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Twin Phenomena of Hypertrophic Cardiomyopathy: A Reported Case Series

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a prevalent genetic cardiovascular disease characterized by asymmetric thickening of the left ventricular wall, frequently occurring in families predisposed genetically. While HCM in twins is rare, it presents a unique opportunity to explore the disease's genetic and epigenetic underpinnings due to the phenotypic heterogeneity observed even among genetically identical individuals. This review collates and analyzes global clinical studies that focus on the twin phenomena in HCM. It explores the genetic foundations of HCM, examines the influence of environmental and epigenetic factors on disease expression, and emphasizes the crucial role of genetic screening in the early and differential diagnosis of HCM. By focusing on twin cases in HCM, this review aims to enhance our understanding of HCM's complex genetic background, which could lead to more personalized approaches in the management and treatment of this condition, thus drawing significant interest from researchers and clinicians alike.

Keywords: Hypertrophic cardiomyopathy, twin, cases, inheritance, genetic testing

REVIEW

INTRODUCTION

Cardiomyopathies represent a heterogeneous group of diseases characterized by structural and functional abnormalities of the heart muscle.[1] These disorders are associated with high mortality and morbidity rates.[2] The classification of cardiomyopathies has evolved over the years, with the American Heart Association (AHA) proposing a classification system in 2006 that categorizes these diseases into primary (genetic, acquired, mixed) and secondary form.[1] Common cardiovascular conditions such as valvular heart diseases, hypertension, and congenital heart defects are generally not classified as cardiomyopathies.[3] Hypertrophic cardiomyopathy (HCM) is the most common form of genetic cardiomyopathy,[4] primarily characterized by asymmetric thickening of the left ventricular wall (Figure 1).[5] The most frequent site of left ventricular wall thickening in HCM is located at the junction of the basal septum and the right anterior and inferior ventricles.[6] Clinical manifestations can range from asymptomatic to heart failure (HF) and sudden cardiac death (SCD).[1,7] This review aims to explore the unique role of twins in HCM research, particularly by analyzing twin cases to understand the interplay of genetic and non-genetic factors (such as environmental or epigenetic factors) in HCM. The analysis of twin cases helps to deepen our understanding of the genetic basis and phenotypic heterogeneity of HCM, thereby enhancing disease diagnosis, the development of personalized treatments, and patient prognosis. Additionally, it reveals the potential of genetic research in predicting disease progression and treatment responses.

EPIDEMIOLOGY AND DIAGNOSIS OF HYPERTROPHIC CARDIOMYOPATHY

Epidemiological data indicate that the incidence of HCM is approximately 1 in 500 in the general population,[8] but in populations with a family history of the disease, the incidence may rise to as high as 1 in 200.[5,9,10] In the United States, it is estimated that around 750 000 people are affected by HCM, yet only about 100 000 are diagnosed, indicating that the majority of HCM patients may go undiagnosed throughout their lives.[11] Although the prevalence of HCM has shown an increasing trend in recent

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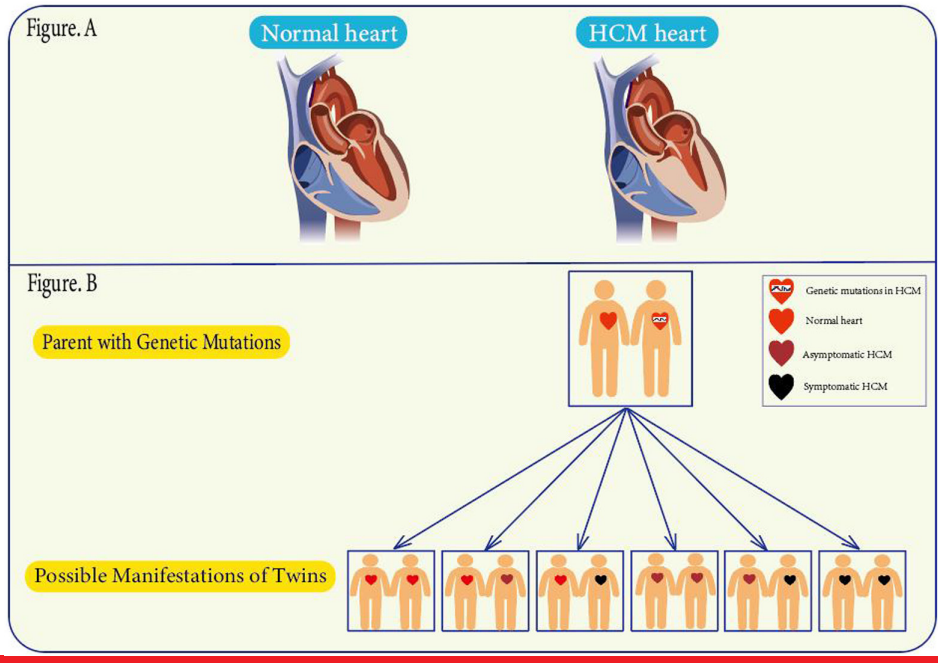

