Mutations in Sarcomere Protein Genes in Left Ventricular Noncompaction

Sabine Klaassen, MD*; Susanne Probst, MSc*; Erwin Oechslin, MD; Brenda Gerull, MD; Gregor Krings, MD; Pia Schuler, MD; Matthias Greutmann, MD; David Hürlimann, MD; Mustafa Yegitbasi, MD; Lucia Pons, MD; Michael Gramlich, MD; Jörg-Detlef Drenckhahn, MD; Arnd Heuser, MD; Felix Berger, MD; Rolf Jenni, MD; Ludwig Thierfelder, MD

Background—Left ventricular noncompaction constitutes a primary cardiomyopathy characterized by a severely thickened, 2-layered myocardium, numerous prominent trabeculations, and deep intertrabecular recesses. The genetic basis of this cardiomyopathy is still largely unresolved. We speculated that mutations in sarcomere protein genes known to cause hypertrophic cardiomyopathy and dilated cardiomyopathy may be associated with left ventricular noncompaction.

Methods and Results—Mutational analysis in a cohort of 63 unrelated adult probands with left ventricular noncompaction and no other congenital heart anomalies was performed by denaturing high-performance liquid chromatography analysis and direct DNA sequencing of 6 genes encoding sarcomere proteins. Heterozygous mutations were identified in 11 of 63 samples in genes encoding β-myosin heavy chain (MYH7), α-cardiac actin (ACTC), and cardiac troponin T (TNNT2). Nine distinct mutations, 7 of them in MYH7, 1 in ACTC, and 1 in TNNT2, were found. Clinical evaluations demonstrated familial disease in 6 of 11 probands with sarcomere gene mutations. MYH7 mutations segregated with the disease in 4 autosomal dominant LVNC kindreds. Six of the MYH7 mutations were novel, and 1 encodes a splice-site mutation, a relatively unique finding for MYH7 mutations. Modified residues in β-myosin heavy chain were located mainly within the ATP binding site.

Conclusions—We conclude that left ventricular noncompaction is within the diverse spectrum of cardiac morphologies triggered by sarcomere protein gene defects. Our findings support the hypothesis that there is a shared molecular etiology of different cardiomyopathic phenotypes. (Circulation. 2008;117:2893-2901.)

Key Words: cardiomyopathy ■ genetics ■ heart failure ■ remodeling ■ myocardium

Left ventricular noncompaction (LVNC) has recently been classified as a primary cardiomyopathy with a genetic origin.1 LVNC is morphologically characterized by a severely thickened, 2-layered myocardium, numerous prominent trabeculations, and deep intertrabecular recesses.2-3 LVNC may be an isolated finding in the absence of any coexisting cardiac anomaly or may be associated with other congenital heart anomalies.1 The heterogeneity of the clinical features includes both asymptomatic and symptomatic patients with progressive deterioration in cardiac function that results in congestive heart failure, arrhythmias, thromboembolic events, and sudden cardiac death.2

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As in other heart muscle disorders, LVNC shows genetic heterogeneity. Mutations in genes encoding taffazin (G4.5), LIM domain binding protein 3/ZASP (LDB3), and α-dystrobrevin have been reported5-6 but are infrequent causes of the disease.5-8 Therefore, the genetic basis of disease in a large proportion of patients with LVNC is still unresolved.

Molecular genetic studies have shown that dilated cardiomyopathy (DCM) and an apparently distinct clinical entity, hypertrophic cardiomyopathy (HCM), are allelic diseases caused by mutations in the α-cardiac actin gene (ACTC).9 Moreover, mutations in several sarcomeric protein genes, first identified in familial HCM, have been implicated in DCM.10 In patients with familial LVNC, relatives may have features consistent with DCM rather than LVNC.11 Biagini et al12 reported a series of LVNC patients in which patients fulfilled criteria for DCM, HCM, and restrictive cardiomyopathy. Mutations in 4 distinct sarcomere protein genes lead to a specific type of HCM, apical HCM.13 As in apical HCM, the predominant location of LVNC is the ventricular apex.

