Mutations of the Light Meromyosin Domain of the $\beta$-Myosin Heavy Chain Rod in Hypertrophic Cardiomyopathy

Edward Blair, Charles Redwood, Marisa de Jesus Oliveira, J. C. Moolman-Smook, Paul Brink, V. A. Corfield, Ingegerd Östman-Smith, Hugh Watkins

Abstract—Familial hypertrophic cardiomyopathy (HCM) is caused by mutations in 9 sarcomeric protein genes. The most commonly affected is $\beta$-myosin heavy chain ($MYH7$), where missense mutations cluster in the head and neck regions and directly affect motor function. Comparable mutations have not been described in the light meromyosin (LMM) region of the myosin rod, nor would these be expected to directly affect motor function. We studied 82 probands with HCM in whom no mutations had been found in MYH7 exons encoding the head and neck regions of myosin nor in the other frequently implicated disease genes. Primers were designed to amplify exons 24 to 40 of $MYH7$. These amplimers were subjected to temperature modulated heteroduplex analysis by DHPLC. An Ala1379Thr missense mutation in exon 30 segregated with disease in three families and was not present in 200 normal chromosomes. The mutation occurred on two haplotypes, indicating that it was not a polymorphism linked with another disease-causing mutation. The position of this residue within the LMM region of myosin suggests that it may be important for thick filament assembly or for accessory protein binding. A further missense mutation in exon 37, Ser1776Gly, segregated with disease in a single family and was absent from 400 population-matched control chromosomes. Because the Ser1776 residue occupies a core position in the myosin rod at which the substitution of glycine is extremely energetically unfavorable, it is likely to disrupt the coiled-coil structure. We conclude that mutation of the LMM can cause HCM and that such mutations may act through novel mechanisms of disease pathogenesis involving myosin filament assembly or interaction with thick filament binding proteins. (Circ Res. 2002;90:1045–1052.)

Key Words: hypertrophic cardiomyopathy $\boxminus$ myosin

Familial hypertrophic cardiomyopathy (HCM) is an autosomal dominant disorder, characterized by myocardial hypertrophy and histological evidence of myocyte disarray. It can predispose to cardiac arrhythmia, cardiac failure, and, in some cases, sudden death. Understanding of the molecular pathogenesis of HCM has greatly increased in recent years with the description of disease-causing mutations in genes encoding proteins of the cardiac sarcomere. The gene most commonly mutated in patients with HCM is that encoding $\beta$-myosin heavy chain ($\beta$-MyHC), which is the predominant myosin isoform in adult human ventricular muscle. The $MYH7$ gene contains 40 exons spread over $\approx$25 kb of genomic DNA. Initial studies suggested that mutations of $MYH7$ were typically missense and clustered within the globular head and neck regions of the protein. Of more than 60 missense mutations identified subsequently in this gene, none have been 3’ of exon 23. A single report of a deletion truncating the carboxy-terminal portion of the rod is of uncertain significance, because the mutation could not be shown to segregate with disease. Because HCM is complicated by its allelic and genetic heterogeneity, mutation detection is extremely laborious and many laboratories focus their mutation detection strategies for HCM in analyzing regions of the genome where success is most likely. It is not clear to what extent this practice may have falsely reinforced the impression that $MYH7$ mutations are confined to exons 3 to 23.

Myosin is the main component of cardiac muscle thick filaments accounting for $\approx$30% of total myofibrillar protein. It is a hexamer comprising two myosin heavy chains (MyHCs) and two nonidentical myosin light chains per MyHC, and its structure consists of two globular heads attached to a long $\alpha$-helical coiled-coil (the myosin rod). Each head, or subfragment-1 (S1), is composed of a terminal residue of one MyHC and one of each light chain. The heads contain the actin and ATP binding regions of the protein and are responsible for the force transduction properties of myosin. The myosin rod is a parallel $\alpha$-helical coiled-coil dimer of the C-terminal MyHC tails (each $\approx$1100 amino acids). The N-terminal region of the rod, termed subfragment-2 (S2),
oligonucleotides were designed from flanking intronic sequence. 21 Mutation analysis 20 Index cases were then selected from each family in sufficient size, linkage analysis performed using flanking microsatellite markers. 20 

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Most laboratories recognize incomplete mutation detection among families with HCM. Whereas some of the families in which no mutation is identified are presumably accounted for by mutations in genes as yet not implicated in causing HCM, we hypothesized that some of the “missing” mutations might be located in regions of known genes not routinely investigated. To test this hypothesis, we screened for mutations in exons 24 to 40 of MYH7 in a panel of 82 probands in whom a mutation could not be found after screening of MYH7 exons 3 to 23 and the other commonly implicated disease genes.

