Novel Locus for an Inherited Cardiomyopathy Maps to Chromosome 7

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Background—Genetic mutations are the most common cause of hypertrophic cardiomyopathy (HCM) and an increasingly recognized cause of dilated cardiomyopathy. Autosomal dominant HCM is caused by mutations in sarcomere proteins; such mutations are not universally present, however, and fail to account for \( \approx 40\% \) of cases of phenotypic HCM. To add further complexity, other genetic origins can mimic the gross clinical phenotype of HCM, and mutations in sarcomere genes have been demonstrated to cause dilated cardiomyopathy.

Methods and Results—To explore novel genetic causes of inherited cardiomyopathies, genome-wide linkage analysis was used to study one kindred (4 generations, 32 individuals) with predominant clinical features of left ventricular hypertrophy in addition to cardiac dilation, end-stage heart failure, and sudden death. Of note, histopathology from 2 family members did not demonstrate myocyte disarray and fibrosis, indicating that this phenotype is not typical sarcomere mutation HCM. Direct DNA sequencing was performed on sarcomere genes known to cause HCM and dilated cardiomyopathy, and no mutations were identified. Linkage was then established to a novel locus on chromosome 7 (7p12.1-7q21). A maximum 2-point logarithm of odds score of 4.11 was obtained. Recombination events refine the disease interval between D7S506 and D7S3314, corresponding to a distance of 27.2 megabases.

Conclusions—The discovery of a novel genetic locus in this family provides more evidence that molecular pathways leading to inherited cardiac hypertrophy extend beyond the sarcomere. Identification of the causal gene mutation and additional genotype-phenotype correlation studies will provide fundamental insight into mechanisms of cardiac remodeling. (Circulation. 2006;113:2186-2192.)

Key Words: cardiomyopathy genetics hypertrophy remodeling

The heart undergoes 2 predominant patterns of remodeling in response to mechanical or hemodynamic stress: ventricular hypertrophy or dilation. In hypertrophic remodeling of the heart, ventricular wall thickness increases without concomitant cavity enlargement. In dilated remodeling, the ventricular cavity enlarges without a proportional increase in wall thickness. The molecular pathways and signaling cascades responsible for these divergent morphological changes remain largely unknown. However, the study of gene mutations that primarily remodel the heart provides a unique opportunity to identify critical molecules involved in these pathways.

Clinical Perspective p 2192

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained cardiac hypertrophy: thickening of the myocardial wall in the absence of any other identifiable cause for left ventricular hypertrophy (LVH) such as systemic hypertension or valvular heart disease. Myocyte hypertrophy, disarray, and fibrosis are the histopathological hallmarks of this disorder. Although diverse, arrhythmias, sudden cardiac death, and heart failure are clinical features of HCM.1 With an estimated prevalence of 1 in 500,2,3 HCM is the most common cardiovascular genetic disease and the most common cause of sudden death in competitive athletes in the United States.4

Genetic studies established the paradigm that HCM is a disease of the sarcomere caused by sporadic or dominantly inherited mutations in contractile proteins.5-7 To date, >400 causal mutations for HCM have been identified in 11 sarcomere proteins (http://cardiogenomics.med.harvard.edu), including components of the thick filament, thin filament, and sarcomere-related structural proteins. As a whole, sarcomere gene mutations account for \( \approx 60\% \) of cases of unexplained cardiac hyper-
In addition to mutations in contractile proteins, other molecular pathways, namely those involved in glucose metabolism and energetics, recently have been shown to result in a similar gross phenotype of unexplained LVH. These glyco-
gen storage cardiomyopathies can be difficult to distinguish from HCM by routine clinical evaluation. To add a further layer of complexity, gene mutations are increasingly recognized as a cause of idiopathic dilated cardiomyopathy (DCM). Family studies in which relatives of probands who presented with DCM were systematically studied suggest that 30% to 50% of DCM has a genetic origin involving a broad spectrum of mutations, including sarcomere proteins, components of the cytoskeleton, and mitochondrial genes.

