Expression Patterns of Cardiac Myofilament Proteins
Genomic and Protein Analysis of Surgical Myectomy Tissue From Patients With Obstructive Hypertrophic Cardiomyopathy

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Background—Mutations in myofilament proteins, most commonly MYBPC3-encoded myosin-binding protein C and MYH7-encoded β-myosin heavy chain, can cause hypertrophic cardiomyopathy (HCM). Despite significant advances in structure-function relationships pertaining to the cardiac sarcomere, there is limited knowledge of how a mutation leads to clinical HCM. We, therefore, set out to study expression and localization of myofilament proteins in left ventricular tissue of patients with HCM.

Methods and Results—Frozen surgical myectomy specimens from 47 patients with HCM were examined and genotyped for mutations involving 8 myofilament-encoding genes. Myofilament protein levels were quantified by Western blotting with localization graded from immunohistochemical staining of tissue sections. Overall, 25 of 47 (53%) patients had myofilament-HCM, including 12 with MYBPC3-HCM and 9 with MYH7-HCM. As compared with healthy heart tissue, levels of myofilament proteins were increased in patients manifesting a mutation in either gene. Patients with a frameshift mutation predicted to truncate MYBPC3 exhibited marked disturbances in protein localization as compared with missense mutations in either MYBPC3 or MYH7.

Conclusions—In this first expression study in human HCM tissue, increased myofilament protein levels in patients with either MYBPC3- or MYH7-mediated HCM suggest a poison peptide mechanism. Specifically, the mechanism of dysfunction may vary according to the genetic subgroup suggested by a distinctly abnormal distribution of myofilament proteins in patients manifesting a truncation mutation in MYBPC3. *(Circ Heart Fail. 2009;2:325-333.)*

Key Words: cardiomyopathy ■ hypertrophy ■ genetics ■ protein ■ tissue
**MYBPC3** mutations involve frameshifts that are predicted to result in a truncated protein product.\(^{16–18}\)

The intimate association of **MYBPC3** with **MYH7** and the recognition that their corresponding genes are the 2 most common genotypes in HCM prompt the question of how a mutation would affect levels and subcellular localization of these proteins in HCM patients. We hypothesize that a mutation in **MYBPC3** or **MYH7** causes the mutant protein to perturb the wild-type protein, resulting in disrupted localization and impairment of their roles in mediating or regulating contraction in myocardium.

### Methods

#### Study Population

Between July 1998 and May 2002, 209 patients underwent surgical septal myectomy to relieve symptoms of obstructive HCM refractory to pharmacotherapy. Of these, 47 unrelated patients consented to participate in this study. Following receipt of written consent for this Mayo Foundation Institutional Review Board-approved protocol, a portion of myocardium tissue was divided and either flash frozen in liquid nitrogen or fixed in formalin for paraffin embedding.

#### Mutational Analysis

DNA was extracted from the myocardium tissue using the Purgene DNA extraction kit (Genta, Inc, Minneapolis, Minn). Polymerase chain reaction was performed on the 34 translated exons of **MYBPC3** and the 38 translated exons of **MYH7** including all flanking splice junctions. To exclude patients manifesting compound heterozygosity, mutational analysis was performed on 6 additional myofilament genes which, together with **MYBPC3** and **MYH7**, comprise commercially available HCM genetic tests. Each individual exon was evaluated for sequence variation using denaturing high-performance liquid chromatography (Transgenomic, Omaha, Neb). All samples with an abnormal elution profile were directly sequenced (ABI Prism 377; Applied Biosystem, Foster City, Calif) to characterize the precise genetic variant. Furthermore, a panel of 400 reference alleles of amino acids within human **MYBPC3** (LLKKRDSFRPRDSKLEA; amino acids 296 to 315) (available on request). Horseradish peroxidase-conjugated rabbit antismouse (ab67280) (1:5000) and goat antirabbit (ab6721) (1:5000) antibodies were purchased from Abcam.

#### Immunohistochemistry

Formalin-fixed, paraffin-embedded myectomy tissue blocks were sectioned at 5 μm for immunohistochemical staining. Deparaaffinization with xylene and subsequent rehydration with graded alcohol preceded heat-induced epitope retrieval with EDTA buffer (pH 8) in a Laboratory Vision PT Module (Fremont, Calif). The staining procedure was carried out by an automated immunohistochemistry staining machine (DAKO Techmate 500, DAKO, Denmark) using the Envision program. The antibodies against myosin-binding protein C and myosin heavy chain were diluted 1:1000 and scored for 2 parameters, which assessed overall homogeneity of protein expression using a whole-slide imaging platform. Evaluation of intercellular distribution was observed at a lower magnification (20×) followed by assessment of the intracellular distribution at a higher magnification (400×). Interpretation of the final scores was done blinded to the genotype, and all results were confirmed by a cardiac pathologist (D.V.M.). The initial score was based on the average percentage of sarcomass showing disruption of protein expression: 0, normal (0% loss); 1, <25% loss; 2, 25% to 50% loss; 3, 50% to 75% loss; and 4, 75% to 100% loss. The second score used the same scoring system but now analyzed the overall percentage of the cell population showing disruption of staining. These 2 scores were multiplied and converted to a percentage ultimately representing the total disruption in protein localization with 0 representing normal distribution and a score of 16 indicating 75% to 100% disruption of the protein.

