Sarcomere Mutations in Cardiomyopathy With Left Ventricular Hypertrabeculation

Lisa M. Dellefave, MS; Peter Pytel, MD; Stephanie Mewborn, PhD; Bassem Mora, MD; Deborah L. Guris, MD, PhD; Savitri Fedson, MD; Darrel Waggoner, MD; Ivan Moskowitz, MD, PhD; Elizabeth M. McNally, MD, PhD

Background—Mutations in the genes encoding sarcomere proteins have been associated with both hypertrophic and dilated cardiomyopathy. Recently, mutations in myosin heavy chain (MYH7), cardiac actin (ACTC), and troponin T (TNNT2) were associated with left ventricular noncompaction, a form of cardiomyopathy characterized with hypertrabeculation that may also include reduced function of the left ventricle.

Methods and Results—We used clinically available genetic testing on 3 cases referred for evaluation of left ventricular dysfunction and noncompaction of the left ventricle and found that all 3 individuals carried sarcomere mutations. The first patient presented with neonatal heart failure and was referred for left ventricular noncompaction cardiomyopathy. Genetic testing found 2 different mutations in MYBPC3 in trans. The first mutation, 3776delA, Q1259fs, rendered a frame shift at 1259 of cardiac myosin-binding protein C and the second mutation was L1200P. The frameshift mutation was also found in this mother who displayed mild echocardiographic features of cardiomyopathy, with only subtle increase in trabeculation and an absence of hypertrophy. A second pediatric patient presented with heart failure and was found to carry a de novo MYH7 R369Q mutation. The third case was an adult patient with dilated cardiomyopathy referred for ventricular hypertrabeculation. This patient had a family history of congestive heart failure, including pediatric onset cardiomyopathy where 3 individuals in the family were found to have the MYH7 mutation R1250W.

Conclusion—Genetic testing should be considered for cardiomyopathy with hypertrabeculation. (Circ Cardiovasc Genet. 2009;2:442-449.)

Key Words: gene mutation ■ myosin heavy chain ■ myosin-binding protein C ■ sarcomere ■ cardiomyopathy ■ contractility ■ genetics ■ heart failure ■ myocardial contraction

Mutations in the genes encoding sarcomere proteins are well established to cause hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM). The most common genetic causes of HCM are mutations in either MYH7 encoding β myosin heavy chain or MYBPC3 encoding cardiac myosin-binding protein C. Together, these 2 genes account for 70% to 80% of the mutational spectrum in HCM. In vivo, HCM is morphologically classified by thickening of the left ventricle (LV) that preferentially affects the septum but may also affect the left ventricular free wall. Apical variants of HCM, where the apex is preferentially targeted, have also been associated with sarcomeric gene mutations; the mutations associated with apical HCM display the similar genetic spectrum found in HCM, and in some cases, apical variants have the identical gene mutations.

Clinical Perspective on p 449

Noncompaction of the ventricular myocardium is characterized by a spongy morphological appearance of the myocardium that occurs in the LV and is most evident in the apical portion of the heart. During cardiac development, the embryonic myocardium forms as a hypertrabeculated ventricle thought to enhance blood flow to the developing but avascular myocardium. During embryonic weeks 5 and 8, the ventricular myocardium transforms from a hypertrabeculated morphology to a compacted layer, and this process is concomitant with coronary artery development. Myocardial remodeling begins at the base of the heart and over time progresses to the apex; the intertrabecular spaces form capillaries and the larger residual spaces flatten to become normal compacted myocardium. Left ventricular noncompaction (LVNC) is believed to arise from premature cessation of embryonic endomyocardial morphogenesis, resulting in the presence of persistent trabeculated myocardium in the region where compaction arrested. Because of the base to apex progression, early termination of myocardial remodeling leaves the apex preferentially affected. Other portions of the