Materials and Methods

Subjects
Family members were ascertained through our clinical practice or the practices of referring physicians and evaluated by physical examination, ECG, and echocardiography, allowing the diagnosis of HCM to be made in those clinically affected. Cohorts of probands from the UK and from South Africa were each of mixed ethnic background and control subjects were selected from the appropriate populations to be ethnically matched. All participants gave informed consent and local ethical committee approval was granted.

Short Tandem Repeat (STR) Analysis
DNA was extracted from peripheral lymphocytes and, in families of sufficient size, linkage analysis performed using flanking microsatellite markers. 20 Index cases were then selected from each family in whom linkage to MYH7 could not be excluded to undergo direct mutation screening.

Mutation Analysis
Oligonucleotides were designed from flanking intronic sequence 21 for exons 24 to 40 of the MYH7 gene. Amplifications were performed with “touchdown” PCR using high-fidelity polymerases. Annealing temperatures were optimized for each exon and touched down from 7.5°C above the final annealing temperature in 0.5°C decrements. Mutation analysis was undertaken using temperature-modulated heteroduplex analysis (TMHA) on an automated HPLC instrument equipped with a DNASep column (Transgenomic Inc). Mobile phase gradients and melting temperatures for TMHA of each exon were calculated using the Wavemaker (Transgenomic Inc) software package. Exons with an abnormal TMHA profile were sequenced using an ABI377 (Applied Biosystems), following product purification by QIAquick PCR purification (Qiagen) and compared with published genomic sequence of the MYH7 gene (GenBank accession number X52889).

Single-Nucleotide Polymorphism (SNP) Haplotyping
Common DNA variants in exons 3, 8, 24, and 33 of MYH7 were selected for haplotype analysis (Table 1). The exon 8 SNP was genotyped by direct sequencing of PCR products. The remaining variants created restriction fragment-length polymorphisms and were genotyped by restriction digest: exon 3, Ddel; exon 24, BsrDI; and exon 33, FokI. Haplotypes of these SNPs and STR alleles were constructed after typing of all family members.

Results
Mutation screening was performed on a final panel of 82 probands in whom no mutations had been found on screening exons 3 to 23 of MYH7 or on screening the other frequently implicated HCM disease genes (cardiac troponin T, cardiac myosin binding protein-C, regulatory myosin light chain, and cardiac actin). Our initial screening panel had contained isolated cases where the mode of inheritance could not be determined as well as families with clear evidence of autosomal dominant transmission. Of those families showing evidence of autosomal dominant inheritance, no mutation had been found in five, three of whom are presented in this study (J1, JH1, and J9).

Screening of exons 24 to 40 in this panel revealed a number of heterozygous variants (Table 1). Most of the variants found were neutral polymorphisms predicted not to change the amino acid sequence of the encoded protein, all of which were found in normal control populations. In addition, a C-to-G transversion encoding a Ser1491Cys substitution was found in ∼3% of affected and control chromosomes.

The three index cases of families J1, JH1, and J9 (Figure 2) also showed a clear heteroduplex abnormality in exon 30 of the MYH7 gene (Figures 3a and 3b). Screening all members of these families by TMHA showed that the variant was present in all 15 clinically affected individuals and absent in all clinically unaffected adults. Sequencing of this variant showed that it was due to a heterozygous G-to-A transition at nucleotide 19227 (Figure 3c). This DNA variant is predicted to replace alanine with threonine at residue 1379 (Ala1379Thr). This base change causes loss of an HgaI restriction site in the exon 30 amplifier, allowing independent confirmation of its presence in all affected family members.

A 2-point logarithm of odds (LOD) score was calculated for
this base change in these three families: LOD=3.6 for penetrance 0.8, LOD=3.8 for penetrance 0.95. We did not find the Ala1379Thr variant in any of 200 normal control chromosomes typed by restriction digest, excluding the possibility that this is a common polymorphism. Furthermore this residue is conserved in the myosin rod across mammalian species and myosin isoforms.

Haplotype analysis using intragenic coding region SNPs and flanking STRs showed that this mutation was present on the same SNP/STR haplotypes in families J1 and JH1. Both of these families are of Caucasian origin and reside in the same county. We have not been able to determine any known link between these two pedigrees, but a remote common ancestor seems likely. In contrast, family J9 segregated the Ala1379Thr mutation on a different haplotype (Figure 4). These data indicate that this mutation has arisen at least twice and is not an ancestral founder in these families or indeed a rare polymorphism in linkage disequilibrium with another, as yet undetected, MYH7 mutation. These findings satisfy conventional criteria for defining as a pathogenic mutation the G-to-A base substitution in families J1, JH1, and J9.

