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Twin Phenomena of Hypertrophic Cardiomyopathy: A Reported Case Series

Zeng JT[1], Zhang YA[2], Ma TY[1], Huang K[1], Lu SJ[1], Zhong JH[1]* and Li JJ[3]**

[1]Department of Cardiology, Xiangya School of Medicine, Haikou Affiliated Hospital of Central South University, China

[2]Central Laboratory, Xiangya School of Medicine, Haikou Affiliated Hospital of Central South University, China

[3]Cardiometabolic Center, State Key Laboratory of Cardiovascular Diseases, Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, China

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Correspondence:

Shi-Juan Lu, Department of Cardiology, Xiangya School of Medicine, Haikou Affiliated Hospital of Central South University, No. 43 Renmin Avenue, Meilan District, Haikou, 570208, Hainan, China,

Jiang-Hua Zhong, Department of Cardiology, Xiangya School of Medicine, Haikou Affiliated Hospital of Central South University, No. 43 Renmin Avenue, Meilan District, Haikou, 570208, Hainan, China,

Jian-Jun Li, Cardiometabolic Center, State Key Laboratory of Cardiovascular Diseases, Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No 167 BeiLiShi Road, Xicheng District, Beijing, 100037, China,

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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 delves into the genetic foundations of *HCM*, the impact of environmental and epigenetic factors on disease expression, and underscores the critical role of genetic screening in the early and differential diagnosis of *HCM*. By focusing on the 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; Case; Inheritance

Abbreviations

HCM: Hypertrophic Cardiomyopathy; AHA: American Heart Association; HF: Heart Failure; SCD: Sudden Cardiac Death; CMR: Cardiac Magnetic Resonance; LVOT: Left Ventricular Outflow Tract; SAM: Systolic Anterior Motion; LGE: Late Gadolinium Enhancement; *MYH7*: β-Myosin Heavy Chain 7; *MYBPC3*: Myosin-Binding Protein; TNNT2: Cardiac Troponin T; MYL2: Myosin Light Chain 2; MZ: Monozygotic; DZ: Dizygotic; ECG: Electrocardiogram; WGS: Whole Genome Sequencing; WES: Whole Exome Sequencing; ASA: Alcohol Septal Ablation; ICD: Implantable Cardioverter Defibrillator

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 forms [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 *HCM*

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 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 thrombus obstruction. When any part of the left ventricular thickening reaches 30 mm or more the risk of SCD is extremely high [6]. CMR 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. Especially 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].

HCM 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 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 *HCM*

HCM 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 7 (*MYH7*: OMIM #160760) and myosin-binding protein C3 (*MYBPC3*, OMIM #600958) mutations account for approximately 50% of cases [30,31]. Other less common genes include cardiac 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 support 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 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 *HCM* 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 two fetuses. Twins are classified into Monozygotic (MZ) and Dizygotic (DZ) twins. MZ twins result from the division of a single egg sharing nearly 100% of their genetic material [4,39], while DZ twins originate from two 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

HCM can exhibit a variety of clinical symptoms Electrocardiogram (ECG) features morphological changes and disease progression. Since

Table 1: Clinical features of reported cases in HCM twins.

