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. (Circ Cardiovasc Genet. 2011;4:367-374.)

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.1,2 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.3,4 Variable clinical features are seen in symptomatic patients with the triad of congestive heart failure, thrombembolic events, and arrhythmias, including sudden cardiac death.5–12 Familial cases range in frequency between 18% and 64% based on variation in clinical assessment.5–7,13 As in other cardiomyopathies, index cases represent the most severe spectrum of the disease.5,7 Milder and asymptomatic forms and a more favorable prognosis of the disease have been identified during family screening.10,11,13,14 In addition to reports on some very rare disease genes,15 mutations in genes encoding sarcomere proteins have been identified in a significant proportion of patients with LVNC.16–18 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.18 In a study by Hoedemaekers et al,13 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-
Mutation Screening

Mutation screening was carried out with genomic DNA samples from 63 probands as described previously. Denaturing high-performance liquid chromatography analysis of TP1 and MYBPC3 was performed on the WAVE Nucleic Acid Fragment Analysis System model 3500HT (Transgenomic; 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 mutations in the control population was assumed to be 0.01, 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.

Clinical Perspective on p 374

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. Probands 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.).

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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 α-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 and is suggested to have 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>
<thead>
<tr>
<th>Table 1. Mutations of 63 LVNC Probands</th>
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<tbody>
<tr>
<td><strong>Proband</strong></td>
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<tr>
<td>-----------------</td>
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<tr>
<td><strong>New mutations, present study</strong></td>
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<tr>
<td><strong>TPM1</strong></td>
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<tr>
<td>LVNC-117</td>
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<tr>
<td><strong>MYBPC3</strong></td>
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<tr>
<td>Sporadic</td>
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<tr>
<td>LVNC-102</td>
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<td>Sporadic</td>
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<td>Sporadic</td>
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<tr>
<td>Sporadic</td>
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<tr>
<td><strong>Mutations previously published by Klaassen et al</strong>18</td>
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<tr>
<td><strong>MYH7</strong></td>
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<tr>
<td>LVNC-101</td>
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<tr>
<td>LVNC-107</td>
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<tr>
<td>LVNC-108</td>
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<td>LVNC-109</td>
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<tr>
<td>Sporadic</td>
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<td>Sporadic</td>
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<tr>
<td>Sporadic</td>
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<tr>
<td>Sporadic</td>
</tr>
<tr>
<td><strong>ACTC1</strong></td>
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<tr>
<td><strong>TNNT2</strong></td>
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<tr>
<td>Sporadic</td>
</tr>
</tbody>
</table>

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.
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 Lys248Glu mutation in MYBPC3 was 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 endoventricular fibroelastosis and minimal interstitial fibrosis. After follow-up. The duration of follow-up was slightly shorter in the mutation-negative group (16 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 genes: MYH7, MYBPC3, TPM1, ACTC1, and TNNI3. No mutations were found in TNNT2. 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 negative and 8 mutation positive 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

