

# The Dilemma of Genotype Positive-Phenotype Negative Hypertrophic Cardiomyopathy

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## Abstract

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease and the leading cause of sudden death in athletes. An autosomal dominant disorder affecting approximately 1 in 500 individuals, HCM has been linked to multiple mutations and exhibits variable phenotypic expression. The utility of cardiovascular screening in diagnosing risk factors for sudden cardiac death continues to be debated intensely. Genetic testing has been employed increasingly in diagnosing HCM, resulting in a subset of patients with genotype positive-phenotype negative disease; these patients carry the mutation for HCM but lack pathologic evidence of disease. These individuals pose a dilemma in the clinical management of HCM: should treatment guidelines for phenotypically normal HCM patients be the same as that of symptomatic patients? Governing bodies continue to disagree, providing conflicting guidelines for sports participation. This review examines the current fund of knowledge regarding HCM and the debate regarding screening.

## Prevalence

HCM is the most common genetic cardiovascular disease (10) and the number one cause of sudden cardiac death (SCD) in athletes in the United States (21). An autosomal dominant disorder with an estimated prevalence of 1:500 (25), HCM is characterized clinically by asymmetric, concentric LV hypertrophy without an obvious root cause (10). However HCM is phenotypically heterogeneous, varying widely in age of onset, severity of symptoms, and relative risk of sudden cardiac events (16).

## Introduction

C.F. is a very active 10-year-old male whose father was discovered to have hypertrophic cardiomyopathy (HCM). Familial genetic testing indicated C.F. was heterozygous for causative mutation in the MYBPC3 gene. Further testing indicated that C.F. was phenotypically normal, without cardiac hypertrophy or left ventricular (LV) outflow tract obstruction. Given his active sports involvement, the question arose whether or not to prevent his involvement in athletic activities. As genetic testing becomes more mainstream, more cases like that of C.F. will emerge. This review examines the current fund of knowledge regarding HCM and the debate regarding screening.

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## Clinical Presentation

HCM may manifest itself at any age and unfold with a wide spectrum of initial clinical presentations ranging from an incidental finding in an asymptomatic person to SCD (27). Symptoms of HCM may include dyspnea, atypical chest pain, syncope, presyncope, insidious congestive heart failure, and SCD. However findings such as LV outflow tract obstruction or bifid arterial pulse are often absent on initial presentation (23).

Physicians may suspect HCM in asymptomatic patients who present with a family history of HCM (30), SCD, or cardiac disability prior to the age of 50 years (1), or a personal history of exertional chest pain or excessive dyspnea, unexplained syncope or presyncope, prior heart murmur, or hypertension. Physical examination may reveal the stereotypical systolic murmur that increases with Valsalva maneuver (23). However given the relative frequency of the above in the general population, history and physical examination are unreliable in this clinical diagnosis. Electrocardiogram (EKG) screening may be utilized to discover more asymptomatic cases of HCM in the general population. In Italy, inclusion of EKG in preparticipation evaluations has resulted in increased detection of asymptomatic HCM and decreased all-cause SCD in young athletes (26). The debate surrounding EKG screening in athletes in the United States continues and is beyond the scope of this article.

## Evaluation

Upon suspicion of possible HCM, patients typically undergo 12-lead EKG and 2D echocardiogram. Studies have shown that 75% to 95% of HCM patients will demonstrate an abnormality on EKG (27), most commonly Q waves and repolarization abnormalities (20). One study found Q waves to be 98% specific for HCM when observed in phenotypically normal family members of individuals with known HCM (26). However EKGs often appear normal during screening of family members of individuals with HCM. Although HCM is characterized by LV hypertrophy, voltage criteria for LV hypertrophy is not an acceptable marker for HCM when observed in isolation (26). On echocardiography, HCM is defined as LV wall thickness greater than 15 mm. LV wall thicknesses of 13 to 14 mm constitute a gray zone of clinical diagnosis and must be evaluated carefully in context of each individual's medical history (13). Within this criterion, there is further risk stratification for SCD, with LV thickness  $\geq 30$  mm at highest risk. The pattern of LV hypertrophy is asymmetric, most commonly affecting the anterior wall or interventricular septum (32).

