Proposal for Contemporary Screening Strategies in Families With Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a familial cardiac disease caused by a variety of mutant genes encoding protein components of the cardiac sarcomere, transmitted to each consecutive generation as an autosomal dominant trait with variable penetrance and heterogeneous clinical expression (1–36). Hypertrophic cardiomyopathy is the most common of the genetic cardiovascular diseases, occurring in about 1 in 500 of the general population (based on echocardiographic recognition of the phenotype) (37–41). This estimate suggests that as many as 500,000 people in the U.S. may be affected by this condition (42). However, the relatively low prevalence of HCM in clinical cardiologic practice (43) suggests that many affected (and largely asymptomatic) relatives remain undiagnosed and unaware of their underlying disease or genetic status, possibly due in some instances to the variable and incomplete age-dependent penetrance now known to be associated with certain disease-causing mutant genes.

The Mendelian autosomal dominant inheritance pattern of HCM has been established during the more than 40 years since the earliest clinical descriptions of the disease in the late 1950s and early 1960s (44,45). However, not until the application of molecular biology to HCM over the past 15 years has the genetic complexity and heterogeneity of HCM been fully appreciated (1–36,46–49). Advances in our understanding of HCM, as a consequence of the power implicit in mutational analysis, have occurred in two principal areas. The first of these is the development of genetic markers for stratification of sudden death risk and other adverse consequences of HCM (1–36,47). However, the extent to which precise knowledge of particular disease-causing mutations will prove useful in predicting prognosis and designing management strategies for individual HCM patients is incompletely resolved (48,49) and has not been included in the present discussion.

Second, the capability of achieving an unequivocal diagnosis of HCM with deoxyribonucleic acid (DNA)-based laboratory methods is irrefutable and has led to enhanced recognition of the HCM disease state, and consequently to more complete definition of its broad clinical spectrum, as well as providing practical insights into appropriate genetic counseling (1–36,46–49). Indeed, there is substantial justification for pursuing and encouraging the clinical and genetic screening of families for HCM in order to recognize affected individuals who would otherwise be unaware of their disease. This includes the opportunity to identify patients who may be at high risk for sudden death and, therefore, eligible for preventive strategies (42,50). Although such considerations importantly affect ambulatory medical practice for many cardiologists (as well as general internists and pediatricians), the clinical implications of
virtue of detecting pathologic mutations as well as access to definitive laboratory-based diagnosis by provided important insights into the genetics of HCM, as molecular studies with clinical genotype-phenotype correlations, conducted intensively over more than a decade, have demonstrated convincingly that HCM is caused by mutations in any one of 10 genes, each encoding a protein component of the cardiac sarcomere, i.e., either of the thick or thin filaments with contractile, structural, or regulatory functions. Therefore, from the perspective of these basic observations, it is presently possible to regard most of the diverse clinical spectrum of HCM as both a unified disease entity and a fundamental and primary disorder of the sarcomere (7). Two of the HCM-causing mutant genes, beta-myosin heavy chain (the first identified) and myosin-binding protein C, appear to predominate in frequency. The other eight genes appear to account for far fewer cases of HCM and include troponin T and I, regulatory and essential myosin light chains, titin, alpha-tropomyosin, alpha-actin, and alpha-myosin heavy chain. This genetic diversity is compounded by the considerable intragenic heterogeneity, with more than 200 mutations now identified. These are most commonly missense mutations with a single amino acid residue substituted for another, but also include insertions, deletions, and splice (split site) mutations encoding truncated sarcomeric proteins. The characteristic morphologic diversity of the HCM phenotype is largely attributable to the disease-causing mutations, but also probably to the influence of modifier genes and environmental factors on phenotypic expression.

In addition, non-sarcomeric protein missense mutations have been recently reported to be responsible for primary cardiac disease with the clinical presentation of HCM. The first of these involves the gene encoding the gamma-2-regulatory subunit of the AMP-activated protein kinase (PRKAG2) which may occasionally cause familial, relatively mild left ventricular (LV) hypertrophy associated with ventricular pre-excitation (54–56). Patients harboring PRKAG2 mutations are distinguished from those with typical sarcomere protein gene mutations by absence of histopathologic features characteristic of HCM (i.e., myocyte disarray), progressive conduction system disease with heart block, and a distinct metabolic-based cause for the hypertrophy with glycogen accumulation evident in myocytes (54).

