Sarcomere Gene Mutations in Isolated Left Ventricular Noncompaction Cardiomyopathy Do Not Predict Clinical Phenotype

Susanne Probst, PhD*; Erwin Oechslin, MD*; Pia Schuler, MD; Matthias Greutmann, MD; Philipp Boyé, MD; Walter Knirsch, MD; Felix Berger, MD; Ludwig Thierfelder, MD; Rolf Jenni, MD; Sabine Klaassen, MD

Background—Left ventricular noncompaction of the myocardium (LVNC) has been recognized as a cardiomyopathy with a genetic etiology. Mutations in genes encoding sarcomere proteins were shown to be associated with LVNC. We evaluated the potential clinical impact of genetic analysis of sarcomere genes in patients with LVNC.

Methods and Results—We identified 5 mutations in cardiac myosin-binding protein C (MYBPC3) and 2 mutations in α-tropomyosin (TPM1) in a cohort of unrelated adult probands with isolated LVNC. The mutations in MYBPC3 and TPM1 and in 6 other previously reported sarcomere genes in this cohort resulted in a total of 18 (29%) heterozygous mutations in 63 probands. β-myosin heavy chain (MYH7) was the most prevalent disease gene and accounts for 13% of cases, followed by MYBPC3 (8%). Comparing sarcomere mutation-positive and mutation-negative LVNC probands showed no significant differences in terms of average age, myocardial function, and presence of heart failure or tachyarrhythmias at initial presentation or at follow-up. Familial disease was found in 16 probands of whom 8 were sarcomere mutation positive. Nonpenetration was detected in 2 of 8 mutation-positive families with LVNC.

Conclusions—Mutations in sarcomere genes account for a significant (29%) proportion of cases of isolated LVNC in this cohort. The distribution of disease genes confirms genetic heterogeneity and opens new perspectives in genetic testing in patients with LVNC and their relatives at high risk of inheriting the cardiomyopathy. The presence or absence of a sarcomere gene mutation in LVNC cannot be related to the clinical phenotype.

Key Words: cardiomyopathy • genetics • noncompaction • myocardium • sarcomere

Left ventricular noncompaction of the myocardium (LVNC) has been recognized by the American Heart Association as a distinct primary cardiomyopathy with a genetic etiology, although it is still considered an unclassified cardiomyopathy according to the European Society of Cardiology. LVNC is characterized by a unique myocardial morphology, hypertrophic segments that consist of a thin, compacted epicardial layer and a thick, noncompacted endocardial layer. The noncompacted layer contains numerous prominent trabeculations and deep intertrabecular recesses. Variable clinical features are seen in symptomatic patients with the triad of congestive heart failure, thrombembolic events, and arrhythmias, including sudden cardiac death. Familial cases range in frequency between 18% and 64% based on variation in clinical assessment. As in other cardiomyopathies, index cases represent the most severe spectrum of the disease. Milder and asymptomatic forms and a more favorable prognosis of the disease have been identified during family screening. In addition to reports on some very rare disease genes, mutations in genes encoding sarcomere proteins have been identified in a significant proportion of patients with LVNC. Heterozygous mutations in genes encoding β-myosin heavy chain (MYH7), α-cardiac actin (ACTC1), and cardiac troponin T (TNNT2) account for 17% of cases of isolated LVNC in adult patients. In a study by Hoedemaekers et al., LVNC was associated with genetic variants in 11 of 17 genes: 6 sarcomere; 2 calcium handling; and other cardiomyopathy genes, such as lamin A/C (LMNA), ZASP (LDB3), and taffazin (TAZ). Mutations in the genes encoding cardiac myosin-
binding protein C (MYBPC3), α-tropomyosin (TPM1), and cardiac troponin I (TNNI3) further support the concept that sarcomere genes are associated with LVNC. Nevertheless, except in 1 report, mutation screening efficiency of sarcomere genes is uncertain, and penetrance and genotype/phenotype correlations in LVNC are unknown. In this systematic study, we investigated the prevalence, distribution of disease genes, and spectrum of mutations in 8 sarcomere disease genes in 63 adult patients with isolated LVNC. We extended our previous mutation analyses to MYBPC3 and TPM1. The purpose of this study was to combine genetic and phenotypic analyses of this LVNC cohort to compare mutation-positive versus mutation-negative probands for possible differences in clinical phenotypes.

