Prevalence and Severity of “Benign” Mutations in the \( \beta \)-Myosin Heavy Chain, Cardiac Troponin T, and \( \alpha \)-Tropomyosin Genes in Hypertrophic Cardiomyopathy

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Background—Genotype-phenotype correlative studies have implicated 8 particular mutations that cause hypertrophic cardiomyopathy (HCM) as “benign defects,” associated with near-normal survival: N232S, G256E, F513C, V606M, R719Q, and L908V of \( \beta \)-myosin heavy chain (MYH7); S179F of troponin T (TNNT2); and D175N of \( \alpha \)-tropomyosin (TPM1). Routine genetic screening of HCM patients for specific mutations is anticipated to provide important diagnostic and prognostic information. The frequency and associated phenotype of these mutations in a large, unselected cohort of HCM is unknown.

Methods and Results—A total of 293 unrelated HCM patients were genotyped for the presence of a benign mutation. DNA was obtained after informed consent; specific MYH7, TNNT2, and TPM1 fragments were amplified by polymerase chain reaction; and the mutations were detected by denaturing high-performance liquid chromatography and automated DNA sequencing. Only 5 (1.7%) of the 293 patients possessed a benign mutation. Moreover, all 5 subjects with an ascribed benign mutation had already manifested clinically severe expression of HCM, with all 5 requiring surgical myectomy, 3 of the 5 having a family history of sudden cardiac death, and 1 adolescent requiring an orthotopic heart transplant.

Conclusions—These findings demonstrate the rarity of specific mutations in HCM and challenge the notion of mutation-specific clinical outcomes. Fewer than 2% of the subjects harbored a benign mutation, and those patients with a benign mutation experienced a very serious clinical course. (Circulation. 2002;106:3085-3090.)

Key Words: hypertrophy ■ cardiomyopathy ■ genetics ■ death, sudden

Hypertrrophic cardiomyopathy (HCM) manifests as left ventricular hypertrophy without obvious cause, with myocyte disarray, interstitial fibrosis, and preserved systolic function.1–4 HCM affects 1 in 500 persons according to echocardiographic criteria.3 The clinical outcomes of HCM range from asymptomatic longevity to chronic, progressive heart failure or premature sudden arrhythmic death. In young persons, HCM remains the most common cause of sudden cardiac death (SCD).4 To date, 10 genes encoding components of the cardiac sarcomere have been implicated in HCM.4–6 The Familial Hypertrophic Cardiomyopathy Mutation Database2 lists more than 150 unique mutations scattered throughout these genes. Several genotype-phenotype correlative studies have suggested that specific mutations are associated with a “malignant” clinical course (decreased survival), whereas other mutations cosegregate with families having a “benign” phenotype (see reviews8,9). Within the \( \beta \)-myosin heavy chain gene (MYH7), at least 4 mutations have been ascribed as malignant mutations: R403Q, R453C, G716R, and R719W.8,10,11 In contrast, 6 particular missense mutations in MYH7 (N232S, G256E, F513C, V606M, R719Q, and L908V), as well as the S179F mutation in troponin T (TNNT2) and the D175N mutation in \( \alpha \)-tropomyosin (TPM1), have been designated as benign mutations with no increased risk of SCD.8–10,12–17

Several studies have reported exceptions to these genotype-phenotype correlations12–14,18,19; however, the veracity with which the genetic substrate predicts the clinical outcome and the frequency of specific mutations are unknown. From a cohort of nearly 300 unrelated individuals with HCM seen at a single tertiary referral center, we sought to determine the frequency of 8 published benign mutations and to examine the clinical course of the individuals harboring these mutations.

Methods

Clinical Characterization of Unrelated HCM Cases

Informed written consent was obtained in accordance with the Mayo Foundation Institution Review Board. Between April 1997 and
TABLE 1. Demographics of HCM Cohort (n=293)