Most recently, a non-sarcomeric mutant gene has been identified involving the lysosome-associated membrane proteins 2 alpha-galactosidase or acid alpha-1, 4-glucosidase, and causing clinically diagnosed HCM (52). This results in a glycogen storage disease (Danon disease) with clinical manifestations largely limited to the heart, usually associated with ventricular pre-excitation and massive degrees of LV hypertrophy (52). Undoubtedly, many other mutations causing HCM in sarcomere (as well as non-sarcomere) related genes remain to be identified.

Although laboratory DNA analysis for mutant genes is the most definitive method for establishing the diagnosis of HCM, important obstacles remain for translating such research-based genetic technology into practical clinical strategies on a widespread or routine basis (1,2,6,10,48,49). These factors include the aforementioned genetic heterogeneity of HCM, as well as the methodologic difficulties associated with identifying a single disease-causing mutation among a total of at least 12 possible HCM genes, given the complex, time-consuming and expensive laboratory techniques required. However, when an HCM mutation is successfully identified in a proband, accurate definition of genetic status can be achieved in all family members much more efficiently and inexpensively. Academic diagnostic molecular laboratories have recently begun to address these challenges and opportunities by offering DNA testing for a subset of HCM disease genes.

HCM GENOTYPE

Molecular studies with clinical genotype-phenotype correlations, conducted intensively over more than a decade, have provided important insights into the genetics of HCM, as well as access to definitive laboratory-based diagnosis by virtue of detecting pathologic mutations, even in the absence of obvious clinical evidence of the disease (1–36, 46–49,51–56). This substantial investigative effort has demonstrated convincingly that HCM is caused by mutations in any one of 10 genes, each encoding a protein component of the cardiac sarcomere, i.e., either of the thick or thin filaments with contractile, structural, or regulatory functions. Therefore, from the perspective of these basic observations, it is presently possible to regard most of the diverse clinical spectrum of HCM as both a unified disease entity and a fundamental and primary disorder of the sarcomere (7). Two of the HCM-causing mutant genes, beta-myosin heavy chain (the first identified) and myosin-binding protein C, appear to predominate in frequency. The other eight genes appear to account for far fewer cases of HCM and include troponin T and I, regulatory and essential myosin light chains, titin, alpha-tropomyosin, alpha-actin, and alpha-myosin heavy chain. This genetic diversity is compounded by the considerable intragenic heterogeneity, with more than 200 mutations now identified. These are most commonly missense mutations with a single amino acid residue substituted for another, but also include insertions, deletions, and splice (split site) mutations encoding truncated sarcomeric proteins. The characteristic morphologic diversity of the HCM phenotype is largely attributable to the disease-causing mutations, but also probably to the influence of modifier genes and environmental factors on phenotypic expression.

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within the LV chamber such as the anterolateral free wall or apex.

It has been a historical dictum in HCM that, in the absence of another cardiac disease capable of producing the magnitude of LV hypertrophy evident, an abnormally increased LV wall thickness (usually ≥15 mm in adults) associated with a non-dilated chamber represents the clinical marker and evidence of an underlying mutant HCM gene (2,5,10,37,58,61). Borderline LV wall thicknesses of 13 or 14 mm in an adult patient are regarded as possible evidence of HCM, but often elicit a differential diagnosis with the physiologically based athlete’s heart or systemic hypertension—which may be difficult to resolve on clinical grounds alone (2,10,62,63). However, clinical and molecular genotype-phenotype studies have triggered the emergence of novel diagnostic criteria for HCM (1,2,8,10,20–22,24,64,65). As a consequence of these data, it is now evident that there is no true minimum LV wall thickness diagnostic or pathognomonic for HCM (1,2,6,10,18–24,28,29,64,65). Indeed, virtually any value for LV wall thickness, even when within the normal range (i.e., ≤12 mm for adults), is consistent with the presence of a HCM-causing mutant gene.

DEVELOPMENT OF LV HYPERTROPHY

Individuals harboring a genetic defect for HCM do not necessarily express clinical markers of their disease, such as LV hypertrophy on echocardiogram, ECG abnormalities, or disease-related symptoms, at all times during life (2,5,10,18–24,28,29,64–76). Indeed, there are probably three phases of life during which LV hypertrophy (identifiable on a diagnostic echocardiogram) may appear for the first time in HCM, i.e., most commonly during adolescence, but also earlier in preadolescent children or later in adulthood.

However, these diverse clinical profiles, although discussed separately here, do not imply different etiologies, genetic substrates, or nature of the LV hypertrophy, but only that LV wall thickening may appear or be evident at different ages in a given lifetime.

