Shared Genetic Causes of Cardiac Hypertrophy in Children and Adults

Hiroyuki Morita, M.D., Heidi L. Rehm, Ph.D., Andres Menesses, M.D., Barbara McDonough, R.N., Amy E. Roberts, M.D., Raju Kucherlapati, Ph.D., Jeffrey A. Towbin, M.D., J.G. Seidman, Ph.D., and Christine E. Seidman, M.D.

ABSTRACT

BACKGROUND
The childhood onset of idiopathic cardiac hypertrophy that occurs without a family history of cardiomyopathy can portend a poor prognosis. Despite morphologic similarities to genetic cardiomyopathies of adulthood, the contribution of genetics to childhood-onset hypertrophy is unknown.

METHODS
We assessed the family and medical histories of 84 children (63 boys and 21 girls) with idiopathic cardiac hypertrophy diagnosed before 15 years of age (mean ±SD age, 6.99±6.12 years). We sequenced eight genes: MYH7, MYBPC3, TNNT2, TNNI3, TPM1, MYL3, MYL2, and ACTC. These genes encode sarcomere proteins that, when mutated, cause adult-onset cardiomyopathies. We also sequenced PRKAG2 and LAMP2, which encode metabolic proteins; mutations in these genes can cause early-onset ventricular hypertrophy.

RESULTS
We identified mutations in 25 of 51 affected children without family histories of cardiomyopathy and in 21 of 33 affected children with familial cardiomyopathy. Among 11 of the 25 children with presumed sporadic disease, 4 carried new mutations and 7 inherited the mutations. Mutations occurred predominantly (in >75% of the children) in MYH7 and MYBPC3; significantly more MYBPC3 missense mutations were detected than occur in adult-onset cardiomyopathy (P<0.005). Neither hypertrophic severity nor contractile function correlated with familial or genetic status. Cardiac transplantation and sudden death were more prevalent among mutation-positive than among mutation-negative children; implantable cardioverter–defibrillators were more frequent (P=0.007) in children with family histories that were positive for the mutation.

CONCLUSIONS
Genetic causes account for about half of presumed sporadic cases and nearly two thirds of familial cases of childhood-onset hypertrophy. Childhood-onset hypertrophy should prompt genetic analyses and family evaluations.
The diagnosis of childhood cardiomyopathies can be prompted by abnormal physical findings that occur without symptoms or by life-threatening events, including sudden death, which is the presenting manifestation in 3.5% of affected children. Despite sophisticated medical management, rates of death and cardiac transplantation among children with symptomatic childhood-onset cardiomyopathy approach 40%. The early age at diagnosis and the striking differences in morbidity and mortality that distinguish childhood cardiomyopathies from adult-onset cardiomyopathies have been interpreted to indicate distinct causes of these pathologic conditions.

Adult-onset hypertrophic cardiomyopathy is a prevalent genetic condition caused by inherited or new mutations in genes that encode sarcomere proteins, including cardiac β-myosin heavy chain (MYH7), cardiac myosin-binding protein C (MYBPC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), essential myosin light chain (MYL3), regulatory myosin light chain (MYL2), α-tropomyosin (TPM1), cardiac actin (ACTC), and titin (TTN). Less commonly, hypertrophic cardiomyopathy is caused by mutations in other genes.

The range of ages at clinical diagnosis of hypertrophic cardiomyopathy is broad; however, manifestations before 14 years of age are atypical, even in children with an inherited gene mutation.

Mutations affecting the γ2 regulatory subunit of AMP-activated protein kinase (PRKAG2) (which regulates substrate use for energy production) cause early-onset left ventricular hypertrophy with arrhythmias and, more rarely, fatal infantile cardiac glycogenosis. Mutations in the gene encoding lysosome-associated membrane protein 2 (LAMP2), which is located on the X chromosome, cause massive left ventricular hypertrophy in boys in whom systemic manifestations (the Danon disease) may also develop. Because LAMP2 mutations are usually clinically silent in female carriers, affected boys appear to have sporadic rather than inherited disease.

To determine whether some childhood-onset left ventricular hypertrophies share a genetic cause with hypertrophic cardiomyopathy, we sequenced genes encoding eight sarcomere proteins, PRKAG2, and LAMP2 in 84 children with isolated, idiopathic left ventricular hypertrophy diagnosed before 15 years of age.