<table>
<thead>
<tr>
<th>Age at diagnosis, y (range)</th>
<th>42.5±18.9 (0–89.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% &gt;25 y at diagnosis</td>
<td>82</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>156/137</td>
</tr>
<tr>
<td>Mean LVWT, mm (range)</td>
<td>21±6 (15–46)</td>
</tr>
<tr>
<td>% with extreme hypertrophy (LVWT ≥30 mm)</td>
<td>6.1</td>
</tr>
<tr>
<td>Peak resting gradient, mm Hg (range)</td>
<td>60.4±40 (4–231)</td>
</tr>
<tr>
<td>LVOTO &gt;30 mm Hg at rest, n (%)</td>
<td>155 (52.9)</td>
</tr>
<tr>
<td>LVOTO &gt;30 mm Hg with provocation, n (%)</td>
<td>51 (17.4)</td>
</tr>
<tr>
<td>Midcavity obstruction, n (%)</td>
<td>9 (3.1)</td>
</tr>
<tr>
<td>History of syncope at presentation, n (%)</td>
<td>30 (10.2)</td>
</tr>
<tr>
<td>No cardiac symptoms at presentation, n (%)</td>
<td>133 (45.4)</td>
</tr>
<tr>
<td>Negative family history of HCM, n (%)</td>
<td>198 (67.6)</td>
</tr>
<tr>
<td>Negative family history of SCD, n (%)</td>
<td>224 (76.5)</td>
</tr>
<tr>
<td>Surgical myectomy, n (%)</td>
<td>83 (28.3)</td>
</tr>
<tr>
<td>ICD implantation, n (%)</td>
<td>25 (8.5)</td>
</tr>
</tbody>
</table>

LVWT indicates left ventricular wall thickness; LVOTO, left ventricular outflow tract obstruction; and ICD, implantable cardioverter-defibrillator.

October 2000, 293 unrelated individuals (age 42.5±18.9 years, 137 females) were evaluated at the Mayo Medical Center HCM outpatient clinic in Rochester, Minn, and provided a blood sample for molecular genetic testing. Each of these subjects met the clinical diagnostic criterion for HCM: left ventricular wall thickness >13 mm in the absence of another confounding diagnosis. Relevant data for cohort analysis were extracted from the patients’ clinical records. Positive family history of SCD was defined as having any family member with instantaneous and unexpected death with or without documented ventricular fibrillation within 1 hour after a witnessed collapse in patients who previously were in stable clinical condition, or nocturnal death with no antecedent history of worsening symptoms.

Benign MYH7, TNNT2, and TPM1 Mutation Genotyping

Purgene DNA extraction kits (Gentra, Inc) were used to extract genomic DNA from peripheral blood lymphocytes. Previously published intron/exon-based primers or novel primers were used to amplify exons hosting benign mutations from genomic DNA by the polymerase chain reaction. The 8 exons containing these mutations were amplified: N232S (exon 8), G256E (exon 9), F513C (exon 15), V606M (exon 16), R719Q (exon 19), and L908V (exon 23) in MYH7; S179F (exon 11) of TNNT2; and D175N (exon 5) of TPM1. Sequence variations were detected by denaturing high-performance liquid chromatography (DHPLC; WAVE, Transgenic).21 For samples with an abnormal DHPLC elution profile, the precise sequence anomaly was determined by automated dye terminator cycle-sequencing with an ABI Prism 377.22

Profile of HCM Cohort

Table 1 summarizes the demographics for the 293 unrelated individuals with HCM. Nearly half of the patients (n=133; 45%) were asymptomatic. The mean New York Heart Association (NYHA) functional class of the 160 symptomatic patients was 1.9±0.8, with 27 patients being class 3 or 4 at presentation. In addition, two thirds (67.6%) reported no clinically apparent family history of HCM, and three fourths (76.5%) had no family history of SCD.

Results

Benign mutations detected by DHPLC. Depicted are elution profiles for normal samples and MYH7 benign mutations detected in 5 of 293 patients: R719Q (A) and L908V (B).

Benign Mutations

Overall, 5 (1.7%) of 293 patients possessed a previously published benign mutation: 2 with R719Q-MYH7 and 3 with L908V-MYH7 mutations (Figure). No patient had an N232S-MYH7, G256E-MYH7, F513C-MYH7, V606M-MYH7,
TABLE 2. Clinical Profiles of HCM Patients With Benign Mutation

<table>
<thead>
<tr>
<th>Index Case</th>
<th>Age at Study, y/SEX</th>
<th>Age at Dx</th>
<th>Presentation</th>
<th>Subsequent Symptoms</th>
<th>NYHA Class*</th>
<th>LVWT, mm</th>
<th>LVOTO, mm Hg*</th>
<th>Resting LVOTO, mm Hg*</th>
<th>Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16/F</td>
<td>9 y</td>
<td>Murmur</td>
<td>Angina, dyspnea, presyncope</td>
<td>3</td>
<td>29</td>
<td>75</td>
<td>No</td>
<td>NO              HCM</td>
</tr>
<tr>
<td>2</td>
<td>15/M</td>
<td>3 mo</td>
<td>Murmur</td>
<td>No</td>
<td>1</td>
<td>33</td>
<td>95</td>
<td>Yes</td>
<td>Yes             HCM</td>
</tr>
<tr>
<td>3</td>
<td>29/F</td>
<td>29 y</td>
<td>Murmur</td>
<td>Angina, dyspnea</td>
<td>3</td>
<td>22</td>
<td>144</td>
<td>No</td>
<td>No              HCM</td>
</tr>
<tr>
<td>4</td>
<td>43/F</td>
<td>38 y</td>
<td>Dyspnea</td>
<td>Angina, dyspnea, syncope</td>
<td>3</td>
<td>28</td>
<td>92†</td>
<td>Yes</td>
<td>Yes             HCM</td>
</tr>
<tr>
<td>5</td>
<td>52/M</td>
<td>44 y</td>
<td>Dyspnea</td>
<td>Murmur</td>
<td>3</td>
<td>21</td>
<td>40</td>
<td>Yes</td>
<td>Yes             HCM</td>
</tr>
</tbody>
</table>