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From the Departments of Medicine (L.M.D., S.M., S.F., E.M.M.), Section of Cardiology, Pathology (P.P., I.M.), Surgery (B.M.), Section of Cardiothoracic Surgery, Pediatrics (B.M., D.G., S.F., D.W., I.M.), and Human Genetics (D.W., E.M.M.), The University of Chicago, Chicago, Ill. Correspondence to E. McNally, MD, PhD, 5841 South Maryland, MC6088, Chicago, IL 60637. E-mail emcnally@uchicago.edu
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ventricle, including midventricular lateral wall midventricular inferior wall, and midposterior wall, may also be involved.2–4

LVNC may occur in the setting of other developmental defects, such as cognitive impairment and developmental delay, where it is referred to as “syndromic LVNC.” Nonsyndromic LVNC refers to the absence of any extracardiac defects, and nonsyndromic LVNC may be familial. Nonsyndromic LVNC can be familial and may or may not be associated with structural cardiac malformations, such as septal defects.5 LVNC can be difficult to diagnose because some degree of trabeculation may be normally present in the heart.6 With the enhanced sensitivity of echocardiographic imaging, there has been an increased recognition of hypertrabeculation and LVNC. The American Heart Association reclassified LVNC as a primary cardiomyopathy in 2006.7 The clinical symptoms of LVNC range from none to severe heart failure. Like other forms of cardiomyopathy, LVNC may be associated with arrhythmias, including ventricular tachycardia and atrial fibrillation.8 ECGs in adult and pediatric patients with LVNC are typically abnormal with left or right bundle branch block, tachyarrhythmias, and ventricular preexcitation.2,9–11 Thromboembolic events are increased and may arise from dislodged thrombi from the trabeculations of the LV and/or the associated arrhythmias.

The genetic etiology of LVNC includes both autosomal dominant and X-linked recessive inheritance. X-linked recessive inheritance of neonatal LVNC has been described with mutations in the G4.5 gene (TAZ).12 A single mutation in DTNA encoding α-dystrobrevin was associated with LVNC and congenital heart disease, including ventricular septal defects, patent ductus arteriosus, and hypoplastic left heart syndrome.13 LVNC has also been attributed to mutations in the gene encoding Cypher/ZASP.14 Overall, however, mutations in DTNA, G4.5, and the LDB3 gene encoding Cypher/ZASP are rare causes of LVNC.15,16 Most recently, sarcomeric protein genes have been associated with isolated LVNC. Specifically, mutations in β myosin heavy chain (MYH7), α-cardiac actin (ACTC), and cardiac troponin T (TNNT2) have been described.17–19 Where families and probands have been studied, sarcomere gene mutations have been identified in up to 17% of isolated LVNC cases.20 We now used clinical genetic testing for sarcomeric gene mutations in 3 patients who were referred for LVNC and hypertrabeculation in the setting of cardiomyopathy. Two patients were pediatric and 1 was an adult, and mutations were identified in all three. These data support the utility of using genetic testing to define the etiology and risks to relatives in LVNC.

Methods

Diagnostic Criteria
The criteria of Jenni et al20 were used to diagnose LVNC consisting of: (1) a 2-layered left ventricular wall structure with a compacted thin epicardial band (C) and the noncompacted endocardial layer (NC) of trabecular meshwork with deep endomyocardial spaces, with a maximal end-systolic ratio of noncompacted to compacted layers (NC/C) greater than two; (2) the segments of noncompacted myocardium mainly involve the apex and the inferior mid and lateral mid of the left ventricular wall; (3) the visualization of blood flow from the ventricular cavity into the intertrabecular recesses by color Doppler imaging; and (4) absence of coexisting cardiac abnormalities.

Molecular Analysis

Genetic Testing
Peripheral blood was collected from index patients in families A, B, and C (AII.2, BII.3, and CII.1). Genomic DNA was extracted and clinical mutation analysis for 11 genes was performed using the CardioChip that includes MYH7, cardiac myosin-binding protein C (MYBPC3), TNNT2, cardiac troponin I (TNNI3), troponymosin 1 (TPM1), ACTC, myosin regulatory light chain (MYL2), cardiac myosin essential light chain (MYL3), lysosomal-associated membrane protein 2 (LAMP2), γ subunit 5-AMP-activated protein kinase (PRKAG2), and α-galactosidase a (GLA). For family C, genomic DNA was amplified by polymerase chain reaction for direct sequencing of the genes: ACTC, MYBPC3, MYH7, MYL2, MYL3, troponin C (TNNC1), TNNI3, TNNT2, and TPM1.