Currently cardiovascular magnetic resonance (CMR) is the preferred modality for further characterizing HCM. Compared with echocardiography, CMR is superior in detecting early morphologic changes in myocardium, such as fibrosis (35) and basilar hypertrophy (38). Furthermore CMR has greater specificity than echocardiography in characterizing LV size and ventricular mass, and is a more sensitive indicator of HCM outcomes (13). In addition, CMR can demonstrate focal areas of hypertrophy, which may be confused for potential neoplastic lesions on echocardiogram. Furthermore CMR better assesses right ventricular hypertrophy and diastolic function. Considering its diagnostic effectiveness, CMR has the potential to assist clinicians in clearance decisions in individuals with asymptomatic HCM.

LV hypertrophy is not pathognomonic for HCM; the differential diagnosis includes congenital glycogen storage diseases, hypertension, aortic stenosis, and athletic heart (23,30). Athletic heart results in physiologic symmetric hypertrophy, often of all cardiac chambers (23), in contrast to HCM's asymmetric LV hypertrophy. In cases of suspected athletic heart, deconditioning can assist in differentiating physiologic from pathologic hypertrophy. In a 1993 study of Olympic athletes with borderline LV hypertrophy (atrioventricular septal wall 13 to 15 mm) who underwent an average of 13 wk of deconditioning period, the athletes experienced a 2- to 5-mm reduction in LV wall thickness (28). Similarly a more recent case report of an elite adolescent swimmer demonstrated resolution of mild LV hypertrophy following 8 wk of exercise cessation (2). There is currently no consensus regarding a standard duration of time needed to produce sufficient decreases in LV wall thickness. Postdeconditioning echocardiograms demonstrating no change in LV wall thickness are therefore more suspicious for HCM versus athlete's heart.

## Family Screening

HCM has been associated with more than 1,400 mutations (10,14) in 13 sarcomere genes (21). Many of these mutations are considered "private," having been identified in only one person or family. It is likely that more mutations

will be discovered in the future, as an estimated 40% to 50% of HCM cases have an unknown genetic source. Thus genetic testing may be utilized in family members of individuals with known HCM but its utility is limited (3,16,21,27). Current guidelines recommend screening family members of affected individuals beginning at the age of 12 years (23). However, studies have shown that family members with identical mutations may follow markedly different manifestations of disease and overall clinical courses (16). As such, clinical outcomes cannot be predicted absolutely based solely upon mutations.

The other implication of genetic screening is that it has created a new subtype of HCM patients who possess known genetic mutations for disease but are currently phenotypically normal.

## Genotype Positive — Phenotype Negative HCM

Genetic testing of individuals for HCM continues to be more readily available, causing a new subdivision of HCM patients to emerge who possess the genetic mutation for HCM but are phenotypically normal. This subset is referred to as "genotype positive-phenotype negative" or "preclinical" HCM. Little research has been done on this subset of asymptomatic individuals, leaving a number of unresolved issues for consideration (listed hereafter).

### *Influences upon phenotype*

With more than 1,400 specific mutations implicated in the development of HCM, the sheer number of mutations could account for the heterogeneity of disease expression. However family members carrying identical HCM mutations have been shown to differ in their phenotypic expression and individual disease progressions, indicating that exogenous factors must impact disease development as well (16). Gene dosage appears to play a role in severity of disease, as those individuals possessing multiple mutations for HCM tend to have earlier onset of symptoms and an overall more severe disease course (16,36,39,41).