*Preoperative value.
†‡ indicates first-degree relative; 2, second-degree relative; and 3, third-degree relative.

None of the cases had atrial fibrillation.

Family History:
- HCM: Hypertrophic cardiomyopathy
- SCDF: Sudden cardiac death
- L: Left
- R: Right

S179F-TNN1, or D175N-TPM1 mutation. All 5 individuals harboring a benign mutation have a significant clinical phenotype. All 5 have undergone septal myectomies, and 4 are still undergoing therapy with β-blockers and calcium channel blockers. Three of the 5 individuals have a positive family history of SCD. In addition, 1 of the patients (case 1, Table 2) received an orthotopic heart transplant as a teenager for end-stage HCM with severe restrictive hemodynamics. Table 2 summarizes the clinical profiles of the 5 patients harboring a benign mutation. The average age at diagnosis was 25 years, with 3 of the 5 cases (cases 1, 2, and 3) being less than 30 years old at diagnosis.

Case 1
An adolescent white female was identified with the R719Q-MYH7 mutation. She was diagnosed at age 9 years during the evaluation of a murmur. An echocardiogram revealed extreme hypertrophy with a maximal septal thickness of 29 mm and a gradient of 75 mm Hg at rest. Although asymptomatic at diagnosis, she experienced progressive dyspnea, angina, and presyncope unresponsive to pharmacological therapy over the next 2 years. She underwent surgical septal myectomy at age 11 years that resulted in immediate symptom relief. However, progressive dyspnea and congestive heart failure later recurred. Comprehensive echocardiography and hemodynamic catheterization (τ=68 ms, mean left atrial pressure=20 mm Hg, left ventricular end-diastolic pressure=24 mm Hg) demonstrated severe residual diastolic dysfunction. Orthotopic heart transplantation was performed at age 16 years. There is no documented HCM or SCDF in her family.

Case 2
An adolescent white male also harbored the R719Q-MYH7 mutation. He was diagnosed during infancy when he presented with a cardiac murmur and a positive family history of HCM. Because of the severity of obstruction and symptoms of dyspnea, he underwent surgical septal myectomy at age 5 years. He gradually redeveloped outflow obstruction and severe symptomatic mitral regurgitation that necessitated repeat surgical myectomy at age 15 years. In addition, an implantable cardioverter-defibrillator was implanted prophylactically at the time of his repeat myectomy, prompted by the SCDF of the patient’s 12-year-old brother. This younger brother was also diagnosed with HCM during infancy, and asymmetric hypertrophy and myocyte disarray were confirmed at autopsy. The patient’s father had been diagnosed with HCM at age 18 years and manifested progressive nonobstructive HCM that culminated in his recent death at the age of 46 years of acute pulmonary edema and cardiac arrest. Finally, a paternal-paternal great-uncle and the paternal-paternal great-grandfather died in their early 30s of SCDF.

Case 3
A 29-year-old woman was diagnosed with HCM when a murmur was detected in the second trimester of pregnancy. The L908V-MYH7 mutation was identified. She had experienced exertional dyspnea for a number of years but had 1 prior uncomplicated pregnancy and 1 prior miscarriage. Because of severe obstruction at rest (gradient >140 mm Hg), NYHA class 3 symptoms, and potential fetal compromise, a surgical septal myectomy was performed during the 30th week of pregnancy without complications. A normal infant was delivered at 38 weeks of pregnancy. She remains symptom-free 7 years after the surgical myectomy. There is no family history of HCM or SCDF.

