Sarcomere Protein Gene Mutations in Patients With Apical Hypertrophic Cardiomyopathy

Christiane Gruner, MD; Melanie Care, MSc; Katherine Siminovitch, MD; Gil Moravsky, MD; E. Douglas Wigle, MD; Anna Woo, MD; Harry Rakowski, MD

Background—Apical hypertrophic cardiomyopathy (HCM) is a unique form of HCM with left ventricular hypertrophy confined to the cardiac apex. The purpose of our study was to report genetic findings in a large series of unrelated patients with apical HCM and compare them with a nonapical HCM cohort.

Methods and Results—Overall, 429 patients with HCM underwent genetic testing. The panel included 8 sarcomere protein genes and 3 other genes (GLA, PRKAG2, and LAMP2). Sixty-one patients were diagnosed with apical HCM. A positive genotype was found in 8 patients with apical HCM. The genotype-positive and genotype-negative patients had similar maximal wall thicknesses (17.5 ± 3.5 mm versus 17.6 ± 3.3 mm, P = 0.71) and similar frequency of HCM-related events (2/8; 25% versus 13/53; 25%; P = 0.98). Thirteen percent with apical HCM and 40% with nonapical HCM had a positive genotype (P < 0.001) most often involving the MYBPC3 and MYH7 genes.

Conclusions—In apical HCM, a positive genotype was found less frequently than in nonapical HCM, and it was most often involving MYBPC3 and MYH7 genes. Only 13% of patients with apical HCM were found to be genotype positive, indicating that genome-wide association studies and gene expression profiling are needed for better understanding of the genetic background of the disease. There was no significant genotype-phenotype correlation in our cohort with apical HCM. (Circ Cardiovasc Genet. 2011;4:288-295.)

Key Words: hypertrophic cardiomyopathy ■ genotyping ■ sarcomere

Hypertrophic cardiomyopathy (HCM) is the most common cardiovascular genetic disorder, affecting approximately 1 in 500 people within the general population.1 HCM is an autosomal dominant condition, and >900 unique mutations in 13 genes encoding sarcomere or sarcomere-related proteins have been described.2-4 According to the American College of Cardiology guidelines, HCM is defined as left ventricular hypertrophy (LVH) in the absence of another cardiac or systemic disease (eg, hypertension, aortic stenosis, or metabolic cardiomyopathy) capable of producing the magnitude of hypertrophy evident.5

Clinical Perspective on p 295

Apical HCM is a specific variant of HCM, in which the myocardi6al hypertrophy is mainly confined to the cardiac apex. Epidemiological studies showed that about 3% to 10% of HCM patients worldwide express the apical variant, excluding Japan, where the prevalence of apical HCM is considerably higher.3,6,7 In apical HCM, sarcomere protein gene mutations have been found to be present in up to 30% of this specific patient population.3 A few select sarcomere protein gene defects (ie, ACTC; p.Glu101Lys) have been reported in the apical HCM phenotype.8,9 To date, no consistent genotype-phenotype correlation has been established, and most of the reports underscore the heterogeneity of the clinical disease expression in patients with mutations within the same sarcomere protein gene.10-13 There is some evidence to suggest that the presence of multiple sarcomere protein gene mutations in a given patient may be associated with an earlier onset of disease and a more severe disease course compared with patients with only 1 sarcomere protein gene mutation.14,15

To date, literature reporting sarcomere protein gene mutations in patients with apical HCM is limited to a relatively small number of unrelated patients.3,9 This report describes sarcomere protein gene mutations in a larger series of unrelated patients with apical HCM at a tertiary referral center. In addition, we compared the prevalence and distribution of mutations in apical HCM with a nonapical HCM population studied at the same time.