Continued study is required to determine the full spectrum of gene mutations that lead to cardiac remodeling. We report a locus on chromosome 7p12.1-7q21 that is linked to a phenotype with clinical features of both HCM and DCM in a large multigenerational family. Mutations in known HCM- and DCM-associated genes, including sarcomere proteins, components of the cytoskeleton, and mitochondrial genes.

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**Methods**

**Clinical Evaluations**

Informed consent was obtained in accordance with human subjects' committee guidelines and the institutional review boards at Brigham and Women's Hospital and the Minneapolis Heart Institute Foundation. Family members were evaluated by the use of clinical history, physical examination, 12-lead ECG, and transthoracic echocardiography. Individuals were considered affected if they demonstrated unexplained LVH (wall thickness >13 mm) in the absence of chamber dilatation or if left ventricular enlargement was present (left ventricular end-diastolic dimension >5.7 cm). The disease status of deceased individuals was based on review of medical records. The disease status of individuals <29 years of age without evidence of LVH or cardiac enlargement was considered to be unknown for purposes of linkage analysis (Figure 1).

**Histology**

Cardiac pathology was available on 2 family members: individual III-2 (explanted heart at the time of cardiac transplantation (Figure 2) and individual III-3 (autopsy after sudden cardiac death). Myocardial specimens were handled in standard fashion with dehydration through increasing concentrations of ethanol and embedding in paraffin wax. Tissues were serially sectioned by microtome at 5-μm intervals. A subset of the slides was stained with hematoxylin and eosin, metallothionein, Masson’s trichrome, and periodic acid-Schiff, according to standard procedures.

**Linkage Analysis and DNA Sequencing**

Genomic DNA was extracted from whole blood or Epstein Barr virus–transformed lymphocytes in standard fashion. A candidate gene approach was initially used. The coding regions and intron/exon boundaries of HCM-associated sarcomere genes MYH7, MYL2, MYL3, MYBP3, TNN1, TNN3, TPM1, and ACTC, as well as glycogen storage cardiomyopathy-associated PRKAG2, were sequenced as previously described in an attempt to identify disease-causing DNA sequence variants. Linkage analysis was then performed using 383 short tandem repeat markers spaced an average of 10 cM apart (Human Linkage Screening Set MD-10, Applied Biosystems, Inc, Foster City, Calif) from chromosomes 1 through 22. Seventy-three additional M13 dinucleotide markers were used to narrow the primary interval on chromosome 7. Polymerase chain reaction amplification was performed in a 10-μL reaction containing 20 ng genomic DNA,
symptomatic heart failure, left ventricular enlargement, and sudden cardiac death. The clinical characteristics of affected family members are summarized in Table 1. Distinguishing features of surviving affected individuals include LVH on echocardiography (asymmetric septal hypertrophy and concentric pattern) and ECG abnormalities (voltage criteria for LVH, T-wave abnormalities, or dysrhythmias).

Two family members (III-3 and III-14) had suspicious clinical features but did not meet defined phenotypic criteria. Specifically, individual III-3 died suddenly at 40 years of age (DNA not available), and clinical information is limited. He was reported to have a history of a congenital subaortic membrane resected at 16 years of age. Serial echocardiographic studies were performed in adulthood. A study performed 11 years after membrane resection reports asymmetric septal thickening (20 mm), systolic anterior motion of the mitral valve, and a left ventricular outflow tract obstruction. Echocardiograms 4 years, 3 years, and 1 year before his death described “mild septal hypertrophy” (accurate measurements are not available) and mild cavity enlargement to an end-diastolic dimension of 5.7 cm. Systolic function is preserved. An autopsy was performed, and cardiomegaly was present with a heart weight of 600 g. Limited histopathological examination is notable for mild interstitial fibrosis and myocyte hypertrophy but no disarray. In this individual, persistent LVH and sudden death 24 years after surgical treatment of subvalvular stenosis raises suspicion for the inheritance of a primary cardiomyopathy, distinct from secondary changes resulting from subvalvular stenosis.