Figure 1. Comparison of normal and HCM hearts and variable expression in twins. Figure A depicts the differences between a normal heart and an HCM heart. The normal heart shows typical cardiac anatomy, while the HCM heart demonstrates characteristic ventricular wall thickening. Figure B illustrates the possible phenotypic manifestations of twins born to a parent with HCM-associated genetic mutations. It demonstrates the parent's genetic mutation (indicated by the icon) and various potential cardiac conditions in their twins. Given that HCM follows an autosomal dominant inheritance pattern, the twins may exhibit a range of cardiac phenotypes: both normal; 1 normal and 1 asymptomatic HCM; 1 normal and 1 symptomatic HCM; both asymptomatic HCM; both symptomatic HCM. The icons represent the presence of genetic mutations, normal heart, asymptomatic HCM, and symptomatic HCM.

years, reported rates vary due to differences in the study populations and diagnostic tools used. Despite HCM being reported across all races, the definitions of racial disparities remain controversial and are primarily associated with variations in disease prevalence, severity, and disparities related to genetic testing and the distribution of medical resources.[12]

The diagnosis of HCM is exclusionary[13] made after ruling out other cardiovascular and metabolic diseases that could cause ventricular wall thickening, associated with mutations in sarcomere protein genes.[14] In adults, an echocardiographic or cardiac magnetic resonance (CMR) measurement of the maximum left ventricular wall thickness ≥15 mm at end-diastole, in the absence of other causes of left ventricular hypertrophy, is sufficient for diagnosis.[15] If there is a positive family history of HCM or a positive genetic test, a left ventricular wall thickness ≥13 mm is also diagnostic.[5,12,16,17] Before a definitive diagnosis, suspected patients should undergo echocardiography to assess left ventricular wall thickness, diastolic function, and the extent of left ventricular outflow tract obstruction. When any part of the left ventricular thickening reaches 30 mm or more the risk of SCD is extremely high.[6] Cardiac magnetic resonance holds higher diagnostic accuracy for detecting key indicators such as myocardial fibrosis and systolic anterior motion (SAM) of the mitral valve, which are primary causes of left ventricular outflow tract (LVOT) obstruction.[18,19] Compared to echocardiography, CMR provides greater accuracy and reproducibility in confirming morphological features. Specifically, the presence, location, and extent of late gadolinium enhancement (LGE) in CMR can more accurately define the etiology and prognosis of the HCM hypertrophic phenotype.[6]

HIGHLIGHTS

- Twins with hypertrophic cardiomyopathy (HCM) can show significant phenotypic differences despite identical genetics, highlighting non-genetic factors.
- Hypertrophic cardiomyopathy expression involves a complex interplay of genetic predispositions and environmental or epigenetic factors, as evident from twin case studies.
- Genetic screening enhances early HCM diagnosis and personalized treatment by assessing individual risk.
- Twin studies provide insights into the genetic and environmental aspects of HCM, guiding personalized medicine.