Methods

Study Population

The study subjects were identified through the multidisciplinary HCM clinic at Toronto General Hospital, which serves as a large

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tertiary referral center. Subjects were serially ascertained as they attended routine clinic visits. This cohort represents the first individuals who chose to proceed with genetic testing for HCM between July 2005 and December 2009. During this time, 429 probands with the clinical expression of HCM underwent genetic testing, 61 of whom showed the morphological features of apical HCM. For the population with apical HCM, detailed clinical, genetic, ECG, and echocardiographic data were collected. Clinical follow-up data were abstracted between the first and latest clinic visit at our institution. Special attention was paid to HCM-related events including sudden cardiac death (SCD), atrial fibrillation, development of heart failure, stroke, syncope, and the need for the implantation of a permanent pacemaker (PPM) or an automated implantable cardioverter-defibrillator (AICD). Arterial hypertension was defined either as blood pressure values \( <110/90 \text{ mm Hg} \) measured during a clinic visit or if patients were medically treated for arterial hypertension. Heart failure events were defined as progression to New York Heart Association functional class III and IV, unexpected hospital admission for heart failure, or death due to heart failure. Family history information was ascertained and assessed through detailed pedigree analysis by genetic counselors specialized in cardiac genetics. A positive family history was defined as either documented evidence of HCM in a family member (based on a review of clinical investigations or autopsy reports), or by highly convincing patient report. The study was approved by the Research Ethics Board of the University Health Network.

**Diagnostic Criteria**

The diagnosis of HCM was made by 2-dimensional echocardiography findings, based on the presence of otherwise unexplained LVH with a maximal wall thickness \( \geq 15 \text{ mm} \). In borderline cases with a maximal wall thickness between 13 and 15 mm, concomitant ECG changes were required to establish the diagnosis of HCM, as shown by an example in Figure 1. Apical HCM was defined as LVH predominantly confined to the LV apex demonstrating maximal wall thickness within the apical segments and absence of significant hypertrophy at the basal level. Two different apical HCM patterns were distinguished: (1) the “pure apical” form, with hypertrophy limited to the apical segments, and (2) the “distal dominant” form, with hypertrophy extending to the midventricular level, clearly sparing the basal segments (Figure 2).

**Genetic Testing**

Patients underwent a commercially available genetic test for HCM using a combination of oligonucleotide hybridization–based DNA sequencing and dideoxy-based DNA sequencing. Testing initiated after February 2008 assessed 8 HCM-associated myofilament-encoding genes involving myosin-binding protein C (MYBPC3), \( \beta \)-myosin heavy chain (MYH7), essential and regulatory myosin light chains (MYL2, MYL3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), \( \alpha \)-tropomyosin (TPM1), and cardiac actin (ACTC) as well as 3 genes associated with metabolic cardiomyopathies: GLA for Fabry disease, LAMP2 for Danon disease, and PRKAG2 for PRKAG2 cardiomyopathy. Testing initiated before February 2008.
did not include the GLA gene, and testing was initiated only in the setting of a clinical presentation suggestive of Fabry disease.

Gene variants detected by genetic testing are reported as pathogenic, presumed pathogenic, variant of unknown significance (VUS), and probably benign. Our definition of a positive genotype for HCM comprises the presence of a sarcomere protein gene mutation that is classified as pathogenic or presumed pathogenic. We deliberately did not classify patients with VUS as having a positive genotype because of the ambiguity of these variants with respect to a pathogenic role and that in our clinical experience it is not uncommon for those variants to be reclassified as probably benign.

ECG
The ECG closest to the time of genetic testing was analyzed regarding the presence of LVH, using the Sokolow-Lyon criteria.19 “Giant” T-wave negativity was defined as a voltage of negative T wave ≥1 mV (≥10 mm) in any of the leads.

Echocardiography
Routinely, each patient underwent echocardiography during the outpatient visit at the HCM clinic according to the standards of the American Society of Echocardiography.20 The studies were performed using commercially available ultrasound equipment. For the purposes of the present study, the echocardiogram closest to the time of genetic testing was analyzed. Echocardiographic images were interpreted by one of the investigators (C.G.), and a subset of cases was reviewed by one of the senior investigators (H.R.). Borderline cases (n=6) with suspicious ECGs and inconclusive echocardiographic findings were further investigated by cardiac MRI regarding the presence of apical hypertrophy.

Statistics
Continuous data are presented as mean±SD. An unpaired Student t test was used to compare continuous variables, and χ² or Fisher exact test was used to assess categorical data, where appropriate. A probability value <0.05 was considered significant.