#### Statistical Analysis

Student’s \( t \) test and Fisher’s exact test were used to compare clinical characteristics among the genotypes utilizing the JMP statistical software (JMP 6.0, 2005; SAS Institute Inc, Cary, NC). Student’s \( t \) test was also used to compare localization patterns in different genotype groups. Generalized estimating equations, using a gamma distribution and a log link, were used to determine variation in levels of myosin-binding protein C and myosin heavy chain protein. This type of analysis was used because the distribution of protein levels was highly skewed and could not be transformed to the normal distribution. The gamma distribution provided a much better fit than any other distribution available. Levels observed in healthy heart tissue were compared with patients having a missense mutation in either protein and with those having a truncation mutation in **MYBPC3**.

### Results

#### Clinical and Genetic Analysis of Cohort

The demographics of this cohort (n=47, 25 men) are summarized in Table 1. The mean age at diagnosis was 33.8±19.9 years with a mean left ventricular wall thickness...
of 24.2±7.7 mm. Mutational analysis of 8 HCM-associated myofilament genes revealed that 25 of 47 (53%) were mutation positive including 12 with MYBPC3-HCM and 9 with MYH7-HCM. For the purpose of the study, we focused on these 21 patients manifesting a single mutation in either MYBPC3 or MYH7. Because of small quantity and low quality of tissue, 5 patients were excluded from further experimental analysis; the excluded patients are annotated in Table 2.

Consistent with prior investigations, the 22 patients who were sarcomere genotype negative were significantly older than those with myofilament-negative group. Similar to our previous findings, statistically significant differences to genotype negative group were confirmed by an unpaired Student’s t test ($P<0.05$).

### Spectrum and Prevalence of MYBPC3- and MYH7-HCM

Table 2 summarizes the clinical profiles of the 21 patients having either MYBPC3-HCM or MYH7-HCM. Although all mutations in MYH7 were missense mutations, 7 of the 12 (58%) mutations accounting for MYBPC3-HCM were insertion/deletions or splice site mutations predicted to result in an in-frame deletion (case 6) or C-terminal truncation (cases 7 to 12).

Examination of the clinical phenotypes of these patients failed to reveal significant genotype-phenotype differences between MYBPC3-HCM and MYH7-HCM; however, those with a mutation in MYBPC tended to be older than those with a mutation in MYH7 (Table 1). As compared with the myofilament-negative group, MYH7-HCM patients were significantly younger at diagnosis (24.3±24.7 versus 41.1±19.1 years; $P=0.03$) and had greater hypertrophy as evidenced by left ventricular wall thickness (24.3±7.1 versus 21.8±5.2 mm; $P=0.05$).

### Spectrum of MYBPC3 Insertion/Deletions and Splice Site Mutations

Table 3 presents detailed protein characteristics for those individuals with an insertion/deletion mutation or mutation at the canonical splice site. Investigation of the cardiac transcriptome permitted elucidation of the precise splicing defect: 3 transcripts in case 7 and 2 transcripts in case 8 (data not shown). Case 6 had a splice defect that yielded an in-frame deletion of 89 amino acids resulting in a protein product lacking the CO domain. A summary of proteins that would result including the domains present in the truncated proteins are indicated (Table 3).

### Levels of Protein Expression

Analysis of whole-protein lysate from patients with either MYBPC3- or MYH7-mediated HCM revealed that a mutation results in increased protein levels as compared with healthy tissue. Loading for individual samples was controlled by running a replicate gel for Coomassie, and quantitative normalization was performed using GAPDH (Figure 1). In each subgroup, the levels of myosin-binding protein C and myosin heavy chain were significantly increased as compared with that observed in healthy heart tissue (Figure 2). Although the antibody against myosin heavy chain recognizes the $\beta$ and $\alpha$ isoforms, it is still plausible that this increase may be secondary to activation of the fetal gene program.