**METHODS**

**SUBJECTS**

Studies were performed in accordance with institutional guidelines and approved by the ethics committees of Brigham and Women’s Hospital and Baylor College of Medicine. Written informed consent was provided by the parents and age-appropriate assent was provided by the children. Subjects were participants in the Pediatric Cardiomyopathy Registry of the National Heart, Lung, and Blood Institute or were identified through referrals to investigators. All subjects had isolated, unexplained left ventricular hypertrophy (defined as a wall thickness >2 SD above the normal-population mean for body-surface area) that was diagnosed at or before 15 years of age. Subjects with extracardiac disease (suggesting the Danon disease, glycogen storage disease [types I through VI], Diamond–Blackfan anemia, muscular dystrophies, skeletal myopathies, or mitochondrial diseases) or secondary causes of hypertrophy (e.g., congenital malformations, hypertension, or drug exposure) were excluded.

Family histories were obtained from parents and, when possible, medical records were reviewed. The ancestry of subjects and controls was determined by parental report or self-report with the use of a list of options (see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

**DNA SEQUENCING AND CONFIRMATION OF SEQUENCE VARIANTS**

DNA was extracted from whole blood. Exons of MYH7, MYBPC3, TNNT2, TNNI3, TPM1, MYL2, MYL3, ACTC, PRKAG2, and LAMP2 were amplified from genomic DNA with the use of previously described primers and methods. After polymerase-chain-reaction (PCR) purification with the use of a QIAquick purification kit (Qiagen), DNA was sequenced with a dye-terminator cycle-sequencing system (ABI PRISM, Applied Biosystems).

DNA sequence variants were confirmed by means of restriction-enzyme digestion of PCR-amplified fragments with the use of oligonucleotide primers (Table 2 of the Supplementary Appendix). Previously unreported nonsynonymous sequence variants (Table 1, and Table 3 of the Supplementary Appendix) were assessed with the
use of the described procedures in DNA samples obtained from 180 unrelated persons who were matched by ancestral origin to the subjects.

**STATISTICAL ANALYSIS**

Descriptive data for continuous clinical values were expressed as means ±SD or discrete values (numbers or percentages). Differences in clinical characteristics between groups were assessed with the use of Proc GLM software for continuous variables (SAS Institute) or the Proc Logistic procedure for discrete variables (SAS Institute). \(^{16}\)

Distributions of types of sarcomere-protein gene mutations in groups were compared with the use of two-tailed exact \(P\) values, with a \(P\) value of less than 0.05 considered to indicate statistical significance.

**RESULTS**

We studied 84 unrelated children (63 boys and 21 girls) with unexplained left ventricular hypertrophy diagnosed at or before 15 years of age (mean age, 6.99±6.12 years) (Table 1). Hypertrophy was determined by means of echocardiography (Fig. 1) and defined as a mean left ventricular wall thickness of at least 2 SD above the normal value, stratified according to body-mass index or age. \(^{1}\)

The ages of the children at diagnosis ranged from 2 days to 15 years. Initial clinical evaluations were prompted by abnormal physical findings (e.g., murmur or cardiomegaly) identified during routine examinations or by symptoms that were nonspecific (e.g., irritability or lack of feeding in an infant) or suggestive of heart disease (e.g., chest pain). Three children died suddenly from cardiac causes, and in one child this was the presenting manifestation. Over a 5-year follow-up period, 10 children received implantable cardioverter–defibrillators and 5 children underwent cardiac transplantation.

Family histories were positive for cardiomyopathy in 33 children but negative in 51 children who were presumed to have sporadic disease. There were no significant differences with regard to sex distribution, age at presentation, maximum left ventricular wall thickness, contractile function, sudden death, or cardiac transplantation between the group of children with familial disease and the group of children with presumed sporadic cardiomyopathy (Table 1). However, significantly more children with a family history of cardiomyopathy received implantable cardioverter–defibrillators (8 of 33 children, vs. 2 of 51 children with no family history; \(P=0.007\)).

Nucleotide sequences encoding eight sarcomere-protein genes (MYH7, MYBPC3, TNNT2, TNNI3,
Among children with presumed sporadic cardiomyopathy, 112 sequence variants were identified (Fig. 1 of the Supplementary Appendix). Seventy-nine synonymous variants or intronic polymorphisms distant from conserved splicing sequences were not predicted to alter the protein structure. Six nonsynonymous MYBPC3 variants (Val158Met, Ser236Gly, Arg326Gln, Val1677Met, Arg495Gly, and Gly1248Arg), disrupted RNA splicing (detailed above). Each of these previously unreported variants caused missense residues, 1 is predicted to delete an amino acid, and 1 is predicted to prematurely terminate protein translation.