Report	Twin Type	Sex/Age*	Clinical Manifestations	ECG	Cardiac Morphology	Treatments	Results
Karatzas et al. [66]	MZ	F/22	All had symptoms such as shortness of breath and palpitation	All have T wave inversion; Only one had AF	The wall thickness of LV is obviously different	Unknown	Diverse progression rates of HCM
Harley et al. [34]	DZ	F/22	All had symptoms of chest pain	All had S-ST segment changes	Normal	Only one needs medication	Variability in HCM treatment approaches
Littler et al. [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 one required a ventricular myectomy	Clinical symptoms and LV hypertrophy vary in HCM
Epstein et al. [21]	MZ	F/Unknown	Unknown	Unknown	Only one had the LOVT obstruction	Only one 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. [70]	MZ	F/38	Only one 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 one had severe breathing difficulties	Only one had the ST-T segment changes	The degree of ventricular septal hypertrophy was different	Only one required the ASA	Environmental factors can impact HCM morphology and clinical presentations
Araujo et al. [61]	MZ	M/19	Only one had severe breathing difficulties	Only one had LV hypertrophy	All had similar interventricular septal hypertrophy and LOVT obstruction	Only one 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 one 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 one experienced syncope due to malignant tachycardia	Only one had malignant ventricular tachycardia	There was a difference in LV hypertrophy	Only one has had an ICD implanted	Emphasizes potential genetic susceptibility to cardiac arrest in twins with HCM
Kovács et al. [48]	MZ	F/70	Systolic murmurs vary in severity	Only one 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 one required the ASA	The HCM cardiac morphology in twins is largely genetically determined
Rodríguez Junquera et al. [46]	MZ	F/89	Unknown	Unknown	Only one had the LOVT obstruction	Only one required the ASA	The twins share the same pathogenic gene but exhibit distinct cardiac morphologies

F: Female; M: Male; MZ: Monozygotic; DZ: Dizygotic; ECG: Electrocardiogram; ICD: Implantable Cardioverter Defibrillator; LVOT: Left Ventricular Outflow Tract; SAM: Systolic Anterior Movement; SCD: Sudden Cardiac Death; AF: Atrial Fibrillation; RBBB: Right Bundle Branch Block; SSS: Sick Sinus Syndrome; ASA: Alcohol Septal Ablation; LV: Left Ventricle; HF: Heart Failure; *Age at diagnosis of first twin

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 such as those by Wang et al. [47] observed that a pair of MZ twins both carrying the same *MYH7* gene mutation presented similar morphological characteristics of *HCM* but differed in clinical manifestations and the extent of myocardial fibrosis pointing to environmental factors and methylation modifications as 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 [36,54-57,61-65] 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 [36,59,66,67]. 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 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 [68]. 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].

ECG is a valuable diagnostic tool for *HCM* [23] and typically identifies abnormalities such as left ventricular hypertrophy ST-T changes and pathological Q-waves [69]. 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 plays 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

HCM 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 [68] 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]. WES 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,

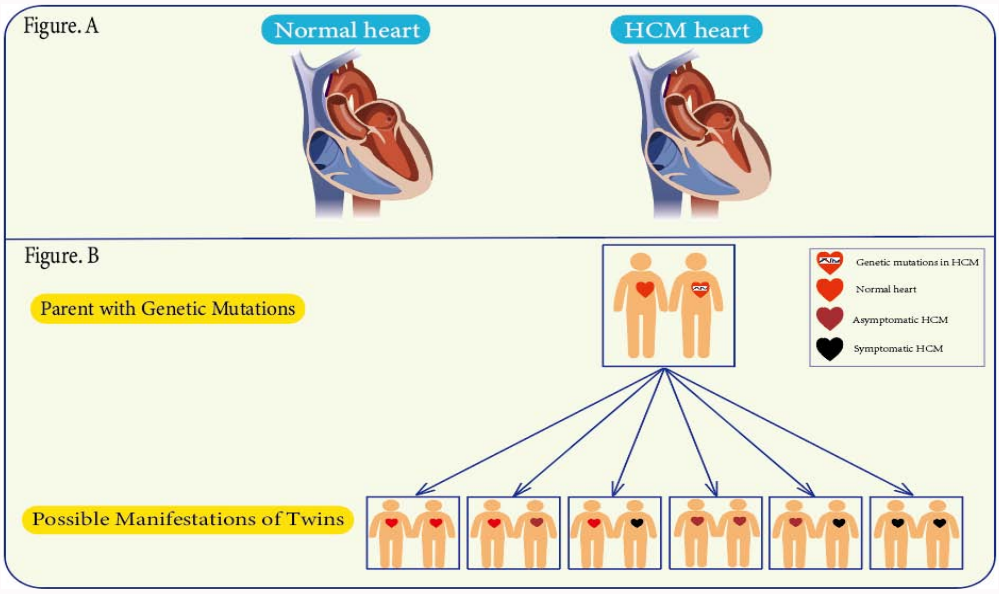

Figure 1: Comparison of normal and HCM hearts and variable expression in twins.

