Cardiac Myosin Binding Protein-C Mutations in Families With Hypertrophic Cardiomyopathy
Disease Expression in Relation to Age, Gender, and Long Term Outcome

Stephen P. Page, MD, MRCP; Stavros Kounas, MD; Petros Syrris, PhD; Michael Christiansen, MD; Rune Frank-Hansen, PhD; Paal Skytt Andersen, PhD; Perry M. Elliott, MD, FRCP; William J. McKenna, MD, FRCP

Background—Small selected cohort studies suggest that mutations in the cardiac myosin binding protein-C (MYBPC3) gene cause late-onset, clinically benign hypertrophic cardiomyopathy (HCM). The aim of this study was to test this hypothesis in a large series of families with HCM associated with MYBPC3 mutations.

Methods and Results—The initial study population comprised 57 probands with 42 mutations (26 [61.9%] novel) in MYBPC3. Missense mutations (15, 45.6%) were the most frequent, and multiple mutations occurred in 4 (7.0%) probands. Another 110 mutation carriers were identified during familial evaluation; 38 were clinically affected with left ventricular hypertrophy/H1135013 mm. Disease penetrance was, therefore, incomplete (56.9% in all mutation carriers, 34.5% in relatives), related to age (38.4%/H1102140 versus 68.6%/H1135040 years, P/110001), and was greater in males than females (65.1% versus 48.1%, P/110005). In 9 families (25 individuals) with the R502W mutation, there was marked heterogeneity in age at diagnosis (5 to 80 years), pattern of hypertrophy (11 none, 9 asymmetrical, 3 concentric, 1 apical, 1 eccentric), and prognosis (premature sudden death in 2 individuals compared with survival to advanced age in 6 individuals). During follow up of 7.9+/−4.5 years, in 82 clinically affected individuals the annual risk of sudden death and all cause mortality was 0.46% and 0.93% per year, respectively.

Conclusions—Disease expression in families with HCM related to MYBPC3 mutations shows marked heterogeneity with incomplete, age-related, and gender specific penetrance. Importantly, complex genetic status is observed and should be considered when mutation analysis and cascade screening is used in the evaluation of at risk family members. (Circ Cardiovasc Genet. 2012;5:156-166.)

Key Words: hypertrophic cardiomyopathy ■ penetrance ■ genetic heart disease ■ disease expression ■ MYBPC3

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease, with an estimated prevalence of 1 in 500.1 It is inherited as an autosomal dominant trait caused by mutations in cardiac sarcomeric protein genes2 in approximately 60%/3,4 of affected individuals. The most frequent gene to be implicated is cardiac myosin binding protein-C (MYBPC3).3,5,6

Clinical Perspective on p 166

HCM is typified by marked variation in clinical phenotype. Small studies specifically examining individuals or families with MYBPC3 mutations suggest that disease onset occurs later in life and has a more benign prognosis in comparison with that associated with mutations in other sarcomeric protein genes, such as β-myosin heavy chain (MYH7) and troponin T.7,8 Such data have been used to support long-term periodic screening in unaffected adult family members to identify those with late onset disease.9 Early studies, however, often were based on highly selected large families with relatively few mutations and may not accurately reflect disease expression in the broader population of families with MYBPC3 mutations. Developments in genomics technology, such as intronic sequencing, also may yield pathogenic mutations not identified using previous techniques.10 Accurate clinical and longitudinal follow up data are also lacking in this subset of patients with HCM.

The primary aim of this study was to determine clinical disease expression, penetrance, and outcomes in a large cohort of patients and relatives with mutations in MYBPC3.

Methods

The study was approved by the local research ethical committee and informed written consent was obtained from all participants.

The study cohort consisted of 585 consecutive, unrelated individuals fulfilling diagnostic criteria for HCM referred to a dedicated...
cardiomyopathy clinic at St. George’s Hospital (London, United Kingdom) over a 10-year period. HCM was defined in probands as unexplained left ventricular hypertrophy (maximum left ventricular wall thickness ≥13 mm or >2 standard deviations corrected for body surface area in children). Relatives also were considered to be affected if they fulfilled diagnostic criteria within the context of familial HCM.11,12

Clinical Evaluation
At the time of the initial assessment and subsequent clinic visits probands underwent full clinical evaluation with physical examination, 12-lead ECG, transthoracic echocardiography using a dedicated protocol combining 2-D imaging and Doppler studies, 24-hour ambulatory ECG monitoring, and exercise stress testing using a bicycle ramp protocol with respiratory gas exchange measurements.

Twelve-lead ECGs were analyzed by 1 observer (S.P.) for the following: abnormal Q waves (duration ≥40 ms and voltage greater than one third of the ensuing R wave) and presence of T wave inversion, and a Romhilt Estes score was calculated for each patient.13

Nonsustained ventricular tachycardia (NSVT) during ambulatory ECG monitoring was defined as 3 or more ventricular premature complexes at a rate of ≥120 bpm. Unless otherwise stated, disease penetrance was defined as the proportion of mutation carriers with echocardiographic left ventricular hypertrophy >13 mm (or >2 standard deviations corrected for body surface area in children). However, to determine the relationship between ECG and echocardiographic abnormalities, disease penetrance (where stated) also was evaluated in relation to unexplained ECG abnormalities (Romhilt Estes score ≥4, abnormal T wave inversion, or abnormal Q waves). Longitudinal follow up was defined as 2 or more clinical evaluations at least 12 months apart.

