Mutations in the Sarcomere Gene MYH7 in Ebstein Anomaly

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**Background**—Ebstein anomaly is a rare congenital heart malformation characterized by adherence of the septal and posterior leaflets of the tricuspid valve to the underlying myocardium. An association between Ebstein anomaly with left ventricular noncompaction (LVNC) and mutations in MYH7 encoding β-myosin heavy chain has been shown; in this report, we have screened for MYH7 mutations in a cohort of probands with Ebstein anomaly in a large population-based study.

**Methods and Results**—Mutational analysis in a cohort of 141 unrelated probands with Ebstein anomaly was performed by next-generation sequencing and direct DNA sequencing of MYH7. Heterozygous mutations were identified in 8 of 141 samples (6%). Seven distinct mutations were found; 5 were novel and 2 were known to cause hypertrophic cardiomyopathy. All mutations except for 1 3-bp deletion were missense mutations; 1 was a de novo change. Mutation-positive probands and family members showed various congenital heart malformations as well as LVNC. Among 8 mutation-positive probands, 6 had LVNC, whereas among 133 mutation-negative probands, none had LVNC. The frequency of MYH7 mutations was significantly different between probands with and without LVNC accompanying Ebstein anomaly (P<0.0001). LVNC segregated with the MYH7 mutation in the pedigrees of 3 of the probands, 1 of which also included another individual with Ebstein anomaly.

**Conclusions**—Ebstein anomaly is a congenital heart malformation that is associated with mutations in MYH7. MYH7 mutations are predominantly found in Ebstein anomaly associated with LVNC and may warrant genetic testing and family evaluation in this subset of patients. (Circ Cardiovasc Genet. 2011;4:43-50.)

**Key Words:** heart defects ■ congenital ■ genetics ■ cardiomyopathy

**Clinical Perspective on p 50**

The genetic basis of Ebstein anomaly is largely unresolved. Although Ebstein anomaly is more common in patients with a family history of congenital heart disease, most cases are sporadic and familial Ebstein anomaly is rare. Mutations in the cardiac transcription factor NKX2.5 are responsible for a
variety of cardiac structural anomalies including Ebstein anomaly and ASD. In 1 LVNC family carrying a mutation in MYH7 encoding the sarcomere gene β-myosin heavy chain (MYH7), 4 individuals had Ebstein anomaly.7

Mutations in sarcomere genes are a major cause of cardiomyopathy. LVNC has recently been classified as a primary cardiomyopathy with a genetic etiology, and is morphologically characterized by a severely thickened 2-layered myocardium, numerous prominent trabeculations, and deep intertrabecular recesses.9 Mutations in 6 sarcomere genes, MYH7, α-cardiac actin (ACTC1), cardiac Troponin T (TNNT2), α-tropomyosin (TPM1), cardiac Troponin I (TNNI3), and cardiac myosin-binding protein C (MYBPC3) have been described in familial or nonfamilial LVNC.10–14 MYH7 is the most frequent disease gene (13%) in adult patients with LVNC, in the absence of other congenital heart anomalies.12

Interestingly, mutations in ACTC1 have been associated with ASD and cardiomyopathy,15,16 and some individuals have both defects.10 Because a possible association between Ebstein anomaly with LVNC and MYH7 mutations previously was shown, this led us to test the association between Ebstein anomaly and MYH7 mutations in a large cohort. We performed mutational analysis of MYH7 in a cohort of 141 unrelated probands with Ebstein anomaly using both next generation sequencing and direct DNA sequencing. Mutations were identified in 8 of 141 probands (6%), the largest resequencing study of Ebstein anomaly so far. We provide further evidence for a link between structural proteins, cardiomyopathy, and congenital heart malformations.