Eleven sequence variants were not previously reported: MYH7 Val1763Met, MYH7 Arg787Cys, MYH7 Leu1414Met, MYBPC3 Arg495Gly, MYBPC3 Thr1028Ser, MYBPC3 IVS31+2t→g, MYBPC3 Gly1248Arg, TNNT2 Glu96del, ACTC His90Tyr, ACTC Arg97Cys, and PRKAG2 His530Arg. Nine of these previously unreported variants caused missense changes and altered amino acid residues that are highly conserved during mammalian evolution (Fig. 3 of the Supplementary Appendix), one variant deleted a highly conserved glutamic acid residue in TNNT2, and one variant altered MYBPC3 splicing (detailed above). Each of these 11 previously unreported variants was absent in 180 unrelated persons matched by ancestral origin to the subjects (data not shown) and in more than 1000 chromosomes of unaffected persons (unpublished data). Furthermore, sequence analyses of these eight sarcomere-protein genes in 34 persons without left ventricular hypertrophy revealed no variants. On the basis of a chi-square analysis, the probability that 25 nonsynonymous sequence variants occurred by chance in 51 cases of pediatric-onset left ventricular hypertrophy is less than 1 in 500,000. We conclude that each of these previously unreported variants, like the 14 mutations known to cause hypertrophic cardiomyopathy, caused left ventricular hypertrophy in these children.

Three of the 25 children with presumed sporadic cardiomyopathy who had mutations (12%) had two different sarcomere-gene mutations: MYH
Gene Mutations in Childhood-Onset Cardiac Hypertrophy

MYH7
- Arg663His
- Val606Met
- Arg663His
- Val763Met
- Arg719Gln
- Leu908Val
- Glu924Lys
- Leu1414Met
- Gly278Glu
- Gly490Arg
- Arg495Gly
- Arg502Gln
- Asp605Asn
- Arg943ter
- Thr1028Ser
- IVS31+2t→g
- Gly1248Arg
- Arg92Gln
- Glu96del
- Lys178del
- His90Tyr
- Arg97Cys
- His530Arg

MYBPC3
- Gly1248Arg
- Thr1028Ser
- IVS31+2t→g
- Gly1248Arg
- Arg92Gln
- Glu96del
- Lys178del
- His90Tyr
- Arg97Cys
- His530Arg

ACTC
- His90Tyr
- Arg97Cys
- His530Arg

PRKAG2
- His90Tyr
- Arg97Cys
- His530Arg

Table 2. Gene Mutations in Patients with Childhood-Onset Cardiac Hypertrophy and Presumed Sporadic Cardiomyopathy.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Sequence</th>
<th>Consequence</th>
<th>Charge</th>
<th>Previously Reported Hypertrophic Cardiomyopathy Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td>Lys146Asn</td>
<td>G→T</td>
<td>Missense</td>
<td>−1</td>
<td>Yes</td>
</tr>
<tr>
<td>MYH7</td>
<td>Val606Met</td>
<td>G→A</td>
<td>Missense</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>MYH7</td>
<td>Arg663His</td>
<td>G→A</td>
<td>Missense</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>MYH7</td>
<td>Arg719Gln</td>
<td>G→A</td>
<td>Missense</td>
<td>−1</td>
<td>Yes</td>
</tr>
<tr>
<td>MYH7</td>
<td>Val763Met</td>
<td>G→A</td>
<td>Missense</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>MYH7</td>
<td>Arg787Cys</td>
<td>C→T</td>
<td>Missense</td>
<td>−1</td>
<td>No</td>
</tr>
<tr>
<td>MYH7</td>
<td>Leu908Val</td>
<td>C→G</td>
<td>Missense</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>MYH7</td>
<td>Glu924Lys</td>
<td>G→A</td>
<td>Missense</td>
<td>+2</td>
<td>Yes</td>
</tr>
<tr>
<td>MYH7</td>
<td>Leu1414Met</td>
<td>C→A</td>
<td>Missense</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Gly278Glu</td>
<td>G→A</td>
<td>Missense</td>
<td>−1</td>
<td>Yes</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Gly490Arg</td>
<td>G→A</td>
<td>Missense</td>
<td>+1</td>
<td>Yes</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Arg495Gly</td>
<td>C→G</td>
<td>Missense</td>
<td>−1</td>
<td>No</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Arg502Ter†</td>
<td>C→T</td>
<td>Missense</td>
<td>−1</td>
<td>Yes</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Arg502Gln</td>
<td>G→A</td>
<td>Missense</td>
<td>−1</td>
<td>Yes</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Asp605Asn</td>
<td>G→A</td>
<td>Missense</td>
<td>+1</td>
<td>Yes</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Arg943Ter</td>
<td>C→T</td>
<td>Truncation</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Thr1028Ser</td>
<td>C→G</td>
<td>Missense</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>IVS31+2t→g‡</td>
<td>t→g</td>
<td>Truncation</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Gly1248Arg</td>
<td>G→a</td>
<td>Missense</td>
<td>+1</td>
<td>No</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Arg92Gln</td>
<td>G→A</td>
<td>Missense</td>
<td>−1</td>
<td>Yes</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Glu96del</td>
<td>ΔGAG</td>
<td>Codon 96 deleted</td>
<td>+1</td>
<td>No</td>
</tr>
<tr>
<td>TNNT3</td>
<td>Lys178del</td>
<td>ΔAAG</td>
<td>Codon 178 deleted</td>
<td>−1</td>
<td>Yes</td>
</tr>
<tr>
<td>ACTC</td>
<td>His90Tyr</td>
<td>C→T</td>
<td>Missense</td>
<td>−1</td>
<td>No</td>
</tr>
<tr>
<td>ACTC</td>
<td>Arg97Cys</td>
<td>C→T</td>
<td>Missense</td>
<td>−1</td>
<td>No</td>
</tr>
<tr>
<td>PRKAG2</td>
<td>His530Arg</td>
<td>A→G</td>
<td>Missense</td>
<td>0</td>
<td>No</td>
</tr>
</tbody>
</table>