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 *HCM* 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 [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 [5,67]. 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 [27]. 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, in a study by Reid et al. [49] one twin required ventricular myectomy at age 12 due to progressive severe exercise-induced dyspnea and significant LVOT obstruction: Whereas 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 and the American Heart Association 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 case 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 confirmed 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

HCM 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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References

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. Circulation. 2006;113(14):1807-16.
2. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: Present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol. 2014;64(1):83-99.
3. Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. Br Heart J. 1980;44(6):672-3.
4. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: A position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29(2):270-6.
5. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-79.
6. Licordari R, Trimarchi G, Teresi L, Restelli D, Lofrumento F, Perna A, et al. Cardiac magnetic resonance in HCM Phenocopies: From diagnosis to risk stratification and therapeutic management. J Clin Med. 2023;12(10):3481.
7. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. Circ Res. 2017;121(7):722-30.
8. Yotti R, Seidman CE, Seidman JG. Advances in the genetic basis and pathogenesis of sarcomere cardiomyopathies. Annu Rev Genomics Hum Genet. 2019;20:129-53.
9. Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, et al. Management of hypertrophic cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2022;79(4):390-414.
10. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2015;65(12):1249-54.
11. Maron MS, Hellawell JL, Lucove JC, Farzaneh-Far R, Olivotto I. Occurrence of clinically diagnosed hypertrophic cardiomyopathy in the United States. Am J Cardiol. 2016;117(10):1651-4.
12. Melas M, Beltsios ET, Adamou A, Koumarelas K, McBride KL. Molecular Diagnosis of Hypertrophic Cardiomyopathy (HCM): In the heart of cardiac disease. J Clin Med. 2022;12(1):225.
13. Geske JB, Ommen SR, Gersh BJ. Hypertrophic cardiomyopathy: Clinical update. JACC Heart Fail. 2018;6(5):364-75.
14. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: A report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. J Am Coll Cardiol. 2020;76(25):e159-e240.
15. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;124(24):e783-831.
16. Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, et al. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: Expanded panels offer limited additional sensitivity. Genet Med. 2015;17(11):880-8.
17. Teekakirikul P, Kelly MA, Rehm HL, Lakdawala NK, Funke BH. Inherited cardiomyopathies: Molecular genetics and clinical genetic testing in the postgenomic era. J Mol Diagn. 2013;15(2):158-70.
18. Rickers C, Wilke NM, Jerosch-Herold M, Casey SA, Panse P, Panse N, et al. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. Circulation. 2005;112(6):855-61.
19. Silbiger JJ. Abnormalities of the mitral apparatus in hypertrophic cardiomyopathy: Echocardiographic, pathophysiologic, and surgical insights. J Am Soc Echocardiogr. 2016;29(7):622-39.
20. Greaves SC, Roche AH, Neutze JM, Whitlock RM, Veale AM. Inheritance of hypertrophic cardiomyopathy: A cross sectional and M mode echocardiographic study of 50 families. Br Heart J. 1987;58(3):259-66.
21. Epstein ND, Lin HJ, Fananapazir L. Genetic evidence of dissociation (generational skips) of electrical from morphologic forms of hypertrophic cardiomyopathy. Am J Cardiol. 1990;66(5):627-31.
22. Harper AR, Parikh VN, Goldfeder RL, Caleshu C, Ashley EA. Delivering clinical grade sequencing and genetic test interpretation for cardiovascular medicine. Circ Cardiovasc Genet. 2017;10(2):e001221.
23. Arad M, Seidman JG, Seidman CE. Phenotypic diversity in hypertrophic cardiomyopathy. Hum Mol Genet. 2002;11(20):2499-506.
24. Vermeer AMC, Clur SB, Blom NA, Wilde AAM, Christiaans I. Penetrance of hypertrophic cardiomyopathy in children who are mutation positive. J Pediatr. 2017;188:91-5.
25. Sen-Chowdhry S, Jacoby D, Moon JC, McKenna WJ. Update on hypertrophic cardiomyopathy and a guide to the guidelines. Nat Rev Cardiol. 2016;13(11):651-75.
26. Maron BJ, Rowin EJ, Casey SA, Garberich RF, Maron MS. What do patients with hypertrophic cardiomyopathy die from? Am J Cardiol. 2016;117(3):434-5.
27. Maron BJ, Rowin EJ, Maron MS. Evolution of risk stratification and sudden death prevention in hypertrophic cardiomyopathy: Twenty years with the implantable cardioverter-defibrillator. Heart Rhythm. 2021;18(6):1012-23.
28. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the diagnosis and treatment of