Case 4
A 43-year-old woman presented for evaluation of known HCM and possessed the L908V-MYH7 mutation. She had been diagnosed 5 years previously when she complained of moderate exertional dyspnea and a family history of HCM. Her symptoms had continually progressed to NYHA class 3 despite appropriate pharmacological therapy. She underwent an uncomplicated surgical septal myectomy for severe midcavitary obstruction (maximum instantaneous gradient 92 mm Hg, left ventricular wall thickness 28 mm). The patient’s mother had received pacemaker therapy elsewhere for symptomatic HCM and later died of complications of a stroke at age 71 years. Her maternal-paternal great-grandfather had unexplained SCDF while running at age 45 years.

Case 5
A 44-year-old man was diagnosed with obstructive HCM (resting gradient 40 mm Hg) during evaluation of a cardiac
murmur; he had an extensive family history of HCM that spanned 4 generations, with 13 confirmed diagnoses of HCM, including SCD in 2 nephews (ages 16 and 18 years). In addition, 2 siblings died of unexplained causes in early childhood. The patient was found to have the L908V-MYH7 mutation. Despite pharmacological therapy, he continued to experience severe exertional dyspnea and presyncope. A pacemaker was implanted at age 47 years. This initially resulted in symptomatic improvement. However, 18 months later, his symptoms returned, and he underwent surgical septal myectomy without complication.

Discussion

In spite of exceptions to previously published genotype-phenotype correlations,12–14,18,19 hopes that genetic testing will become a routine clinical test with prognostic value remain.9,23–26 An HCM gene chip containing known mutations has been reported.27 Previously, we demonstrated that the prevalence of 5 malignant mutations in MYH7 and TNNT7 was only 1%.28 This type of study design, with large, unselected cohorts of individuals with HCM rather than selected, large families, is necessary to translate the profound molecular breakthroughs of HCM pathogenomics to clinical practice. Specifically, the frequency of specific mutations and the veracity with which the genetic substrate predicts the clinical outcome are necessary to define the feasibility, yield, and precise clinical role of genetic testing for HCM.

Genetic Heterogeneity in HCM

HCM is the final common pathway for many distinct sarcomeric defects. To date, more than 150 mutations scattered throughout 10 different sarcomeric genes have been reported. Unlike monogenic diseases, such as cystic fibrosis, in which a single mutation (F508del) causes the majority of cases, an HCM “hot spot” does not exist.29 New mutations are continually discovered, and many families with HCM will have personal disease-causing mutations. This profound heterogeneity is underscored in the present study, in which fewer than 2% of 293 patients possessed 1 of these 8 benign mutations. Within this entire HCM cohort, ~35% would be considered to have a benign clinical phenotype thus far (ie, no symptoms, no family history of HCM, and no family history of SCD). Yet, no patient within this benign subset was found to possess one of these benign mutations, which indicates that targeted screening for mutations based on phenotype may not be robust.

These factors hinder the future widespread application of an HCM gene chip. Present-generation diagnostic sequencing chips that host known mutations are technically feasible27 but potentially uninformative for the next family with HCM. A diagnostic genetic test that can comprehensively screen the known HCM-causing genes without an a priori assumption of the mutation’s location is required but is not yet available. Thus, in addition to the complexities introduced by genotype-specific interactions with environmental influences and gene modifiers, significant technological challenges must be surmounted before routine HCM genotyping becomes a clinical reality.

Malignant Versus Benign Mutations

One of the purposes of the Human Genome Project is to enable translation of molecular revelations to the clinical setting for diseases such as HCM by establishing precise and accurate genotype/phenotype relationships. However, it appears that for every genotype/phenotype association, there is an exception. These exceptions constitute a major impediment to the use of routine genotyping alone as a clinical and prognostic tool for the individual patient within the general population.

Initially, these 8 particular mutations appeared to confer a benign clinical phenotype (ie, near-normal life expectancy) based on a limited number of families: 1 large family with G256E,12 1 family with F513C,10 4 families with V606M,13,14 1 family with R719Q,15 and 1 family with L908V19 in MYH7. The S179F-TNNT2 mutation has been reported in a single family,16 and 3 families were evaluated for the D175N-TPM1 mutation.17

Furthermore, several studies have cast doubt on the widespread applicability of these specific genotype-phenotype associations to other families. Previous studies associating the V606M mutation with a low risk of SCD nonetheless included individuals who experienced SCD or premature death.13,14 In a larger kindred family study, 8 people were affected in 1 family, 4 of whom died of SCD.12 A more recent study has provided additional examples of V606M associated with a high risk of SCD at a young age, which hinders the interpretation of V606M as a benign mutation.18 In the present study, none of the 293 patients possessed this particular mutation.