Hypertrophic cardiomyopathy follows an autosomal dominant inheritance pattern,[20] leading to variability in expression and penetrance among affected individuals,[21] thus affecting clinical manifestations and disease progression, posing challenges for diagnosis and treatment.[22] Clinically, HCM is diverse, ranging from asymptomatic to severe SCD or HF outcomes (Table 1).[1,7,23,24] Common clinical presentations

Table 1. Summary of Demographic and Clinical Features of Twins with HCM

Reports	Twin Type	Sex/Age*	Clinical Manifestations	ECG	Cardiac Morphology	Treatments	Results
Karatzas et al[67]	MZ	F/22	All had symptoms such as shortness of breath and palpitation	All have T-wave inversion; Only 1 had AF	The wall thickness of LV is obviously different	Unknown	Diverse progression rates of HCM
Harley and Orgain[34]	DZ	F/22	All had symptoms of chest pain	All had S-ST segment changes	Normal	Only 1 needs medication	Variability in HCM treatment approaches
Littler[57]	MZ	M/Unknown	Unknown	Unknown	All had the LOVT obstruction	Unknown	Differences in HCM clinical progression suggest environmental influences
Reid et al[49]	MZ	M/11	The severity of the dyspnea varies	All had the LV hypertrophy and T-wave inversion	There was a difference in LV hypertrophy	Only 1 required a ventricular myectomy	Clinical symptoms and LV hypertrophy vary in HCM
Epstein et al[21]	MZ	F/Unknown	Unknown	Unknown	Only 1 had the LOVT obstruction	Only 1 required a ventricular myectomy	Emphasis on genetic testing and supplementary assessments for HCM family members
Ko et al[52]	MZ	M/35	All asymptomatic	There are differences in the degree of T-wave inversion	There was a difference in LV hypertrophy	All require medical treatment	Differences in LV hypertrophy not solely attributable to genetics, environmental factors also influential
Agirbasli et al[66]	MZ	F/38	Only 1 person had chest pain	All had LV hypertrophy	All had asymmetric septal hypertrophy and mitral valve SAM	All require medical treatment	The HCM course was identical in twins
Wylie et al[58]	MZ	F/62	All asymptomatic	The ECG results were all normal	Asymmetric septal hypertrophy is similar	No medical treatment is required	HCM morphology was similar
Maron et al[56]	MZ	M/18	All asymptomatic	All have T wave inversions	The hypertrophic parts of LV were the same	No medical treatment is required	Heredity is the primary factor influencing HCM morphology
Palka et al[50]	MZ	F/69	Only 1 had severe breathing difficulties	Only 1 had the ST-T segment changes	The degree of ventricular septal hypertrophy was different	Only 1 required the ASA	Environmental factors can impact HCM morphology and clinical presentations
Araujo et al[61]	MZ	M/19	Only 1 had severe breathing difficulties	Only 1 had LV hypertrophy	All had similar septal hypertrophy and LVOT obstruction	Only 1 required a ventricular myectomy	Raises further questions about HCM pathogenesis
Zenovich et al[54]	MZ	F/44	There were no obvious symptoms	All had the LV hypertrophy and T-wave inversion	All had LV hypertrophy and apical ventricular aneurysm	Only 1 has had an ICD implanted	Apical ventricular aneurysm was first found in twin HCM
Maron et al[55]	MZ	F/18	All asymptomatic	One has ST-T changes, the other a pathological Q-wave	Mitral SAM is similar	Unknown	Heredity primarily determines HCM morphology
Goh et al[53]	MZ	M/62	Only 1 experienced syncope due to malignant tachycardia	Only 1 had malignant ventricular tachycardia	There was a difference in LV hypertrophy	Only 1 has had an ICD implanted	Emphasizes potential genetic susceptibility to cardiac arrest in twins with HCM

(*Continued*)

Table 1. Summary of Demographic and Clinical Features of Twins with HCM (*Continued*)