### Patterns of Protein Localization

To determine how a mutation might affect the localization of these proteins, we performed immunohistochemistry on paraffin-embedded tissue sections. Within healthy heart tissue, we observed that staining with either protein had an even, homogeneous pattern throughout the entire tissue section (Figure 3A). Patients with a missense mutation in either...
Table 2. Clinical Profiles of HCM Patients With Mutations in MYBPC3 or MYH7

<table>
<thead>
<tr>
<th>Case</th>
<th>Mutation</th>
<th>Exon</th>
<th>Gender</th>
<th>Age at Dx, y</th>
<th>Age at Myectomy, y</th>
<th>LVWT, mm</th>
<th>Family Hx HCM*</th>
<th>Family Hx SCA*</th>
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<td></td>
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<td>Sigmoidal</td>
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LWWT indicates left ventricular wall thickness.
*In a first-degree relative.
†Indicates patient samples not used in expression studies.

Table 3. Mutations and Predicted Protein of Patients Having a Genetic Variation Resulting in a Truncated Protein

<table>
<thead>
<tr>
<th>Genetic Variation</th>
<th>Affected Exon</th>
<th>Predicted Protein Size</th>
<th>Intact Domains</th>
<th>Consequence of Mutation</th>
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<td>C0-C10</td>
<td>Full length</td>
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<td>C.58-2 A&gt;G</td>
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<td>C1-C10</td>
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<td>C.821+1 G&gt;A</td>
<td>7</td>
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<td>C0-C1</td>
<td>H257 fs/15</td>
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<tr>
<td>C.1580_1581ins CACT</td>
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<td>C0-C2</td>
<td>LS27 fs/3</td>
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<tr>
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<td>CS66 fs/3</td>
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<tr>
<td>C.3226_3227ins T</td>
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<td>C0-C8</td>
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<tr>
<td>C.3776del A</td>
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<td>147 kD</td>
<td>C0-C9</td>
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protein had a small degree of disruption in the even distribution (Figure 3B and 3C) but were not significantly different from normal. Interestingly, analysis of these proteins in patients with a mutation resulting in the truncation of MYBPC3 showed a marked disturbance in protein localization. In these patients, both proteins demonstrated a heterogeneous pattern, suggesting regional variations in expression or incorporation of protein (Figure 3D and 3E). This irregular staining pattern in patients with a truncation mutation was confirmed by staining with a monoclonal antibody that specifically recognizes the intact N terminus of MYBPC3 (Figure 3D and 3E). Interestingly, the heterogeneity in the staining did not correlate with the degree of disarray and was observed throughout the tissue section. Furthermore, the presence of striations in areas of light staining confirms that these are cardiomyocytes and excludes the presence of fibrosis as an explanation for decreased staining (Figure 4A through 4C). Figure 5 summarizes the expression score data...
from the 3 groups of interest based on the percent disruption in either myosin-binding protein C (Figure 5A) or myosin heavy chain (Figure 5B). Greater disruption of both proteins was observed in patients having a MYBPC3 mutation resulting in premature truncation MYBPC3.

**Discussion**

Even though >20 genes have been implicated in the pathogenesis of HCM,2 most genetically established HCM is explained by mutations within MYBPC3 or MYH7. In vitro work and animal models have guided our understanding of how a mutation in either protein may lead to disease15,21–31 yet little is known about the effects of these mutations in the human heart. As a tertiary referral center for the surgical treatment of HCM, our unique ability to collect and flash freeze human cardiac tissue from myectomies was essential for our characterization of the expression and localization patterns of myosin heavy chain and myosin-binding protein C in myocardium from patients with HCM.

MYBPC3 and MYH7 are the principal constituents of the thick filament and are essential for proper function of the cardiac sarcomere. In fact, the activity of MYH7 is regulated/modulated by MYBPC3 that has dual roles in stabilizing the sarcomere and regulating contraction.32 In mice lacking myosin-binding protein C, septal hypertrophy and impaired contractile function were observed,19,28 whereas in the human, the vital necessity for myosin-binding protein C is evidenced by neonatal lethality when both alleles encode for a premature truncation.33,34

Our studies of protein levels in human HCM illustrate that both proteins are present at normal to increased levels as compared with healthy tissue. These data suggest that the disease is not mediated by a decrease in total protein in these patients and mirror what has been observed previously, both in animal models21,22,24 and in human myectomy tissue.35,36 Although we were unable to identify the truncated MYBPC3 product in patients manifesting an insertion/deletion or splice site variation, this protein product may be present at levels that are too low to be detected by Western blotting. It is still plausible that minute quantities may lead to disease as evidenced in a homozygous knock-in mouse expressing truncated MYBPC3.30