hypertrophic cardiomyopathy: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58(25):e212-60.

29. Bos JM, Will ML, Gersh BJ, Kruisselbrink TM, Ommen SR, Ackerman MJ. Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy. Mayo Clin Proc. 2014;89(6):727-37.

30. Millat G, Bouvagnet P, Chevalier P, Dauphin C, Jouk PS, Da Costa A, et al. Prevalence and spectrum of mutations in a cohort of 192 unrelated patients with hypertrophic cardiomyopathy. Eur J Med Genet. 2010;53(5):261-7.

31. Kaski JP, Syrris P, Esteban MT, Jenkins S, Pantazis A, Deanfield JE, et al. Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. Circ Cardiovasc Genet. 2009;2(5):436-41.

32. Thomson KL, Ormondroyd E, Harper AR, Dent T, McGuire K, Baksi J, et al. Analysis of 51 proposed hypertrophic cardiomyopathy genes from genome sequencing data in sarcomere negative cases has negligible diagnostic yield. Genet Med. 2019;21(7):1576-84.

33. Lorca R, Gómez J, Martín M, Cabanillas R, Calvo J, León V, et al. Insights into hypertrophic cardiomyopathy evaluation through follow-up of a founder pathogenic variant. Rev Esp Cardiol (Engl Ed). 2019;72(2):138-44.

34. Harley A, Orgain ES. Hypertrophic cardiomyopathy with unusual features in a family. Br Heart J. 1971;33(1):55-61.

35. Bos JM, Towbin JA, Ackerman MJ. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54(3):201-11.

36. Ashraf M, Samad F, Jahangir A, Jan MF, Galazka P, Tajik AJ. Hypertrophic cardiomyopathy in identical twins: A case series. Eur Heart J Case Rep. 2022;7(1):ytac452.

37. Jansweijer JA, van Spaendonck-Zwarts KY, Tanck MWT, van Tintelen JP, Christiaans I, van der Smagt J, et al. Heritability in genetic heart disease: The role of genetic background. Open Heart. 2019;6(1):e000929.

38. Shur N. The genetics of twinning: from splitting eggs to breaking paradigms. Am J Med Genet C Semin Med Genet. 2009;151C(2):105-9.

39. Hall J G. Twinning. Lancet. 2003;362(9385):735-43.

40. Balasubramanian R, Vuppalapati S, Avanthika C, Jhaveri S, Peddi NC, Ahmed S, et al. Epidemiology, genetics and epigenetics of congenital heart diseases in twins. Cureus. 2021;13(8):e17253.

41. Jaenisch R, Bird A. Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. Nat Genet. 2003;33 Suppl:245-54.

42. Boomsma D, Busjahn A, Peltonen L. Classical twin studies and beyond. Nat Rev Genet. 2002;3(11):872-82.

43. Craig JM, Calais-Ferreira L, Umstad MP, Buchwald D. The value of twins for health and medical research: A third of a century of progress. Twin Res Hum Genet. 2020;23(1):8-15.

44. Ji F, Ning F, Duan H, Kaprio J, Zhang D, Zhang D, et al. Genetic and environmental influences on cardiovascular disease risk factors: A study of Chinese twin children and adolescents. Twin Res Hum Genet. 2014;17(2):72-9.

45. McGue M, Osler M, Christensen K. Causal inference and observational research: The utility of twins. Perspect Psychol Sci. 2010;5(5):546-56.