Onset in adolescence. It is well established that LV hypertrophy may be absent on echocardiogram in preadolescent children affected by a mutant HCM gene (1–6, 10,18–24,28,29,65,68,69,73,75). However, marked LV remodeling with spontaneous de novo appearance or striking evolution of hypertrophy frequently occurs in association with accelerated body growth during the crucial five-year period of the adolescent years (i.e., usually 13 to 17 years) (10,68,69,73,75). Morphologic expression is usually complete when physical maturity is achieved at about 18 years of age. Within this period of time, dramatic increases in LV wall thickness are often evident, averaging about 100% in a group of patients (compared to an expected average increase of only about 10%) (68). Therefore, it is common for young affected family members <13 years old to represent “silent” gene carriers during the pre-hypertrophic phase of HCM. These dramatic structural changes in adolescence appear to be spontaneous events generally unrelated to the onset of symptoms, disease progression, or cardiac events (10,68,69,73,75). Also, during this period of life, as LV outflow tract geometry is altered with accelerated body growth, systolic anterior motion of the mitral valve causing dynamic obstruction to LV outflow may develop for the first time (69).

Of note, abnormal 12-lead ECG patterns may be evident even before LV hypertrophy is detectable on echocardiogram, thereby potentially providing early clinical evidence for mutant HCM genes (10,18,19,21,24,73,74,76). However, although a distinctly abnormal ECG can in some cases be regarded as a surrogate clinical marker for the HCM phenotype, relatively minor ECG alterations often represent nonspecific or normal variants completely unrelated to HCM. Therefore, prudence should be exercised in assigning genetically affected status to a HCM family member based solely on an altered ECG in the absence of LV hypertrophy. Recent imaging studies with reduced load-dependent tissue Doppler echocardiography provide evidence that diastolic dysfunction may also precede the appearance of the HCM phenotype on echocardiogram (66,67). Nevertheless, in the absence of LV hypertrophy, neither the scalar ECG nor tissue Doppler echocardiography would appear at present to convey sufficient sensitivity or specificity to represent reliable diagnostic alternatives to laboratory DNA testing.

Early onset. Left ventricular hypertrophy and clinical manifestations of HCM may occasionally appear in symptom-atic or asymptomatic infants or young children well before adolescence, although the precise significance of this presentation is incompletely understood in terms of the natural history of the disease and clinical management (77–80). Indeed, young and often asymptomatic children of about 4 to 12 years of age with marked LV wall thickening relative to body size are being recognized with greater frequency, probably owing to the increasingly widespread practice of clinical and genetic family screening. At present, however, specific data are sparse (and follow-up relatively short) in this subset of patients, and it is largely unresolved as to whether or not (or how often) the appearance of hypertrophy particularly early in life represents a malignant genetic substrate and an unfavorable clinical feature of the disease associated with premature death or disease progression. Nevertheless, when the HCM phenotype has been recognized in infants and young children, it has often been associated with severe heart failure and increased mortality (77–79,81).

Late onset. Recognition of age-related and incomplete penetrance, with the initial appearance of LV hypertrophy in HCM family members delayed well into adulthood, has altered the landscape of clinical pedigree screening in this disease (1,2,6,10,18,19,21,22,24,28,71,82), and is the primary focus of the present discussion. Over the past five years
there have been numerous observations and reports supporting morphologic conversions to the HCM phenotype (i.e., from normal wall thickness to LV hypertrophy) during mid-life and even beyond in relatives who could be regarded as “silent” affected gene carriers of mutant genes (10,21,22,24,28,29,71) (Fig. 1). This aspect of the natural history of HCM was first described in cross-sectional investigations of families genotyped to myosin-binding protein C mutations (28). In these studies, penetrance of the HCM phenotype was often incomplete in children and young adults, increased progressively with age, and was virtually complete in the oldest patients.

Delayed development of LV hypertrophy well until into adulthood in affected HCM relatives has been confirmed by serial observations in individual patients studied with echocardiography over substantial periods of time (21,28,71), as well as in the previously unreported patient depicted in Figure 1. These striking adult morphologic conversions involve an increase in LV wall thickness averaging about 60% over 5 years and have been documented at 30 to 60 years of age, largely unassociated with the development of significant symptoms or outflow obstruction (21).

However, the precise frequency with which delayed-onset LV hypertrophy occurs in HCM is unknown owing to the practical difficulties in assembling such data and documenting these clinical occurrences. Indeed, adult morphologic conversions could ultimately prove to be a relatively common phenomenon, as suggested by the cross-sectional data (28), or are possibly rare as implied by the anecdotal clinical experience at present. This is largely because it has not been customary clinical practice to perform repeated echocardiographic examinations in adult family members or patients suspected of having HCM (after obtaining a normal echocardiogram over about 18 years of age), given the prior assumption that LV hypertrophy did not initially appear in adulthood as well as the potentially long time intervals over which serial echocardiograms would be required to reliably demonstrate (or exclude) LV wall thickness changes in adult patients.