Standard echocardiographic findings for individual III-14 were normal and without criteria for LVH or enlargement. ECG showed inferior T-wave inversions. Her adult daughter, IV-9, was unambiguously clinically affected on the basis of echocardiographic evidence of unexplained LVH. Individual III-14 was considered an obligate carrier and was scored as having an unknown phenotype for purposes of linkage. Both III-14 and IV-9 are asymptomatic.

Review of family history and medical records revealed 9 definitely affected individuals, described also in Table 1. Individual III-2 required cardiac transplantation for end-stage heart failure at 49 years of age. She presented with what was initially thought to be DCM and had precipitous progression of symptomatic heart failure. Pretransplantation echocardiography demonstrated mild septal hypertrophy; accurate measurement of left ventricular cavity size was not available, however. The finding of left ventricular enlargement was confirmed by pathological examination of her explanted heart, which revealed marked cardiomegaly (1035 g) caused by chamber dilation. Histological findings were nonspecific and nondiagnostic. A representative transmural section of left ventricular free wall was stained by hematoxylin and eosin, Masson’s trichrome (Figure 2), and periodic acid–Schiff. There is moderate diffuse myocyte hypertrophy with hyperchromatic “boxcar” nuclei and well-defined nucleoli. There is also minimal to mild interstitial and minimal focal replacement fibrosis.

The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Clinical Evaluations

Thirty-two individuals from a 4-generation family were available for analysis (Figure 1). The phenotype present in this family is notable for autosomal dominant inheritance of a mixed cardiomyopathy represented by unexplained LVH, fluorescent-labeled primers, and standard reagents for standard reaction times (Applied Biosystems, Inc). Product sizes were determined with an ABI Prism automated 3700 sequencer and Genescan and Genotyper software (Perkin-Elmer, Wellesley, Mass). Alleles were determined independently of clinical status. Two-point logarithm of odds (LOD) scores and the maximum LOD score were calculated with MLINK (version 5.1)/FASTLINK (version 4.0P),17 assuming a penetrance of 95% and disease gene frequency of 0.001. The coding regions and intron/exon boundaries of 9 candidate genes located in the disease interval were sequenced from genomic DNA through the use of standard methods.16

The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the manuscript as written.

Figure 2. Histopathology of the explanted heart from individual III-2. There was gross cardiac hypertrophy with a heart weight of 1035 g. A, A ×40 magnification of a section stained with hematoxylin and eosin shows moderate diffuse myocyte hypertrophy with boxcar nuclei. There is no myocyte disarray or intramyocardial arteriolar medial hypertrophy. There is no evidence of myocarditis, acute ischemic insult, or deposition. B, A ×40 magnification of a section stained with Masson’s trichrome demonstrates only minimal to mild interstitial fibrosis and minimal focal replacement fibrosis.
 Individuals II-5 and II-9 both have severe asymmetric unexplained LVH (interventricular septum [IVS] thickness, 25 and 20 mm, respectively) on echocardiography and no ECG abnormalities. They have mild, nonlimiting symptoms. II-7 had a similar degree of LVH (IVS thickness, 23 mm), along with mitral valve prolapse and sinus bradycardia. III-4 was diagnosed at 37 years of age on the basis of LVH (IVS thickness, 20 mm, plus free-wall hypertrophy to 25 mm) and ECG abnormalities of LVH with repolarization changes. III-10 was diagnosed at 44 years of age and has clinical features of LVH (IVS thickness, 18 mm), ECG criteria for LVH with repolarization changes, and refractory atrial fibrillation that ultimately was treated with AV nodal ablation. He is the only family member to have documented resting left ventricular outflow tract obstruction with a baseline gradient of 30 mm Hg resulting from systolic anterior motion of the mitral valve. Individual IV-12 was last evaluated at 13 years of age. He was active and asymptomatic at that time but had an abnormal ECG with right-axis deviation and voltage criteria for LVH. Echocardiography revealed mild LVH (IVS thickness, 13 mm) and mitral valve prolapse.