The pertinent clinical findings in families J1, JH1, and J9 are shown in Table 2. In family J1, two siblings of the proband died suddenly and prematurely; four surviving affected individuals were available for study. In families JH1 and J9, all 11 known affected individuals were alive and took part in the study, with no known family history of premature disease-related deaths. Penetrance in these families was complete in both adults and children, with demonstrable abnormalities on ECG and/or echocardiogram in children under the age of 5 years in each family. However, hypertrophy in adults was only moderate, with mean maximal wall thickness of ~18 mm. Diastolic filling abnormalities, as are well recognized in HCM, are a prominent feature of the disease in these three families, despite the moderate degree of hypertrophy. Some individuals had notably prolonged isovolumic relaxation times, but on average these were not statistically different in this small sample from those of patients with other MYH7 mutations (data not shown).

A unique abnormality of exon 37 was found in family SA6. Sequencing of this PCR product showed a G-to-A transition at nucleotide 22240 (Figure 3d). This is predicted to change the amino acid sequence in the final protein from serine to glycine at position 1776 (Ser1776Gly). This base change introduced a second MspI site in the PCR amplimer, allowing independent confirmation of this mutation. Screening of 400 ethnically matched control chromosomes did not detect this base change, showing that it is not a common polymorphism. The mutation cosegregated with disease in this family, as it was present in the two affected siblings and absent in the unaffected sibling. Ser1776 is conserved across mammalian species and myosin isoforms. The pedigree of family SA6 is shown in Figure 2, and the clinical details of the affected individuals within this family are shown in Table 2.

**Discussion**

Most of the mutations described so far in β-MyHC cluster in functionally significant regions of myosin S1, eg, in the actin binding region, the ATP binding pocket, on the lever arm helix, and near the sites of interaction with the myosin light

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**TABLE 1. Neutral Polymorphisms Used in Haplotype Analysis or Found During Mutation Screening of the Myosin Rod**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Polymorphism*</th>
<th>Amino Acid Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ACC→ACT; 4582</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>TTT→TTC; 6528</td>
<td>None</td>
</tr>
<tr>
<td>24</td>
<td>ATT→ATC; 14438</td>
<td>None</td>
</tr>
<tr>
<td>32</td>
<td>TCC→TGC; 20271</td>
<td>Ser1491Cys</td>
</tr>
<tr>
<td>33</td>
<td>ACC→ACT; 20525</td>
<td>None</td>
</tr>
<tr>
<td>34</td>
<td>ATC→ATT; 21217</td>
<td>None</td>
</tr>
<tr>
<td>40</td>
<td>ATC→ATT; 23646</td>
<td>None</td>
</tr>
<tr>
<td>40</td>
<td>GCC→GCT; 23577</td>
<td>None</td>
</tr>
<tr>
<td>40</td>
<td>GCC→GCT; 23649</td>
<td>None</td>
</tr>
</tbody>
</table>

*All of these polymorphisms were shown to be present in unaffected, unrelated ethnically matched control subjects.*
chains. A few further mutations located in the N-terminus of the myosin S2 region, which links the S1 to the backbone of the thick filament, have been described and these are thought to alter β-MyHC binding to the N-terminal regulatory domain of myosin binding protein-C. A combination of structure-function prediction and direct experimental observations has begun to clarify how mutations in the myosin head and neck regions cause HCM. Although recent work has suggested that two β-MyHC mutants result in increased filament sliding and force, most studies have indicated that the previously reported mutations in directly reduce force generation and the efficiency of ATP utilization. Thus, the β-MyHC mutations are predicted to produce a hypocontractile deficit with compensatory hypertrophy and, most probably, energetic compromise in the myocyte. The mutations described in the present study are the first definite HCM-causing mutations found in the rod proper and cannot easily be made to fit into this model of pathogenesis.

In myosin heavy chain dimers, the LMM region is a parallel α-helical coiled-coil, which forms the core of the thick filament and hence is very unlikely to influence directly the crossbridge cycle and the interaction of the myosin head with actin. This suggests the interesting possibility that mutation of the LMM may give rise to HCM by novel mechanisms mediated by perturbed thick filament structure and/or assembly. Missense mutations in the myosin rod have previously been shown to cause a significant dominant phenotype in both nematode and Drosophila; in these models, dysfunction is caused, at least in part, by aberrant thick filament assembly and, in the case of Drosophila, by

Figure 3. a, Normal TMHA trace from a control sample. b, Abnormal analysis obtained from exon 30 of affected individuals from families J1, JH1, and J9. c, Sequence of the heterozygous sequence variant (G→A) underlying this abnormality. d, DNA sequence variant (G→A) underlying the Ser1776Gly mutation.