Delayed development of LV hypertrophy into adulthood has most commonly been reported with mutations in cardiac myosin-binding protein C (10,18,19,21–24,28,35,67). However, other HCM-causing mutant genes have been associated with gene-positive, phenotype-negative adult relatives (e.g., troponin-T and beta-myosin heavy chain genes) (18,19,66,67), raising the distinct possibility that late-onset hypertrophy may occur with other genetic substrates and be much more common than generally regarded at this early juncture. For example, not uncommonly, HCM may be recognized for the first time when symptoms of heart failure appear at advanced ages of ≥60 years (2,5,10,41,57,82–87), although all such patients probably have not harbored a dormant HCM phenotype since early in life. It should also be noted, in light of these observations and conjectures regarding increasing wall thickness in adult HCM patients that it is also possible for gradual LV remodeling with regression of hypertrophy to occur during this period of life (74,88), particularly in women (88).

Based on the aforementioned novel echocardiographic-molecular observations in HCM families, it is now an unavoidable conclusion that any HCM family member of full adult maturity (and with normal echocardiographic
studies) can harbor the potential to develop LV hypertrophy and HCM at virtually any age. These considerations have particular relevance for screening relatives in high-risk families in which HCM-related sudden deaths may have already occurred. In such a clinical circumstance it is not only possible that a HCM family member will develop phenotypic expression of the disease for the first time as an adult, but in the process also acquire risk factors for sudden death such as extreme magnitude of LV hypertrophy with wall thickness \( \geq 30 \text{ mm} \) (81,89). At present, conclusive data linking adult patients with late-onset hypertrophy to any particular prognosis are lacking and treatment algorithms are unresolved, although the longitudinal follow-up of this newly recognized subset of patients is still brief. It should be emphasized, however, that although sudden-death events occurring in HCM in the advance of obvious phenotypic expression have been reported (10,20,64,65,70,72), at this time they appear to be quite rare (2,10).

**RECOMMENDATIONS FOR CLINICAL SCREENING STRATEGIES IN HCM FAMILIES**

In clinical practice, prospective screening of HCM family members to ascertain affected or unaffected genetic status usually takes place without access to DNA analysis, and is performed primarily with two-dimensional echocardiography and 12-lead ECG, as well as history and physical examination. Furthermore, most family screening is carried out by clinical cardiologists in the community; the relatively small number of HCM research centers do not possess the resources necessary to routinely perform such clinical testing.

The traditional recommended strategy for screening relatives in most HCM families calls for such evaluations on a 12- to 18-month basis, usually beginning at least by 12 years of age (Table 1). If these studies do not show evidence of LV hypertrophy, with one or more segments of increased wall thickness, by the time full growth is achieved (at the age of about 18 to 21 years), it has been customary practice to conclude that a HCM-mutant gene is probably absent and reassure family members accordingly that further echocardiographic testing would therefore be unnecessary.

However, recognition of the aforementioned adult morphologic conversions to the HCM phenotype has created a new proposed paradigm for screening families and genetic counseling in this disease, i.e., it is no longer possible to routinely hold to the traditional tenet that a normal echocardiogram (and ECG) obtained at maturity itself defines a genetically unaffected relative. Consequently, we believe that it is now probably prudent to revise current practice strategies and extend the time period into adulthood for the clinical-morphologic surveillance of those phenotype-negative relatives judged to potentially harbor a mutant HCM gene (Table 1).

Specifically, at present, the recommended clinical model for diagnosis of HCM would include serial two-dimensional echocardiographic (and ECG) examinations performed in adult family members without LV hypertrophy at about five-year intervals, past the end of adolescence and into mid-life, unless a clinical development intervenes that justifies a shorter interval (Table 1). Also, a family history suggestive of late-onset HCM (or malignant clinical course) may justify repeated echocardiographic screening at somewhat more frequent intervals during the adult years.