The R719Q-MYH7 mutation represents a distinct missense mutation that occurs at the same codon as a previously ascribed malignant mutation, R719W, which has been reported with a high incidence of premature death through severe arrhythmia or SCD within 4 families.10,13 Previously, we failed to identify a single patient with R719W.28 In contrast to R719W, R719Q has been associated with near-normal survival.15 Nevertheless, the 2 patients found to possess this mutation in the present study have not experienced the natural history ascribed to this mutation: one received an orthotopic heart transplant at the age of 16 years, and the other had a brother who died suddenly at the age of 12 years.

The L908V-MYH7 mutation has also been associated with a benign prognosis. However, even in the large kindred family study, there were reports of SCD.19 In the present study, SCD before age 20 years was encountered.

Mutation-Specific Prognostication

In the present study, genotype-guided prognostication would have been misleading. In fact, 3 of the 5 individuals with benign mutations had family members who succumbed to SCD, and 2 individuals had a family history of SCD before age 20 years. Moreover, the 5 patients found to possess 1 of these benign mutations have not experienced a favorable clinical course. Rather, all 5 patients have required a surgical myectomy, including 1 adolescent female who received an orthotopic heart transplant at 16 years of age for end-stage heart failure. Holistically, these observations weaken the premise that clinical severity and risk for SCD can be associated with any certain mutation. We do not yet have a sufficient understanding of the complex disease entity or
entities comprising the diagnosis of HCM necessary to
determine which mutation, combinations of mutations, or
combinations of mutations and environmental factors portend
either an ominous or a favorable clinical outcome.

**Study Limitations**

Because they were associated with a tertiary referral center
known for expertise with myectomy, the present cohort may
not be representative of all patients with HCM. Compared
with a cohort of 744 patients seen in 3 regional centers, the
age at initial evaluation and left ventricular wall thickness are
not significantly different. However, the present cohort has a
larger representation of patients with outflow tract obstruc-
tion (53% versus 22% in regional centers) and myectomy
(28% versus 5% in regional centers). 

It is possible that the mutations not detected in the present
cohort were missed by DHPLC. However, this is most
unlikely. For each of the MYH7 and TPM1 amplicons
analyzed, other mutations were identified (unpublished data),
which demonstrates the sensitivity of DHPLC to detect
variants in these fragments. No mutations were found in
TTNT2 exon 11, but the D175N-TTNT2 mutation has been
reported in only 1 family, which indicates its rarity.

Importantly, previous studies assigned a mutation as be-
ign on the basis of survival curves that indicated near-
normal life expectancy for mutation-positive family mem-
bers. However, the focus of the HCM clinic, the clinical
database, and the genomics program at our institution is
on the individual patient and translation of pathogenomic
information to clinical practice. As such, the clinical database
does not contain expansive pedigree data, which precludes
generation of Kaplan-Meier survival curves for the families
represented by the 5 individuals who harbor benign muta-
tions. Nevertheless, documentation of a benign mutation in
only 5 of 293 unrelated patients, an orthotopic transplant in 1
patient, SCD in another’s 12-year-old brother and 46-year-old
father, and SCD in 2 nephews, aged 16 and 18 years, of a
third individual succinctly underscore the present-day chal-
lenges and limitations to translating the pathogenomics of
HCM to clinical practice for risk stratification.

Finally, the present study did not address the frequency of
mutations in the gene encoding myosin binding protein C
(MYBPC3), a gene associated with a benign course and
delayed onset of hypertrophy. The present study focused on
the prevalence and associated phenotype of specific muta-
tions ascribed as benign, rather than comprehensive muta-
tional analysis of an entire gene. Future studies involving a
comprehensive analysis of MYBPC3 should confirm whether
its present status as a benign HCM gene is maintained after
examination of this large referral population of HCM.

**Conclusions**

Yesterday’s discoveries regarding the molecular basis for
HCM, combined with new insights from genotype-phenotype
correlative studies, have provided a framework for tomor-
row’s improved understanding of the exact mechanisms that
mitigate hypertrophy and SCD. Although it has been sug-
gested that routine screening will identify those individuals
who harbor malignant and benign mutations, our evaluation
of a tertiary referral population of individual patients with
HCM suggests that such a targeted screen will elucidate very
few cases.

Currently, prognostication based solely on genotype may
be premature and inappropriate. Informing a patient that they
have a benign or malignant mutation has profound clinical
implications. Therapy, particularly prophylactic therapy with
an implantable cardioverter-defibrillator, should not be dic-
tated for the individual patient based on their specific genetic
substrate. Nonetheless, genotyping undoubtedly will play a
critical role in identifying family members who harbor a
sarcomeric perturbation but have not yet manifested any signs
or symptoms indicative of HCM.

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