Methods

Clinical Evaluation

Unrelated patients were recruited from 3 sources: (1) CONCOR (National Registry and DNA bank of congenital heart defects), The Netherlands (n = 114); (2) National Registry for Congenital Heart Defects, Berlin, Germany (n = 19); and (3) The Institute of Human Genetics, Newcastle University, United Kingdom (n = 8). Informed consent was obtained from all participants according to established guidelines. Probands and available family members were evaluated by history taking, review of medical records, physical examination, guidelines. Probands and available family members were evaluated by history taking, review of medical records, physical examination, and transthoracic echocardiography. All probands had a physical examination for dysmorphic features, and patients with abnormalities pointing to syndromic features or neuromuscular involvement were excluded. Echocardiography in Ebstein anamoly shows apical displacement of the septal leaflet of the tricuspid valve from the insertion of the anterior leaflet of the mitral valve by at least 8 mm/m2 body surface area.3,4 Marked enlargement of the right atrium and atrialized right ventricle may be present, as well as varying degrees of regurgitation of the tricuspid valve. The diagnosis of LVNC was made by echocardiography, based on the presence of the established criteria by Jenni et al.4 In partially penetrant cases of LVNC, the ratio of noncompacted to compacted myocardium is <2. A diagnosis of LVNC was made irrespective of the presence of heart failure or left ventricular systolic dysfunction.8 Echocardiographic studies were performed/reviewed by 2 independent observers.

Mutation Screening

Mutation screening was carried out with genomic DNA samples from 141 probands. Fusion primers were designed using Primer3 and IDT primer design portal to amplify MYH7 (Genbank accession No. NM_000257) coding and 5′/3′ untranslated regions; 20 ng of genomic DNA was amplified using FastStart HighFidelity enzyme in a total reaction volume of 50 μL. Amplification was performed by initial denaturation at 94°C for 3 minutes followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at the recommended temperatures for 45 seconds, extension at 72°C for 1 minute, and a final extension at 72°C for 2 minutes. Amplicons were purified using Solid-Phase Reversible Immobilization beads (Beckman Coulter Genomics, High Wycombe, Buckinghamshire, United Kingdom). Amplicon quality was assessed using the DNA 1000 LabChip on an Agilent Bioanalyzer and quantified using Quant-iT PicoGreen dsDNA Assay Kit (Invitrogen, Paisley, United Kingdom). Fifty PCR amplicons from 141 patients were pooled at equimolar ratios and sequenced on 3 GS FLX LR70 PicoTiterPlates. Library immobilization and emulsion PCR were performed using genome sequencer (GS) emPCR kits II and III (Roche, Welwyn Garden City, Hertfordshire, United Kingdom). After DNA bead recovery, bead enrichment and sequencing-primer annealing, the DNA beads, packing beads, and enzyme beads were deposited on a GS FLX PicoTiter Plate and sequenced using GS LR70 Sequencing kit (Roche). GS reference mapper was used to map sequence reads obtained with reference sequences from the Human genome hg18 assembly (NCBI build 36.1). The average read length was 244 bp, and average fold coverage was 45X per allele. Putative variants detected by GS Amplicon Variant Analyzer software (Roche) that were supported by both forward and reverse reads or with a variant frequency of >1.0% on either the forward or reverse reads were selected for further analyses by MassARRAY MALDI-TOF (Sequenom, San Diego, CA) to validate changes and, as the sequencing had been carried out in pooled samples, to identify in which samples they were present. After this, each change was confirmed by Sanger sequencing as previously published.12 When a putative mutation was identified, at least 490 ethnically matched controls (980 chromosomes) were screened for the absence of the sequence variation (P < 0.0001). The microsatellite marker D14S990 was used to rule out a founder mutation for MYH7.12

The Fisher exact test was used to analyze noncontinuous data; probability values <0.05 were considered significant.
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A cohort of 141 unrelated white individuals of western European descent (61 men and 80 women; 138 adults and 3 children; mean age, 46 years; range, 4 months to 77 years) with the diagnosis of Ebstein anomaly were investigated. Sixty-four probands had no associated cardiac anomalies, the most common associated cardiac malformation being ASDII (48 probands) and cardiomyopathy (7 probands) (Table 1).