Relatives underwent clinical evaluation with physical examination, ECG, and transthoracic echocardiography, irrespective of genotype.

Genetic Evaluation
Blood was drawn for mutation analysis from HCM patients and family members, and DNA was extracted from peripheral blood leukocytes using standard methods. The following genes were screened for sequence variations in the probands: MYBPC3, MYH7, troponin T, troponin I, essential and regulatory light chains, α-tropomyosin, and alpha cardiac actin using fluorescent SSCP, and direct sequencing as previously described.14,15 If clinically suspected, α-galactosidase and AMP-kinase also were sequenced. All exons and flanking intronic sequences were analyzed for sequence variations. Sequence variants were considered to be disease causing if 1 or more of the following applied: (1) the sequence variant was present in all relatives with disease, (2) the sequence variation was not identified in 200 matched control alleles, (3) the mutation occurred in a highly conserved region of DNA (for missense mutations), and (4) the sequence variation was predicted to result in an abnormal protein. In relatives, only the mutation identified in the proband was screened for unless otherwise stated. The potential effect of the certain mutations (Table 1) was evaluated by calculating Shapiro–Senapathy splice site scores. Neural network predictions of splice sites were performed using NetGene2 and Alternative Splice Site Predictor.

Statistical Analysis
Data are presented as mean±SD and range where appropriate. Normally distributed continuous data were compared with paired and unpaired 2-tailed student t tests. Multiple groups were compared using ANOVA. Noncontinuous variables were compared using Chi-squared test. Probability values of <0.05 were considered statistically significant.

Results
Mutation Spectrum
Mutation analysis of 585 consecutive, unrelated probands with HCM identified 54 sequence variations in MYBPC3 in 69 families. Of these, 11 had not been reported before and were excluded from further analysis as the sequence variation either did not cosegregate with disease or it was of uncertain biological significance. One further proband was found to have both the MYBPC3 G148R variant and the α-galactosidase N215S variant associated with an overlap phenotype between HCM and Anderson Fabry disease. This family was excluded from further analysis, leaving a total of 42 putative pathogenic mutations identified in 57 probands (9.7% of the total cohort).

Of the 42 pathogenic mutations, 26 were novel (61.9%). The spectrum of identified sequence variants is shown in Table 1. In the 57 probands, mutation types were as follows: missense in 26 (45.6%), insertions/deletions in 11 (19.3%), intronic in 11 (19.3%), nonsense in 5 (8.8%), and complex genetic status in 4 (7.0%). Of the 4 probands with complex genetic status, 2 were compound heterozygotes and 2 double heterozygotes. Importantly, in 1 family with the R502W variant (which is an established disease causing mutation,16,17 2 asymptomatic relatives were found to be affected but did not carry the family mutation (both were cousins of the proband; their mother was the maternal aunt of the proband). One (54-year- old male) had a Romhilt Estes score of 6, 14 mm of asymmetrical septal hypertrophy, and no history of hypertension. The second individual (a 51-year-old hypertensive male) had a Romhilt Estes score of 12 and 20 mm of asymmetrical septal hypertrophy. Further sarcomeric protein gene analysis in these individuals did not identify a different mutation. Further sarcomeric protein gene mutation analysis in these individuals did not identify an additional mutation.

Clinical Characteristics of Probands
Thirty-four of 57 probands were male (59.6%). Mean age at diagnosis was 39.7±16.1 years, range 5 to 76. The reasons for diagnosis were: symptoms 30 (52.6%), incidental finding 16 (28.0%), family screening 10 (17.5%), and in 1 individual (1.8%) the diagnosis was made at autopsy following sudden cardiac death. Fifty-three of 57 probands (92.9%) were of white European ethnic origin, 2 (3.4%) were black, and 2 (3.5%) were Asian. Fifty-three of 57 probands were in sinus rhythm at diagnosis (93.0%), with 2 (3.5%) in atrial fibrillation, 1 in a paced rhythm, and 1 unknown (presented with sudden cardiac death). NSVT on 24 hour ECG monitoring was present in 13 (22.8%) individuals. Thirty-five (61.4%) had left atrial enlargement on ECG, 2 (3.5%) had right bundle branch block, and 39 (68.4%) had a Romhilt Estes score ≥4.