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Methods

Clinical Evaluation
Unrelated adult patients were recruited from 2 tertiary referral centers (University Hospital Zürich, Switzerland, and the German Heart Institute Berlin, Germany). Informed consent was obtained from all patients according to institutional guidelines. Proband and available family members were evaluated by history taking, review of medical records, physical examination, 12-lead electrocardiography, 24-hour Holter monitoring, and transthoracic echocardiography. Neuromuscular abnormalities were excluded by physical examination. The diagnosis of isolated LVNC was made based on the presence of the established echocardiographic criteria by Jenni et al. Echocardiographic studies were performed and reviewed by 2 independent observers (R.J. and E.O.).

Mutation Screening
Mutation screening was carried out with genomic DNA samples from 63 probands as described previously. Denaturing high-performance liquid chromatography analysis of TPM1 and MYBPC3 was performed on the WAVE Nucleic Acid Fragment Analysis System model 3500HT (Transgenicom; Glasgow, UK), and samples with an abnormal peak were sequenced as described previously. A total of 360 control chromosomes were screened for the absence of a sequence variation to recognize common polymorphisms. The allele frequency of the putative mutation in the control population was assumed to be <0.003, given that 360 control chromosomes were free of the mutation. Mutations were not reported as variants in the 1000 Genomes Project, December 2010 release, which is based on the 20100804 sequence and alignment release (www.1000genomes.org).

Statistical Analysis
Statistical analyses were performed with SPSS for Windows version 15.0 (SPSS Inc; Chicago, IL). Mann–Whitney test was used for categorical variables. Unpaired Student t test analysis was used for continuous variables, and a normal distribution of the data was confirmed by the Kolmogorov-Smirnov test. Descriptive data for continuous variables are presented as mean ± SD. P < 0.05 was considered to be significant. Probability of the event-free rate for the combined end point of death or heart transplantation was calculated by the Kaplan–Meier method of life table estimation. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results
A cohort of 63 unrelated white individuals of western European descent (43 men and 20 women; mean age at diagnosis, 40.2 ± 15.6 years; age range, 15 to 70 years) underwent genetic screening of 8 sarcomere genes. The diagnosis in family members with LVNC was ascertained at an age range of 6 weeks to 73 years. Results of a subset of 6 sarcomere genes, MYH7, ACTC1, TNNT2, TNNI3, MYL2, and MYL3 in this cohort have been reported previously. In the present study, heterozygous mutations in the same cohort were identified for 2 other sarcomere genes in 5 probands in MYBPC3 and in 2 probands in TPM1 (Figure 1). Clinical phenotypes were assessable in 4 families of the 7 probands with MYBPC3 and TPM1 mutations, and familial disease was found in 2 of them (Figure 1A). Table 1 shows the mutations of probands. The clinical charac-
teristics of affected family members at initial diagnosis are presented in Table 2. A comparison of the clinical characteristics between sarcomere mutation-positive and sarcomere mutation-negative probands was performed (Table 3).

Mutations in \(\alpha\)-Tropomyosin

Two novel mutations were found in \(TPM1\). A Glu192Lys missense mutation in exon 6 of \(TPM1\) (Figure 1B) was detected in proband KR, who was experiencing sudden chest pain and dyspnea at initial diagnosis. The echocardiogram revealed pronounced LVNC and increased right ventricular trabeculations. The mutation affects a glutamic acid with a high degree of conservation throughout evolution suggested its functional importance (Figure 1B). Cardiac MRI revealed normal left ventricular (LV) mass and extensive diffuse fibrosis of the LV (Figure 2A and 2B). Fibrosis was predominantly located on the epicardial side of the LV myocardium and extended transmurally into the anterior and inferior LV wall. The hypertrophic interventricular septum was spared by fibrosis and appeared without recesses or prominent trabeculations. This unusual pattern of fibrosis is not seen in hypertrophic cardiomyopathy (HCM), myocardial infarction, or myocarditis. Family history revealed that the proband’s father had died from heart disease at age 60 and that his uncle died of sudden cardiac death at age 40. Echocardiography performed on his son, who did not carry the \(TPM1\) mutation, showed normal LV morphology and function.