Heterozygous mutations were identified in 8 of 141 samples (6%). Seven distinct mutations were found; 5 were novel and 2 were known to cause hypertrophic cardiomyopathy. Two probands had the same mutation. All mutations except for 1 3-bp deletion are missense mutations. In 6 of 8 probands with MYH7 mutations LVNC was identified in addition to Ebstein anomaly. One of 8 mutation-positive probands had partially penetrant LVNC (kindred 109.787, III-2, Figure 1), and in 1 other proband (AD) LVNC was uncertain. MYH7 mutations were not reported in the subcohort of 133 probands with Ebstein anomaly without evidence of LVNC. The frequency of MYH7 mutations between those Ebstein patients with LVNC and those without LVNC was significant (P=2 e-07, P<0.0001). Clinical phenotypes were assessed in all available family members of the 8 probands with mutations, and familial congenital heart malformations or cardiomyopathy was found in 3 of them. In these kindreds, MYH7 mutations segregated with LVNC, and there was an additional individual with Ebstein anomaly (110.647). The clinical characteristics of all family members with mutations are presented in Table 2 and described below.

Familial Cases

Kindred 110.647

We identified a missense mutation at nucleotide 933 in exon 10, which replaces tyrosine with aspartic acid at residue 283 (designated Tyr283Asp) in the proband. She had been (III-6) diagnosed with Ebstein anomaly and ASDII at 29 years of age, which were surgically corrected. At age 49 years, echocardiography revealed LVNC with abnormal LV diastolic function. Family screening identified Ebstein anomaly and LVNC in the proband’s 24-year-old niece (IV-2) (Figure 2A and 2B). Individuals III-2 and III-3 showed only mild left ventricular apical hypertropectulation (partially penetrant phenotype). III-10 had been diagnosed with a perimembranous ventricular septal defect at 18 years. MRI performed at age 59 years because of palpitations, and the unexplained sudden...
death in her 40-year-old sister (III-9) showed marked LVNC with mildly abnormal systolic function. A cardioverter-defibrillator was implanted. Her asymptomatic father (II-4) was subsequently diagnosed with LVNC (Figure 1A).

Kindred 110.240
In the proband (III-4), a missense mutation (Asn1918Lys) in exon 39 was found. Ebstein anomaly was established after evaluation of a cardiac murmur at 3 years of age. She has always been asymptomatic despite significant tricuspid regurgitation from the age of 30 years. Marked LVNC was found at age 39 years (Figure 2E and 2F). Her youngest son (IV-4) had a bicuspid aortic valve and aortic coarctation, and echocardiography at age 5 years showed LVNC. The proband’s asymptomatic brother (III-1) had LVNC and LV dilatation with LV dysfunction; her mother (II-2) was also found to have LVNC (Figure 2G and 2H). Echocardiography of III-6 could not rule out cardiomyopathy because of poor imaging quality (Figure 1B).

Kindred 109.787
A Glu1573Lys missense mutation in exon 34 was detected in the proband (III-2) and her asymptomatic father. Evaluation of a cardiac murmur in the proband’s first year of life led to the diagnoses of Ebstein anomaly and a small doubly committed subarterial ventricular septal defect. Echocardiography at age 33 years showed mild hypertrabeculation of the apex, not fulfilling the criteria for LVNC (partially penetrant phenotype). The parents of the proband had normal echocardiography (Figure 1C).

Kindred 16875
The proband (III-1) and his father (II-2) carried the same Tyr283Asp missense mutation as in kindred 110.647. Haplotype analyses ruled out a founder mutation in these 2 families. The proband presented with Ebstein anomaly, LVNC, and pulmonary hypoplasia as a neonate and had an aortopulmonary shunt at the 2nd day of life (Figure 2C and 2D). By family screening, his asymptomatic father was