Most individuals had asymmetrical septal hypertrophy (86.0%) but other patterns of hypertrophy were observed including concentric (5.3%), eccentric (5.3%), apical (1.8%), and 1 (1.8%) undetermined (presented with sudden cardiac death). One female (28 years old at diagnosis) had progressive wall thinning and predominant restrictive physiology requiring cardiac transplantation age 43. A resting left ventricular outflow tract obstruction (peak gradient ≥30 mm Hg) was seen in 17 (29.8%) individuals. Both age at diagnosis and maximal wall thickness were similar comparing missense, insertion/deletion, nonsense, and intronic mutations (p=NS); those with complex genetic status were not more severely affected, although because of the small number of individuals...
<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Mutation Description</th>
<th>Novel</th>
<th>Reference</th>
<th>Total No. of Affected Individuals</th>
<th>Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsense (4 mutations in 5 families)</td>
<td>Q425X</td>
<td>No</td>
<td>†</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R943X</td>
<td>No</td>
<td>‡</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O969X §</td>
<td>No</td>
<td>II</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>K1055X</td>
<td>Yes</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Deletions/insertions (10 in 11 families)</td>
<td>g7040_7041delTT</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g14274delC</td>
<td>No</td>
<td>**</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g14291insA</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g1591insG</td>
<td>No</td>
<td>**</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g16190_16196delGGGCTA</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g16225delG</td>
<td>Yes</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g18567delCT</td>
<td>No</td>
<td>**</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>g20350insT §</td>
<td>Yes</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Missense (15 in 26 families)</td>
<td>G148R</td>
<td>No</td>
<td>††</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E258K §</td>
<td>No</td>
<td>**</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G341R</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G490R</td>
<td>No</td>
<td>†</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R495G§</td>
<td>No</td>
<td>‡‡</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R502W§</td>
<td>No</td>
<td>§§§</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R502Q§</td>
<td>No</td>
<td>**</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E542Q</td>
<td>No</td>
<td>II</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D605N</td>
<td>No</td>
<td>†</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T750 mol/L</td>
<td>Yes</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R820Q</td>
<td>No</td>
<td>***</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P873Q</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T957S</td>
<td>No</td>
<td>†††</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F1177L</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C1266Y</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intronic (9 in 11 families)</td>
<td>IVS1–2A&gt;G</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td>In silico analysis</td>
</tr>
<tr>
<td></td>
<td>IVS7 + 1G&gt;A</td>
<td>No</td>
<td>†††</td>
<td>1</td>
<td>In silico analysis</td>
</tr>
<tr>
<td></td>
<td>IVS9–36G&gt;A</td>
<td>No</td>
<td>§§§</td>
<td>1</td>
<td>RNA analysis</td>
</tr>
<tr>
<td></td>
<td>IVS13–23G&gt;A§</td>
<td>No</td>
<td>§§§</td>
<td>4</td>
<td>RNA analysis</td>
</tr>
<tr>
<td></td>
<td>IVS13–2A&gt;G</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td>RNA analysis</td>
</tr>
<tr>
<td></td>
<td>IVS14–13G&gt;A§</td>
<td>Yes</td>
<td></td>
<td>2</td>
<td>RNA analysis</td>
</tr>
<tr>
<td></td>
<td>IVS17 + 4A&gt;T</td>
<td>No</td>
<td>II II</td>
<td>3</td>
<td>RNA analysis</td>
</tr>
<tr>
<td></td>
<td>IVS20–2A&gt;G</td>
<td>No</td>
<td>§§§</td>
<td>3</td>
<td>RNA analysis</td>
</tr>
<tr>
<td></td>
<td>IVS27 + 16G&gt;A</td>
<td>No</td>
<td>††</td>
<td>1</td>
<td>In silico analysis</td>
</tr>
<tr>
<td>Complex genetic status (4 in 4 families)</td>
<td>MYBPC3 IVS14–13G&gt;A§ and MYH7 T1854 mol/L</td>
<td>No</td>
<td></td>
<td>2</td>
<td>In silico analysis</td>
</tr>
<tr>
<td></td>
<td>MYBPC3 R502W § and MYH7 N602S</td>
<td>No</td>
<td>****</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>††††</td>
<td>(Continued)</td>
<td></td>
</tr>
</tbody>
</table>
with complex genetic status, this study is limited in its ability to draw strong conclusions about phenotype in this subgroup.

### Disease Penetration

In addition to the 57 probands, familial evaluation identified a further 110 mutation carriers and 118 relatives in whom the family mutation was absent. Of the 167 mutation carriers, at the last clinical evaluation 95 fulfilled diagnostic criteria for HCM, whereas 72 were unaffected. Disease penetrance in all mutation carriers was 56.9%, and 34.5% in relatives undergoing familial evaluation. Disease penetrance increased with age until the 6th decade (Figure 1). Disease penetrance at first assessment was 38.4% in those aged <40 years and 68.6% in those aged ≥40 (P=0.001). Disease penetrance reached a plateau by the 6th decade, and was 30.0% in 10 mutation carriers aged ≥70 years. Of the 7 unaffected mutation carriers aged ≥70 years the spectrum of mutations was as follows: 1 nonsense, 1 deletion, 3 missense, 1 intronic, and 1 compound heterozygote. Among mutation carrying relatives, an abnormal ECG was more common than left ventricular hypertrophy >13 mm, and therefore defining disease penetrance among relatives by ECG criteria (defined as either Romhilt Estes score >4, abnormal T wave inversion, or abnormal Q waves) was more sensitive than criteria based on echocardiography alone (Figure 2).

During familial evaluation, the genotype and phenotype of the proband’s parents was identified in 19 families. Two of 5 (40%) mutation carrier fathers were unaffected, while 5 of 13 (39%) mutation carrier mothers were unaffected (P=0.95). The clinical characteristics of the families in whom the parent was an unaffected mutation carrier are shown in Table 2.