Reports	Twin Type	Sex/Age*	Clinical Manifestations	ECG	Cardiac Morphology	Treatments	Results
Kovács et al[48]	MZ	F/70	Systolic murmurs vary in severity	Only 1 had the RBBB	There was a difference in LV hypertrophy	All require medical treatment	Epigenetic and environmental influences on cardiac morphology
Wang et al[47]	MZ	F/49	One fainted, the other had difficulty breathing	One has SSS, the other has AF	The LV hypertrophy position and degree were similar	One was recommended for an ICD. The other needs medication	Carrying the same pathogenic gene with similar morphology but differing clinical presentations
Maron et al[59]	MZ	M/49	Both had AF and HF findings	Both patients had AF and bundle branch block	The hypertrophic parts of LV were the same	All underwent septal myectomy	Heredity is considered the primary determinant of cardiac morphology and clinical manifestations
Ashraf et al[36]	MZ	F/57	Unknown	All had LV hypertrophy	The hypertrophic parts of LV were the same	Only 1 required the ASA	The HCM cardiac morphology in twins is largely genetically determined
Rodríguez Junquera et al[46]	MZ	F/89	Unknown	Unknown	Only 1 had the LOVT obstruction	Only 1 required the ASA	The twins share the same pathogenic gene but exhibit distinct cardiac morphologies

*Age at diagnosis of first twin. AF, atrial fibrillation; ASA, alcohol septal ablation; DZ, dizygotic; ECG, electrocardiogram; F, female; HF, heart failure; ICD, implantable cardioverter defibrillator; LV, left ventricle; LVOT, left ventricular outflow tract; M, male; MZ, monozygotic; RBBB, right bundle branch block; SAM, systolic anterior movement; SCD, sudden cardiac death; SSS, sick sinus syndrome.

include dyspnea, chest pain, and palpitations.[25] Patients are also prone to malignant arrhythmias and adverse cardiac events such as SCD,[21,26] with HCM being a major cause of SCD in young adults.[27] Given the high lethality of SCD, improving risk stratification is crucial.[28] Understanding the genetic background and epidemiological characteristics of HCM is essential for guiding disease management.

GENETIC BACKGROUND OF HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is primarily inherited in an autosomal dominant manner, involving mutations in at least 11 sarcomere protein genes.[16,29] These genetic variants directly affect cardiomyocyte function and cardiac contractility, leading to the abnormal thickening of the heart muscle. The most common genetic variants are found in the β-myosin heavy chain (*MYH7*, OMIM #160760) and myosin-binding protein C (*MYBPC3*, OMIM #600958); these mutations account for approximately 50% of cases.[30,31] Other less common genes include cardiac muscle troponin T (*TNNT2*, OMIM #191045) and myosin light chain 2 (*MYL2*, OMIM #160781).[32] The clinical presentation of these gene mutations shows significant individual variability, and phenotypic heterogeneity complicates the prognosis and treatment responses in HCM (Table 1). Indeed, it has been suggested that mutations in sarcomeric proteins may not be the sole cause of HCM.[14] The likelihood of developing HCM in relatives carrying the same disease-causing variant is high, but it is also age-related.[14,33] However, the age of onset and clinical manifestations of HCM vary,[14] which supports the hypothesis that non-genetic factors may influence the clinical course of the disease. Given the high penetrance but variable expression of HCM genes,[12] intrauterine factors may also contribute to the differences observed in twins.[34] To better understand how these genetic variants influence disease phenotypes, clinicians must conduct comprehensive genetic counseling and individualized disease management strategies. These should include not only genetic testing to identify mutations but also assessments of family history and monitoring of the health of other family members. Such an approach is essential for preventing complications and facilitating early interventional treatment, which improves both survival rates and the quality of life of patients.[35]

THE SIGNIFICANCE OF TWINS IN HYPERTROPHIC CARDIOMYOPATHY RESEARCH

Globally, reports on twins with HCM are rare, and the related research is relatively limited,[36,37] but some preliminary studies have delved deeply into this area (Table 1). Twin pregnancies account for about 3% of all pregnancies,[38] resulting in the simultaneous development of 2 fetuses. Twins are classified into monozygotic (MZ) and dizygotic (DZ) twins. Monozygotic twins result from the division of a single egg, sharing nearly 100% of their genetic material,[4,39] while DZ twins originate from 2 different eggs, sharing about 50% of their genetic material.[40] This close genetic relationship makes twins uniquely valuable in the study of genetic diseases like HCM. Despite their genetic closeness, twins can exhibit significant variability in the expression of diseases such as HCM, highlighting the impact of environmental and epigenetic