Table 2. Clinical Characteristics of Family Members With MYH7 Mutations

<table>
<thead>
<tr>
<th>Family ID</th>
<th>Age, y/Sex</th>
<th>Mutation</th>
<th>Site of LVNC*</th>
<th>RV†</th>
<th>LVED Z Score</th>
<th>EF/FS, %</th>
<th>Type CVM</th>
<th>Cardiovascular Complications</th>
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<tr>
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<td>II-4</td>
<td>78/M</td>
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<td>No</td>
<td>−2.8</td>
<td>47/NA</td>
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<td></td>
<td>III-2</td>
<td>54/F</td>
<td>p.Y283D</td>
<td>1‡</td>
<td>No</td>
<td>−1.9</td>
<td>68/36</td>
<td>None</td>
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<tr>
<td></td>
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<td>50/M</td>
<td>p.Y283D</td>
<td>1‡</td>
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<td>−2.2</td>
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<td>Ebstein, ASDII</td>
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<td>Perimembranous VSD</td>
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<td>p.Y283D</td>
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<tr>
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<td>0</td>
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<td>None</td>
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<td>No</td>
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<td>Coarctation of the aorta, BAV</td>
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<td>42/M</td>
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<td>−2.2</td>
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<td>p.K1459N</td>
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<td>No</td>
<td>−3.0</td>
<td>65/NA</td>
<td>Ebstein</td>
</tr>
</tbody>
</table>

LVED indicates left ventricular end-diastolic diameter; Z score, normal reference range −2 < −2; EF/FS, left ventricular ejection fraction/fractional shortening; NL, normal limits; NA, not available; AF, atrial fibrillation; NSAT, nonsustained atrial tachycardia; CHF, congestive heart failure; CVM, cardiovascular malformation; DCM, dilated cardiomyopathy; ICD, intracardiac defibrillator; EPI, electrophysiologic investigation; CVI, cerebrovascular insult; PFO, patent foramen ovale; VSD, ventricular septal defect; and TV, tricuspid valve.

*Noncompacted segments: None=0; apex=1; apex, midventricular wall=2; and apex, midventricular wall, basis=3.
†Right ventricular involvement.
‡Partially penetrant phenotype; inheritance of sporadic mutations: not tested, AO, BT, and AD; de novo, DB.
§ID probands.
diagnosed with LVNC. The paternal aunt (II-1) was reported to have heart failure and the paternal grandfather (I-1) had received an implantable cardioverter-defibrillator (Figure 1D).

Nonfamilial Cases
There were 4 sporadic cases with MYH7 mutations. These included 1 de novo mutation; in 3 probands, the parental DNA or clinical information was unavailable. In proband AO, who presented with LVNC and LV diastolic dysfunction, a 3-bp in-frame deletion was detected, leading to the removal of a glutamic acid at residue 1220 in exon 27 (1220delGlu). In proband DB, a tyrosine was substituted by an asparagine at residue 350 in exon 12, which was not present in her unaffected parents and had occurred de novo (Tyr350Asp). This patient presented with biventricular non-compaction with preserved function. In proband BT, a missense mutation (Leu390Pro) was found in exon 13. Cardiac MRI was undertaken as echocardiography of left ventricular morphology was uninformative because of weight-related imaging difficulties and revealed extensive LVNC. In proband AD, a Lys1459Asn substitution in exon 32 was present.

Echocardiography of left ventricle morphology was also uninformative; this patient had not had an MRI.

Genetic and Clinical Evaluation of the Cohort With MYH7 Mutations
Three of the 7 distinct mutations reside within the genomic sequence of exon 10 to exon 13 of MYH7, which encode the head region of the molecule (Figure 3A). Four mutations are located throughout the rod domain of the β-myosin heavy chain molecule. All identified missense mutations affect amino acids with high degrees of conservation throughout evolution, underscoring the functional importance of these residues (Figure 3B). The Tyr350Asn substitution occurred de novo. Together with the observation that none of the mutations are present in more than 980 chromosomes from a control population of western European descent, our findings strongly support a disease-causing role for these mutations.