One potential avenue by which a mutation in a protein could poison the cell is through mislocalization caused by the inability to interact properly with partner proteins. Our immunohistochemistry study revealed that the effect of a missense mutation on the localization of either protein was modest as shown by an even distribution of protein throughout the cardiomyocyte and tissue. In contrast, in myocardium from patients predicted to have a truncation in MYBPC3, a heterogeneous expression pattern was observed. Even within an individual cardiomyocyte, the protein seems to be localized to discrete zones in patterns that affect myocardial contraction. This mislocalization of the protein in human tissue may be secondary to the absence of a complete C terminus, which is necessary for proper incorporation of the protein into the sarcomere.15,37

We surmise that this disrupted localization of MYBPC3 in patients with a truncation mutation may be caused by disruption of the cooperative assembly of proteins known to exist within the sarcomere.38 Although degradation of truncated MYBPC3 through the ubiquitin proteasome system has been
observed, it is plausible that as the proteasome ages, truncated MYBPC3 could integrate into the sarcomere. Previous work by others has demonstrated that truncation of the C terminus can result in misincorporation of the protein and a diffuse pattern throughout the sarcomere. This misincorporation of mutant protein may consequently act as a nidus for aggregation of wild-type protein at these locations.

Regardless the mechanistic basis for the maldistribution of MYBPC3, the juxtaposition of sarcomeres with and without MYBPC3 would be expected to affect myocardial function profoundly during a twitch. Previously, myocardium lacking MYBPC3 was shown to have an accelerated stretch activation response, suggesting that MYBPC3 normally constrains cross-bridges and thereby reduces both the probability of binding to actin and the rate of force development. Ablation of MYBPC3 would relieve this constraint and accelerate the rate of force development.

Ablation of MYBPC3 would relieve this constraint and accelerate the rate of force development. In myocardium in which the incorporation of MYBPC3 is not uniform, as in the patients with a truncation yielding MYBPC3 allele, sarcomeres without MYBPC3 would develop force more rapidly than sarcomeres with normal or greater amounts of MYBPC3. This mismatch in contraction kinetics would set up an oscillating system of reciprocal stretch activation during a twitch: zones without MYBPC3 would quickly develop more force than zones with MYBPC3. Because of the force differential, the former would stretch the latter and thereby stretch-activate the zone with MYBPC3. Because stretch activation occurs with a time delay, the net effect would be to delay the time to full relaxation of the twitch. Moreover, because of its faster kinetics, the zone without MYBPC3 will begin to relax before the zone with MYBPC3. This again sets up a force differential between the zones so that the zone without MYBPC3 is now stretch activated by the zone with MYBPC3. This asynchronous reciprocal stretch activation is similar to what is observed in the antagonist asynchronous flight muscles of insects. In the present case, the oscillation would rapidly decay because of the intracellular sequestration of Ca\(^{2+}\), but the net effect is a slowing of relaxation, which notably, is a distinct functional feature in mice lacking MYBPC3.

Accordingly, a more severe clinical phenotype might be expected among patients with a premature truncation in MYBPC3 as compared with those with MYBPC3 missense mutations. However, in this study, the phenotypes of these 2 subsets were similar between the 7 patients with truncations and the 5 patients with missense mutations in MYBPC3. A much larger sample size with longitudinal follow-up will be necessary to explore this possibility further.
Conclusion
This study is the first characterization of the localization and expression patterns of myofilament proteins in the largest known cohort of patients from whom flash-frozen myectomy tissue has been collected. The levels of myosin-binding protein C and myosin heavy chain in patients with either MYBPC3- or MYH7-mediated HCM support the notion that these mutations lead to dysfunction and disease through a poison peptide mechanism. More specifically, the mechanism may vary according to the genetic subgroup, a conclusion that is suggested by the distinctly abnormal distribution of MYBPC3 in patients manifesting a truncation mutation in this gene.

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Disclosures
Dr. Ackerman is a consultant for PGxHealth.

References


CLINICAL PERSPECTIVE
Although >20 genes have been associated with hypertrophic cardiomyopathy, mutations in MYBPC3-encoded myosin-binding protein C and MYH7-encoded β-myosin heavy chain are known to cause >80% of genetically explained hypertrophic cardiomyopathy. Among these 2 most common subtypes of hypertrophic cardiomyopathy, a variety of genotype-phenotype associations have been reported. Here, from detailed immunohistochemical analysis of human septal myocardium flash frozen following surgical myectomy, a novel genotype/phenotype observation has emerged. As compared with patients with missense mutations in either gene, patients having MYBPC3 frame-shift mutations exhibited a significant disruption in their myofilament architecture. The observed maldistribution of myosin-binding protein C may precipitate the abnormal diastolic relaxation commonly observed among patients with MYBPC3-hypertrophic cardiomyopathy.
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