For the assessment of HCM-related events during follow-up, a combined end point was created including SCD, atrial fibrillation, heart failure, stroke, insertion of a PPM, or implantation of an AICD for secondary prophylaxis of SCD.

Results
The HCM population who underwent genetic testing comprised 429 patients, 61 of whom were found to have apical HCM. Our entire apical HCM cohort consists of 143 patients; thus 43% of patients with apical HCM underwent genetic testing.

Within the apical HCM population, 35 of 61 patients and within the nonapical HCM population 117 of 368 were not tested for Fabry disease. The patients not tested for Fabry disease did not show clinical evidence for the presence of this disorder. Overall, there were no cases with metabolic disease detected in the apical HCM population. However, in the nonapical HCM group, 4 patients did show disease-causing mutations for metabolic cardiomyopathies, including 2 patients with Fabry disease and 1 patient each with Danon disease and PRKAG2 cardiomyopathy (4/368; 1.1%). Those were excluded from further analysis, which left 364 patients with nonapical HCM.

Clinical Findings of the Apical HCM Cohort
Clinical characteristics, ECG and echocardiographic features, and reasons for diagnosis are listed in Table 1. The mean age of the patients was 47±14 years at diagnosis of apical HCM, and 45 of 61 (74%) were male. In 51 of 61 (84%), no known family history for HCM was present. One-third of the patients (20/61; 33%) were hypertensive and 37 of 61 (61%) were asymptomatic in New York Heart Association functional class I. The majority of the patients were diagnosed with apical HCM either due to pathological ECG changes, symptoms such as chest pain or shortness of breath, or in the setting of family screening.

The mean follow-up for this population was 6.7 years. Four patients were lost to follow-up. None of the patients had SCD. However, 5 of 61 patients (8%) had a stroke, 10 of 61 patients (16%) had episodes of atrial fibrillation, and 3 of 61 patients (5%) had heart failure. An AICD was placed in 7 of 61 patients (11%), and 1 of 61 patient (2%) received a PPM. Only 1 patient required the AICD for secondary prophylaxis and 2 patients received an AICD because they had 1 risk factor for SCD and qualified for a PPM because of significant bradycardia. Overall, 15 of 61 patients (25%) had HCM-related events during their disease course, and 6 had multiple events.

Genetic Findings and Association With Clinical Findings of the Apical HCM Cohort
In 8 of 61 patients (13%), 9 disease-causing sarcomere gene mutations were found. Overall, we found 5 mutations of the MYH7 gene, 2 mutations of the MYBPC3 gene, and 1 mutation each of the TNNT2 and TNNI3 genes. One patient was a double heterozygous carrier, with the MYH7 and TNNI3 genes being involved. A detailed listing of the specific mutations and the clinical features of the patients is given in Table 2. Within the entire apical HCM cohort, 7 VUS were found, which are listed in Table 3. One of these (MYH7 p.Gly541Asp) occurred in a patient with another mutation that has been classified as pathogenic or presumed pathogenic (MYH7 p.Pro211Leu). We compared the genotype-positive (genotype+) patients with those who were found to have a negative genotype regarding demographic and clinical data, echocardiographic findings, and HCM-related events (Table 1). The only signif-
The significant difference was that patients with a disease-causing sarcomere gene mutation were more likely to have a positive family history for HCM compared with the genotype-negative (genotype \( ^-/H11002 \)) probands (genotype \( ^+/H11001 \) 4/8; 50% versus genotype \( ^-/H11002 \) 6/53; 11%, \( P = 0.02 \)).

The genotype was not associated with a higher rate of HCM-related events even after creating a combined end point including stroke, atrial fibrillation, heart failure, or PPM insertion or AICD implantation for secondary prophylaxis of SCD (genotype \( ^+/H11001 \) 2/8; 25% versus genotype \( ^-/H11002 \) 13/53; 25%, \( P = 0.98 \)). Also, the percentage of patients with the distal dominant form was not significantly higher in the genotype \( ^+/H11001 \) group compared with the genotype \( ^-/H11002 \) group (genotype \( ^+/H11001 \) 2/8; 25% versus genotype \( ^-/H11002 \) 15/53; 28%, \( P = 1.0 \)).

