Patients With Familial Hypertrophic Cardiomyopathy Caused by a Phe110Ile Missense Mutation in the Cardiac Troponin T Gene Have Variable Cardiac Morphologies and a Favorable Prognosis

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Background—Mutations that cause familial hypertrophic cardiomyopathy have been identified in several genes that encode contractile proteins. Patients with mutations in the cardiac troponin T (cTnT) gene have particularly poor prognosis but only mild hypertrophy. To date, no benign mutation in the cTnT gene has been reported. The clinical characteristics and prognosis of patients with the Phe110Ile mutation in the cTnT gene is unclear because few affected individuals have been identified.

Methods and Results—Forty-six probands with familial hypertrophic cardiomyopathy were screened for mutations in the cTnT gene. The Phe110Ile missense mutation was found in 6 probands. Individuals in the 6 families were analyzed genetically and clinically. Haplotype analysis was performed with markers encompassing the cTnT gene. Left ventricular hypertrophy was classified as type I, II, III, or IV according to the criteria of Maron et al. The Phe110Ile mutation in the cTnT gene was identified in 16 individuals. Two of the 6 families shared the same flanking haplotype, and 4 were different from each other. Affected individuals exhibited different cardiac morphologies: 4 had type II, 6 had type III, and 3 had type IV hypertrophy with apical involvement. Three individuals with the disease-causing mutation did not fulfill clinical criteria for the disease. The product-limit survival curve analysis demonstrated a favorable prognosis.

Conclusions—Multiple independent mutations of residue 340 in the cTnT gene have been described, suggesting that this may be a “hot spot” for such events. The Phe110Ile substitution causes hypertrophic cardiomyopathy with variable cardiac morphologies and a favorable prognosis. (Circulation. 1998;98:391-397.)

Key Words: cardiomyopathy • echocardiography • genetics • prognosis

Familial hypertrophic cardiomyopathy is a complex cardiac disease with unique pathophysiological characteristics and a great diversity of morphological, functional, and clinical features.1 Mutations in 7 genes that encode proteins in the sarcomere have been associated with familial hypertrophic cardiomyopathy: the β-cardiac myosin heavy chain, α-tropomyosin, cardiac troponin T (cTnT), cardiac troponin I, cardiac myosin binding protein C, cardiac myosin regulatory light chain, and cardiac myosin essential light chain genes.2–6

The clinical characteristics of patients with familial hypertrophic cardiomyopathy differ depending on the particular genetic mutation. Mutations in the β-cardiac myosin heavy chain gene are associated with substantial cardiac hypertrophy.7,8 In contrast, cTnT defects are associated with mild cardiac hypertrophy.9

Patients with some mutations in the β-cardiac heavy chain gene have hypertrophic cardiomyopathy with a poor prognosis, whereas those with others have a benign prognosis.3,8 The described mutations in the cTnT gene have all been associated with a poor prognosis.5–11 Six mutations in the cTnT gene (Ile79Asn, Arg92Gln, Arg92Trp, Ala104Val, ΔGlu160, and Intron 15G>A) are characterized by a high incidence of sudden death.5–11 However, the characteristics and prognosis of patients with other mutations in the cTnT gene are not known because the number of affected patients is small. To date, no benign mutation in the cTnT gene has been reported. Only 1 family with 2 affected individuals with a Phe110Ile mutation in the cTnT gene has been reported,9 and the clinical characteristics and prognosis of patients with such mutations are not known. Moolman et al10 emphasized that independent clinical data are necessary to confirm the characteristic phenotype of patients with cTnT gene mutations. To further clarify the genetic and clinical features of familial hypertrophic cardiomyopathy caused by mutations in the cTnT gene, we analyzed this gene in individuals from families with familial hypertrophic car-

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diomyopathy. Sixteen patients in 6 families with a Phe110Ile mutation in the cTnT were identified, and the clinical features of this mutation were studied. Here we report that the Phe110Ile mutation in the cTnT gene is associated with hypertrophic cardiomyopathy with variable cardiac morphologies and a favorable prognosis.