Molecular Analysis
Exons 32 and 33 of MYBPC3 were amplified as 1 amplicon from DNA from patient AII.2, ligated into a plasmid vector and then sequenced to determine phase. Polymerase chain reaction was performed using the following primers: MYBPC3 32F GGCCTGTCCGTTACCAAGCTCTGTC and MYBPC3 33R CGCGCCGTCCTTTCCATCTC. The polymerase chain reaction products were ligated using the TOPO TA Cloning Kit (Invitrogen, Carlsbad, Calif., USA). Three independent clones were sequenced.

This study was performed under the approval of the University of Chicago Internal Review Board.

Results

Family A
The proband (AII.2) was a white male, born after an uncomplicated term gestation by an emergent cesarean section for low heart rate; he was intubated briefly. His birth weight was 7lb 14oz. Polycythemia was treated with 2 blood draws, and he was discharged within 4 days. He was the second child of healthy nonconsanguineous parents (Figure 1). At 11 days of life, he presented in cardiogenic shock with profound hypotension, anuria, and acidosis. His hospital course included inotropic support that was subsequently weaned, allowing him to be discharged briefly. He presented with cardiogenic shock at 6 weeks of age and was readmitted to the hospital. He was listed for heart transplantation. However, at 7 weeks of age, he had a cardiac arrest and was placed on an extracorporeal membrane oxygenation. He had a biventricular assist device placed in efforts to stabilize his cardiac status and allow time for a potential organ donor; his immediate postoperative course was complicated by a large left middle cerebral artery stroke with hemorrhagic conversion. The proband expired at 9 weeks of age.

Echocardiography between 11 days and 9 weeks showed a fractional shortening ranging from 6.5% on initial presentation to a transient improvement with inotropic and mechanical support to 22.8%, but then with a slow decline as his heart failure progressed. LVNC was noted on his initial echocardiogram (Figure 2), and an ECG showed biventricular hypertrophy (Figure 3). The proband’s autopsy showed LV hypertrophy with coarse trabeculations, which was most severe at the apex, with a LV free wall thickness of 14 mm. The right ventricle was hypertrophied, with a right ventricular free wall thickness of 5 mm. The left and right atria were hypertrophied, each with a free wall thickness of 2 to 3 mm. Microscopic examination revealed right ventricular and left
atrium myocyte hypertrophy and disarray. The LV apex and base had interstitial fibrosis with myocyte hypertrophy and disarray. Electron microscopy showed wooly densities and disorganized cristae within the mitochondria. The sarcomeres were well organized without evidence of disarray. Minimal Z line distortion was seen. The I bands were occasionally stretched and were of uneven width. The M bands were strikingly abnormal in that they lacked definition and were difficult to discern (Figure 4).

Genetic testing of the proband identified 2 mutations in MYBPC3, a gene previously not associated with LVNC. The first mutation, in exon 33 of the MYBPC3 gene, was 3776delA, Q1259fs. This frameshift mutation alters the protein’s terminal 16 amino acids and leads to the addition of 55 amino acids. A second mutation was also identified in his MYBPC3 gene in exon 32, 3599T->C, L1200P. This missense mutation has not been previously reported in the literature and was not identified in >600 ethnically matched (white) probands. To determine whether these 2 mutations were in cis or trans in the proband, exons 32 and 33 were amplified as 1 amplicon and ligated into a vector, and multiple independent clones were sequenced. This analysis demonstrated that the 2 mutations were not found on the same allele and thus were in trans, consistent with no normal MYBPC3 protein and the microscopic absence of normal M bands in his sarcomeres (Figure 4).