Six of 57 probands (10.5%) and 8 of 95 affected relatives (8.4%) were diagnosed before the age of 20 years (Figure 3). When affected individuals were grouped into early diagnosis (<40 years) and late diagnosis (≥40 years) there were

### Table 1. Continued

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Mutation Description</th>
<th>Novel</th>
<th>Reference</th>
<th>Total No. of Affected Individuals</th>
<th>Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYBPC3 G490R and MYBPC3 Q642X</td>
<td>No</td>
<td>†</td>
<td>1 (proband only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYBPC3 V1125 mol/L and MYBPC3 IVS9–1G:C</td>
<td>No</td>
<td>††††</td>
<td>2 (trans)</td>
<td>RNA analysis</td>
<td></td>
</tr>
</tbody>
</table>

*All listed mutations were not found in 384 UK controls, or 200 Danish controls.
§Mutation found in more than 1 family.
no apparent important clinical differences in terms of septal thickness, maximal wall thickness, left ventricular (LV) cavity size, percent symptomatic (Table 3), or prevalence of confirmed familial disease (defined as at least 1 other affected relative; 76.7% versus 67.3%, \( P = 0.3 \)). However, the percent predicted VO\(_2\) was greater in those diagnosed before 40 years of age (81.9 \( \pm \) 24.0 versus 68.4 \( \pm \) 16.2, \( P = 0.021 \)).

Of 167 mutation carriers, 86 (51.5%) were male and 81 (48.5%) were female. Disease penetrance, however, was higher in males than in females (65.1% versus 48.1%, \( P = 0.03 \)) despite a similar age at evaluation (39 \( \pm \) 16 versus 43 \( \pm \) 20 years, \( P = 0.08 \)). Disease penetrance was also higher in males than females (47.4% versus 27.6%, \( P = 0.03 \)) when considering only those identified during familial evaluation. Mean age at diagnosis in affected individuals was no different between males and females (40.4 \( \pm \) 15.4 years versus 43.3 \( \pm \) 17.3, \( P = 0.44 \)). Affected male mutation carriers had greater left atrial diameter (42.8 \( \pm \) 7.4 versus 39.6 \( \pm \) 6.8 mm, \( P = 0.04 \)) and greater LV cavity dimensions (left ventricular end-diastolic diameter 45.4 \( \pm \) 6.5 versus 41.4 \( \pm \) 6.0 mm, \( P = 0.005 \), left ventricular end-systolic diameter 27.8 \( \pm \) 6.5 versus 23.4 \( \pm \) 9.4 mm, \( P = 0.002 \)), but similar degrees of ventricular hypertrophy (septal thickness 18.4 \( \pm \) 5.5 versus 17.1 \( \pm \) 5.3 mm, \( P = 0.28 \), maximal wall thickness 19.1 \( \pm \) 5.4 versus 17.9 \( \pm \) 5.8 mm, \( P = 0.34 \); Table 4). The differences in left ventricular end-diastolic diameter between males and females remained when measurements were adjusted for body surface area (\( P = 0.02 \)), but not LVESD (\( P = 0.9 \)). The proportion of individuals who were symptomatic was similar between the males and females, but males have better exercise capacity (percent predicted VO\(_2\): 80.9 \( \pm \) 24.5 versus 68.6 \( \pm \) 14.7, \( P = 0.038 \)).

**Families Sharing the Same Mutation**

Eight different mutations were identified in 2 or more families, affording the opportunity to compare families with an identical genotype.

Of particular interest was the finding of the previously reported\(^3,16,17\) R502W mutation in 9 apparently unrelated families. All of these families were Caucasian and haplotype analysis identified a common founder effect in these families. Of 25 mutation carriers, 12 fulfilled diagnostic criteria for HCM, while 13 were unaffected. Overall disease penetrance was 48%. In 1 family all 3 mutation carriers were clinically affected (100% penetrant), whereas in 3 other families with at least 2 adult mutation carriers the penetrance was incomplete. Three patients were diagnosed incidentally, 4 presented with symptoms, and 1 was diagnosed at family screening following the sudden death of a child. Age at diagnosis was markedly different between the families, with 1 boy presenting at age 5 with breathlessness, and 1 woman presenting at age 80 with an abnormal ECG (Figure 4).
mutation carriers, pattern and extent of hypertrophy varied: 10 (40%) had no hypertrophy, 10 (40%) had asymmetrical septal hypertrophy, 3 (12%) were concentric, 1 (4%) was apical, and 1 (4%) was eccentric. Prognosis varied between families with multiple premature sudden cardiac deaths occurring in 2 families, and a more benign prognosis in 7 families.

Two families shared a similar missense mutation at the same locus, the previously reported R502Q mutation. Over-all, 15 mutation carriers were identified, of which 7 were affected (disease penetrance = 47%). The proband of 1 family was diagnosed incidentally at age 14. Investigations showed severe septal hypertrophy (37 mm) but the patient, now aged 23, remains asymptomatic. His sister is a gene carrier with an asymptomatic septal hypertrophy (37 mm) but the patient, now aged 23, remains asymptomatic. Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an 81-year-old male with mild concentric hypertrophy), and 2 did not fulfill diagnostic criteria (53-year-old female with abnormal ECG and normal echo and a 23-year-old female with normal ECG and echo). There were no premature sudden deaths or strokes in this family. In contrast in another family sharing the same mutation, 8 adult mutation carriers were identified during family screening following the sudden death of a 16-year-old girl. Of these, 3 were clinically affected: the 51-year-old male with dilated-phase HCM and heart failure, the 14-year-old asymptomatic female with apical hypertrophy, and the 54-year-old male with mild septal hypertrophy, maximal wall thickness 24 mm) and is asymptomatic.