Methods

Study Patients

Informed consent was obtained in accordance with the local institutional review committees for human subject investigations. Forty-six probands with familial hypertrophic cardiomyopathy were enrolled in the study. Six families whose probands had a Phe110Ile mutation in the cTnT gene were studied further. Members of the 6 families were studied both genetically and clinically.

Genetic Studies

DNA was isolated from peripheral blood lymphocytes by use of a DNA extractor WB kit (Wako Pure Chemical Industries, Ltd). On the basis of the published sequences and the sequences obtained from GenBank (accession numbers X98477, X98478, X98480, X98481, and Y09626-Y09628), the cTnT gene was amplified by the polymerase chain reaction with 400 ng of genomic DNA and 500 ng each of the 2 primers. After polymerase chain reaction amplification, cycle sequencing was done with the cyclist DNA sequencing kit (Stratagene) and a primer end-labeled with [32P]ATP (Amersham). The sequence was obtained directly from the product of polymerase chain reaction. Exon 9 of the cTnT gene was amplified with primers 277F (5′-GACATCCACCGGAACGCATGGGA-3′) and 393R (5′-GATCCTGCTTTGGAGAAGCC-3′).

Exon 9 in the cTnT was sequenced in members of the 6 families to confirm cosegregation of the mutation with clinical status. Samples from 50 normal individuals were also analyzed.

To determine whether the mutation arose independently or reflected a founder effect in these 6 families, the haplotype associated with the gene defect was identified. Five flanking short tandem repeat markers (AFM123yc7, AFMb309xe1, AFM289ye9, AFMb334zeb1, and AFM234wf6) encompassing 19 cM flanking the cTnT gene were analyzed.

Clinical Evaluations

Forty-six probands were evaluated by echocardiography and ECG. A diagnosis of familial hypertrophic cardiomyopathy was based on the presence of unexplained cardiac hypertrophy. Family members of the 6 probands with the Phe110Ile mutation in the cTnT gene were studied further. Twenty members of families KC, KD, KE, KF, KG, and KH were genetically studied and clinically evaluated (Figure 1).

Sixteen of the 20 individuals studied had Phe110Ile mutation in the cTnT gene (Figure 1). The results of the haplotype analysis are shown in Table 1 and Figure 1. The disease gene haplotype (5,5,2,3,6) was identical in the KD and KG families. The disease gene haplotypes were different in 2 other families: 5,5,2,4,6 in the KE and 5,10,2,1,2 in the KH family.

In the KC and KE families, the haplotypes were not determined because only the probands were available for the study. The haplotype of the KE family may have been identical to those of the KD and KG families. However, the haplotype of AFMb309xe1 was 2 or 9 in the KE family, which was different from that present in the KD and KG families. The haplotypes may have been identical in the KC and KH families. However, the haplotype of AFM234wf6 was 1 or 6 in the KC family, which was different from that present in the KH family.

The origin of the mutation was the same in 2 families (the KD and KG families) and different in the other 4 families studied.

Clinical Results

Sixteen individuals (5 men and 11 women; mean age, 48±17 years) of 20 studied had the Phe110Ile mutation in the cTnT gene (Figure 1 and Table 2). Chest pain was seen in 1 individual (KE I-1). No individual complained of dyspnea or syncope. One patient (KG I-1) had hypertension and was on a calcium channel blocker.

Table 2 shows the echocardiographic findings of the 16 affected individuals. Three individuals with the Phe110Ile mutation (KE II-2, KG II-3, and KH III-2) did not show left ventricular hypertrophy, and they were classified as having a nonpenetrant mutation. No individual showed type I left ventricular hypertrophy, 4 showed type II, 6 showed type III, and 3 showed type IV. All 3 individuals with type IV left ventricular hypertrophy showed apical hypertrophy.