Mutation-positive probands and family members showed various congenital heart disease including ASDII, ventricular septal defect, coarctation of the aorta, bicuspid aortic valve, and pulmonary artery stenosis/hypoplasia as well as cardiomyopathy including LVNC (Table 2). All individuals with
LNVNC, including the 3 partially penetrant cases (kindred 110.647, III-2, III-3; kindred 109.787, III-2), carried a MYH7 mutation. There was only 1 mutation carrier with a normal echocardiogram (kindred 109.787, II-3). All individuals with MYH7 mutations, 16 positive probands and family members showed various congenital heart malformations as well as LNVNC. Significant pleiotropy and reduced penetrance were characteristic of MYH7 mutation-positive congenital heart malformations. The LNVNC phenotype had a higher penetrance, with only 1 mutation carrier having a normal echocardiogram. Mutations in MYH7 can cause hypertrophic cardiomyopathy, dilated cardiomyopathy, and LNVNC.

The 8 probands with MYH7 mutations were in New York Heart Association class I at the time of genetic evaluation. Except for the infant with additional pulmonary artery hypoplasia (16875, III-1), congestive heart failure had not been present at initial diagnosis. Severe regurgitation required surgical reconstruction of the tricuspid valve in 2 patients. LVNC was always observed in the left ventricular apex, and left systolic function was preserved in 7 of 8 probands (Table 2). Sustained ventricular tachycardias or sudden cardiac deaths were not seen in probands; however, in kindred 110.647, there had been 1 sudden cardiac death. In 2 probands, nonsustained atrial tachyarrhythmias were present.

**Discussion**

Comprehensive genetic analyses of 141 unrelated probands with Ebstein anomaly identified 8 disease-associated mutations in the gene encoding β-myosin heavy chain. Mutation-positive probands and family members showed various congenital heart malformations as well as LVNC. Significant pleiotropy and reduced penetrance were characteristic of MYH7 mutation-positive congenital heart malformations. The LVNC phenotype had a higher penetrance, with only 1 mutation carrier having a normal echocardiogram. Mutations in MYH7 can cause hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, and LVNC. This study further broadens the spectrum of phenotypes associated with a defect in a structural protein from cardio-myopathies to congenital heart malformations.

The main hemodynamic abnormality in Ebstein anomaly producing symptoms is tricuspid regurgitation. When the tricuspid dysplasia or right ventricular myocardial hypoplasia is severe or associations with other cardiac lesions are present clinical symptoms occur in infancy as seen in the proband III:1 of kindred 16875. In contrast, Ebstein anomaly may be asymptomatic in adolescents and adults, as in most of the
mutation-positive probands in the present cohort. In such cases, supraventricular arrhythmias may be the main clinical problem as in probands BT and AD.

The frequency of MYH7 mutations between those patients with LVNC and those without LVNC was significantly different. All 8 MYH7 mutations were found in 8 probands with LVNC or with LVNC being partially penetrant or uncertain. There were no MYH7 mutations in 133 probands without LVNC. Because there was no family screening by echocardiography in the 133 mutation-negative probands, the true prevalence of cardiomyopathy or congenital heart malformations in the families of the 133 mutation-negative probands remained unknown. In mutation-positive probands, several family members were shown to have congenital heart malformations as well as LVNC, of which some were not known before family screening. In Ebstein anomaly associated with mutations in NKX2.5 mutations, carriers were also more likely to have a positive history of heart disease in the young.8 Familial Ebstein anomaly was found in 1 kindred (110.647). In general, familial Ebstein anomaly is rare and only a few families with autosomal dominant inheritance have been described.18,19 Several genetic loci for Ebstein anomaly have been reported in humans and in animal models. Chromosomal abnormalities as well as mutations in NKX2.5 were found in patients with Ebstein anomaly.6,20 Andelfinger et al21 demonstrated linkage between tricuspid valve formation and canine chromosome 9 in a region systemic to human chromosome 1q12-q23. Of interest, penetrance of Ebstein anomaly in the dog was estimated to be 68%. This may represent the polygenic or multifactorial inheritance pattern proposed in humans with Ebstein anomaly.