Two families shared a similar missense mutation at the same locus, the previously reported R502Q mutation. Overall, 15 mutation carriers were identified, of which 7 were affected (disease penetrance = 47%). The proband of 1 family was diagnosed incidentally at age 14. Investigations showed severe septal hypertrophy (37 mm) but the patient, now aged 23, remains asymptomatic. His sister is a gene carrier with an abnormal ECG but has shown no evidence of hypertrophy on echo during 17 years of follow up. Their father was diagnosed with HCM during familial evaluation (asymmetrical septal hypertrophy, maximal wall thickness 24 mm) and is asymptomatic. Four other family members were found to be mutation carriers. Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo). Two of these fulfilled diagnostic criteria for HCM (45-year-old male with mild septal hypertrophy and an asymptomatic 72-year-old male, normal ECG and echo).
hypertrophy who died of a hemorrhagic stroke at age 64. The other 4 had a normal ECG and echo during 18 years of follow up (now aged 57, 39, 37, and 34).

Two families shared the Q969X mutation, totaling 9 individuals of which 7 were clinically affected (disease penetrance 78%). One of these families was characterized by a benign phenotype with no sudden cardiac death observed. In contrast, the other Q969X family was characterized by high disease penetrance and multiple sudden cardiac deaths. The proband presented at age 29 with breathlessness and was found to have asymmetric septal hypertrophy. His mother was affected with a mild phenotype, but 2 of her siblings died subsequently at a young age and a further sibling survived a cardiac arrest and underwent implantable cardioverter-defibrillator (ICD) implantation. Three other siblings were clinically affected with a variable phenotype (a 51-year-old male with asymmetrical septal hypertroph and a 46-year-old female with advanced heart failure, previous stroke, and atrial fibrillation). In contrast, the youngest sibling was also a mutation carrier, but was asymptomatic and had a normal ECG and echo.

Two families shared the E258K mutation (3 of 4 mutation carriers affected, penetrance 75%). A 48-year-old woman was found to have asymmetrical septal hypertrophy during familial evaluation following the sudden death of her 19-year-old son (genotype unknown). No other mutation carriers were identified in this family. In the other family, the proband was diagnosed at 16 years of age, having been found to have an incidental murmur. His mother died suddenly awaiting cardiac transplantation for severe left ventricular hypertrophy and restrictive physiology. His sister was also a mutation carrier and had an abnormal ECG but no hypertrophy on transthoracic echo.

Three families shared the IVS13–23G>A mutation (4 of 6 mutation carriers were affected, penetrance 67%). In 1 Asian family the proband presented aged 43 years old with chest pain and was found to have asymmetrical septal hypertrophy. In a Caucasian family the proband presented aged 25 years with obstructive asymmetrical septal hypertrophy and subsequently underwent surgical myomectomy. Three other mutation carriers were identified in this family, 1 of whom had asymmetrical septal hypertrophy without obstruction. In the third family the proband presented at age 15 with syncope and had asymmetrical septal hypertrophy.

The IVS14–13G>A mutation was found in 1 family as a single variant. The index case died suddenly while exercising at age 32 years in the context of nonobstructive asymmetric septal hypertrophy, previous syncope, and NSVT on ambulatory ECG monitoring. Her mother was also affected. Her brother (32 years old) was a mutation carrier with a borderline phenotype (maximal wall thickness of 12 mm). In another family the same mutation was seen in combination with a missense mutation in MYH7. Both affected individuals in this family carried both mutations. Two families shared the R495G mutation (disease was fully penetrant in the 3 mutation carriers). The index case of 1 family presented at age 67 years with atrial arrhythmias and heart failure in the context of dilated-phase HCM. In the other family a 26-year-old male with asymmetrical septal hypertroph and a 46-year-old female with advanced heart failure, previous stroke, and atrial fibrillation). In contrast, the youngest sibling was also a mutation carrier, but was asymptomatic and had a normal ECG and echo.

Longitudinal Follow-Up Data
Longitudinal follow up data were available for 82 mutation carriers (56 probands, 26 relatives). Of these, 65 were

---

**Table 4. Gender Differences in 95 Affected Mutation Carriers**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>56</td>
<td>39</td>
<td>...</td>
</tr>
<tr>
<td>Age at diagnosis (affected only, y)</td>
<td>40.4+/−15.4</td>
<td>43.0+/−17.3</td>
<td>0.44</td>
</tr>
<tr>
<td>% symptomatic</td>
<td>53.8%</td>
<td>67.6%</td>
<td>0.20</td>
</tr>
<tr>
<td>% predicted VO2</td>
<td>80.9+/−24.5</td>
<td>68.6+/−14.7</td>
<td>0.04</td>
</tr>
</tbody>
</table>

LA indicates left atrial; LVEDD, left ventricular end-diastolic diameter; LVESP, left ventricular end-systolic diameter; and FS, fractional shortening.