Individual II-3 is essentially asymptomatic at 87 years of age despite moderate asymmetric septal hypertrophy (IVS thickness, 16 mm) and ECG findings of left-axis deviation and diffuse T-wave abnormalities. His clinical status was considered unknown for the purposes of linkage analysis because he has concomitant systemic hypertension that is controlled with medication. Individuals IV-2, IV-3, IV-4, IV-6, IV-8, IV-10, IV-11, and IV-13 had no echocardiographic evidence of LVH, normal left ventricular systolic and diastolic function, and no ECG abnormalities. Given their young age (ranging from 17 to 29 years at last evaluation), they were deemed to be of unknown clinical status. Individual IV-7, 25 years of age, has borderline LVH (IVS and posterior wall, 12 mm) but a background of suboptimally controlled hypertension. He was deemed to be of unknown clinical status.

No other available family members had evidence of cardiac hypertrophy or dilation by echocardiographic or ECG assessment. Of the 32 phenotyped family members, 14 (II-3, III-10, III-14, III-16, IV-1, IV-2, IV-3, IV-4, IV-7, IV-8, IV-9, IV-10, IV-11, and IV-13) had echocardiographic studies performed since November 2004 with contemporary equipment. All had good to excellent image quality for analysis and showed no evidence of abnormal LV trabeculation or noncompaction to suggest alternative morphological processes.

### Candidate Gene Analysis

A candidate gene approach was initially used, and direct DNA sequence analysis was performed on all coding exons and intron/exon splice junctions of the 8 sarcomere genes most commonly associated with HCM (MYH7, MYL2, MYL3, MYBPC3, TNN2, TNNI3, TPM1, and ACTC). PRKAG2, encoding the γ2-regulatory subunit of adenosine monophosphate kinase, also was sequenced. Disease associated with mutations in these genes is characterized by unexplained cardiac hypertrophy, and they have been well established as the genetic origin of HCM and glycogen storage cardiomyopathies, respectively.

Mutations in sarcomere genes MYH7, TNN2, and ACTC also have been demonstrated to be a genetic origin of DCM. No mutations were identified in this family.

### Linkage Analysis

Genome-wide linkage analysis was then performed to map the disease locus. Analysis of 456 polymorphic loci excluded 42.5% of the genome (θ at LOD = -2.0) before linkage was identified with markers at 7p12.1-7q21 (Table 2). A maximum LOD score of 4.11 (at θ = 0%) was achieved at loci D7S669. Because this marker is fully informative, a multipoint calculation achieved no higher LOD score.

To refine the disease interval, genotypes were analyzed using additional markers at nearby loci, and a disease haplotype was identified with markers at markers at 7p12.1-7q21 (Table 2). A maximum LOD score of 4.11 (at θ = 0%) was achieved at loci D7S669. Because this marker is fully informative, a multipoint calculation achieved no higher LOD score.

