myocardial ischemia and fibrosis in HCM, with strong links to adverse outcomes reported.[38] With respect to genotype variation, a CMR study that studied the degree of oxygenation and perfusion in HCM with LVH, genotype positive without LVH, and controls found that HCM with LVH phenotype had oxygenation and perfusion deficits, whereas genotype-positive patients without LVH had oxygenation deficits but similar perfusion compared with controls.[39] A more recent study found a worse CMR-derived myocardial perfusion reserve in genotype-positive patients without LVH compared with controls.[40] This implies that microvascular autoregulation may impact genotype-positive patients before the manifestation of overt LVH and autoregulation is worsened in patients with HCM with LVH phenotype (Figure 1). There are few articles studying perfusion in PHCM. Jablonowski et al used CMR-derived estimates of perfusion and late gadolinium enhancement (LGE) to study fibrosis in PHCM compared with controls. They found that there was decreased perfusion in areas of hypertrophy, and the level of hypoperfusion was accentuated when LGE was found within hypertrophy. Furthermore, the areas of hypoperfusion at rest and in areas of fibrosis expanded on adenosine stress testing.[41] This suggests that CMD may play an important role in the development of PHCM. More research needs to be done in children and adults with HCM to translate these findings into clinical management.[42]

Fibrosis

CMR is the primary noninvasive clinical modality used to assess fibrosis because of its good correlation with histological specimens.[43] Traditionally, fibrosis has been classified in 2 forms. Localized replacement fibrosis is the deposition of collagen where there was previously necrosed or apoptotic myocytes and is quantitatively assessed using LGE. Diffuse interstitial fibrosis is a reversible pathologic remodeling process consisting of deposition of collagen by myofibroblasts. CMR T1 mapping-derived parameters, such as native T1 values and extracellular volume fraction, have recently emerged as promising techniques to quantitatively estimate myocardial fibrosis and could prove useful in disease monitoring.[44] In children, Axelsson Raja et al reported that there was no LGE in genotype-positive patients without LVH, but there is LGE in 46% of patients with LVH.[45] Interestingly, among the pathogenic or likely pathogenic carriers without LVH, they had enlarged left atrial volumes (left atrial volume index=41±10 mL/m^2), which suggests that DD is present in PHCM before manifestation of LVH. Of note, although there was no LGE detected in genotype-positive patients without LVH, T1 mapping techniques, which are more sensitive

to subtle changes in diffuse interstitial fibrosis, were not used.[43] It may be possible that the elevated left atrial volume index in this genotype-positive group could be attributable to both delayed relaxation as well as undetected diffuse interstitial fibrosis. In particular, Hussain et al used T1 mapping methods (partition coefficient) to estimate diffuse myocardial fibrosis in patients with PHCM and found elevated partition coefficient levels compared with controls. Moreover, there was no significant difference in partition coefficient in patients with PHCM who are LGE positive versus LGE negative.[8] These findings suggest that fibrosis, especially diffuse interstitial fibrosis, is prevalent in children with HCM and is likely underestimated when using LGE alone to detect fibrosis in PHCM. More pediatric studies focusing on fibrosis quantification should include native T1/extracellular volume methods and assess genotype-positive, phenotype-negative PHCM. Unfortunately, few studies relate fibrosis to outcomes in PHCM, whereas the evidence in the adult population is strong enough to be a diagnostic tool useful in the risk stratification for implantable cardioverter-defibrillator placement decision making.[42]

Additional research in understanding the pathophysiological characteristics of the fibrosis phenotype as they impact HCM could help us better apply tools extensively researched for fibrosis to improve PHCM. Raman et al had investigated potential causative factors of fibrosis in HCM. Through CMR techniques, they found that inefficient energy use (a low phosphocreatine/ATP ratio via phosphorous magnetic resonance spectroscopy) and CMD (via CMR-derived myocardial perfusion reserve index) on baseline CMR correlated with significantly higher increases in LGE.[46] Although their study design did not include mediation analysis, one could speculate the possibility that inadequate perfusion (eg, CMD) is a mediator that explains the relationship between inefficient energy use and fibrosis.

Electrocardiographic Phenotype

Children with HCM are more likely to have malignant life-threatening arrhythmias than adults with HCM.[2] This has led to guideline-recommended regular arrhythmia screening, including serial 12-lead ECG and ambulatory monitoring.[1] Interestingly, studies have found ECG patterns unique to patients with HCM and have validated their prognostic value in assessing SCD risk in PHCM. Lorenzini et al found that children who had pathogenic or likely pathogenic sarcomeric gene mutations with normal echocardiograms but abnormal ECG (LVH by Sokolow-Lyon criteria, abnormal Q wave, and repolarization abnormalities) were more likely to develop pathologic ventricular hypertrophy.[47] This suggests that visible patterns seen in ECG are a phenotypic expression of genetic variation. Furthermore,

there is evidence that ECG phenotype by itself could be a promising screening tool for SCD risk in PHCM. An extensive body of work generated from a large national Swedish registry of patients with HCM has yielded an ECG risk score composed of morphological, repolarization, and voltage-amplitude criteria from a surface ECG. This score was predictive of SCD and cardiac arrest in this cohort.[48] When this risk score is combined with a clinical SCD risk score (which uses clinical criteria, such as echocardiographic findings, clinical signs and symptoms, and cardiac rhythm monitor findings), they found it was synergistic and its ability to predict SCD and cardiac arrest was improved.[49] These findings provide strong evidence that ECG phenotype should be incorporated into SCD risk stratification going forward. In addition, it is well known that ECG findings are strongly associated with changes to conductive, functional, and morphological changes of the myocardium. This is supported by the fact that the ECG risk score is associated with positive LGE and perfusion deficits by CMR.[50] Other pathophysiological features that ECG phenotype could represent include myocardial disarray and ion-channel mutations, which are both implicated in HCM.[12,51]