factors as well as genetic susceptibility (Table 1). Epigenetics involves changes that do not alter the DNA sequence fundamentally but mainly include DNA methylation and histone modifications.[41] Literature suggests that any observed similarities between MZ twins living in the same environment should be attributed to genetic factors.[42,43] Both genetic and environmental factors can lead to cardiovascular diseases in twins.[44] The natural comparison between HCM twins enhances causal inference in research,[45] thereby facilitating clinical research on HCM.[43] Twin studies can reveal the genetic heterogeneity of HCM and the interaction of genetic factors with environmental influences. By comparing studies of MZ and DZ twins, researchers can identify both genetic and non-genetic factors that influence HCM. In this context, the analysis of twins provides a favorable approach to addressing these issues.[46] However, twin studies also face challenges such as difficulties in sample acquisition and controlling environmental variables. Nonetheless, their potential value in exploring how genetic and non-genetic factors together shape the clinical manifestation of HCM cannot be overlooked.

TWIN CASES STUDIES IN RESEARCH

Hypertrophic cardiomyopathy can exhibit a variety of clinical symptoms, electrocardiogram (ECG) features, morphological changes, and disease progression. Since twins share most or all of their genetic information, the study of twins serves as an ideal natural model to explore the genetic foundations of diseases. Although the molecular mechanisms underlying HCM remain largely undefined, twin studies enhance understanding of how mutations in disease-causing genes are linked to disease phenotypes, as well as the impact of epigenetic and environmental factors.[47-58] These studies provide crucial insights into the interplay between genetic and non-genetic factors in HCM.

Clinically, HCM manifests variably not only across different individuals but also within the same family.[46] Historically, researchers like Maron et al[59] have underscored the value of analyzing genetic characteristics in twins to elucidate disease phenotypes. For instance, in a study of middle-aged MZ twins, despite sharing identical genetic information, the twins exhibited a high consistency in clinical presentation and disease progression, suggesting a strong genetic influence.[59] Other case also reported a case where twins, despite living in distinct geographical regions of Australia and leading different lifestyles, experienced cardiac arrests at the same age but showed variations in left ventricular hypertrophy, underscoring the significance of genetic factors in such critical outcomes.[53] Conversely, Wang et al[47] observed that a pair of monozygotic twins carrying the same *MYH7* gene mutation exhibited similar morphological characteristics of HCM but showed differences in clinical manifestations and the extent of myocardial fibrosis, suggesting that non-genetic factors, such as environmental influences and epigenetic modifications, may be potential drivers of phenotypic diversity. Similarly, Reid et al[49] documented variations in clinical symptoms, the degree of left ventricular hypertrophy, and outflow tract obstruction between MZ twins, implicating epigenetic modifications and environmental factors in the regulation of gene expression and myocardial structure, thereby influencing disease severity and presentation. This phenotypic variability underscores not only the role of genetic predisposition in the pathogenesis of HCM but also the importance of external factors in disease expression. One study analyzed 11 pairs of identical twins and noted clinical inconsistencies, further highlighting the significant impact of environmental and epigenetic influences.[51] Many current reports in the literature describing clinical and phenotypic characteristics of HCM twins are mixed in terms of genetic and environmental determinants, with most researchers describing twins with different clinical characteristics that tend to be influenced significantly by environmental and epigenetic factors.[47-52] However, other reports have also highlighted the presence of significant clinical and phenotypic similarities in twins.[53-58] This similarity extends to clinical manifestations including almost the same frequency of paroxysmal AF and the degree and timing of heart failure symptoms caused by left ventricular outflow obstruction.[60] These novel observations strongly support the genetic determinants of HCM.