---

**Figure 4.** Age at diagnosis in affected individuals with the R502W mutation. Bars represent number of individuals in each age group.
clinically affected at baseline (mean age 36.8 +/- 16.4 years, range 5–76). Mean duration of follow up was 7.9±4.5 years (range 1–19). Overall survival was 94.0%: there were 5 deaths (3 sudden, 1 heart failure, 1 stroke), 1 underwent cardiac transplantation, and 1 was lost to follow up. The overall annual mortality rate was, therefore, 0.93%, with an annual sudden death rate of 0.46%. The 3 individuals who died suddenly were a 32-year-old woman with 2 risk factors (syncope and NSVT) who died suddenly during exertion, a 58-year-old symptomatic man with 2 risk factors (abnormal blood pressure response and family history of sudden cardiac death) who died suddenly at rest, and a 31-year-old symptomatic man with a single risk factor (NSVT) who died suddenly during exertion.

The proportion of patients who were symptomatic was no different at baseline compared with follow up (65.5% and 64.6%); 3 underwent alcohol septal ablation and 2 had surgical myomectomy for symptomatic outflow tract obstruction, while 13 individuals received an ICD (11 prophylactic, 2 following cardiac arrest). No appropriate ICD therapies (either antitachycardia pacing or direct current shock therapy) were detected in 3.0 years (range 1–6). There were 5 strokes (1 fatal, annual risk of stroke 0.77%). Arrhythmias were common, however, with 28.0% of individuals having documented NSVT on ambulatory ECG monitoring and 17.0% developing at least 1 episode of paroxysmal atrial fibrillation during follow up. Table 5 shows echocardiographic data for affected individuals at baseline and at follow up. Table 5 shows echocardiographic data for affected individuals at baseline and at follow up. Longitudinal follow up was associated with a reduction in septal thickness (15.1 versus 16.3 mm, P=0.04), increased LV end-systolic diameter (28.7 versus 25.7 mm, P=0.001), reduced fractional shortening (36.9% versus 41.6%, P=0.001), and increase in left atrial diameter (42.6 versus 39.9 mm, P=0.001). Clinical symptoms of heart failure developed in 11.0% of individuals during follow up and dilated-phase HCM (defined as left ventricular end-diastolic diameter >55 mm and fractional shortening <25%) occurred in 2 individuals (2.4%).

Seventeen individuals who were clinically unaffected at baseline were followed up for a mean 9.4±7.1 years (range 1–18). Mean age at baseline was 25.0±14.3 years (range 10–53) and 33.1+/− 14.8 years (range 11–66) at second evaluation. Of these 17 individuals, 3 (17.6%) developed ventricular hypertrophy during follow up. Two of the 3 developed evidence of disease expression at ages 13 and 14. The third individual (from a large family with a deletion mutation [g14274delC] with multiple affected family members) was first evaluated at age 39 and found to have a normal ECG and echo. He was subsequently diagnosed with HCM during a routine health check at the age of 53 on the basis of T wave inversion in the anterior chest leads and asymmetrical septal hypertrophy on transthoracic echocardiography (maximal wall thickness 15 mm). He had not been evaluated in the interim period so it is not known more precisely at what age hypertrophy developed. There was no history of hypertension or athletic training and he remains asymptomatic.

**Discussion**

This study presents data on penetrance, disease expression, and outcome in a large cohort of families with HCM associated with mutations in MYBPC3. The major findings were (1) clinical disease expression is heterogeneous and unrelated to mutation type or specific mutation, (2) disease penetrance is incomplete throughout life, (3) disease penetrance is higher in males than females, (4) development of hypertrophy in adulthood is infrequent, and (5) from long term serial assessment, symptoms and non life-threatening arrhythmias are common, but the occurrence of major complications is relatively low.

The broad spectrum of clinical disease expression seen in individuals and families with HCM is well established. Early studies attempted to explain this phenotypic diversity in terms of gene-specific or mutation-specific correlates, leading to suggestions that mutations in MYBPC3 cause a more benign, late-onset form of the disease. Such data led to recommendations for screening unaffected mutation carriers throughout adult life, and a perception that families with MYBPC3 mutations can be reassured that their prognosis is relatively favorable. The results of our study do not support these recommendations. Clinical disease expression among families with MYBPC3 mutations was heterogeneous, with first diagnosis throughout life from the first to the ninth decades. Prognosis ranged from sudden death in childhood to symptom free survival to advanced age, and all patterns of hypertrophy were observed, including severe obstructive asymmetrical septal hypertrophy, apical, concentric, and biventricular hypertrophy with midcavity obstruction, dilated-phase HCM, and HCM with restrictive physiology. Neither mutation type (eg, nonsense, missense, etc) nor specific mutation appeared to manifest a particular phenotype, with marked phenotypic diversity seen in families sharing identical mutations. Furthermore, there were no differences in terms of age at diagnosis and maximal wall thickness comparing different mutation types. In addition, age at diagnosis, cardiac morphology, and prognosis were heterogeneous, both within and between families sharing an identical mutation. The finding of 9 families sharing the previously reported mutation (R502W) was unexpected, and haplotype analysis confirmed a common founder, the first described in a United Kingdom cohort. A recent report confirms the pathogenicity...
of R502W sequence variation, being found in 2.4% of apparently unrelated probands of European descent.\(^1\) Identifying families sharing an identical mutation allows a unique opportunity to observe phenotypic disease expression having controlled for genetic heterogeneity. In our cohort we observed a broad spectrum of clinical disease with no specific phenotype apparent. Disease penetrance was only 48%, all morphological variants of cardiac hypertrophy were observed in these patients, and disease was diagnosed over a broad age range (5–80 years). That disease expression can vary to such a degree among mutation carriers confirms that disease modifying factors are very powerful and exert as much of an effect on disease expression as the mutation itself.