PERSPECTIVES

The traditional paradigm in the natural history of PHCM is linear: a sarcomeric coding variant may lead to the typical HCM phenotype of ventricular hypertrophy, and those with more severe phenotypes have an increased risk of adverse events, such as SCD. However, much research over the past 10 years has significantly broadened our approach to this PHCM paradigm. It is now known that multiple other components of the genome can lead to the classic HCM phenotype of pathologic ventricular hypertrophy. Furthermore, genetic variation can impact the form and function of the heart beyond just ventricular hypertrophy, and these phenotypes have a complex relationship in their impact of SCD risk (Figures 1 and 2).

Each phenotype is likely a result of influences that are both innate and acquired; genes play a major role in each phenotype, but also the environment heavily influences phenotypic expression. Restrictions on exercise in patients with PHCM have been the norm because of concern for worsening of the HCM phenotype and triggering arrhythmia. However, recent murine models have found a protective effect in reducing pathologic hypertrophy in HCM, and there are several ongoing human trials (eg, exercise in genetic cardiovascular disease/lifestyle and exercise in hypertrophic cardiomyopathy and randomized exploratory study of exercise training in hypertrophic cardiomyopathy) that have preliminary findings corroborating the benefit of exercise in HCM.[52]

Furthermore, more contemporary studies have found that HCM-related SCD in athletes is rare.[52] This environmental impact is an important aspect of prognostication and management that requires additional study.

Much of the research to further elucidate the association between genotype and phenotype is ongoing, but there are areas of research that could directly improve our understanding of PHCM. Although noncoding variants are mentioned in this review, the development of high-throughput DNA sequencing has led to the discovery of many other potential noncoding variants in HCM, such as in RNA missplicing.[53] In addition, the pathogenesis of HCM attributable to epigenetic causes is an emerging field that is worth investigating.[54] There has been increased emphasis on the noninvasive phenotyping of patients with PHCM. For example, a more direct assessment of DD could be possible using shear wave elastography to estimate myocardial stiffness.[26] The noninvasive assessment of the myocardial perfusion could also play a major role in the future.[55,56] Finally, machine learning methods can synergize the nonlinear and complex interactions between the described diagnostic phenotyping techniques in this review to create accurate risk predictions.[5,9] There are other phenotypes that genotype could impact that were not described herein, which include, but are not limited to, nonventricular morphological characteristics (mitral valve leaflet elongation and ventricular aneurysms) and obstructive HCM.

Finally, the precise diagnosis of genotypic variation and phenotypic progression should provide a better understanding of HCM pathophysiological characteristics to accurately predict SCD risk. Not only would our prognostic ability improve, but this granular understanding of disease progression could permit us the opportunity to assess if intervention improves the development of disease at the patient level. For example, delayed relaxation is a direct consequence of MYH7 variations that cause abnormal myosin function at the molecular level with subsequent delayed relaxation and inefficient energy use at the myocardial tissue level. This DD can then predispose to interstitial fibrosis. Interstitial fibrosis is implicated in pathologic remodeling attributable to heart failure with preserved ejection fraction, of which several causes exist in HCM (eg, DD and LV outflow tract obstruction).[57] Knowing this pathophysiology, we could more closely monitor DD and fibrosis progression in patients with this genetic variation. Interventions that improve fibrosis and DD could then be tracked in an individual patient to assess management efficacy and prognosis. Understanding the impact of all aspects of a genotype on phenotypic expression, combined with a comprehensive understanding of the phenotypes that can interact with genotype, may improve our ability to improve adverse event assessment and management in PHCM.

CONCLUSIONS

The goal in understanding the association between genotype and phenotype in PHCM is to improve the outcomes of this high-risk population of children. This may result in broadening the genetic variants classically associated with "genotype-positive" HCM as well as expanding the definition of HCM phenotype beyond ventricular hypertrophy. Precision medicine, the personalization of health care based on an individual's unique genetic and phenotypic makeup, could directly benefit by solidifying the link between genotype and phenotype.

ARTICLE INFORMATION

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Disclosures

Dr Jeewa is the site principal investigator for industry-sponsored (Novartis) heart failure drug trial in pediatric heart failure. Dr Jeewa is a Canadian Institutes of Health Research coinvestigator for SCRIPT (Survival and Cardiac Recovery in Pediatric Cardiomyopathy) Study. Dr Mital is a member of the Cardiovascular Advisory Board of Bristol Myers Squibb.

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