In terms of morphology: Numerous studies have demonstrated that twins with HCM often display identical or similar cardiac morphological features,[36,54-57,61-66] including the site of left ventricular hypertrophy, LVOT obstruction, and SAM of the mitral valve. Some researchers contend that these morphological similarities are primarily determined by genetic factors with minimal or no environmental impact.[36,59,67,68] For instance, Zenovich et al[54] detailed the case of middle-aged female MZ twins, both presenting with mitral valve motion abnormalities and outflow obstruction, and both exhibiting aneurysms at the ventricular apex accompanied by significant wall thinning, suggesting a strong genetic basis for the development of left ventricular apical aneurysms. Ashraf et al[36] described twins with basal septal hypertrophy and fibrosis detected by cardiac CMR, yet their clinical trajectories differed. These findings underline the strong genetic predisposition in HCM morphology while also highlighting the potential roles of epigenetic and environmental factors in the expression and progression of the disease. Although the morphological phenotype of HCM is generally considered to be consistent in twins, discussions on the heterogeneity of HCM morphological manifestations in twins have emerged.[21,37,46,48,49,53] One study examined septal thickness in 11 pairs of HCM MZ twins and found that septal thickness was not significantly inherited in HCM.[37] In twin studies, there are significant differences in the morphological manifestations of HCM, even in studies with the same myotome-associated protein mutation.[46] This precisely indicates the difference in gene expression and penetrance.[21] This variability highlights the influence of non-genetic factors, including intrauterine environmental conditions, which can influence early heart development and contribute to the differences in disease presentation between twins.[48] The complex interplay of genetic predisposition and external factors in determining heart morphology in HCM twins is evident from existing studies. While a single gene mutation can trigger disease, the multiple phenotypes observed in twins suggest that

epigenetic modifications and broader environmental influences significantly modulate disease expression.[69] Previous studies have shown that in some cases of HCM, there is an underlying recessive pattern of inheritance which increases the complexity of the genetic situation.[57]

Electrocardiogram is a valuable diagnostic tool for HCM[23] and typically identifies abnormalities such as left ventricular hypertrophy, ST-T changes, and pathological Q-waves.[70] However, ECG findings in twins with HCM can also display significant variability, even among twins with identical genetic profiles.[47,53,59] For instance, while a pair of twins may show similar clinical features and disease expression in middle age, their ECG results can differ significantly with one exhibiting a right bundle branch block and the other a left bundle branch block, possibly due to uncontrolled epigenetic phenomena.[59] These findings are crucial for understanding the ECG manifestations in twins with HCM where gene expression may be consistent, yet numerous cases exhibit varying ECG results due to the presence of epigenetic and environmental factors (Table 1). Monitoring ECG in twins, particularly those who are less affected or asymptomatic, is crucial as it facilitates early detection of abnormalities. Comparative ECG analysis of twins with HCM provides valuable insights into the heterogeneity of the disease.

Although genetics play a pivotal role in the clinical presentation, morphology, and ECG of HCM, the influence of environmental and epigenetic factors is significant, highlighting the complexity of the disease. Twin studies offer crucial insights into the interaction of genetic and non-genetic factors in HCM. A comprehensive assessment of clinical manifestations, ECG, and cardiac morphology in twins with HCM not only facilitates early diagnosis but also improves patient outcomes by preventing disease progression and protecting cardiac function through aggressive management strategies. This comprehensive approach has important clinical implications, especially for genetically susceptible populations, such as twins or those with a family history of HCM.