A novel Lys248Glu missense mutation was identified in exon 8 in the proband of family LVNC-117, individual I-1. The patient presented with congestive heart failure at age 63 (Figure 2C and 2D). His 2 affected, asymptomatic children, a 32-year-old daughter (II-2) and a 34-year-old son (II-3), were

<table>
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<th>Table 1. Mutations of 63 LVNC Probands</th>
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<td><strong>Proband</strong></td>
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<tr>
<td>New mutations, present study</td>
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<tr>
<td>(TPM1)</td>
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<td>(MYBPC3)</td>
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<tr>
<td>Sporadic</td>
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<tr>
<td>Mutations previously published by Klaassen et al[18]</td>
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<tr>
<td>(MYH7)</td>
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<td>LVNC-107</td>
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<td>LVNC-108</td>
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<td>LVNC-109</td>
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<tr>
<td>(ACTC1)</td>
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<tr>
<td>LVNC-111</td>
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<td>(TNNT2)</td>
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Sporadic indicates that only the proband of a family was affected with LVNC; LVNC-101, -102, -107, -108, -109, -110, -111, and -117 indicate familial disease, meaning that, apart from the proband, at least 1 individual in a family was affected LVNC indicates left ventricular noncompaction of the myocardium.
identified only by family screening (Figure 1A). The daughter of individual II-2 (III-1) was suspected to have experienced congestive heart failure because of myocarditis several years before description of this family history of cardiomyopathy. She received a diagnosis of dilated cardiomyopathy (DCM) without signs of LVNC, and an echocardiogram performed at age 6 weeks showed biventricular impaired systolic function. At age 5, she received an LV assist device and a successful transplant 3 months later. A diagnostic myocardial tissue sample taken from the LV apex revealed pronounced endo-
ventricular tachycardia; NYHA, New York Heart Association; PHT, pulmonary hypertension. Other abbreviation as in Table 1.

Sporadic indicates that only the proband of a family was affected by LVNC; LVNC-102 and -117 indicate familial disease, meaning that, apart from the proband, at least 1 individual in a family was affected AF indicates atrial fibrillation; CHF, congestive heart failure; EPI, electrophysiological investigation; HTX, heart transplantation; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF/LVFS, left ventricular ejection fraction/left ventricular fractional shortening; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PHT, pulmonary hypertension. Other abbreviation as in Table 1.

*Noncompacted segments: no = 0; apex = 1; apex, midventricular wall = 2; midventricular wall = 3.
† Z score is the normal reference range −2 to +2.

### Mutations in Cardiac Myosin-Binding Protein C

In MYBPC3, 5 mutations were identified, 4 of which were described before in individual patients with HCM (Figure 1C). Proband AY presented with atypical chest pain, and a Gly5Arg sequence variation in exon 2 was detected in this otherwise asymptomatic patient. This mutation also was present in his 47-year-old unaffected mother and has been reported as a compound heterozygous mutation in a patient with HCM. Two probands, individual I-1 of LVNC-102 and LD, carry the same missense mutation (Gly490Arg) in exon 18. The proband of LVNC-102 received the first diagnosis at age 70 because of dyspnea. Family screening revealed that his asymptomatic 32-year-old son also was affected. Proband LD received the diagnosis as a result of unclear syncope. In the 2 individuals with the Gly490Arg mutation, the apex was not affected, only the midventricular inferior and lateral wall (Figure 2E). Proband SN presented with decompensated congestive heart failure. In this patient, the Pro873Leu substitution in exon 27 is a novel mutation. Proband NS had nonsustained ventricular flutter at electrophysiological investigation and received an implantable cardioverter-defibrillator (Figure 2F). A 2-bp deletion Pro955ArgfsX95 was detected in this patient and in 1 of her unaffected daughters (aged 14 years) that led to an amino acid frameshift and a premature stop codon, resulting in a predicted truncated protein. Variants Pro955ArgfsX95 and Gly5Arg represent the only 2 cases with familial nonpenetrance in our series.

### Genetic and Phenotypic Analysis of the Cohort

Sixty-three unrelated probands with LVNC underwent genetic screening of 8 sarcomere genes. Eighteen mutations were identified, which accounts for 29% of all probands with isolated LVNC. Fifteen distinct heterozygous mutations were found in 5 sarcomere protein genes: MYH7, MYBPC3, TPM1, ACTC1, and TNNT2. No mutations were found in TNNI3, MYL2, and MYL3. Mutations occurred most frequently in MYH7 (13%) and MYBPC3 (8%). The frequency of mutations in the 3 other disease genes were 3% in TPM1, 3% in ACTC1, and 2% in TNNT2. Eight of the 15 distinct heterozygous mutations were novel mutations: 6 in MYH7, 1 in TPM1, and 1 in MYBPC3. The majority of mutations were missense mutations (13/18), but 3 splice-site mutations and 2 deletions, 1 with and 1 without producing a frameshift, were identified. Probands did not carry multiple sarcomere mutations. Familial disease was present in 16 probands of whom 8 were mutation positive and 8 mutation negative for sarcomere genes.