Figure 4. Schematic representing the 2 haplotypes segregating with the Ala1379Thr mutation. The mutation in families J1 and JH1 is found on haplotype A. In family J9, the mutation segregates with haplotype B. The fact that the mutation occurs on different SNP/STR haplotypes indicates that the mutation has arisen as independent events at least twice.
possible altered interaction with flightin, a myosin-binding protein in indirect flight muscle. Disruption of $\alpha$-helical coiled-coil structures has also been associated with human disease: altered stability of the $\alpha$-helical coiled-coil has been demonstrated for the Asp175Asn and Glu180Gly HCM mutations in $\alpha$-tropomyosin, and a missense mutation in the desmin rod domain causes autosomal dominant distal myopathy through a dominant-negative effect on filament formation.31 It is possible that some of the reported MyBP-C mutations may also act by affecting thick filament assembly/stability, although it is equally likely that they act by disrupting the modulating effect of MyBP-C on contractility.

The heptad repeat motif forms the structural basis of the $\alpha$-helical coiled-coil and is found in a wide variety of proteins. Each seven amino acid repeat ($a$, $b$, $c$, $d$, $e$, $f$, and $g$), the $a$ and $d$ positions are typically occupied by small nonpolar residues, allowing stabilization of the coil as a result of the packing of the apolar side chains when two helices interact. The coiled-coil may be further stabilized by salt bridges formed between charged side chains in the $g$ and $e$ positions of opposing helices. Figure 5 shows the sequence of the human $\beta$-MyHC rod arranged to emphasize the heptad repeat. The 7-fold repeat is interrupted in four positions by insertion of “skip” residues, single amino acids that serve to provide flexibility in the rod, important for packing. The Ala1379Thr mutation affects an $e$ position and does not involve a change in charge. It may therefore be less likely to disrupt the coiled-coil structure than a mutation in the core positions $a$ or $d$, or one in the $e$ position that changed charge and so perturbed interhelical salt bridge formation.

### Table 2: Clinical Findings in Affected Members of Families J1, JH1, J9, and SA6

<table>
<thead>
<tr>
<th></th>
<th>Age/Age at Diagnosis, years</th>
<th>Symptoms</th>
<th>LVH/ST</th>
<th>Q-Wave Abnormalities</th>
<th>LA Size</th>
<th>SAM</th>
<th>LVWT, mm</th>
<th>IVRT, ms</th>
</tr>
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<tr>
<td><strong>J1</strong> (Ala1379Thr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II:2</td>
<td>60/54</td>
<td>Dyspnea, PAF</td>
<td>...</td>
<td>...</td>
<td>4.2</td>
<td>+</td>
<td>20</td>
<td>Sinus bradycardia, slow isovolumic relaxation</td>
</tr>
<tr>
<td>II:3</td>
<td>Sudden death at age 19</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>II:4</td>
<td>Sudden death at age 40</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>III:2</td>
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<td>Dyspnea</td>
<td>+</td>
<td>-</td>
<td>3.3</td>
<td>-</td>
<td>18</td>
<td>170</td>
</tr>
<tr>
<td>IV:1</td>
<td>7/4</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>...</td>
<td>-</td>
<td>10.8*</td>
<td>90</td>
</tr>
<tr>
<td>IV:2</td>
<td>4/2</td>
<td>-</td>
<td>SL 25</td>
<td>-</td>
<td>...</td>
<td>+</td>
<td>9.1*</td>
<td>80</td>
</tr>
<tr>
<td><strong>JH1</strong> (Ala1379Thr)</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>74/60+</td>
<td>Dyspnea, PAF</td>
<td>-</td>
<td>-</td>
<td>5.2</td>
<td>-</td>
<td>20</td>
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<td>3.8</td>
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<tr>
<td>IV:1</td>
<td>13/3</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>...</td>
<td>...</td>
<td>12.5*</td>
<td>110</td>
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<tr>
<td><strong>J9</strong> (Ala1379Thr)</td>
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<td>...</td>
<td>6.4</td>
<td>+</td>
<td>22.7</td>
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<tr>
<td>II:3</td>
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<td>-</td>
<td>-</td>
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<td>115</td>
</tr>
<tr>
<td>II:4</td>
<td>62/52</td>
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<td>-</td>
<td>-</td>
<td>...</td>
<td>5.9</td>
<td>-</td>
<td>19</td>
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<td>63/53</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>...</td>
<td>...</td>
<td>12.7</td>
<td>...</td>
</tr>
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<td>-</td>
<td>+</td>
<td>-</td>
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<td>93</td>
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<td>III:2</td>
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<td>-</td>
<td>LVH</td>
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<td>...</td>
<td>3.5</td>
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<tr>
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<td>?/5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>...</td>
<td>-</td>
<td>9.6*</td>
<td>90</td>
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<tr>
<td>IV:2</td>
<td>?/4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>...</td>
<td>-</td>
<td>8.6*</td>
<td>50</td>
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<tr>
<td><strong>SA6</strong> (Ser1776Gly)</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>II:1</td>
<td>37/32</td>
<td>CP</td>
<td>-</td>
<td>+</td>
<td>3.1</td>
<td>+</td>
<td>17.3</td>
<td>...</td>
</tr>
<tr>
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<td>49/49</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>...</td>
<td>3.0</td>
<td>+</td>
<td>13</td>
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</table>
position of Ala1379 on the outside of the core raises the interesting possibility that it may act by altering the interactions of the LMM with other sarcomeric proteins such as titin or MyBP-C. At present, the regions of the LMM involved in interaction with other sarcomeric proteins are not defined; however, recurrent mutation of this particular residue in families with HCM suggests that Ala1379 may occupy a key position for LMM function. The Ser1776Gly mutation occupies a core a position within the myosin rod. This mutation appears to be particularly significant in that studies on model peptides have shown that glycine in a core position is the least energetically favorable of all amino acids, with the exception of proline. Moreover, in all of the 312 core a or d positions throughout the rod, glycine occurs just twice, each time in areas of local unwinding. Therefore, the Ser1776Gly mutation may disrupt the coiled-coil structure of the LMM and thus thick filament assembly.