ROLE OF GENETIC TESTING

Hypertrophic cardiomyopathy exhibits significant genetic heterogeneity with family history playing a pivotal role in diagnosis.[71] In twin studies of HCM, familial clustering is observed in more than 50% of cases,[69] complicating the diagnosis, particularly in familial HCM where phenotypic heterogeneity is prominent. For instance, twin studies have demonstrated substantial variations in disease severity and cardiac structural changes between individuals, even among those harboring the same *MYH7* or *MYBPC3* gene mutations.[46,47] This variability underscores the influence of epigenetic and intrauterine environmental factors, such as differences in placental and chorionic conditions along with other environmental determinants on disease progression.[36,46,48,72-74] Individuals carrying multiple mutations, such as those who are double-heterozygous or compound heterozygous, often present with a more severe disease phenotype and are at increased risk of premature mortality. At present, the inconsistencies observed within the same family, which cannot solely be explained by mutation heterogeneity, are often attributed to environmental influences,[12] highlighting the critical necessity for genetic testing. The American College of Cardiology and the American Heart Association strongly recommend genetic testing for HCM as a Level 1 measure.[75] The diagnostic yield of genetic testing is approximately 30% in sporadic cases and about 60% in familial cases.[76] In children, HCM may necessitate more specialized assessments and diagnostic tests due to a higher prevalence of syndromic conditions and inborn metabolic errors associated with the disease at these ages.[77] Typically, individuals presenting with the most severe phenotypes and/or the earliest onset are prioritized for genetic testing. When a specimen from an affected individual is unavailable, comprehensive genomic testing should be performed on another affected family member. However, the primary objective of genetic testing is to identify asymptomatic family members. The detection of genetic variants facilitates targeted sequencing for other family members utilizing this information for ongoing genetic counseling and surveillance.[78]

Given the genetic heterogeneity of HCM, whole genome sequencing (WGS) and whole exome sequencing (WES) have emerged as crucial tools for diagnosing familial HCM or other cases where the underlying genetic cause remains elusive.[79] Whole exome sequencing identifies pathogenic gene variants in up to 60% of HCM cases,[5] efficiently sequencing all exons to facilitate the discovery of novel genes and deepen our understanding of HCM's genetic underpinnings. Next-generation sequencing technologies enable high-throughput sequencing of the entire human genome, assessing not only known single-nucleotide variants and insertions/deletions but also transcriptome variants, copy number variants, and complex genomic structural variants, thus, advancing our comprehension of the genetic etiologies of HCM.[80-84] In situations where initial genetic testing fails to detect pathogenic variants, particularly in individuals presenting with severe symptoms but lacking a clear family history, WGS may be employed to search for novel variants or conduct more comprehensive genetic analyses.[12] However, WES and WGS have occasionally sparked controversy regarding their role in expanding our knowledge of HCM's genetic basis, primarily due to the potential generation of a large number of variants of unknown significance (VUS) and incomplete exome coverage caused by probe design limitations. Genetic variants associated with cardiovascular diseases must be managed carefully as they may be linked to serious conditions such as SCD or HF[85] posing challenges for individuals without a personal or familial history of HCM.[86] Thus, the interpretation of genetic test results must be conducted in conjunction with clinical presentations and family history, with genetic counseling playing a pivotal role in this process. This counseling helps patients and their families understand the test results and their potential implications.[87] Owing to the genetic heterogeneity of cardiomyopathy, recent studies recommend the use of multi-gene panels for genetic testing over single-gene testing via Sanger sequencing.[16] The advantage of using gene panels for targeted sequencing is that the sequencing region is highly specific, and multiple

samples can be analyzed simultaneously, providing extensive coverage. Furthermore, considering the 50% risk of genetic transmission of HCM,[5] genetic screening is imperative to assess familial genetic risk, even in the absence of clinical symptoms.[46]

When HCM is diagnosed in one twin, it is crucial to screen the other twin and additional family members; a positive result necessitates further cardiac morphological evaluation to confirm the HCM diagnosis, with at least annual follow-up recommended as the disease's presentation may evolve over time.[88] Investigating the medical history of other family members, including those not diagnosed with HCM but who may exhibit related symptoms, is essential to construct a comprehensive genetic profile of the disease. An in-depth understanding of the family genetic background enhances the interpretation of twin data, particularly in analyzing the influence of genetic factors on HCM development. Moreover, genetic testing data could be pivotal for developing future preventive screenings and interventions for high-risk family members. A comprehensive assessment of familial HCM will not only lead to a better understanding of the mechanisms of genetic transmission and expression but also to more effective health management and treatment strategies for twin patients and their families.