The mean maximal wall thickness of the affected individuals was 17.3±4.8 mm, and the penetrance of the mutation was 81%. Left ventricular end-diastolic dimension and fractional shortening of the left ventricle were normal in all the affected individuals. Left ventricular outflow obstruction was seen in 1 individual with type III hypertrophy (KC II-1). Seven individuals showed asymmetrical septal hypertrophy.
Table 3 shows the ECG findings of the affected individuals. All these individuals had sinus rhythm, and 1 (KG III-1) had sinus bradycardia. One elderly individual (KG I-1) showed first-degree atrioventricular block, with a PR interval of 0.22 second. QRS width was normal in all individuals. SV1+RV5 was >3.5 mV in 9 of 16 individuals (56%). Abnormalities in ST-T waves were seen in 15 individuals (94%), and 2 of the 3 individuals with apical hypertrophy showed giant negative T waves in the left precordial leads.

**Figure 1.** Pedigrees of the 6 families studied. Circles represent females; squares, males. Solid symbols indicate affected individuals; open symbols, unaffected individuals. Slashed symbols indicate deceased members, and shaded symbols indicate unknown disease status. Arrow indicates proband of family. Alleles are listed (top to bottom) for markers AFM123yc7, AFMb309xe1, AFM289ye9, AFMb334zb1, and AFM234wf6. Boxed alleles indicate affected alleles.

**TABLE 1. Disease-Gene Haplotypes in the 6 Families**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Locus</th>
<th>KC</th>
<th>KD</th>
<th>KE</th>
<th>KF</th>
<th>KG</th>
<th>KH</th>
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<td>5</td>
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<td>D1S2757</td>
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<td>5</td>
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<td>2/9</td>
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<td>10</td>
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<td>D1S477</td>
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<td>2</td>
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<tr>
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<td>D1S2773</td>
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<td>3</td>
<td>4</td>
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<td>1</td>
</tr>
<tr>
<td>AFM234wf6</td>
<td>D1S249</td>
<td>1/6</td>
<td>6</td>
<td>6</td>
<td>2/6</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

**Prognosis**

Two individuals (1 in family KD and 1 in family KH) died suddenly at the age of 33 and 52 years, respectively. No other disease-related deaths were observed. Six of 16 affected individuals were >50 years old. To analyze the survival of the patients with the Phe110Ile mutation in the cTnT gene, the data were combined for members of the 6 families.

Figure 2 shows the Kaplan-Meier product-limit curves for survival of the individuals with a Phe110Ile mutation and 2 other mutations in the β-cardiac myosin heavy chain gene. Survival among patients with the Phe110Ile mutation in the cTnT gene...
was similar to that seen in patients with Phe513Cys \(\beta\)-cardiac myosin heavy chain gene mutation. A significant difference (\(P=0.0002\)) in life expectancy was observed in individuals with the Phe110Ile versus the malignant Arg719Trp mutation in the \(\beta\)-cardiac myosin heavy chain gene.

**Discussion**

Eleven different mutations in the cTnT gene have been reported to cause familial hypertrophic cardiomyopathy.\(^3,9 –11,14\) Only 2 of these, Arg92Gln and Glu160, have been recognized, in 3 and 2 families, respectively.\(^3,9\) Characterization of the Phe110Ile mutation in 6 different families adds to our understanding of the consequences of these mutations.

**Genotype**

When a mutation is found in \(\geq 2\) unrelated families, it reflects either a founder effect or recurrent identical mutations occurring independently. To test this hypothesis, we studied the cTnT haplotypes associated with the disease-causing mutation in each family.