Clinical outcomes cannot be predicted absolutely based upon mutations (16), but clinical correlations can be made based upon the implicated gene. Mutations in different proteins will exhibit HCM with varying degrees of severity, ranging from unaffected to increasingly severe LV hypertrophy, heart failure, and SCD (15). Approximately 40% of all HCM cases involve mutations in MYBPC3 and MYH7 genes, which code for the thick filament of the sarcomere (10,22). However, individuals with these mutations tend to encounter markedly different natural histories of disease. MYBPC3 accounts for approximately 25% of all identified mutations (22,39) and is associated clinically with an older age of symptom onset, a decreased risk of SCD, and a relatively asymptomatic clinical course (15,39). Individuals with MYBPC3 mutations who develop clinical HCM often begin experiencing symptoms in their 20s and 30s (15). As in the case described previously, C.F.'s father began experiencing symptoms of HCM in his late 20s, prompting family screening and early detection of the same mutation in his asymptomatic 10-year-old son. Conversely patients affected by mutations to MYH7 often experience overt cardiac hypertrophy, an earlier onset of symptoms, and an overall worse outcome (39).

Heterogeneity in HCM mutations and phenotypic expression has made predicting outcomes very difficult in affected individuals. The overall variability of genotypic correlation to phenotypic outcome makes genetic typing an ineffective method of assessing risk of SCD in patients with HCM.

#### *Molecular abnormalities prior to hypertrophy*

Although patients with phenotypically silent HCM may not display outward indications of disease, recent studies have made several discoveries demonstrating altered cardiac function preceding clinical disease. Impaired relaxation of the myocardium has been observed in genotype positive-phenotype negative individuals when compared with relaxation velocities of control subjects. This relaxation is further impaired with onset of clinical disease (16). Other studies have demonstrated impaired energy metabolism in patients with genetically identified HCM, regardless of phenotypic expression (9). These biochemical effects on cardiac function may occur prior to the onset of clinical symptoms (16). Using CMR imaging, Germans *et al.* (6,11) demonstrated a reduced strain rate of the myocardium in the basal LV segments of nonhypertrophied HCM patients, indicating decreased diastolic function. CMR imaging also has revealed other morphologic changes in some individuals with genotype positive-phenotype negative HCM; specifically the presence of “crypts” along the anterior inferoseptum has been identified in nearly 70% of individuals with the HCM mutation (6,12).

Although these differences between prehypertrophy HCM hearts and genotypically negative counterparts have been discovered, the impact of these changes on clinical course, onset of symptoms, severity of disease, and risk of SCD has yet to be determined. Due to this knowledge gap, some researchers maintain that the identification of phenotypically normal individuals with mutations for HCM will allow for further study to determine the full continuum of the clinical development of disease, resulting in a more complete understanding of its pathogenesis (16).

#### *Onset of hypertrophy*

Given the uncertainty of disease prognosis and timeline of progression, the value of identifying sarcomere gene mutations in children without phenotypic manifestations of HCM is unclear. One study by Gray *et al.* (14) surveyed 32 patients ( $n = 16$ , <18 years old;  $n = 16$ , >18 years old) with genotype positive-phenotype negative HCM and followed them for an average of  $4.1 \pm 2.8$  years. During this follow-up period, the under-18 cohort experienced an increase in LV wall thickness that was “consistent with physiologic growth,” while the over-18 cohort did not experience a statistically significant change in LV wall thickness. Overall none of the patients reported clinical symptoms of HCM, although one patient developed HCM as diagnosed by LV wall thickness ( $\geq 15$  mm).

A recent study examined the long-term outcomes of familial genetic screening in the first-degree relatives of individuals with HCM (6). Sixty-six children <18 years old were included in the study. Twenty-six of these had an unknown HCM mutation status, and 12 were determined genetically to possess a mutation for HCM and were thus at risk of developing the disease. None of these individuals exhibited clinical signs of HCM at the time of inclusion in the study. After 12 years, all individuals were re-assessed.

At that time, 2 of the 12 HCM carriers had developed HCM, manifested by LV thicknesses of 15 and 17 mm at ages 26 and 28 years (18). Overall the penetrance of HCM in a cohort of phenotypically normal relatives of patients with HCM was demonstrated to be 6%.