**Genetic Findings of the Apical HCM Cohort Compared With the Nonapical HCM Cohort**

Basic demographics such as age at diagnosis, sex, and ethnicity were similar among the cohorts with apical HCM and with nonapical HCM (Table 4).

In the apical HCM cohort 8 of 61 patients (13%) and in the nonapical HCM cohort 145 of 364 patients (40%) were found to have a positive genotype, which demonstrates a significantly lower prevalence of mutations in the apical cohort than in the nonapical cohort (\( P < 0.001 \)). We compared those 2 populations regarding their distribution of sarcomere gene mutations (Table 5), and there was no significant difference present (\( \chi^2 \) test, \( P = 0.78 \)). Because this observation is only based on 8 positive genotypes within the apical HCM cohort,
relevant differences may be overcome by the lack of statistical power.

Discussion

The present study provides results regarding the frequency and distribution of disease-causing sarcomere protein gene mutations in a large cohort of 61 unrelated patients with apical HCM who underwent genetic testing for clinical purposes at a tertiary referral center in Canada. In our population, 13% of patients were found to have disease-causing sarcomere gene mutations that predominantly occurred in genes encoding proteins for the thick sarcomere filament, with 5 mutations affecting the MYH7 gene and 2 mutations affecting the MYBPC3 gene. Additionally, 1 mutation each of the TNNT2 and TNNI3 genes encoding proteins for the thin sarcomere filament was present. One patient was a double heterozygote, carrying both a TNNI3 and MYH7 disease-causing sarcomere gene mutation.

Patients with a positive genotype were more likely to have a positive family history for HCM than were patients with a negative genotype. Otherwise, there were no further differences present, especially no higher incidence of HCM-related events compared with the patients with a negative genotype. The lack of difference in terms of the apical morphology pattern (pure apical versus distal dominant) as well as the lack of any difference in wall thickness are indicative that the amount of left ventricular muscle mass is not associated with the genotype. We are aware that the statistical power, with only 8 patients having a positive genotype, is limited. However, this is the largest cohort of apical HCM with genetic testing that has been reported to date, and, importantly, apical HCM has a good prognosis compared with the other morphologies, which implies a lower event rate.17

Binder et al3 and Arad et al7 report a positive genotype in their apical HCM cohort in 30% and in 47% of cases, respectively (see Table 6). Compared with those numbers, our proportion of patients with a positive genotype (13%) seems to be low. Similarly, both of them report a higher rate of patients with a positive family history for HCM (Binder et al, 22%; Arad et al, 40%; our cohort, 16%). A possible explanation for this difference may be a variable accessibility of genetic testing as a result of differences in the health care systems in the United States versus Canada. This may create a referral bias in the United States, with higher rates for genetic testing in patients with a positive family history of HCM increasing the likelihood of finding a known disease causing sarcomere gene mutation. An additional factor explaining our low percentage of patients with positive genotype may be that patients with a VUS were not classified as having a positive genotype. If VUS were included, 23% of patients would have a positive genotype.

<table>
<thead>
<tr>
<th>Table 3. Variants of Unknown Significance in the Apical HCM Cohort</th>
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<tbody>
<tr>
<td>Gene</td>
</tr>
<tr>
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</tr>
<tr>
<td>MYBPC3</td>
</tr>
<tr>
<td>58 MYBPC3</td>
</tr>
<tr>
<td>02 MYH7</td>
</tr>
<tr>
<td>49 MYH7</td>
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<tr>
<td>21 MYH7</td>
</tr>
<tr>
<td>05 MYH7</td>
</tr>
<tr>
<td>50 TNNT2</td>
</tr>
<tr>
<td>29 TNNI3</td>
</tr>
</tbody>
</table>

ID indicates identification code; Apical, with or without apical morphology; TWN, T-wave negativity, giant being defined as voltage of negative T wave \(\geq 1 \text{ mV}\) or TWN, maximal wall thickness; LVEF, left ventricular ejection fraction; AA, apical aneurysm; Pattern: PA, pure apical; DD, distal dominant; MYBPC3, myosin-binding protein C; MYH7, \(\beta\)-myosin heavy chain; TNNI3, cardiac troponin I.