* Mutations are denoted by normally encoded amino acid residue number, substituted amino acid or termination signal (ter), or altered splice signal (intervening sequence). Sequence refers to nucleotide substitution, and consequence refers to the mutational effects on protein. Charge is the altered charge by the mutant amino acid change. NA denotes not available. Three children had compound mutations: MYH7 Arg663His and MYH7 Val763Met, MYBPC3 Thr1028Ser and MYBPC3 IVS31+2t→g, and MYH7 Arg787Cys and ACTC Arg97Cys.
† This mutation was identified in three children.
‡ This mutation was identified in two children.

7Arg663His and Val763Met; MYH7 Arg787Cys and ACTC Arg97Cys; and MYBPC3 Thr1028Ser and MYBPC3 IVS31+2t→g. We observed the MYBPC3 IVS31+2t→g mutation in isolation in another child; others27 have reported MYH7 Arg663His in isolation as the cause of hypertrophic cardiomyopathy.

To determine whether sporadic left ventricular hypertrophy in the children reflected new mutational events, we genotyped the parents of 11 probands (Fig. 2) and confirmed parental relationships using 22 polymorphic microsatellite markers (data not shown). Four mutations (MYH7 Lys146Asn, MYH7 Glu924Lys, TNNT2 Arg92Gln, and TNNT2 Glu96del) were absent from both parents, confirming that new mutations accounted for sporadic cardiomyopathy in these children. In contrast, mutations found in seven children were also present in the parents, indicating that these
mutations were inherited (Fig. 2). Clinical studies revealed cardiomyopathy in one parent, were not performed in two parents, and showed no abnormalities in five parents, two of whom carried one of the two MYBPC3 mutations carried by their compound heterozygous (Thr1028Ser and IVS31+2t→g) affected child.

To determine the parental origins of chromosomes for new mutations, closely linked polymorphisms were analyzed. Haplotype analyses were not informative in two subjects (with mutations MYH7 Lys146Asn and TNNT2 Glu96del). Haplotype analyses indicated that the new mutation MYH7 Glu924Lys arose on a maternal chromosome (Fig. 4A of the Supplementary Appendix), and the new mutation TNNT2 Arg92Gln arose on a paternal chromosome (Fig. 4B of the Supplementary Appendix).

We also sequenced genes in 33 patients who had childhood-onset cardiac hypertrophy and family histories of cardiomyopathy but who had not undergone previous genetic studies. Twenty-two nonsynonymous sequence variants (Table 3 of the Supplementary Appendix) were identified in 21 patients (64%); each variant altered a sarcomere-protein gene: MYH7 (in 9 patients), MYBPC3 (in 7 patients), TNNT2 (in 2 patients), TNNI3 (in 1 patient), TPM1 (in 2 patients), and MYL3 (in 1 patient). No variants were found in ACTC or MYL2.