46. Junquera MR, Salgado M, González-Urbistondo F, Alén A, Rodríguez-Reguero JJ, Silva I, et al. Different phenotypes in monozygotic twins, carriers of the same pathogenic variant for hypertrophic cardiomyopathy. Life (Basel). 2022;12(9):1346.

47. Wang J, Li W, Han Y, Chen Y. Different clinical presentation and tissue characterization in a monozygotic twin pair with MYH7 mutation-related hypertrophic cardiomyopathy. Int Heart J. 2019;60(2):477-81.

48. Kovács A, Molnár A, Celeng C, Tóth A, Vágó H, Apor A, et al. Hypertrophic cardiomyopathy in a monozygotic twin pair: Similarly different. Circ Cardiovasc Imaging. 2016;9(6):e004794.

49. Reid JM, Houston AB, Lundmark E. Hypertrophic cardiomyopathy in identical twins. Br Heart J. 1989;62(5):384-8.

50. Palka P, Lange A, Burstow DJ. Different presentation of hypertrophic cardiomyopathy in monozygotic twins. Heart. 2003;89(7):751.

51. Repetti GG, Kim Y, Pereira AC, Ingles J, Russell MW, Lakdawala NK, et al. Discordant clinical features of identical hypertrophic cardiomyopathy twins. Proc Natl Acad Sci U S A. 2021;118(10):e2021717118.

52. Ko YL, Tang TK, Chen JJ, Hshieh YY, Wu CW, Lien WP. Idiopathic hypertrophic cardiomyopathy in identical twins. Morphological heterogeneity of the left ventricle. Chest. 1992;102(3):783-5.

53. Goh CY, Asrar ul Haq M, Mutha V, van Gaal WJ. Synchronous cardiac arrest in monozygotic twins with hypertrophic cardiomyopathy--is sudden cardiac death genetically pre-programmed? BMC Cardiovasc Disord. 2015;15:16.

54. Zenovich AG, Lesser JR, Hanna CA, Maron BJ. Identical twins with hypertrophic cardiomyopathy and apical aneurysm. Am J Cardiol. 2006;97(7):1109.

55. Maron BJ, Haas TS, Lesser JR. Images in cardiovascular medicine. Diagnostic utility of cardiac magnetic resonance imaging in monozygotic twins with hypertrophic cardiomyopathy and identical pattern of left ventricular hypertrophy. Circulation. 2007;115(24):e627-8.

56. Maron BJ, Casey SA, Almquist AK. Images in cardiovascular medicine. Hypertrophic cardiomyopathy in monozygotic twins. Circulation. 2002;105(18):2229.

57. Littler WA. Twin studies in hypertrophic cardiomyopathy. Br Heart J. 1972;34(11):1147-51.

58. Wylie L, Ramage A, MacLeod DC. Hypertrophic cardiomyopathy with shared morphology in identical twins: A case report. Scott Med J. 2002;47(3):64-5.

59. Maron BJ, Rowin EJ, Arkun K, Rastegar H, Larson AM, Maron MS, et al. Adult monozygotic twins with hypertrophic cardiomyopathy and identical disease expression and clinical course. Am J Cardiol. 2020:127:135-8.

60. Maron BJ, Rowin EJ, Udelson JE, Maron MS. Clinical spectrum and management of heart failure in hypertrophic cardiomyopathy. JACC Heart Fail. 2018;6(5):353-63.

61. Araujo AQ, Arteaga E, Mady C. Hypertrophic cardiomyopathy in monozygotic twins. Arq Bras Cardiol. 2004;82(4):396-9.

62. Rowin EJ, Maron BJ, Maron MS. The hypertrophic cardiomyopathy phenotype viewed through the prism of multimodality imaging: Clinical and etiologic implications. JACC Cardiovasc Imaging. 2020;13(9):2002-16.

63. Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. Circulation. 1979;59(4):689-706.

64. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1986;8(3):545-57.

65. Shirani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. J Am Coll Cardiol.

2000;35(1):36-44.