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**Table 2. Echocardiographic Findings in the Affected Individuals**

<table>
<thead>
<tr>
<th>Family</th>
<th>No.</th>
<th>Sex</th>
<th>Age, y</th>
<th>IVSth, mm</th>
<th>PWth, mm</th>
<th>IVSth/PWth</th>
<th>Max LWWT</th>
<th>LVDd, mm</th>
<th>%FS</th>
<th>Type of LV Hypertrophy</th>
<th>Outflow Obstruction</th>
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<td>48</td>
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<td>III</td>
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<td>45</td>
<td>44</td>
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<tr>
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<td>M</td>
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<td>F</td>
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<td>11</td>
<td>11</td>
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<td>20</td>
<td>48</td>
<td>40</td>
<td>IV</td>
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</tr>
<tr>
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<td>13</td>
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<td>III</td>
<td>–</td>
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<tr>
<td>KG</td>
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<td>F</td>
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<td>20</td>
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<td>1.8</td>
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<td>20</td>
<td>48</td>
<td>40</td>
<td>IV</td>
<td>–</td>
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</table>

IVSth indicates interventricular septal wall thickness; PWth, left ventricular posterior wall thickness; Max LWWT, maximal left ventricular wall thickness; LVDd, left ventricular end-diastolic dimension; %FS, % fractional shortening; L, left ventricle; +, presence of a finding; and –, absence of a finding.

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**Table 3. ECG Findings in the Affected Individuals**

<table>
<thead>
<tr>
<th>Family</th>
<th>No.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Rhythm/HR, bpm</th>
<th>PR Interval, s</th>
<th>Width, s</th>
<th>SV1, mV</th>
<th>RV5,mV</th>
<th>ST-T Change</th>
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<tr>
<td></td>
<td>III-1</td>
<td>F</td>
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<td>0.8</td>
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</tbody>
</table>

HR indicates heart rate; SR, sinus rhythm; +, presence of a finding; and –, absence of a finding.
that this may be a “hot spot” for such events.

ple independent mutations of residue 340 in cTnT suggest
recurrent, independently occurring mutational events. Multi-
times reflect a founder effect, and in many cases reflect
conclude that mutations found in different families some-

Arg719Trp mutation in
was observed in individuals with Phe110Ile versus malignant
yses identified 16 individuals with Phe110Ile mutation in the
gene. Our analyses demonstrate that the distribution of
hypertrophy among the affected individuals was the same in
the members of 1 family but was different among the
members of the other 3 families. We conclude that this gene
defect results in varied distributions of hypertrophy within
and between families.

The origin of the mutation in these 6 clinically unrelated
families was identical in 2 families and different in 4. We
suggest that the 2 families sharing the same haplotype have a
common ancestor, whereas the Phe110Ile mutation arose
independently in the 4 other families.

Previous analyses of the role of founding mutations in
familial hypertrophic cardiomyopathy have demonstrated that
the origin of the mutation was identical in 2 of 7 mutations
tested but different in 5 of the 7 mutations tested.9,21,22 We
conclude that mutations found in different families sometimes
reflect a founder effect, and in many cases reflect
recurrent, independently occurring mutational events. Multi-
ple independent mutations of residue 340 in cTnT suggest
that this may be a “hot spot” for such events.

Phenotype
We evaluated left ventricular hypertrophy and morphology in
individuals with distinct cTnT gene mutation. Genetic anal-
yses identified 16 individuals with Phe110Ile mutation in the
cTnT gene. Our analyses demonstrate that the distribution of
hypertrophy among the affected individuals was the same in
the members of 1 family but was different among the
members of the other 3 families. We conclude that this gene
defect results in varied distributions of hypertrophy within
and between families.

Usually, only the maximal wall thickness has been evalu-
ated in genotyped individuals with hypertrophic cardiomyop-
athy.7,9,23,24 Only a few studies have addressed cardiac mor-
phology in genotyped individuals with hypertrophic cardiomyopathy. Solomon et al22 evaluated left ventricular
hypertrophy and morphology in genotyped individuals with
familial hypertrophic cardiomyopathy in patients with
β-cardiac myosin heavy chain gene mutations. They con-
cluded that the cardiac morphology in such genetically
defined adults is broad. We found that the ventricular mor-
phology of individuals with hypertrophic cardiomyopathy
and the Phe110Ile mutation in the cTnT gene was also broad
and that some individuals with the mutations showed apical
hypertrophy.