The proband’s mother and father were evaluated. His father (AI.1) had a structurally normal heart by echocardiography and carried neither the exon 33 nor the exon 32 changes seen in the proband. His mother (AI.2) was in good health at age 28 and denied symptoms of shortness of breath, syncope, or cardiac complications. Echocardiography revealed an end-diastolic LV diameter of 4.9 cm and an ejection fraction of 49%. There was global left ventricular systolic dysfunction and hypertrabeculation of the left ventricular apex (Figure 2, Figure 1. Pedigrees. Solid symbols indicate a clinical diagnosis of LVNC in the setting of clinical heart failure; open symbols, normal cardiac dimensions; shaded symbols, intermediate phenotype. Gene and gene mutation are listed. Mutation positive (+), mutation negative (−). The absence of a + or − indicates that mutation status was not determined. In family A, 2-II had both mutations on 2 separate chromosomes, whereas the mother carried only 1 mutation.

Figure 2. Echocardiographic images. A, Four-chamber view showing the non-compaction of the LV (individual AII.2). B, View of the LV showing mild hypertrabeculation in the mother of individual AII.2 who carried only a single mutant MYBPC3 allele. Maximal wall thickness (septal and LV free wall) was 1.0 cm. C, Four-chamber view showing an area of noncompaction in the lateral and posterior section of the LV (individual BII.3). D, Four-chamber view showing noncompaction of the LV (individual CII.1).
upper right). Genetic testing revealed that she had only 1 of the mutations found in her son, MYBPC3, 3776delA, Q1259fs. MYBPC3 has been linked to later onset HCM,\(^21,22\) and at age 28, she had only mild findings, but notably an absence of hypertrophy.

**Family B**
The proband was an African American female, born after an uncomplicated 38-week term gestation and vaginal delivery. Her birthweight was 6lbs 11oz, and her length was 21 inches. She had normal development and walked at 14 months. She was hospitalized for pneumonia at 8 months with full recovery. At 3.5 years, she presented with acute heart failure. Echocardiography showed a dilated LV (end-diastolic diameter of 5.1 cm, normal range 2.72 to 3.68 cm) with reduced function and fractional shortening of 9.1%. An area of noncompaction in the lateral and posterior section of the LV was seen (Figure 2, lower left). ECG showed left atrial enlargement with T-wave inversion on inferior leads (Figure 3). She was treated with an angiotensin-converting enzyme inhibitor, diuretics, aldactone, and β blocker, with clinical stabilization. Her LV function improved to a fractional shortening of 14.1% and an ejection fraction of 36.7%. Genetic testing on the proband identified a single mutation in the MYH7 gene in exon 12, 1106G>A, R369Q. We evaluated both parents of this child, and both her father (BI.1) and her mother (BI.2) did not have the exon 12 mutation, consistent with a de novo mutation. This missense mutation has not been reported previously in the literature. However, the R369Q mutation has been identified in 2 pediatric individuals with cardiomyopathy, where it was identified in 1 patient as a de novo variant and thus believed to be pathogenic (personal communication, Harvard Partners Laboratories).

**Family C**
The proband (CII.1) was an African American man who was referred to our institution for evaluation of LVNC after presenting at age 55 with new-onset heart failure at an outside institution. Echocardiography showed a dilated heart with a noncompacted segment of the free wall and apex (Figure 2, lower right). The LV end-diastolic diameter was 6.4 cm, the ventricular septal thickness in diastole was 0.83 cm, the left ventricular posterior wall thickness in diastole was 1.0 cm, and the LV ejection fraction was 24%. His ECG showed bradycardia and left ventricular hypertrophy (Figure 3). Genetic testing on the proband identified a single mutation in MYH7 in exon 28, 3748C>T, R1250W. This missense mutation has not been reported previously. The proband has a family history of cardiomyopathy and congestive heart failure. Two siblings (CII.2 and CII.5) were affected with DCM. The proband’s niece (CIII.3) underwent cardiac trans-
planted at age 11 for DCM and congestive heart failure and died 7 years after transplant. Genetic evaluation identified the R1250W mutation identified in 2 of his affected deceased relatives (CII.2 and CIII.3) (Figure 1).