A phenotypic comparison between the 18 mutation-positive and 45 mutation-negative patients was performed (Table 3). Both groups did not differ in sex, age at diagnosis, or age at follow-up. The duration of follow-up was slightly shorter in the mutation-negative group (P < 0.046). The following variables also were not different between the 2 groups at the time of diagnosis: (1) number of symptomatic versus asymptomatic
end point of heart transplantation or death did not demonstrate a difference. However, the Kaplan–Meyer survival curve for the combined time to transplant (mutation negative/mutation positive) was more frequently affected in the mutation-positive group (8%/31%; P=0.046), but no differences in the distribution of the endocardial layers of the myocardium.

The prevalence, distribution of disease genes, spectrum of mutations, and clinical features related to mutations in sarcomere genes were investigated in adult patients with isolated LVNC. The combined genetic and phenotypic evaluation in this study has implications for genetic counseling and testing in LVNC because sarcomere gene mutations are an important determinant of LVNC.

Prevalence and Spectrum of Sarcomere Gene Mutations in Patients With LVNC

In the total cohort studied, 18 mutations in 8 sarcomere genes were identified in 29% of adult patients with isolated LVNC. In the study by Hoedemakers et al,13 mutations of 11 genes, among them 6 sarcomere genes, in 41% of patients with LVNC were identified. In adult patients, mutations in MYH7 were the most frequent genetic defects (present study, 8 of 63 probands [13%]; Hoedemakers et al, 9 of 57 probands [16%]).

Table 3. Comparison of Probands With and Without Sarcomere Gene Mutations

<table>
<thead>
<tr>
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<th>Mutation Positive (n=18)</th>
<th>Mutation Negative (n=45)</th>
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<tr>
<td>Male/female sex, n</td>
<td>13/5</td>
<td>30/15</td>
<td>NS</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>39.2±16.9</td>
<td>43.3±15.0</td>
<td>NS</td>
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<tr>
<td>Age at follow-up, y</td>
<td>45.5±16.6</td>
<td>46.8±15.7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of follow-up, y</td>
<td>6.7±5.5</td>
<td>3.8±4.2</td>
<td>0.046</td>
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At diagnosis
- Cardiac symptoms*    14 (78)   40 (89)   NS
- Heart failure†        10 (56)   28 (62)   NS
- Tachyarrhythmias‡     2 (11)    7 (16)    NS

Echocardiography
- LVEDD at diagnosis, mm 60.0±9.2 60.0±12.3 NS
- LVEDD at follow-up, mm 59.7±9.0 58.4±10.2 NS
- LVFS at diagnosis, % 20.0±9.3 22.9±8.9  NS
- LVFS at follow-up, % 22.2±10.3 23.4±11.1 NS
- LVEF at diagnosis, % 36.1±17.1 38.7±16.1 NS
- LVEF at follow-up, % 39.6±14.4 42.3±15.1 NS

At follow-up
- ICD                    3 (17)    7 (16)    NS
- Alive§                 16 (89)   36 (80)   0.048
- HTX or death§          2 (11)    9 (20)    NS

Data are presented as mean±SD or n (%). NS indicates not significant.

Other abbreviations as in Table 2.

*Dyspnea, syncope, shock, palpitations.
†New York Heart Association functional class II to IV.
‡Atrial flutter/fibrillation, atrioventricular nodal reentrant tachycardia, ventricular tachycardia, ventricular flutter/fibrillation.
§From 18 mutation-positive probands, 16 were alive and 2 were deceased or had received a cardiac transplant. From 45 mutation-negative probands, 36 were alive and 9 were deceased or had received a cardiac transplant.

Discussion

The prevalence and spectrum of sarcomere gene mutations in patients with isolated LVNC were investigated in adult patients. The combined genetic and phenotypic evaluation in this study has implications for genetic counseling and testing in LVNC because sarcomere gene mutations are an important determinant of LVNC.