A significant number of patients with Ebstein anomaly have morphofunctional abnormalities of the left ventricle, which may be explained by increased fibrosis of the left ventricular wall and septum as demonstrated by histological studies.22 Attenhofer Jost et al reviewed 106 consecutive patients with Ebstein anomaly and LVNC was identified in 18%. Also, in several other studies, Ebstein anomaly was associated with LVNC.4,18,23 In 1 large family with autosomal dominant LVNC and Ebstein anomaly, an MYH7 mutation was found.7 Ebstein anomaly in families with autosomal inheritance of LVNC18,23 might represent a specific subtype with a mendelian inheritance pattern. The present study supports the association between Ebstein anomaly with LVNC and MYH7 mutations. Clinical and genetic evaluation is recommended to facilitate the diagnosis of cardiomyopathy and congenital heart disease in probands and their first-degree relatives.14,24

Mutations in MYH7 are a common cause for hypertrophic cardiomyopathy and well recognized in dilated cardiomyopathy and LVNC. Mutations are distributed throughout the molecule, and the relationship between mutation location, cardiomyopathy type, and disease severity is poorly understood.17 The first link between sarcomeric proteins and congenital heart malformations was provided by Ching et al25 by identifying a mutation in α-myosin heavy chain (MYH6) through genetic linkage analysis. Later, a founder mutation in ACTC1 was identified in 2 families with autosomal dominant ASD, in the absence of other cardiac anomalies.15 How mutations in sarcomere genes could have detrimental effects on cardiac morphogenesis and produce septal defects and valve anomalies should be subject to further investigations. Because LVNC is thought to result from altered regulation in cell proliferation, differentiation, and maturation during wall formation,26 arrest in directional growth could account for the association of Ebstein anomaly and LVNC.57,28

Conclusions

Ebstein anomaly is within the diverse spectrum of cardiac morphologies associated with mutations in the gene encoding β-myosin heavy chain. MYH7 mutations are predominantly found in Ebstein anomaly associated with LVNC. In the subset of patients with Ebstein anomaly carrying a MYH7 mutation, genetic and clinical evaluation of family members is recommended to identify congenital heart malformations and cardiomyopathy.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Ebstein anomaly is a rare congenital heart malformation affecting both the tricuspid valve and right ventricle, and is characterized by adherence of the septal and posterior leaflets of the tricuspid valve to the underlying myocardium. Ebstein anomaly is more common in patients with a family history of congenital heart disease but most cases are sporadic and familial. Associated abnormalities of left ventricular morphology and function have been observed. A possible association between Ebstein anomaly and left ventricular noncompaction (LVNC) and mutations in MYH7 encoding β-myosin heavy chain was previously shown in one family with multiple affected members. In the present study, we describe that Ebstein anomaly is within the diverse spectrum of cardiac morphologies triggered by a sarcomere gene defect. A possible association between Ebstein anomaly with left ventricular non-compaction and mutations in MYH7 encoding β-myosin heavy chain was previously shown in one family with multiple affected members. In the present study, we describe that Ebstein anomaly is within the diverse spectrum of cardiac morphologies triggered by a sarcomere gene defect. We performed mutational analysis of MYH7 in a cohort of 141 unrelated probands with Ebstein anomaly. Mutations were identified in 8 of 141 probands (6%), the largest resequencing study of Ebstein anomaly thus far. Mutation-positive probands and family members showed various congenital heart malformations as well as LVNC. Significant pleiotropy and reduced penetrance were characteristic of MYH7 mutation-positive congenital heart malformations. In 6 of 8 probands with MYH7 mutations, LVNC was identified in addition to Ebstein anomaly, whereas among 133 MYH7 mutation-negative probands, none had LVNC. We provide further evidence for a link between structural proteins, cardiomyopathy, and congenital heart malformations. MYH7 mutations are predominantly found in Ebstein anomaly associated with LVNC and may warrant genetic testing and family evaluation in this subset of patients.
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