66. Karatzas NB, Hamill J, Sleight P. Hypertrophic cardiomyopathy. Br Heart J. 1968;30(6):826-34.

67. Ciampi Q, Olivotto I, Gardini C, Mori F, Peteiro J, Monserrat L, et al. Prognostic role of stress echocardiography in hypertrophic cardiomyopathy: The international stress echo registry. Int J Cardiol. 2016:219:331-8.

68. Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: Genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res. 2017;121(7):749-70.

69. Muresan ID, Agoston-Coldea L. Phenotypes of hypertrophic cardiomyopathy: Genetics, clinics, and modular imaging. Heart Fail Rev. 2021;26(5):1023-36.

70. Agirbasli M, Hamid R, Jennings HS, Tiller GE. Situs inversus with hypertrophic cardiomyopathy in identical twins. Am J Med Genet. 2000;91(5):327-30.

71. Braunwald E, Wigle ED. Idiopathic hypertrophic subaortic stenosis. Chest. 1973;64(4):529-32.

72. Castillo-Fernandez JE, Spector TD, Bell JT. Epigenetics of discordant monozygotic twins: Implications for disease. Genome Med. 2014;6(7):60.

73. Singh SM, Murphy B, O'Reilly R. Epigenetic contributors to the discordance of monozygotic twins. Clin Genet. 2002;62(2):97-103.

74. Machin GA. Some causes of genotypic and phenotypic discordance in monozygotic twin pairs. Am J Med Genet. 1996;61(3):216-28.

75. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020;142(25):e558-e631.

76. Ingles J, Sarina T, Yeates L, Hunt L, Macciocca I, McCormack L, et al. Clinical predictors of genetic testing outcomes in hypertrophic cardiomyopathy. Genet Med. 2013;15(12):972-7.

77. Ware SM. Genetics of pediatric cardiomyopathies. Curr Opin Pediatr. 2017;29(5):534-40.

78. Teekakirikul P, Zhu W, Huang HC, Fung E. Hypertrophic cardiomyopathy: An overview of genetics and management. Biomolecules. 2019;9(12):878.

79. Sun Y, Ruivenkamp CA, Hoffer MJ, Vrijenhoek T, Kriek M, van Asperen CJ, et al. Next-generation diagnostics: Gene panel, exome, or whole genome? Hum Mutat. 2015;36(6):648-55.

80. Mardis ER. Next-generation DNA sequencing methods. Annu Rev Genomics Hum Genet. 2008.

81. Hu T, Chitnis N, Monos D, Dinh A. Next-generation sequencing technologies: An overview. Hum Immunol. 2021;82(11):801-11.

82. Reinartz J, Bruyns E, Lin JZ, Burcham T, Brenner S, Bowen B, et al. Massively Parallel Signature Sequencing (MPSS) as a tool for in-depth quantitative gene expression profiling in all organisms. Brief Funct Genomic Proteomic. 2002;1(1):95-104.

83. Wang H, Nettleton D, Ying K. Copy number variation detection using next generation sequencing read counts. BMC Bioinformatics. 2014:15:109.

84. Medvedev P, Stanciu M, Brudno M. Computational methods for discovering structural variation with next-generation sequencing. Nat Methods. 2009;6(11 Suppl):S13-20.

85. Miller DT, Lee K, Chung WK, Gordon AS, Herman GE, Klein TE, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1381-90.

86. Lacaze P, Sebra R, Riaz M, Ingles J, Tiller J, Thompson BA, et al. Genetic variants associated with inherited cardiovascular disorders among 13,131 asymptomatic older adults of European descent. NPJ Genom Med. 2021;6(1):51.

87. Ingles J, Semsarian C. Conveying a probabilistic genetic test result to families with an inherited heart disease. Heart Rhythm. 2014;11(6):1073-8.

88. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: Clinical perspectives. J Am Coll Cardiol. 2012;60(8):705-15.

89. Ralph-Edwards A, Woo A, McCrindle BW, Shapero JL, Schwartz L, Rakowski H, et al. Hypertrophic obstructive cardiomyopathy: Comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score. J Thorac Cardiovasc Surg. 2005;129(2):351-8.

90. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124(24):2761-96.