Maron et al19 classified the distribution of left ventricular
hypertrophy in patients with hypertrophic cardiomyopathy.
Recently, more extensive studies of the morphological vari-
ations in individuals with hypertrophic cardiomyopathy were
reported by Klues et al.25 In those studies, individuals with
hypertrophic cardiomyopathy were not genotyped. Patterns of
hypertrophy in and morphology of genotyped individuals
with familial hypertrophic cardiomyopathy should be evalu-
ated more extensively.

On the ECG, 15 individuals (94%) showed abnormalities
of their ST-T waves. Only 9 individuals (56%) showed left
ventricular high voltage. Two of the 3 individuals with
nonpenetrant mutations showed abnormalities in their ST-T
waves. ECG abnormalities seem to be more sensitive than
abnormalities seen in echocardiograms of individuals with
disease-causing mutations.

Apical hypertrophic cardiomyopathy was first described in
Japan.27,28 The hallmark of the apical hypertrophy in Japanese
individuals is giant negative T waves in the left precordial
leads.27 Recently, Forissier et al14 described a family with an
Arg92Leu mutation in the cTnT gene. An individual in that
family showed apical hypertrophy but not giant negative
T waves, and the 3 other individuals in the family showed
other types of left ventricular hypertrophy.

We observed that 3 individuals with a Phe110Ile mutation
in the cTnT gene showed apical hypertrophy. Two of the 3
individuals with apical hypertrophy showed associated giant
negative T waves in the left precordial leads. The individuals
with apical hypertrophy were members of 2 different families
(the KE and KG families). The haplotypes of these 2 families
were different.

Kimura et al6 recently reported that 3 of 36 individuals with
apical hypertrophy in their study had mutations in the cardiac
troponin I gene and suggested that apical hypertrophy is a
form of hypertrophic cardiomyopathy, which is a disease of
the sarcomere. No individuals with a mutation in the cTnT
gene were identified. Our data reconfirm that apical hyper-

Figure 2. Kaplan-Meier product-limit curves for survival of indi-
viduals with Phe110Ile mutation and 2 other mutations in
β-cardiac myosin heavy chain gene. Survival was good in
patients with Phe110Ile mutation in cTnT gene and similar to
that for benign Phe513Cys β-cardiac myosin heavy chain gene
mutation. A significant difference (P=0.0002) in life expectancy
was observed in individuals with Phe110Ile versus malignant
Arg719Trp mutation in β-cardiac myosin heavy chain gene.

Phenotype
We evaluated left ventricular hypertrophy and morphology in
individuals with distinct cTnT gene mutation. Genetic anal-
yses identified 16 individuals with Phe110Ile mutation in the
cTnT gene. Our analyses demonstrate that the distribution of
hypertrophy among the affected individuals was the same in
the members of 1 family but was different among the
members of the other 3 families. We conclude that this gene
defect results in varied distributions of hypertrophy within
and between families.

Usually, only the maximal wall thickness has been evalu-
ated in genotyped individuals with hypertrophic cardiomyop-
athy.7,9,23,24 Only a few studies have addressed cardiac mor-
phology in genotyped individuals with hypertrophic cardiomyopathy. Solomon et al22 evaluated left ventricular
hypertrophy and morphology in genotyped individuals with
familial hypertrophic cardiomyopathy in patients with
β-cardiac myosin heavy chain gene mutations. They con-
cluded that the cardiac morphology in such genetically
defined adults is broad. We found that the ventricular mor-
phology of individuals with hypertrophic cardiomyopathy
and the Phe110Ile mutation in the cTnT gene was also broad
and that some individuals with the mutations showed apical
hypertrophy.

Maron et al19 classified the distribution of left ventricular
hypertrophy in patients with hypertrophic cardiomyopathy.
Recently, more extensive studies of the morphological vari-
ations in individuals with hypertrophic cardiomyopathy were
reported by Klues et al.25 In those studies, individuals with
hypertrophic cardiomyopathy were not genotyped. Patterns of
hypertrophy in and morphology of genotyped individuals
with familial hypertrophic cardiomyopathy should be evalu-
ated more extensively.