The clinical features of HCM in the four families with the LMM mutations are, broadly, typical of the range of clinical manifestations seen in this disorder. Thus, if these mutations initiate the disease by a different pathogenic mechanism, it seems that the end phenotype likely results from a final common pathway. That said, there are some features shared by the three Ala1379Thr families that, if replicated in subsequent studies, would indicate particular genotype:phenotype correlations of this rod mutation (Table 2). In particular, the combination of complete penetrance in both adults and children, despite only moderate hypertrophy, was striking. Unfortunately, no samples of myocardium were available for histological analysis. Insufficient numbers of Ser1776Gly individuals were available to allow any conclusions about genotype:phenotype correlations.

Evidence for segregation of the mutation with disease status in all individuals investigated was necessary to establish the causative role of these mutations in the families described. A previously reported myosin rod deletion mutation was present in a proband and 3 other relatives (2 adults) who did not have clinical evidence of disease.14 The Ser1491Cys substitution has also been previously reported and presumed to be disease-causing.36 However, in the course of this study, we found this mutation in phenotypically normal control individuals as well as disease probands (Table 1). No evidence for segregation of this mutation with disease could be found in the families of the affected probands; we thus concluded that this was a non–disease-causing polymorphism.

A significant number of our HCM probands still remain to have a disease-causing mutation identified. Disease phenocopies will undoubtedly account for some individuals, but TMHA has been shown to be both an efficient and sensitive means of mutation detection,37,38 so false-negative mutation screens are unlikely to account for many of the screen negative probands. Further, mutations were identified by this technique in every one of the families in which probable or definite linkage to MYH7 was observed. As yet, we have no data to indicate where mutations accounting for HCM in the remainder of this cohort will be found. Mutations in nonsarcomeric protein nuclear genes39 are one possible explanation, as are mutations of the mitochondrial genome.40 It does not seem likely that our remaining cohort of 78 HCM probands can be accounted for by sarcomeric protein mutations, indicating that mutations in other genes, possibly with roles in myocardial energetics,39,40 must be sought.

In conclusion, demonstration of disease-causing mutations within the LMM region of the β-MyHC rod domain has implications for both DNA-based diagnostic strategies and for our understanding of how mutation of this protein causes HCM. In our series, LMM mutations accounted for 14% of all MYH7 mutations observed (four mutations in the LMM versus 25 mutations in myosin head and neck regions). Our
findings therefore suggest that mutation-screening protocols that include the full MYH7 coding sequence are warranted in HCM, not least so as to determine whether other LMM mutations exist. Mechanistic insights from further studies of these mutations may disclose new aspects of HCM pathogenesis and should also highlight novel structure-function relationships in the myosin rod.

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References
34. Trepko B, Wagschal K, Lavigne P, Mant CT, Hedges RS. Effects of side-chain characteristics on stability and oligomerization state of a de


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