TREATMENT OF HYPERTROPHIC CARDIOMYOPATHY IN TWINS

The primary objectives in managing HCM are to alleviate symptoms, reduce cardiac stress, and enhance survival and quality of life. Given the genetic and phenotypic diversity of HCM, including among genetically similar twins, disease manifestations and treatment options can vary, underscoring the need for personalized treatment strategies (Table 1).[21,50,54] Treatment approaches range from conservative management and medical interventions to surgical options tailored to the individual's specific circumstances and disease severity.[5,68] Lifestyle modifications and health education are recommended, such as engaging in low-impact aerobic exercises and avoiding competitive sports to minimize the risk of cardiac events. Medications may be employed to relieve LVOT obstruction. In severe cases, surgical interventions like ventricular myectomy are necessary to alleviate symptoms and improve long-term cardiac function.[28] Alcohol septal ablation (ASA) represents a less invasive option effective in reducing myocardial thickness and symptomatology.[5,89] Clinical case studies of twins with HCM highlight the complexity of treatment decisions. Even within twins, it is crucial to consider their clinical manifestations, morphological characteristics, and associated risk factors to select appropriate treatments. For instance, Reid et al[49] reported that one twin required a ventricular myectomy at age 12 due to progressive severe exercise-induced dyspnea and significant LVOT obstruction, while his brother did not require surgery. Since SCD may be the sole presentation in HCM patients, identifying features associated with a higher SCD risk is crucial.[53] Implantable cardioverter defibrillator (ICD) implantation can prevent SCD in HCM patients. The American College of Cardiology Foundation (ACCF) and AHA categorize risk factors into established risk factors and potential SCD risk modifiers.[90] Established risk factors include prior cardiac arrest or persistent ventricular tachycardia, age under 50 years, family history of SCD, unexplained syncope, and left ventricular thickness greater than 30 mm. Potential risk factors include LVOT obstruction and left ventricular apex aneurysm. Regular risk stratification every 12 to 24 months is recommended for HCM patients without ICD.[53] In a case reported by Zenovich et al[54] middle-aged female MZ twins both had left ventricular apex aneurysms. However, only one twin was eventually implanted with an ICD.[36] This case underscores the importance of preventive treatments in managing high-risk HCM patients. Other cases revealed that even in MZ twins with identical genetic backgrounds, different treatment requirements may emerge. While both twins exhibited similar levels of left ventricular hypertrophy, varying risk factors and comorbidities necessitated different treatment approaches, with one twin requiring an ICD for symptom management related to sick sinus syndrome (SSS) and the other relying primarily on medication for atrial fibrillation and heart failure management.[47] There are also case reports confirming that even in twins with morphologically identical basal septal hypertrophy and LVOT obstruction, responses to treatments varied; one twin required ASA for effective symptom relief, while the other responded well to pharmacotherapy.[36]

These cases highlight the significance of considering each twin's unique clinical manifestations, cardiac morphology, and risk factors as well as their genetic susceptibility and environmental influences to devise the most effective personalized treatment plan. With advances in medical technology and deeper insights into the genetic architecture of HCM, future technologies are anticipated to improve diagnostic precision and discover more efficacious treatments, thereby better controlling disease progression and optimizing patient outcomes.

OUTLOOK

Hypertrophic cardiomyopathy is a common hereditary heart disease characterized by polymorphism in clinical manifestations and variability in cardiac morphology and phenotype. Twin studies have elucidated that even among individuals sharing the same genetic background, disease presentations can vary markedly. This phenotypic diversity underscores the intricate interplay between genetic and environmental factors as well as the pivotal role of epigenetic factors in modulating disease expression. By fostering interdisciplinary collaboration that integrates cardiology, genetics, and data science, the complexities of HCM can be more comprehensively understood. A thorough assessment of family history and precise genetic counseling are crucial for developing effective risk assessment and management strategies. Moreover, personalized treatment adjustments tailored to each patient's specific condition and living environment are key to enhancing treatment outcomes and improving patient quality of life. With ongoing research, particularly in understanding the genetic and environmental determinants of HCM, novel treatment options are anticipated. These

advancements are expected to revolutionize the treatment and management of HCM, thereby improving the prognosis and quality of life for individuals with a familial genetic predisposition.

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