### Table 1. Clinical Features of Affected Family Members

<table>
<thead>
<tr>
<th>ID</th>
<th>Age at Last Evaluation, y</th>
<th>Gender</th>
<th>ECG Findings</th>
<th>LV End-Diastolic Dimension, cm</th>
<th>LV End-Systolic Dimension, cm</th>
<th>IVS Thickness, mm</th>
<th>PW Thickness, mm</th>
<th>Left Atrial Size A-P, cm</th>
<th>LV Ejection Fraction, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-5</td>
<td>83</td>
<td>F</td>
<td>NA</td>
<td>5.1</td>
<td>1.8</td>
<td>25</td>
<td>21</td>
<td>5.3</td>
<td>70–75</td>
<td></td>
</tr>
<tr>
<td>II-7</td>
<td>81</td>
<td>M</td>
<td>NA</td>
<td>4.2</td>
<td>2.7</td>
<td>23</td>
<td>20</td>
<td>5.4</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>II-9</td>
<td>77</td>
<td>M</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-2</td>
<td>61</td>
<td>F</td>
<td>LVH</td>
<td>NA</td>
<td>15</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-4</td>
<td>49</td>
<td>M</td>
<td>LVH, TWA</td>
<td>4.6</td>
<td>2.3</td>
<td>20</td>
<td>8</td>
<td>3.7</td>
<td>60–65</td>
<td>Marked ST/T-wave abnormalities</td>
</tr>
<tr>
<td>III-10</td>
<td>56</td>
<td>M</td>
<td>LVH</td>
<td>5.1</td>
<td>1.9</td>
<td>18</td>
<td>16</td>
<td>5.8</td>
<td>60–65</td>
<td>AV node ablation for atrial fibrillation; resting LV outflow tract gradient 30 mm Hg</td>
</tr>
<tr>
<td>III-16</td>
<td>48</td>
<td>M</td>
<td>TWA</td>
<td>4.6</td>
<td>2.0</td>
<td>16</td>
<td>12</td>
<td>5.2</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>IV-9</td>
<td>30</td>
<td>F</td>
<td>Normal</td>
<td>3.7</td>
<td>1.9</td>
<td>14</td>
<td>13</td>
<td>3.4</td>
<td>60–65</td>
<td></td>
</tr>
<tr>
<td>IV-12</td>
<td>13</td>
<td>M</td>
<td>RAD, LVH</td>
<td>4.4</td>
<td>2.7</td>
<td>13</td>
<td>12</td>
<td>3.0</td>
<td>Normal</td>
<td>Mitral valve prolapse</td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PW, posterior left ventricular wall; TWA, T-wave abnormalities; and RAD, right-axis deviation.
deduced (Figure 1). Recombination events were identified in individual II-7 at D7S506 and in individual II-5 at D7S3314 (dinucleotide repeat marker; forward primer, 5′-agtgctctacacaatc; reverse primer, 5′-gggatggtgacctgaaaaga; located at 79.812 megabases [Mb] on chromosome 7, based on the May 2004 Golden Path Version hg17, UCSC), thereby defining a critical disease interval that spans 27.2 Mb on chromosome 7 (Figure 3).

Candidate Gene Analysis on the Critical Interval Defined by Linkage

Nine genes, SEC61G, FKBP9, PHKG1, POM121, TBL2, WBSCR18, TMPIT, POMZP3, and GNAI1, map to this disease interval and were considered potential candidate genes on the basis of their expression profile and function.17a SEC61G (protein transport protein SEC61, γ subunit) is necessary for protein translocation in the endoplasmic reticulum.18 FKBP9 encodes FK506 binding protein 9 and is abundantly expressed in the heart. It localizes to the endoplasmic reticulum and accelerates protein folding during protein synthesis.19 PHKG1 (phosphorylase kinase, γ1), is involved in the phosphorylation of troponin I via the calmodulin pathway.20 POM121 and POMZP3 (nuclear pore membrane protein 121 and Ap3 fusion) are involved in anchoring the nuclear pore complex to the nuclear envelope.21 TBL2 [transducin (β)-like 2 isoform 1] and WBSCR18 (Williams-Beuren syndrome chromosome region 18) are deleted in Williams-Beuren syndrome, characterized by cardiovascular abnormalities, including supravalvular aortic stenosis.22 TMPIT encodes a protein similar to the transmembrane protein induced by tumor necrosis factor alpha.19 GNAI1 [guanine nucleotide-binding protein G(i), α1 subunit] inhibits adenylate cyclase in response to β-adrenergic stimuli.23 The coding regions of these 9 candidate genes were sequenced (data not shown), and no disease-causing mutations were identified.