### **Guidelines for Sports Participation**

#### *Symptomatic HCM*

International governing bodies agree that those with clinically apparent HCM should not participate in competitive athletics (24). According to the 36th Bethesda Guidelines, which dictate cardiovascular guidelines in the United States, individuals with HCM may only participate in “low-intensity,” 1A athletics such as golf, bowling, or curling. Participation is forbidden regardless of disease severity, absence of physical symptoms (such as exertional chest pain or dyspnea), or treatment (including pharmacologic treatment, septal ablation, and implantable cardioverter defibrillator (ICD) insertion) (24). Similarly the European Society for Cardiology recommends against sports participation for those with HCM (37). Their recommendations slightly are stratified more according to risk: only those athletes with HCM and a “low risk profile” for SCD are permitted to play low-intensity, 1A sports, while all others with clinically apparent HCM are prohibited from all competitive athletics. Athletes with HCM are classified as “low risk” if they lack a family history of SCD, have mild left ventricular hypertrophy, do not have a history of arrhythmia, and have an appropriate blood pressure response to exercise (Table) (37).

#### *Genotype positive-phenotype negative HCM*

Although governing bodies agree that sports restriction is necessary for individuals with observed HCM, they differ in their approach to athletes with genetic predisposition to HCM without evidence of disease. The European Society for Cardiology position is restrictive, stating that individuals with genotype positive-phenotype negative HCM may participate only in recreational athletic activities and are barred from competitive athletics (37).

In contrast, the 36th Bethesda Guidelines are slightly more accommodating, stating that athletes with “probable or unequivocal clinical diagnosis of HCM” should be

**Table.**

**Comparison of guidelines regarding athletic participation for individuals with HCM.**

Disease Severity	European Society for Cardiology	36th Bethesda Guidelines
Definitive clinical HCM	No competitive sports	Class IA sports
Definitive clinical HCM, low risk of SCD	Class IA sports	Class IA sports
Genotype positive-phenotype, negative HCM	Recreational activities only, no competitive sports	No sports restriction, close surveillance

prohibited from participating in competitive sports, with the exception of class IA activities (24). However they recognize the growing cohort of individuals with genetically determined HCM who are phenotypically normal. For these genotype positive-phenotype negative individuals, the 36th Bethesda Guidelines stipulate that there is insufficient evidence to preclude them from physical activity (24). Lastly these guidelines recognize the changing landscape of treatment of HCM, particularly the increasing research and use of ICDs.

#### *Disregarding guidelines*

New research is being conducted frequently regarding the natural history of cardiovascular genetic disorders. One such disorder, long QT syndrome (LQTS), is similar to HCM in that both the Bethesda Guidelines and European Society for Cardiology (ESC) consensus statement recommend individuals diagnosed with LQTS be prohibited from competitive sports. Furthermore those with genotype positive-phenotype negative LQTS are permitted to compete by the Bethesda Guidelines but are prohibited from doing so by ESC. Recently a group studied a cohort of athletes with congenital LQTS who decided to disregard these guidelines and continue participating in competitive athletics. The study monitored the outcomes of these athletes and compared the outcomes to athletes in their practice who were diagnosed with LQTS during a similar time period and chose to discontinue participation in sports. The athletes who chose to continue competing participated in sports from all ranges of Bethesda classifications and ranged in level of competition from city leagues to professional athletics. After an average follow-up period of  $5.5 \pm 3.4$  years, researchers found that none of the 70 genotype positive-phenotype negative LQTS athletes had an adverse event during athletic participation. Of the 60 clinically positive athletes, one experienced an adverse event countered by an appropriate discharge of the ICD (19). While these data cannot be extrapolated to HCM, it presents the argument that little research has been done regarding the rate of adverse events in genotype positive-phenotype negative individuals and that the field warrants further study. It also highlights the need for patient autonomy in this area.