Although early reports suggested that HCM commonly develops in adolescence and early adulthood,\(^2\) over 90% of individuals in this study were diagnosed after the age of 20 years. However, age at diagnosis and the age at which clinical disease becomes apparent are not equivalent. During follow up of 7 years, only 1 of 15 adult unaffected mutation carriers developed left ventricular hypertrophy. Reports of late onset disease in the literature are rare and limited to a small number of individuals with serial clinical evaluation.\(^3\)\(^,\)\(^4\) In our study, of the 15 adults who were clinically unaffected at baseline, only 1 developed left ventricular hypertrophy during an average of over 9 years of longitudinal follow up. Therefore, recommendations for the serial clinical evaluation of unaffected relatives throughout adulthood\(^5\) may be premature. It is anticipated that only a small number of unaffected relatives will develop clinical disease during adulthood, and a significant proportion of those who do are likely to develop symptoms and be identified accordingly.

Consistent with previously published data,\(^5\)\(^,\)\(^7\)\(^,\)\(^8\) this study demonstrated incomplete penetrance in the overall cohort (56.9%) and a penetrance of 34.5% among relatives. The low penetrance in relatives is particularly relevant for counseling during familial evaluation. However, in contrast to previous cross sectional studies demonstrating a linear relationship between penetrance and age to advanced age,\(^7\) this study demonstrated that disease penetrance remains incomplete into the later decades, implying that disease development among mutation carriers is not inevitable (perhaps due to reduced survival in affected individuals), an important message when counseling family members at risk. It is likely that this reduced penetrance in the elderly reflects the large number of mutations and families in our cohort in contrast to previous studies.\(^7\)\(^,\)\(^8\) These data are cross-sectional, however, and only long term longitudinal studies of large cohorts will define accurately the lifetime risk of developing clinical disease. The cross-sectional nature of these data also explains the apparent “fall” in disease penetrance seen in those ages 6 to 60 and 70+, which may simply reflect reduced survival in affected younger groups. It is also of interest that no important differences existed between those diagnosed early in life (<40 years) to those diagnosed late (≥40 years) in terms of gender, prevalence of symptoms at diagnosis, magnitude of hypertrophy, and left ventricular systolic function, suggesting that disease expression represents a continuum rather than consisting of discrete forms of the disease. Indeed, when clinical disease was compared using a range of cut offs for late diagnosis (≥30 years, ≥50 years etc), these parameters remained similar. It is unclear, however, whether outcome varies according to the age that disease becomes apparent, and this study was unable to clarify this due to different follow up periods between those diagnosed early and late.

In this study disease penetrance before the age of 30 years was higher when defined by an otherwise unexplained abnormal ECG compared with conventional echocardiographic criteria (Figure 2). Although cross-sectional, these data highlight the importance of ECG abnormalities when evaluating at risk relatives and are most consistent with an early manifestation of disease expression predating the development of hypertrophy by echo. Such individuals, regardless of whether they represent early disease or incomplete disease expression, highlight the increasingly recognized phenomenon of abnormal ECG, normal echo in families with hypertrophic cardiomyopathy who are both at potential risk of disease complications, and transmission of disease to offspring.

Previously published cohorts of unselected probands with HCM consistently have reported a slight male predominance, with approximately 55% to 60% of affected individuals being male.\(^24\)\(^–\)\(^26\) However, as the condition is inherited in an autosomal dominant pattern, an equal ratio of males to females would be anticipated. A number of explanations for this discrepancy have been proposed, including reduced awareness among female patients, clinician bias, and genetic or hormonal modifying factors.\(^24\) Our study confirmed increased disease penetrance in males compared with females even when only considering those assessed during familial evaluation (therefore removing the possible effect of reduced awareness among female patients and clinician bias). These data, therefore, support the existence of biological gender specific factors that influence disease development, such as chromosomal or hormonal specific factors that may influence the pathogenesis of hypertrophy development such as those seen in experimental models.\(^27\) Modifier genes and gender specific single nucleotide polymorphisms also may play a role and represent a potential new target for investigation.\(^28\) Other environmental or behavioral factors (such as athletic training) also may be relevant. Additionally, in contrast to previous data in nongenotyped cohorts suggesting that females are older and more symptomatic at diagnosis,\(^24\)\(^–\)\(^26\) we observed a similar age at diagnosis and similar proportion symptomatic among male and female individuals in our cohorts.