Fifteen sequence variants were previously reported as cardiomyopathy mutations (Table 3 of the Supplementary Appendix). The remaining seven variants (MYH7 Glu903Gly, MYH7 Ser1836Leu, MYBPC3 Ile154Thr, MYBPC3 Asp605del, MYBPC3 Ser858Asn, TMP1 Ser215Leu, and MYL3 Met173Val) were absent from 180 unrelated, ancestrally matched persons (data not shown) and from more than 1000 chromosomes of unaffected persons (unpublished data). Each of these new variants altered amino acid residues that are highly conserved throughout mammalian evolution (Fig. 5 of the Supplementary Appendix), predicting that the missense residue alters protein structure.

Among mutation-positive children with familial disease, three (14%) had compound mutations (MYBPC3 Arg502Trp and MYBPC3 Ser858Asn; MYBPC3 Arg495Gly and IVS31+2t→g; and MYBPC3 Thr1028Ser and IVS31+2t→g).
Genetic studies of childhood-onset cardiomyopathy characterized by unexplained left ventricular hypertrophy in the absence of systemic disease revealed a gene mutation in 46 of 84 patients (55%). Rates of mutation detection were similar among children with familial cardiomyopathy (64%; 95% confidence interval [CI], 45 to 80) and among children with presumed sporadic cardiomyopathy (49%; 95% CI, 36 to 62). We suggest that unexplained hypertrophy that presents during childhood should prompt evaluation for a potential genetic cause of the cardiac changes.

All but 1 of the 46 mutations identified occurred in a sarcomere-protein gene. Thus, despite considerable clinical differences between childhood-onset hypertrophy and hypertrophic cardiomyopathy in adulthood, our data define an etiologic relationship between these pathologic conditions.

We considered whether the disease gene, mutation type, or mutation number accounted for the early clinical presentation, poor prognosis, or male predilection observed in this study cohort. More than 75% of the children who had mutation-positive hypertrophy with a family history (16 of 21 children) or without a family history (20 of 25 children) had at least one mutation in MYH7 (encoding β-myosin heavy chain) or MYBPC3 (encoding myosin-binding protein C). Mutations in these genes that encode thick filaments also account for the majority of cases of familial hypertrophic cardiomyopathy, elderly-onset hypertrophic cardiomyopathy (onset after 50 years of age), and left ventricular hypertrophy in participants of the Framingham Heart Study (Table 3).

The two types of MYBPC3 mutations are those that are predicted to result in the substitution of one amino acid for another (also called missense mutations) and truncation mutations, which are predicted to foreshorten the protein. A total of

### Table 3. Distribution of Sarcomere-Protein Gene Mutations in Different Populations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sarcomere Mutations</th>
<th>Familial Hypertrophic Cardiomyopathy</th>
<th>Elderly-Onset Left Ventricular Hypertrophy</th>
<th>Childhood-Onset Left Ventricular Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gene (%)</td>
<td>Familial</td>
<td>Elderly-Onset</td>
<td>Childhood-Onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sporadic</td>
<td>Sporadic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>34.4</td>
<td>24.1</td>
<td>10.7</td>
<td>21.2</td>
</tr>
<tr>
<td>MYH7</td>
<td>41.2</td>
<td>23.4</td>
<td>1.6</td>
<td>33.3</td>
</tr>
<tr>
<td>TNNT2</td>
<td>8.0</td>
<td>4.2</td>
<td>0</td>
<td>6.1</td>
</tr>
<tr>
<td>TNNI3</td>
<td>7.4</td>
<td>4.9</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>TPM1</td>
<td>2.9</td>
<td>0.4</td>
<td>0</td>
<td>6.1</td>
</tr>
<tr>
<td>MYL3</td>
<td>1.2</td>
<td>0.5</td>
<td>0</td>
<td>3.0</td>
</tr>
<tr>
<td>MYL2</td>
<td>3.1</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ACTC</td>
<td>1.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mutation detection (%)</td>
<td></td>
<td></td>
<td>NA</td>
<td>59.3</td>
</tr>
<tr>
<td>Probands (no.)</td>
<td>NA</td>
<td>551</td>
<td>122</td>
<td>33</td>
</tr>
</tbody>
</table>