On the ECG, 15 individuals (94%) showed abnormalities
of their ST-T waves. Only 9 individuals (56%) showed left
ventricular high voltage. Two of the 3 individuals with
nonpenetrant mutations showed abnormalities in their ST-T
waves. ECG abnormalities seem to be more sensitive than
abnormalities seen in echocardiograms of individuals with
disease-causing mutations.

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Prognosis
Familial hypertrophic cardiomyopathy caused by mutations
in the cTnT gene is characterized by a high incidence of
sudden death and mild cardiac hypertrophy,7 and no benign
mutations have been reported. Six mutations in the cTnT gene
(Ile79Asn, Arg92Gln, Arg92Trp, Ala104Val, ΔGlu160, and
Intron 15G→A) have been characterized by a high incidence
of sudden death.\textsuperscript{9–11} For example, there were 15 disease-related deaths in 32 affected individuals in the 3 families with the Arg92Gln mutation, and 11 of the 15 disease-related deaths were sudden deaths.\textsuperscript{9} Of 57 disease-related deaths with these 6 mutations, 47 were deemed sudden deaths.\textsuperscript{9–11} The life expectancy of individuals with 4 malignant cTnT mutations (Ile79Asn, Arg92Trp, ΔGlu160, and Intron 15G1→A) has been reported to be \( \approx 35 \) years.\textsuperscript{9} Moolman et al\textsuperscript{10} emphasized the relevance of screening the cTnT gene because of the consistent association of a poor prognosis with deceptively mild clinical features and reduced penetrance.

We found the 6 families with Phe110Ile mutation in the cTnT gene to show a benign disease outcome. Of 18 individuals with the Phe110Ile genotype, there were 2 sudden deaths and no heart transplants. Phe110Ile is the first cTnT gene mutation associated with a favorable prognosis.

The Phe110Ile mutation is not associated with a change in charge of the encoded amino acid, like that seen in benign mutations in the \( \beta \)-cardiac myosin heavy chain gene (Phe513Cys, Val606Met, and Leu908Val).\textsuperscript{7,8,23} We suggest that the absence of a change in charge may in part account for the good prognosis of these patients.

The Phe110Ile mutation is located within a major binding site for \( \alpha \)-tropomyosin.\textsuperscript{3,9} Mutations associated with poor prognosis, such as Ala104Val, are also located within this site. The effects of the Phe110Ile mutation on the binding to \( \alpha \)-tropomyosin may be smaller than those of other malignant mutations in this region. Effects of mutations in cTnT protein have been evaluated in several cases, including Ile79Asn, Arg92Gln, and protein truncation.\textsuperscript{30–32} Arg92Gln and protein truncation impair myocardial contractility,\textsuperscript{30,31} and the Ile79Asn mutation increases the sliding speed of the filaments.\textsuperscript{32} The effects of the Phe110Ile mutation have not yet been evaluated and should be studied, because this is the only cTnT mutation associated with a favorable prognosis.

Conclusions
Six of 46 Japanese families studied shared a Phe110Ile mutation. Haplotype analyses demonstrated a founding mutation in some families and an independent mutation in others. Multiple independent mutations of residue 340 in cTnT suggest that this may be a hot spot for such events. Distribution of the hypertrophy in hypertrophic cardiomyopathy by this defect differs among families and also within families. The Phe110Ile is the first cTnT mutation associated with a favorable prognosis. In conclusion, the Phe110Ile mutation of the cTnT gene shows hypertrophic cardiomyopathy with variable cardiac morphologies and a favorable prognosis.

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References


Patients With Familial Hypertrophic Cardiomyopathy Caused by a Phe110Ile Missense Mutation in the Cardiac Troponin T Gene Have Variable Cardiac Morphologies and a Favorable Prognosis

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