Long term clinical data regarding MYBPC3 mutations are lacking in the literature. Progression to “end stage” HCM associated with LV cavity dilatation, systolic dysfunction, and heart failure (defined as left ventricular end-diastolic diameter >55 mm and fractional shortening <25%) was observed in 7 elderly Japanese individuals sharing the V592fs8 mutation\(^29\) and in 2 of 5 Japanese carriers of the R820Q mutation.\(^30\) This dilated phase phenotype was not observed in the 1 female patient with the same R820Q mutation in our cohort. Progression to “end stage” dilated phase HCM in our cohort (using the same criteria) occurred in 2 individuals (3.0%) with the R495G and R502Q mutations. The incidence of major complications was low in this
cohort (annual mortality risk 0.93%, sudden death 0.46%, and nonfatal stroke 0.77%), risks similar or less than those seen in much larger nongenotyped HCM cohorts.\textsuperscript{31,32} It is also important to note that the 3 individuals who died suddenly were all asymptomatic prior to their deaths and had at least 1 conventional risk factor for sudden cardiac death.\textsuperscript{25} In addition, of the 5 strokes, 2 occurred in individuals with persistent atrial fibrillation (both on warfarin) and 2 occurred in individuals in sinus rhythm with progressive LV dilatation and heart failure (not on warfarin). These data suggest that unheralded adverse events are uncommon in this patient population and a prior opportunity for intervention often exists. Careful, regular risk stratification for sudden death and stroke is therefore vital.

The majority of mutations identified were missense (44%) with insertions, deletions, and in intronic mutations accounting for a further 38%, broadly similar to previous mutation screening studies.\textsuperscript{3,5,6} In this study, however, there were a high proportion of families with complex genetic status (7%), a finding that has major implications for mutation identification strategies and the role of genetic predictive testing in clinical practice. Importantly, in 1 family with the R502W mutation, 2 affected individuals did not carry this mutation. This variant has been reported previously by several groups and is considered to be disease causing.\textsuperscript{17} In this family failure to combine clinical evaluation to complement genetic predictive testing would have resulted in these individuals remaining undiagnosed. We therefore suggest that in clinical practice, mutation detection strategies should be broad, inclusive, and should not be curtailed when 1 mutation has been identified, in contrast to a more targeted strategy proposed by others.\textsuperscript{33,34} At the very least, our data suggest that the 2 most common sarcomeric protein genes (MYBPC3 and MYH7) should be screened in all individuals. Moreover, in families undergoing genetic predictive testing, although uncommon, at risk individuals will occasionally be missed without complementary clinical evaluation. We therefore recommend that clinicians consider combined clinical and genetic evaluation, even in families in whom a disease causing mutation has been identified.

**Conclusion**

In summary, the spectrum of clinical disease expression seen in individuals and families with MYBPC3 mutations is broad and variable, with all patterns and degrees of hypertrophy observed. Gene-specific and mutation-specific data do not adequately explain the observed differences in phenotype or penetrance, and other genetic factors (such as modifier genes, additional mutations) and nongenetic factors (such as hormones and environmental factors) must be important. Given the phenotypic heterogeneity, it is difficult to define a clinically relevant specific phenotype to individuals or families with MYBPC3, and previous suggestions that disease is typically late onset and benign appear premature.\textsuperscript{7,8}

Clinicians should use existing summary genotype-phenotype data cautiously when counseling at risk family members, as the applicability of such data to an individual or a family is unclear and the role of genetic predictive testing remains uncertain.

**Sources of Funding**

Stephen Page was supported by the British Heart Foundation (FS/05/035). William McKenna was supported by the British Heart Foundation (Programme Grant RG/04/010). This work was undertaken at UCLH/UCL, who received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme.

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder, and cardiac myosin binding protein C (MYBPC3) mutations are found in approximately 15% to 30% of probands. This study characterizes the phenotype of a large cohort of individuals with a MYBPC3 mutation. It suggests that powerful disease modifying factors influence the development and severity of disease, as disease expression is highly variable both between and within families sharing the same mutation. It also demonstrates reduced disease expression in female mutation carriers, suggesting the potential influence of hormonal, genetic, and environmental factors. Similar to previous studies, disease penetrance is incomplete throughout life; however, the development of the hypertrophic phenotype in adulthood is uncommon and the incidence of major disease related complications (such as stroke and sudden death) is similar to the rates seen in the HCM population as a whole. Finally, complex genetic status is common, which has implications for counseling family members and when considering predictive testing.
Cardiac Myosin Binding Protein-C Mutations in Families With Hypertrophic Cardiomyopathy: Disease Expression in Relation to Age, Gender, and Long Term Outcome

Stephen P. Page, Stavros Kounas, Petros Syrris, Michael Christiansen, Rune Frank-Hansen, Paal Skytt Andersen, Perry M. Elliott and William J. McKenna

_Circ Cardiovasc Genet._ 2012;5:156-166; originally published online January 20, 2012; doi: 10.1161/CIRCGENETICS.111.960831

_Circulation: Cardiovascular Genetics_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circgenetics.ahajournals.org/content/5/2/156

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Genetics_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Genetics_ is online at:
http://circgenetics.ahajournals.org//subscriptions/