**Discussion**

**Sarcomere Mutations in LVNC, HCM, and DCM**

Sarcomere mutations can produce cardiomyopathy with reduced ventricular function and hypertrabeculation. The normal LV contains 2 layers, a compact layer and the inner trabeculated layer. During development, this inner trabecular layer normally undergoes remodeling, and hypertrabeculation is thought to represent arrest of this normal developmental process. The diagnosis of LVNC is made by identifying a ratio between noncompacted and compacted myocardium and blood flow into the intertrabecular recesses.20 The patients in this study met the criteria of Jenni, however, it should be noted that criteria for LVNC have been evolving. The degree to which the myocardium has not undergone normal compaction may contribute to an appearance of a thickened myocardium. However, typical HCM differs from LVNC because of the spongy nature of the myocardium, and this is visualized by blood flow into the trabecular recesses on Doppler echocardiography. LVNC may be associated with hypertrophy or dilation and may also be associated with reduced LV function. Cardiac magnetic resonance may prove most valuable in quantifying trabeculation to more clearly distinguish hypertrabeculation. A recent study supported that nonischemic DCM was more likely to be associated with hypertrabeculation compared with ischemic or DCM from valvular heart defects.23 Nonetheless, there is clear overlap between HCM and hypertrabeculation.24

**MYBPC3 as a Gene for LVNC With Absent M Bands**

The findings from family A demonstrate that MYBPC3 mutations should also be considered for LVNC. The proband in family A carried 2 different MYBPC3 mutations in trans, which suggests that these mutations may play a role in the pathogenesis of LVNC. This finding supports the hypothesis that MYBPC3 mutations may be a genetic cause of LVNC.

**Table. Sarcomere Mutations in LVNC**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Inherited (No. Affected)</th>
<th>Associated Cardiac Features (No. Affected)</th>
<th>Reference</th>
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<td>Klaassen et al¹⁷</td>
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<td>Klaassen et al¹⁷</td>
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<td>TNNT2</td>
<td>R131W</td>
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<td>Klaassen et al¹⁷</td>
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AS, atrial septal; ASD, atrial septal defect; AV, atrioventricular; HCM, hypertrophic cardiomyopathy; NSVT, nonsustained ventricular tachycardia; VSD, ventricular septal defect.

AS, atrial septal; ASD, atrial septal defect; AV, atrioventricular; HCM, hypertrophic cardiomyopathy; NSVT, nonsustained ventricular tachycardia; VSD, ventricular septal defect.
whereas his mother carried only 1 and she was mildly affected. The exon 33 mutation, 3776delA, Q1259fs was present in both the child and mother, and the mother at the age of 28 was only mildly affected, with decreased LV function and an absence of hypertrophy. The second mutation, L1200P, was not present in either parent, and the 2 mutations carried on 2 alleles are consistent with no normal MYBPC3 protein. MYBPC3 gene mutations cause HCM, and compound heterozygous MYBPC3 mutations with HCM have been identified displaying a more severe presentation of neonatal HCM. HCM in these affected individuals was characterized by biventricular thickening, reduced cardiac function, and histopathology showing myofibrillar disarray and interstitial fibrosis.

Microscopic findings with LVNC can overlap with those in HCM and may include subendocardial fibrosis/fibroelastosis, myocardial fibrosis, myocardial disorganization, myocardial hypertrophy and degeneration, scarring of the myocardium, or signs of inflammation. The histopathology findings identified in this proband are consistent with both HCM and LVNC. The ultrastructure reported was striking for its absence of M bands. Interestingly, electron microscopic analysis of animal models of MYBPC3 gene mutations suggests that defective M lines are a feature of MYBPC3 mutations. Hearts from mice homozygous for an MYBPC3 deletion allele were noted to have an absent M line. Similarly, a Drosophila model expressing a truncated human cMyBP-C in indirect flight muscles also showed M-line distortion. The known association of MYBPC protein and the M line supports a role for this protein in M-line maturation and may represent a specific finding associated with MYBPC3 gene mutations.