Table 4. Demographics of the Apical HCM Cohort Compared With the Nonapical HCM Cohort

| Age at diagnosis, y | Sex M/F | Ethnicity | Apical HCM Cohort (n=61) | Nonapical HCM Cohort (n=364) | P Value |
|---|
| 47±14 | 45 (74%)/16 (26%) | Caucasian | 41 (67%) | 271 (74%) | 0.83 |
| 46±35 | 236 (65%)/128 (35%) | Asian | 6 (10%) | 14 (4%) | 0.17 |
| 0.33 |
| 38 (10%) | 11 (3%) | South Asian | 6 (10%) | 30 (8%) | 0.05 |
| 21 (7%) | 11 (3%) | African American | 6 (10%) | 30 (8%) | 0.05 |
| 0.33 |

- MYBPC3 indicates myosin-binding protein C; MYH7, \(\beta\)-myosin heavy chain; and TNNI3, cardiac troponin I.
- Ethnicity of the apical HCM cohort could be defined completely; however, in the nonapical HCM cohort, ethnicity data were missing for 22 patients (6%).
Table 5. Distribution of Sarcomere Protein Gene Mutations in Genotype+ Patients With Apical HCM Versus Nonapical HCM

<table>
<thead>
<tr>
<th>Sarcomere Protein Gene Mutation</th>
<th>Apical HCM Cohort (n=8)</th>
<th>Nonapical HCM Cohort (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYBPC3</td>
<td>2 (25%)</td>
<td>69 (48%)</td>
</tr>
<tr>
<td>MYH7</td>
<td>4 (50%)</td>
<td>51 (35%)</td>
</tr>
<tr>
<td>TNNI3</td>
<td>0</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>TPM1</td>
<td>0</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>TNNI2</td>
<td>1 (13%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>MYL3</td>
<td>0</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>MYL2</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>ACTC</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Multiple mutations</td>
<td>1 (13%)</td>
<td>6 (4%)</td>
</tr>
</tbody>
</table>

χ² test, P=0.78.
MYBPC3 indicates myosin-binding protein C; MYH7, β-myosin heavy chain; TNNI3, cardiac troponin I; TPM1, α-tropomyosin; TNNI2, cardiac troponin T; MYL2 and 3, essential and regulatory myosin light chains; and ACTC, cardiac actin.

Because the morphology of apical HCM is very distinct, we do not believe that there are any misclassified patients confounding our results. In the context of a low likelihood of misclassification in apical HCM, the low percentage of patients with a positive genotype is somewhat puzzling. It suggests that there must be affected gene loci other than the known sarcomere protein-encoding loci, and genome-wide association studies may be helpful in determining additional causative or modifying gene effects. Also, apical HCM represents an unusual distribution of hypertrophy, and it is not clear why such a pattern should evolve compared with more classic septal involvement. Because in patients with a family history of HCM, affected individuals may have either septal dominant or apical hypertrophy, gene expression and modifying factors rather than genotype appear to be responsible for the variable phenotypic expression of disease. This is further supported by our results showing similar distribution of disease causing sarcomere protein gene mutations in both apical and other phenotypes of HCM. Thus, gene expression profiling may help to better understand the phenotypic differences.

The comparison of the genetic test results of the cohort with apical HCM with the nonapical HCM population did not show any significant difference regarding the distribution of the various sarcomere protein gene mutations, revealing most frequently mutations of the MYH7 and MYBPC3 genes. This confirms findings in various described cohorts with mixed HCM phenotypes where in each cohort, highest prevalences for mutations of the MYH7 and MYBPC3 sarcomere genes were found, including a preadolescent population.3,21–24 However, considering that the observations in our apical HCM population are based on 8 patients with a positive genotype, results must be interpreted with caution because we simply may not be able to detect relevant differences due to lack of statistical power. Regarding specific mutations causing apical HCM, Arad et al9 as well as Olson et al8 described unique ACTC mutations in their patients being associated with the expression of apical HCM. However, in our apical HCM population, no mutation of the ACTC sarcomere gene occurred, which might be due to the geographic and ethnic variation in different referral centers. In our apical HCM cohort, one of the mutations (MYH7 p.Arg1712Glu) has not been described in the literature. The apical HCM patient carrying this mutation does have another disease causing sarcomere protein gene mutation of the TNNI3 gene. This individual has a positive family history but is the only one currently known to carry both mutations.