Sorcin is a 22-kDa calcium binding protein that may modulate excitation-contraction coupling in cardiac and skeletal myocytes via interactions with L-type calcium

![Figure 3](image-url)

**Figure 3.** The disease interval spans 27.2 Mb on 7p12.1-7q21, delimited by markers D7S2422 and D7S3314. The relative positions of candidate genes are indicated. Recombination events in affected (A) and unaffected individuals from family CN were identified by comparing affection status and genotype. White shading indicates concordance between disease status and genotype; black shading, discordance.

**TABLE 2.** Linkage in Family CN to Markers at 7p12.1-7q21

<table>
<thead>
<tr>
<th>Markers</th>
<th>0.00</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>D7S2422</td>
<td>-1.132</td>
<td>0.029</td>
<td>0.365</td>
<td>0.497</td>
<td>0.530</td>
<td>0.427</td>
<td>0.211</td>
</tr>
<tr>
<td>D7S506</td>
<td>-2.972</td>
<td>1.103</td>
<td>1.178</td>
<td>1.119</td>
<td>1.000</td>
<td>0.661</td>
<td>0.252</td>
</tr>
<tr>
<td>D7S1485</td>
<td>4.027</td>
<td>3.681</td>
<td>3.317</td>
<td>2.934</td>
<td>2.528</td>
<td>1.648</td>
<td>0.696</td>
</tr>
<tr>
<td>D7S494</td>
<td>3.884</td>
<td>3.533</td>
<td>3.164</td>
<td>2.775</td>
<td>2.363</td>
<td>1.475</td>
<td>0.569</td>
</tr>
<tr>
<td>D7S502</td>
<td>4.010</td>
<td>3.665</td>
<td>3.302</td>
<td>2.919</td>
<td>2.514</td>
<td>1.637</td>
<td>0.691</td>
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<tr>
<td>D7S3313</td>
<td>2.291</td>
<td>2.105</td>
<td>1.904</td>
<td>1.689</td>
<td>1.460</td>
<td>0.953</td>
<td>0.386</td>
</tr>
<tr>
<td>D7S2421</td>
<td>3.525</td>
<td>3.218</td>
<td>2.895</td>
<td>2.554</td>
<td>2.193</td>
<td>1.411</td>
<td>0.574</td>
</tr>
<tr>
<td>D7S669*</td>
<td>4.105*</td>
<td>3.754</td>
<td>3.385</td>
<td>2.995</td>
<td>2.583</td>
<td>1.687</td>
<td>0.718</td>
</tr>
<tr>
<td>D7S2443</td>
<td>2.644</td>
<td>2.403</td>
<td>2.149</td>
<td>1.881</td>
<td>1.599</td>
<td>0.993</td>
<td>0.395</td>
</tr>
<tr>
<td>D7S3314</td>
<td>-0.822</td>
<td>1.896</td>
<td>1.903</td>
<td>1.773</td>
<td>1.579</td>
<td>1.072</td>
<td>0.461</td>
</tr>
</tbody>
</table>

*The maximum 2-point LOD score.
channels and the ryanodine receptor.²⁴ The gene encoding sarcin is located at chromosome 7q21.1 but was excluded as a potential candidate gene because of its location 7.7 Mb remote from the critical region (Figure 3).

**Discussion**

We report a novel locus on chromosome 7p12.1-7q21 linked to an inherited mixed cardiomyopathy with hypertrophic and dilated features. The prototypical clinical condition associated with unexplained cardiac hypertrophy is hypertrophic cardiomyopathy. Prior linkage studies and candidate gene analysis of large kindreds with HCM identified causal mutations in genes encoding different elements of the contractile apparatus, thus establishing the paradigm that HCM is a disease of the sarcomere.⁶,⁷ Sarcomere gene mutations likely account for ≈60% of unexplained cardiac hypertrophy.⁹