* This category refers to the percentage of mutations that have been detected in each sarcomere-protein gene. Data are from the CardioGenomics Project Web site and unpublished data. NA denotes not available.
† This category refers to the percentage of unrelated probands (persons younger than 50 years of age with a diagnosis of familial hypertrophic cardiomyopathy) with a mutation in each sarcomere-protein gene. Data are from the CardioGenomics Project Web site and unpublished data. NA denotes not available.
‡ This category refers to the percentage of unrelated probands (persons older than 50 years of age with a diagnosis of hypertrophic cardiomyopathy or unexplained left ventricular hypertrophy and without a family history of disease) with a mutation in each sarcomere-protein gene. Data are from Morita et al., Anan et al., and Niimura et al.† The frequency of MYBPC3 and MYH7 in the sporadic pediatric cohort was significantly higher than the frequency in the elderly cohort with unexplained left ventricular hypertrophy (P<0.001) and was not significantly different from the frequency in the cohort with familial hypertrophic cardiomyopathy.
§ This category refers to the percentage of unrelated probands (children in the familial and sporadic cohorts with a diagnosis of unexplained left ventricular hypertrophy) with a mutation in each sarcomere-protein gene.
¶ Mutation detection refers to the percentage of persons in each cohort who had a sarcomere-protein gene mutation or, in this study, a PRKAG2 mutation.
13 of the 17 MYBPC3 mutations found in patients with childhood-onset hypertrophy were missense mutations (8 in patients with presumed sporadic disease and 5 in patients with familial disease), whereas among 162 previously reported MYBPC3 mutations, only 64 were missense mutations (P = 0.005); the remainder encoded truncations. This high proportion of MYBPC3 missense mutations in childhood-onset hypertrophy may imply greater functional consequences of MYBPC3 missense mutations than of truncation mutations. The variable stability of different mutant messenger RNAs, mutant proteins, or both might influence clinical expression. This model is supported by the observation that only small amounts of truncated myosin-binding protein C polypeptides, if any, are incorporated into the sarcomere. Alternatively, earlier clinical expression of MYBPC3 missense mutations than of truncation mutation may result from distinct effects on the biophysical properties of myosin-binding protein C.

Virtually all known MYH7 mutations, including those that we report here, are missense mutations. Background genotypes, lifestyle, and other factors probably contribute to the age at which different MYH7 mutations and other sarcomere-protein genes become clinically manifest. The strikingly unequal sex distribution of patients in this study provides support for the influence of background genotype on clinical expression. Although dominant defects in genes are equally transmitted to male and female offspring, boys predominated among the children with mutations (35 boys vs. 11 girls; P = 0.002) (Table 1). Unequal sex distribution was also observed among patients with presumed sporadic cardiomyopathy (39 boys and 12 girls; P < 0.001), those with cardiomyopathy of unknown cause (18 boys and 8 girls with presumed sporadic cardiomyopathy and 10 boys and 2 girls with familial cardiomyopathy), and subjects enrolled in the Pediatric Cardiomyopathy Registry of the National Heart, Lung, and Blood Institute and the Australian Cardiomyopathy Registry. Understanding the biology that underpins a gene and the Australian Cardiomyopathy Registry. The remainder had inherited an MYBPC3 mutation (Fig. 2). The significant overrepresentation of MYBPC3 mutations in patients without hypertrophy (P = 0.001) is consistent with previous studies that show left ventricular hypertrophy in only 55% of MYBPC3 mutation carriers before 40 years of age. Our clinical evaluations of the parents genotyped in this study revealed only one parent with cardiomyopathy and clinically significant arrhythmias. Given the lifetime penetrance of sarcomere-gene mutations and the increased potential for coexisting conditions (particularly atrial fibrillation, which increases in frequency with disease duration), we recommend clinical management strategies that reduce the risk of sudden death.
evaluations or genetic studies in all first-degree family members of children with unexplained left ventricular hypertrophy.

In conclusion, approximately half of all cases of childhood-onset isolated cardiac hypertrophy are caused by a mutation of genes that are routinely screened in adults with unexplained left ventricular hypertrophy. Analyses of genes encoding some sarcomere-protein genes, PRKAG2, and LAMP2 (the latter only if warranted by clinical findings) can precisely define the cause and help to identify family members at risk. The application of management strategies developed for hypertrophic cardiomyopathy may improve outcomes in children with sarcomere-gene mutations.

Supported by grants from the Howard Hughes Medical Institute (to Dr. C.E. Seidman), the National Heart, Lung, and Blood Institute (to Drs. J.G. Seidman and Towbin), the National Football League Charities Foundation (to Drs. J.G. Seidman and C.E. Seidman), and the Children’s Cardiomyopathy Foundation (to Dr. Towbin).

We thank Josh Gorham, Steven DePalma, and Daniel Herman for excellent technical assistance and statistical support.

REFERENCES


Copyright © 2008 Massachusetts Medical Society.