Some mutations found in the apical HCM cohort have been described more extensively than others in the literature and seem to be more frequent: The MYBPC3 p.Trp792fs mutation is relatively widespread in North Europe as well as in North America, and it is associated with a later disease onset and incomplete penetrance.25–27 In our entire cohort, there are 17 carriers of this gene mutation within 11 different families, and 14 of the carriers have expressed the disease, also underscoring the relative frequency of this mutation. The TNNI2 p.Arg278Cys mutation was described to cause rather mild hypertrophy, and SCD was found in elderly as well as in younger patients carrying this mutation.28–30 In our entire cohort, this mutation was identified in 4 unrelated carriers, whereof one has a significant family history for SCD. The patient with apical HCM and this mutation has also only mild hypertrophy with a maximal wall thickness of 16 mm, and the family history is negative for SCD.

Genetic screening detects the presence of metabolic cardiomyopathy in 1% to 4% of patients initially diagnosed with HCM.31,32 In our HCM population, 2 patients in the nonapical HCM cohort were diagnosed with Fabry disease, 1 with PRKAG2 cardiomyopathy and 1 with Danon disease. None of the patients in the apical cohort revealed a mutation for metabolic disease.

Genetic testing remains useful in patients with apical HCM. It may help to confirm the diagnosis in borderline cases, exclude disease in others, and identify family members who could be carriers with a negative phenotype who probably will have the disease later in life.37,33

Limitations
The proportion of patients with apical HCM is 14% in our genetically tested population with HCM and lies slightly above the values reported in the literature (3% to 10%,3,6,7). This may be due to the fact that at the beginning of the era of genetic testing in HCM, the unique features of apical HCM prompted us to provide those patients with genetic testing. Our proportion of genotype-positive patients with apical HCM is lower than that of other reported series. We believe that difference in referral patterns with fewer patients with a positive family history in our series is a likely explanation.

Table 6. Comparison With Apical HCM Cohorts in Other Study Populations

<table>
<thead>
<tr>
<th></th>
<th>Arad et al3</th>
<th>Binder et al9</th>
<th>TGH</th>
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<tbody>
<tr>
<td>No. of probands with apical HCM</td>
<td>15</td>
<td>37</td>
<td>61</td>
</tr>
<tr>
<td>Percentage with positive genotype</td>
<td>47%</td>
<td>30%</td>
<td>13%</td>
</tr>
<tr>
<td>Percentage with positive family history for HCM</td>
<td>40%</td>
<td>22%</td>
<td>16%</td>
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</table>

TGH indicates Toronto General Hospital.
Conclusion

In a large genetically tested cohort of patients with apical HCM, sarcomere protein gene mutations were most often affecting the MYH7 and MYBPC3 genes. Only 13% of patients with apical HCM were found to have pathogenic sarcomere protein gene mutations, indicating that genome-wide association studies and/or gene expression profiling may be useful in this context. We were not able to establish a significant genotype-phenotype correlation in our cohort with apical HCM. However, this might also be due to lack of statistical power according to the fairly small number of patients with a positive genotype, underscoring the need for multicenter studies allowing data pooling.

Disclosures

None.

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This study describes genetic findings in a patient cohort with apical hypertrophic cardiomyopathy (HCM) who underwent genetic testing for clinical purposes. We compared the frequency and distribution of sarcomere protein gene mutations with those of our cohort of HCM patients with nonapical HCM. Importantly, fewer patients with apical HCM (13%) had a disease-causing mutation compared with 40% in the nonapical HCM cohort. There was no unique gene identified that was specific for apical HCM. Thus, family screening in patients with apical HCM can only be simplified in a relatively small number of affected families by screening for the disease-causing mutation of the index patient within the family members. Hence, conventional clinical screening including ECG and echocardiography over regular intervals remains crucial. The low prevalence of mutations found in patients with apical HCM indicates the need for further genetic studies to detect abnormalities at sites not currently tested for.
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