This recommendation, triggered by the recognized potential for late-onset hypertrophy in family members, seems reasonable at present, and probably unavoidable in the context of current clinical practice—at least until that future time when greater clarity has been achieved regarding this phenotypic evolution of HCM, including its frequency, timing, and predisposing genetic substrates. Nevertheless, we also recognize certain negative implications that could result from this strategy. By extending almost indefinitely the period of morphologic (i.e., echocardiographic) surveillance and clinical indecision regarding the diagnosis of HCM for family members we risk eliciting the psychological perception and stigma of cardiac disease in young healthy individuals, many of whom are not even affected by a mutant gene. Indeed, at least 50% of adult relatives exposed to serial echocardiography (as advocated here) will be, by definition, free of any predisposition toward developing the disease or its consequences. Furthermore, this proposed strategy potentially places a considerable burden on echocardiographic resources considering the not inconsiderable number of HCM patients and families that could be involved.

Our current approach for diffusing unnecessary anxiety in adult phenotype-negative family members includes under-scoring the likelihood that they are unaffected relatives. Performing additional serial echocardiograms may be a prudent measure to more definitively resolve such diagnostic dilemmas in individual family members and enable appropriate disease management. However, dependence on this strategy requires considerable motivation by physicians and at-risk individuals over potentially long periods of time. The associated burden of expense, patient compliance, and

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**Table 1. Clinical Screening Strategies With Echocardiography (and 12-Lead ECG) for Detection of HCM in Families**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Screening Strategy</th>
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<tbody>
<tr>
<td><strong>&lt;12 yrs old</strong></td>
<td>Optional unless:</td>
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<tr>
<td></td>
<td>Malignant family history of premature HCM death or other adverse complications</td>
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<tr>
<td></td>
<td>Competitive athlete in an intense training program</td>
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<tr>
<td></td>
<td>Onset of symptoms</td>
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<tr>
<td></td>
<td>Other clinical suspicion of early LV hypertrophy</td>
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<tr>
<td><strong>12 to 18-21 yrs old†</strong></td>
<td>Every 12–18 months</td>
</tr>
<tr>
<td><strong>&gt;18–21 yrs old†</strong></td>
<td>Probably about every 5 yrs, or more frequent intervals with a family history of late-onset HCM and/or malignant clinical course</td>
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*In the absence of laboratory-based genetic testing. †Age range takes into consideration the acknowledged individual variability in achieving physical maturity. ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; LV = left ventricular.
unnecessary anxiety (created by diagnostic uncertainty) may be potentially alleviated by the recent development of rapid laboratory-based genetic testing for HCM.

Indeed, a rapid genetic test for HCM is now available. The Laboratory for Molecular Medicine (a clinical diagnostic testing facility within the Harvard Partners Center for Genetics and Genomics [90]) currently analyzes by direct DNA sequencing the five most common HCM genes (beta-myosin heavy chain, myosin-binding protein C, cardiac troponin T, cardiac troponin I, and alpha-tropomyosin) for disease-causing mutations. The power of the test lies with its effectiveness and efficiency in determining the sequence of each of the genes involved and also in identifying novel mutations (requiring only 7 cc of blood, and with genotyping results provided within one month). However, there remains the significant potential for false-negative test results (in which a HCM diagnosis cannot be ruled out) owing to the possible presence of mutations in the seven known causal genes not yet part of the test panel, or in other potential HCM genes not yet identified. As this genetic test strategy evolves and comes into more widespread clinical use, with its costs ultimately assumed by insurance companies, reliance on serial echocardiograms into adulthood for the diagnosis of family members will diminish substantially.

Although open to individual clinical judgment, it has been the common and generally accepted practice to avoid routine echocardiographic studies in children younger than about 12 years of age owing to the infrequency with which sudden death or other disease complications occur in very young children, and because LV hypertrophy uncommonly appears this early in life. In addition, identification of the HCM phenotype will, per se, rarely trigger therapeutic interventions and management decisions in this age group. Furthermore, with repeated diagnostic testing in rapidly growing children, difficulties can arise with regard to accurate interpretation of borderline LV wall thickness measurements relative to body surface area for the diagnosis of HCM, which itself may create undue uncertainty and anxiety on the part of patients and families.

However, not uncommonly, circumstances may arise that justify performing serial echocardiographic studies in children earlier than 12 years of age, in particular young family members. These may include relatives in whom cardiac symptoms have already occurred, those involved in particularly intense competitive sports programs at this age (such as swimming, ice hockey, or tennis), or suspected of having HCM by an echocardiogram during preadolescence (e.g., 10 to 12 years of age), as well as members of HCM families in which there have been prior premature deaths and/or other malignant disease expression (2,91). In the latter patients, identification of early-onset hypertrophy could possibly lead to recommendation for withdrawal from particularly vigorous and intense physical activities and competitive sports (92), and in selected patients to a prophylactic intervention with an implantable cardioverter-defibrillator for primary prevention of sudden death (42,50).

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REFERENCES