More recently, mutations have been described in nonsarcomere proteins that result in disease that mimics the gross clinical phenotype of HCM. Genetic studies of families and sporadic cases of unexplained LVH with conduction abnormalities (progressive AV block, ventricular preexitation/Wolff-Parkinson-White syndrome) have been associated with mutations in the γ2 regulatory subunit (PRKAG2) of adenosine monophosphate–activated protein kinase, an enzyme involved with glucose metabolism, as well as mutations in the X-linked lysosome–associated membrane protein (LAMP2) gene. Inherited LVH caused by PRKAG2 or LAMP2 mutations define a new category of glycogen storage cardiomyopathies.¹² This disease is an entity distinct from hypertrophic cardiomyopathy caused by sarcomere protein mutations as confirmed by histopathological hallmarks of prominent nonmembrane bound vacuoles with glycogen and amylopectin accumulation rather than the myocyte disarray in fibrosis diagnostic of HCM. Although incompletely described, the molecular signals triggered by PRKAG2 and LAMP2 mutations are almost certainly different from those produced by sarcomere gene mutations.

Recent studies suggest that a genetic origin underlies idiopathic DCM in 30% to 50% of cases.¹³ A wide variety of mutations have been identified, individually present at low prevalence. Common mechanistic pathways are not obvious, but general themes are suggested. Paradoxically, mutations in contractile proteins give rise to DCM in addition to HCM, perhaps by perturbing force transmission more than force generation.²⁵–²⁷ Along similar lines, mutations in intermediate filaments and cytoskeletal elements also give rise to DCM, possibly via alterations in force transmission in the myocyte (reviewed elsewhere²⁸).

The family described in this report adds to our evolving understanding of the array of pathways that culminate in cardiac remodeling. This family also highlights the limitations of relying on relatively crude and nonspecific clinical characteristics to diagnose disease. Surviving family members display gross clinical phenotypic features that are indistinguishable from HCM; they fail to demonstrate the usual diagnostic histopathological features of HCM, however, and sarcomere gene mutations could not be identified either by direct DNA analysis or by inclusion in the disease interval on chromosome 7. Direct sequence analysis of PRKAG2 also failed to reveal pathological mutations. Two family members developed a lethal phenotype, culminating in sudden cardiac death at 40 years of age and end-stage heart failure necessitating cardiac transplantation at 49 years of age. Both had nonspecific histological features, notably lacking myocyte disarray and interstitial fibrosis, not supportive of typical hypertrophic cardiomyopathy.

Although the critical disease interval on chromosome 7 does not include any sarcomere protein genes, it may include genes encoding proteins that interact with and alter contractile function. Alternatively, given the divergent cardiac phenotypes, this family may indicate the presence of an undiscovered pathway leading to cardiac remodeling that is distinct from perturbing force transmission/generation or myocyte glucose metabolism.


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**CLINICAL PERSPECTIVE**

Genetic mutations are the most common cause of hypertrophic cardiomyopathy (HCM) and an increasingly recognized cause of dilated cardiomyopathy. Understanding the molecular mechanisms by which these mutations remodel the heart will provide insights germane not only to the study of primary cardiomyopathies but also to more prevalent forms of secondary cardiac remodeling, including structural abnormalities caused by hypertension and coronary atherosclerosis. Previous studies have established the paradigm that typical HCM is caused by mutations in sarcomere proteins, yet such mutations are not universally present and fail to account for 40% of HCM cases. Moreover, distinct genetic causes can mimic the gross clinical phenotype of HCM, and mutations in sarcomere genes can cause dilated cardiomyopathy. In this study, we report a family with an inherited cardiomyopathy with predominant features of cardiac hypertrophy, in addition to left ventricular dilation, heart failure, and sudden death. However, characteristic histopathological changes of HCM were not present, and genetic linkage analysis indicated that a novel chromosomal locus was responsible. As such, the disease manifestations of cardiomyopathy oftentimes are nonspecific. As highlighted in this study, the combined use of histopathological and molecular diagnostic tools has particular promise to improve our ability to make accurate diagnoses and to identify pathogenetic mechanisms. A more comprehensive and precise understanding of the varied pathways leading to heart failure is essential for progress in both basic science and clinical medicine.
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