<table>
<thead>
<tr>
<th>Proband</th>
<th>ID</th>
<th>Age, y</th>
<th>Sex</th>
<th>NYHA Class</th>
<th>Site of LVNC*</th>
<th>LVEDD Z Score†</th>
<th>LVEF/LVFS, %</th>
<th>Cardiovascular Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPM1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>LVNC-117</td>
<td>I-1</td>
<td>63</td>
<td>M</td>
<td>4</td>
<td>2</td>
<td>3.4</td>
<td>19/18</td>
<td>CHF</td>
</tr>
<tr>
<td></td>
<td>II-2</td>
<td>32</td>
<td>F</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>37/20</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>II-3</td>
<td>34</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>53/32</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>III-1</td>
<td>0</td>
<td>F</td>
<td>3</td>
<td>0</td>
<td>4.0</td>
<td>22/16</td>
<td>CHF, AF, HTX at 5 y</td>
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<tr>
<td>MYBPC3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sporadic</td>
<td>AY</td>
<td>20</td>
<td>M</td>
<td>1</td>
<td>2</td>
<td>0.7</td>
<td>55/25</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>LVNC-102</td>
<td>I-1</td>
<td>70</td>
<td>M</td>
<td>2</td>
<td>3</td>
<td>0.3</td>
<td>72/33</td>
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<tr>
<td></td>
<td>II-1</td>
<td>32</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0.4</td>
<td>60/38</td>
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<tr>
<td></td>
<td>LD</td>
<td>24</td>
<td>F</td>
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<td>3</td>
<td>0.5</td>
<td>57/29</td>
<td>Syncopes</td>
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<tr>
<td></td>
<td>SN</td>
<td>37</td>
<td>M</td>
<td>4</td>
<td>2</td>
<td>3.0</td>
<td>28/18</td>
<td>CHF, PHT</td>
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<tr>
<td></td>
<td>NS</td>
<td>28</td>
<td>F</td>
<td>2</td>
<td>2</td>
<td>1.7</td>
<td>46/25</td>
<td>NSVT at EPI, ICD</td>
</tr>
</tbody>
</table>

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.

†Z score is the normal reference range $-2$ to $+2$.
patients (dyspnea, syncope, shock, palpitations), (2) tachyarrhythmias (atrial flutter/fibrillation, atrioventricular nodal reentrant tachycardia, ventricular tachycardia, ventricular flutter/fibrillation), and (3) heart failure.

Echocardiographic criteria (LV end-diastolic diameter, LV fractional shortening, and LV ejection fraction) at diagnosis and at follow-up also were indistinguishable between the 2 groups. The LV wall was divided into 9 segments to describe the distribution of affected LVNC segments in the 2 groups, including the whole apex (1 segment) and at the base and at the midventricular level, the LV was divided into 4 segments each (inferior, lateral, anterior, and septal). The number of affected segments was comparable between both groups (mean, 3 affected segments each). The most prevalent locations of LVNC (mutation negative/mutation positive) were the apex (88%/31%), midventricular lateral wall (82%/81%), and midventricular inferior wall (76%/88%). Only the midventricular septum was more frequently affected in the mutation-positive group (8%/31%; P<0.046), but no differences in the distribution of the other 8 segments were found between the 2 groups.

There was no difference between the 2 groups with regard to the number of implantations of an automated cardiac defibrillator. Patients who received a cardiac transplant or died were more likely to be found in the mutation-negative group (P<0.048).

However, the Kaplan–Meier survival curve for the combined end point of heart transplantation or death did not demonstrate any difference between the 2 groups.

### Discussion

The prevalence, distribution of disease genes, spectrum of mutations, and clinical features related to mutations in 8 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 5 sarcomere genes were identified in 29% of adult patients with isolated LVNC. In the study by Hoedemaekers 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%]; Hoedemaekers et al, 9 of 57 probands...
In the present study, the exchange Glu192Lys in apical HCM, LVNC, and septal defects. LVNC-117 in this mutation. For LVNC, this has been documented for 1 family (intrafamilial variability) who carry the same mutation. The penetrance of a mutation is defined as the percentage of individuals with a disease who carry the mutation. Penetrance can be incomplete, but nonpenetrance affected only (2 of 8 probands). Thus, penetrance in our series of patients was incomplete, but nonpenetrance affected only (2 of 8 probands). 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.

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 sacromere 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 investigators32,33 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 al34 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 colleagues37 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 negative probands on the basis of their clinical phenotypes. Positive probands cannot be distinguished from mutation-

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.

In this cohort resulted in a total of 18 (29%) heterozygous mutations in 63 probands.


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Villard E, Duboscq-Bidot L, Charron P, Benaiche A, Conraads V, Sylvius CLINICAL PERSPECTIVE


cardiomyopathy: two homoygous cases with “typical” hypertrophic cardiomyopathy and three


Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semarjan C. Compound and double mutations in patients with hypertrophic cardio-


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