Clinical Genetic Testing for Cardiomyopathy
Clinical genetic testing in cardiomyopathy is rapidly evolving. This study relied on an array-based test that allowed the study of 11 genes simultaneously. Given that >50 genes have been associated with genetic forms of cardiomyopathy, newer technologies that permit higher throughput sequencing will allow analysis of many more genes. Other genes beyond those encoding sarcomere proteins have been associated with LVNC, notably TAZ and DTNA as well as LMNA. The TAZ gene is found on the X-chromosome and mutations associate with neutropenia. The patterns of inheritance and the absence of neutropenia make this diagnosis less likely in the patients presented herein. Sequential gene testing is 1 strategy for genetic diagnosis, but this approach would not identify those cases where there is contribution from >1 gene. The ability to assay multiple genes simultaneously and in a more cost effective manner will not only increase diagnostic yield but also lead to the identification of benign polymorphisms that can complicate interpretation. Our study suggests that evaluating the sarcomere genes in LVNC is valuable diagnostically for the proband as well as for family members. Although cardiomyopathy in this pediatric age group should likely prompt genetic testing regardless of the presence of hypertrabeculation, guidelines are only just now emerging supporting this approach. Genetic evaluation in pediatric cardiomyopathy is warranted and focus on sarcomere genes is supported by other investigations. As newer sequencing modalities become even more cost effective, recommendations for clinical genetic testing in cardiomyopathy will likely evolve.

Hypertrabeculation, Cardiomyopathy, LVNC, and Risk Assessment
Genetic evaluation is highly useful for identifying at-risk relatives, or more importantly, excluding risk. Those with LVNC are likely to have similarly affected family members, and screening should be considered to detect asymptomatic family members with LVNC because they may have an increased risk of thromboembolic events or arrhythmias. In 1 study, 51% of LVNC probands were reported to have a family history of DCM or LVNC. Other studies have suggested that familiality of LVNC is lower, with as few as 3%, 9%, and 12% of LVNC probands having affected family members. The familial incidence likely varies depending on the population, the screening modalities, and the criteria used to define LVNC. The clinical overlap of LVNC with other forms of cardiomyopathy should also be considered when evaluating family members. Neonatal and childhood onset of the proband may indicate a de novo mutation, where other family members would not be affected; and in this setting, genetic testing can be highly effective to help determine risk of disease or absence thereof. Alternatively, >1 mutation, as described here, may explain more phenotypic variability.

A recent study identified hypertrabeculation in as many as 23.6% of individuals with heart failure. Whether these echocardiographic features identify those subjects in whom family screening or genetic testing is indicated has not been determined. LVNC criteria have been the debated, and this debate complicates the sole use of these criteria in determining the need for genetic evaluation. Our findings suggest that genetic testing should be considered for individuals with LVNC and cardiomyopathy with reduced LV function because genetic information may be useful in assessing risk to family members. Together, these findings reinforce the argument that a normally functioning sarcomere is required during cardiac development and the process of LV compaction.

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Disclosures
None.

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Mutations in the gene encoding the sarcomere have been linked to hypertrophic and dilated cardiomyopathy. Recently, mutations in MYH7, ACTC, and TNNT2 have been reported in families and sporadic individuals with left ventricular noncompaction, a disorder where there is hypertrabeculation of the left ventricle and cardiomyopathy. Normally, during heart development, the left ventricle is transiently heavily trabeculated to allow for oxygenation before formation of the coronary arteries. Following vascular development, the inner layer of the left ventricle remodells into the mature compacted appearance. Persistence of deep trabeculae in a postnatal heart is variable, but in its severe form, left ventricular noncompaction can be associated with heart failure and thromboembolic events. We implemented clinically available genetic testing in 3 patients with left ventricular noncompaction cardiomyopathy. Two of these individuals were children and 1 was an adult with similarly afflicted family members. We found dominant mutations in MYH7 in 2 of the individuals, including the family with adult and pediatric affected members. In the third individual, we identified 2 different MYBPC3 mutations carried on different chromosomes, consistent with a complete absence of normal myosin-binding protein C. The myocardium from this individual had an absence of discernable M lines, now implicating cardiac myosin-binding protein C as a potential gene for left ventricular noncompaction. These findings suggest that individuals with hypertrabeculation and cardiomyopathy could be considered for screening for the presence of sarcomere mutations.
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