Figure 2. A and B, MRI short-axis orientation at the midventricular level of individual KR with a Glu192Lys mutation in TPM1. A, Steady-state free precession image of thin epicardial and trabeculated endocardial layer of the myocardium. B, Late gadolinium enhancement image of scar tissue (bright region) in the heavily trabeculated areas (anterior, inferior), although the septum and parts of the lateral wall are not affected (black). C through F, Echocardiographic images of affected individuals with left ventricular noncompaction of the myocardium (LVNC). C, Early diastolic parasternal short-axis view (C) and end-diastolic apical 4-chamber view (D) of individual I-1 of kindred LVNC-117. E, Late diastolic parasternal short-axis view of individual LD with midventricular LVNC. F, End-diastolic 4-chamber view of proband NS with apical and midventricular LVNC.
Therefore, the known prominent role for MYH7 in cardiomyopathies, such as in HCM24 and DCM, is becoming evident in LVNC as well. Hoedemakers et al also included children and probands with nonisolated LVNC; patients with Dutch founder mutations were reported. Nevertheless, the distribution of mutations in 5 sarcomere disease genes was comparable in both cohorts, with MYH7 being the most prevalent disease gene (20% in Hoedemakers versus 13% in the present study) followed by MYBP3 (5% versus 8%), and mutations in TNNT2, ACTC1, and TPM1 were rare and accounted for LVNC in only 1 or 2 probands in the respective cohorts. The most prevalent type of mutations in both cohorts was missense mutations (Hoedemakers et al, 16 of 21 distinct mutations; present study, 11 of 15 distinct mutations) in MYH7, MYBP3, TNNT2, ACTC1, and TPM1. In addition to 18 probands with single mutations, Hoedemakers et al described 4 probands with compound or double heterozygote mutations, and 1 proband had 3 mutations. In contrast, all 18 mutation-positive probands in the present study carried single mutations.

Although 8 of the 15 distinct mutations were novel in our cohort, it can be anticipated that they are not specifically found in LVNC. Seven of the 15 distinct mutations have been described previously in apical HCM, DCM, and HCM. In our previous study, the Arg243His substitution in MYH7 was found in a patient with apical HCM,27 the Glu101Lys exchange in ACTC1 in apical HCM and LVNC,27,28 and the Arg131Trp substitution in TNNT2, ACTC1, and TPM1. In the present study, the exchange Glu192Lys in ACTC1 was found in a patient with apical HCM,27 the Glu101Lys exchange in ACTC1 in apical HCM and LVNC,27,28 and the Arg131Trp substitution in TNNT2, ACTC1, and TPM1. In addition to 18 probands with single mutations, Hoedemakers et al described 4 probands with compound or double heterozygote mutations, and 1 proband had 3 mutations. In contrast, all 18 mutation-positive probands in the present study carried single mutations.

Penetrance and Variable Phenotypes in LVNC

The penetrance of a mutation is defined as the percentage of mutation carriers expressing a phenotype, and most autosomal-dominant cardiomyopathies are characterized by incomplete penetrance or more age-related penetrance.20 Variants Pro955ArgfsX95 and Gly5Arg in MYBP3 represent the only cases with familial nonpenetrance in our series (2 of 8 probands). Thus, penetrance in our series of patients with LVNC was incomplete, but nonpenetrance affected only families with MYBP3 mutations. Mutations in the most prominent disease gene MYH7 in LVNC were fully penetrant. There is also variable expressivity in cardiomyopathies, and there even can be large differences among relatives of the same family (intrafamilial variability) who carry the same mutation. For LVNC, this has been documented for 1 family carrying the Glu101Lys exchange in ACTC1 associated with apical HCM, LVNC, and septal defects.28 LVNC-117 in this series is an interesting example of 2 cardiomyopathy phenotypes, adult LVNC and neonatal DCM, segregating within 1 family and associated with the same mutation. Intrafamilial differences or a more severe or early phenotype sometimes are explained by the presence of a second causal mutation in the family.20 For kindred LVNC-117 individual III-1 with neonatal DCM, compound or double heterozygosity or homozygosity in sarcomere genes was excluded and could not account for the severe phenotype.

Familial cardiomyopathy was detected in 25% of probands. Echocardiography revealed LVNC in affected family members, except for family LVNC-117 in which DCM was present in 1 neonate. The number of familial cases in this study is relatively low compared with that by Hoedemakers et al,13 which detected familial cardiomyopathy in 64% of probands because of the almost complete echocardiographic work-up of their families. In their study, 44% of familial disease would have remained undetected by ascertainment of family history alone without clinical cardiac family screening. One limitation of our study was the incomplete clinical family screening for which position statements have recently been published.20,31 Clinical and echocardiographic screening should be considered to detect asymptomatic family members with LVNC because of the potentially increased risk for arrhythmias, myocardial dysfunction, and thrombembolic events. In addition, genetic evaluation is highly useful for identifying other at-risk relatives without the morphological changes because the penetrance of LVNC may be incomplete in some cases. The duration of follow-up was shorter in the mutation-negative group, and patients who received a cardiac transplant or died were more likely to be found in the mutation-negative group. Therefore, the mutation-positive group seems to have a slightly more benign clinical phenotype. Long-term studies are needed to detect possible relationships among the type of mutation, genetic modifiers, and clinical phenotype.