### **Treatment of Preclinical HCM**

#### *Physiologic basis for treatment*

Genotype positive-phenotype negative presentations of HCM have not been studied sufficiently to determine their relative risk of SCD as compared with both their genotypically nonmutated or clinically affected counterparts. It was thought originally that those with genotype positive-phenotype negative HCM did not experience SCD events, as there was no LV hypertrophy to incite electrical instability or outflow tract obstruction. However recent case studies have pointed to instances where genotype positive-phenotype negative individuals experienced nonfatal ventricular fibrillations (7). Furthermore aforementioned research studies have cited molecular changes in cardiac cells that predate gross observations of hypertrophy. This evidence suggests that genotype positive-phenotype negative cardiac tissue may be inherently abnormal and capable of producing an adverse event. These events are thought to be significantly

less prevalent than the event rate of clinically apparent HCM. Given this information, it is unclear whether antiarrhythmic prophylaxis is warranted in the case of genotype positive-phenotype negative HCM.

#### *ICD prophylaxis in preclinical HCM*

Implantable cardioverter defibrillators (ICDs) have been endorsed recently as a possible preventive tool against SCD in individuals with HCM. Several studies have been completed to determine the benefit of ICDs. A 2007 multicenter study examined the benefit of ICDs in patients who met criteria for the highest clinical risk stratification, such as those with LV walls  $>30$  mm, prior unexplained syncope, prior myocardial infarctions, or sustained ventricular tachyarrhythmias (29). There they found that approximately 20% of study participants experienced an episode that warranted ICD cardioversion (29). However nearly the same number of participants experienced inappropriate attempts at cardioversion. These extraneous shocks were observed more frequently in participants less than 30 years old. Overall the study extrapolated that 1 in 4 participants would experience an appropriately timed ICD shock over the first 5 years of ICD insertion, concluding that ICDs may be a reliable way to decrease incidence of SCD in high-risk individuals and likely would result in prolonging life in these HCM patients (29). However they cede that it is difficult to make the case for ICDs as a primary preventive measure for individuals without clear-cut risk factors for SCD, given the heterogeneity of HCM presentation and risks associated with ICD insertion. They recommend that ICDs be considered for individuals with two or more risk factors for SCD.

The benefit of ICDs as a method of prophylaxis in genotype positive-phenotype negative individuals continues to be controversial. It has not been determined whether or not these individuals are able to become sufficiently electrically unstable to induce lethal episodes of ventricular tachyarrhythmias (31). From an athletics standpoint, ICD placement does not affect an individual's ability to participate in competitive sports, as the 36th Bethesda Guidelines and ESC still prohibit participation in more rigorous athletic endeavors. The ESC recommends that individuals receiving an ICD who have only mild morphologic cardiac abnormalities be able to participate in low-intensity sports (class 1A and 1B), stating that such individuals may benefit from a mild exercise regimen (37). Conversely the 36th Bethesda Guidelines state that ICD placement does not lift the restrictions on competitive athletics in those with HCM.

#### *Rate of sudden death of genotype positive-phenotype negative HCM*

After an extensive literature review, the authors were unable to find any studies or data regarding the rate of SCD in individuals with genotype positive-phenotype negative HCM.

### **Psychological Impact of Diagnosis**

#### *Quality of life*

A diagnosis of clinical HCM has been shown to impact deleteriously patients' quality of life and psychological health (33). However studies examining the impact of a

diagnosis of genotype positive-phenotype negative HCM continue to differ.

A Swedish study that measured the quality of life in adolescents with asymptomatic HCM noted that the experience of being diagnosed with HCM through familial screening had a profoundly negative impact upon their life, as they found such a diagnosis interrupted their daily lives and social environments (5). Most notably, participants who self-identified themselves as athletes noticed a significant shift in social interactions: prior to diagnosis, their social circles had centered on daily interactions with teammates. As patients ceased to play these team sports, they noted that their friendship with former teammates began to diminish, altering their overall social context (5). However in an adjunct study investigating the quality of life of asymptomatic children before and after the HCM diagnosis, there was no statistically significant decrease in quality of life an average of 22 months after diagnosis as compared with prediagnosis levels (4).