LVNC: A Defect of Cardiomyocyte Dysfunction During Myocardial Development?

How mutations in sarcomere genes could have detrimental effects on cardiac morphogenesis is unclear. LVNC still is considered an unclassified cardiomyopathy by the European Society of Cardiology and other investigators who have suggested that it is not clear whether it is a separate cardiomyopathy or merely a morphological trait shared by many phenotypically distinct cardiomyopathies. Biagini et al24 reported a series of patients with LVNC who fulfilled echocardiographic criteria for DCM, HCM, and restrictive cardiomyopathy. The causal role of noncompaction in the pathogenesis of cardiomyopathy recently was questioned by a study of transgenic mice carrying a human troponin T mutation that leads to LVNC.35 Not much is known about the molecular regulation of ventricular trabeculation. Early myocardial development is characterized by a subdivision of the myocardial wall into an outer, highly mitotic compact zone and an inner trabecular zone with much less proliferative activity. A correct balance between proliferation and differentiation of cardiomyocytes seems to be critical in ventricular chamber formation.36 In zebrafish, Aumann and colleagues demonstrated that chamber morphology develops through changes in cell morphology. Their model suggests that even subtle changes of circulation or
contractility caused by mutated sarcomere genes could lead to abnormalities in cell morphology and consequences for chamber morphology. How this model could account for the localized remodeling of the ventricular apex, which is primarily affected in LVNC, remains to be determined.

In the present study, several mutations in MYBPC3 were found in LVNC. In HCM, most MYBPC3 mutations are predicted to produce C-terminally truncated proteins, lacking titin, major myosin-binding sites, or both. Recent work has strongly argued for haploinsufficiency as the disease mechanism for both truncation and missense MYBPC3 mutations. The sarcomeric phenotype in HCM with MYBPC3 mutations includes a primary contractile sarcomeric defect causing deranged secondary alterations in protein phosphorylation. It remains to be determined whether contractile dysfunction is the pivotal link between mutant sarcomeric protein and the pathological morphology observed in LVNC.

Conclusions
In the present cohort of adult patients with isolated LVNC, mutations in sarcomere genes play a prominent role, with a prevalence of 29%. Of the 8 genes tested, MYH7 and MYBPC3 are the most frequently mutated sarcomere genes in LVNC at 13% and 8%, respectively. Sarcomere mutation-positive probands cannot be distinguished from mutation-negative probands on the basis of their clinical phenotypes. However, genetic testing of sarcomere genes is a valuable diagnostic tool for the probands and their relatives at high risk of inheriting the cardiomyopathy.

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Disclosures
None.

References
Left ventricular noncompaction of the myocardium (LVNC) is a cardiomyopathy with a genetic etiology and autosomal-dominant transmission is common. The morphological echocardiographic characteristics include a severely thickened, 2-layered myocardium, numerous prominent trabeculations, and deep intertrabecular recesses. The clinical features range from asymptomatic individuals to symptomatic patients with progressive deterioration of cardiac function; thrombembolic events; and arrhythmias, including sudden cardiac death. LVNC is genetically heterogeneous, and prior reports indicate that mutations in genes encoding sarcomere proteins are associated with LVNC. In the present study, we evaluated the potential clinical impact of genetic analysis of sarcomere genes in patients with isolated LVNC. We describe mutations in cardiac myosin-binding protein C (MYBPC3) and α-tropomyosin (TPM1) in a cohort of unrelated adult probands with isolated LVNC. The mutations in MYBPC3 and TPM1 and in 6 other previously reported sarcomere genes in this cohort resulted in a total of 18 (29%) heterozygous mutations in 63 probands. β-myosin heavy chain (MYH7) was the most prevalent disease gene, accounting for 13% of cases, followed by MYBPC3 (8%). Although mutations in sarcomere genes account for a significant proportion of cases of isolated LVNC, patients who are mutation positive could not be distinguished from those who are mutation negative by their clinical characteristics. However, we provide insight into how mutations of different sarcomere genes lead to diverse clinical phenotypes, with implications for diagnosis, genetic testing, and follow-up. Genetic testing of sarcomere genes is a valuable diagnostic tool for the probands and their relatives who may be at high risk of inheriting the cardiomyopathy.
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