Earlier studies had examined the psychological impact of HCM diagnoses on family members, both with and without the condition. Ingles *et al.* (17) found that individuals at risk for HCM and those with genotype positive-phenotype negative HCM did not differ in self-evaluated health status as compared with the general Australian population, while those with clinically apparent HCM had a comparable mental and statistically worse physical health status. Similarly a Dutch study assessing quality of life and psychological implications of HCM diagnosis based on DNA testing demonstrated that those with genotype positive-phenotype negative HCM did not have a significant difference in overall quality of life as compared with the Dutch population. Conversely those with clinically manifested HCM confirmed by DNA testing significantly had increased psychological distress and a lower quality of life (8).

#### *Effects of not competing in sports*

In addition to the psychological impact of an HCM diagnosis, one also must consider the impact of being barred from competitive physical activity. Studies show that a sedentary lifestyle is a risk factor for developing obesity, metabolic disease, and cardiovascular disease. In addition, adolescents who participated in vigorous sport activities were less likely to express negative adolescent health behaviors, including smoking, alcohol use, sex, truancy, and failure to use a seatbelt (34), while those who participated in few activities more likely were to have low self-esteem (14,34). A 2011 meta-analysis of sedentary behaviors and adolescent health reviewed 232 studies involving more than 983,000 participants revealed sedentary behaviors were linked to increased obesity, decreased overall fitness, and decreased cardiorespiratory fitness (40). Longitudinal investigations of TV viewing and academic performance revealed that those children who spent more time watching TV performed worse on cognitive tests, had more difficulty reading as compared with their peers, and more likely were to develop attention problems in adolescence (14). Overall this meta-analysis found evidence that children who participated in more than 2 h of sedentary behaviors daily developed a number of both physical and psychological issues ranging

from increased blood pressure and cholesterol to decreased self-esteem and poor academic performance (14).

#### **Conclusion**

HCM is a commonly inherited cardiac disorder but is notorious for being the number one cause of SCD in young, healthy athletes — a decidedly uncommon event. However in many ways HCM lacks a “common” presentation, varying widely in both genotype mutation and phenotypic expression. This heterogeneity of expression poses a problem for health care providers in providing guidance and medical treatment to affected patients. The advent of genetic testing in family members of patients with HCM has aided in identifying those individuals with the mutation for the disease prior to expressing overt clinical disease. However there is insufficient data regarding the most effective management modalities in these cases. While molecular studies have shown atypical changes in the myocardium of individuals with preclinical HCM, are these changes sufficient to result in clinically evident adverse effects? Does exercise advance the progression of preclinical HCM to overt disease? Is the risk of experiencing SCD the same in genotype positive-phenotype negative HCM as it is in someone with overt HCM? These questions remain unanswered. Current guidelines disagree, and both are based on estimations and clinical extrapolations based upon studies of overt HCM.

Ultimately longitudinal studies are needed to better characterize the natural history of genotype positive-phenotype negative HCM and determine the risk of SCD, clinical implications of athletic endeavors on cardiac health, and risk factors for progression to overt clinical disease. Are there inciting factors, such as vigorous exercise or other comorbidities that produce a more rapid change in presentation? Are the molecular changes observed in preclinical HCM sufficient to cause arrhythmias or are certain mutations more prone to inciting arrhythmias? If so, are these arrhythmias sufficient to result in SCD? Answers to questions like these would allow for better understanding of the pathophysiology and ultimately the management of genotype positive-phenotype negative HCM.

The psychological effects of a new diagnosis of HCM and the health implications of sedentary lifestyles in adolescence may exert a negative impact on this new subset of individuals. Without sufficient data to delineate the precise natural history of preclinical HCM, providers, patients, and their families must collaborate closely to determine an individual's best course of treatment. Patient autonomy, full disclosure of information, and patient comprehension of their disease is paramount to the management of individuals with genotype positive-phenotype negative HCM. Patients' participation in the management of their care, contingent on full disclosure and shared decision making, is well aligned with the current paradigm shift occurring within the United States health care system as it migrates from a physician-centered to patient-centered model of care.

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