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From the Max Delbrück Center for Molecular Medicine (S.K., S.P., B.G., M. Gramlich, J.-D.D., A.H., L.T.), Berlin, Germany; Clinic of Pediatric Cardiology (S.K., G.K., F.B.) and Helios Clinic Berlin-Buch (L.T.), Charité, Humboldt University of Berlin, Berlin, Germany; Adult Congenital Cardiac Centre at Peter Munk Cardiac Centre (E.O.), University Health Network/Toronto General Hospital, Toronto, Canada; Cardiovascular Center (P.S., M. Greutmann, D.H., R.J.), Division of Echocardiography, University Hospital Zürich, Zürich, Switzerland; Department of Congenital Heart Defects/Pediatric Cardiology (M.Y., F.B.), German Heart Institute, Berlin, Germany; and Ospedale Regionale di Mendrisio Beata Vergine (L.P.), Mendrisio, Switzerland.
*The first 2 authors contributed equally to this work.
Correspondence to Sabine Klaassen, MD, Max Delbrück Center for Molecular Medicine, Robert-Roessle Straße 10, 13092 Berlin, Germany. E-mail klaassen@mdc-berlin.de
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Recently, the ACTC Glu101Lys mutation was shown to lead to a specific phenotype with the diagnosis of apical HCM and LVNC within the same kindred. Therefore, we hypothesized that mutations in sarcomere protein genes may be associated with LVNC. Mutational analysis in a large cohort of unrelated adult probands with LVNC and absence of other congenital heart anomalies was performed. Genes encoding 6 sarcomere proteins were studied. Mutations were found in 3 distinct genes: β-myosin heavy chain (MYH7), ACTC, and cardiac troponin T (TNNT2). These findings underscore the fact that mutations in sarcomere protein genes affect a diverse phenotypic spectrum of cardiomyopathies.

**Methods**

**Clinical Evaluation**

Between April 1999 and April 2007, unrelated adult patients were recruited at 2 tertiary referral centers (University Hospital Zürich, Switzerland and the German Heart Institute Berlin, Germany). Informed consent was obtained from all participants 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 LVNC was made by echocardiography on the basis of the presence of the following established criteria by Jenni et al: a severely thickened, 2-layered ventricular myocardium with a noncompacted/compacted ratio of ≥2, prominent and excessive trabeculations, and deep intertrabecular recesses filled with blood from the ventricular cavity as visualized by color Doppler imaging. The diagnosis of LVNC was performed irrespective of the presence of heart failure or left ventricular systolic dysfunction. There are no diagnostic criteria for the diagnosis of noncompacted myocardium involving the right ventricle. The right ventricular myocardium often presents with prominent trabeculae, which makes it difficult to determine the difference between normal and pathological patterns. The diagnosis of noncompaction involving the right ventricle was made in the presence of markedly more prominent trabeculations than usually seen. All echocardiographic studies were performed and reviewed by 2 independent observers (RJ and EO). Only patients with LVNC without associated congenital heart anomalies were included.

**Mutation Screening**

Mutation screening was performed with genomic DNA samples from 63 probands in 6 genes encoding sarcomere proteins MYH7, TNNT2, cardiac troponin I (TNNT3), ACTC, regulatory myosin light chain (MYL2), and essential myosin light chain (MYL3). Primers were designed and modified according to the CardioGenomics database (http://www.cardiogenomics.org). Polymerase chain reaction (PCR) details are available on request. Denaturing high-performance liquid chromatography analysis was performed on the WAVE nucleic acid fragment analysis system (model 3500HT, Transgenic, Glasgow, United Kingdom). When an abnormal peak was detected, the PCR product was sequenced as described previously. When a putative mutation was identified, at least 360 control chromosomes were screened for the absence of the sequence variation to recognize common polymorphisms, with the assumption of an allele frequency of the putative mutation of <0.003 in the control population. The microsatellite marker D14S990 was used to perform linkage analysis for MYH7. Calculations of 2-point logarithm of the odds (LOD) scores were performed with the assumptions of a disease penetrance of 0.95 and a phenocopy rate of 0.001. For reverse-transcription PCR (RT-PCR), RNA was isolated from peripheral lymphocytes with the QIAamp RNA blood mini kit (Qiagen GmbH, Hilden, Germany), reverse transcribed, amplified by nested PCR (protocol available on request), and sequenced.

<table>
<thead>
<tr>
<th>Family</th>
<th>ID</th>
<th>Transcript</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVNC-101</td>
<td>II-4</td>
<td>c.818+16G&gt;A</td>
<td>p.Arg243His</td>
</tr>
<tr>
<td>LVNC-107</td>
<td>II-3</td>
<td>c.814G&gt;A</td>
<td></td>
</tr>
<tr>
<td>LVNC-108</td>
<td>II-2</td>
<td>c.818+16G&gt;A</td>
<td></td>
</tr>
<tr>
<td>LVNC-109</td>
<td>II-1</td>
<td>c.818+3G&gt;C</td>
<td></td>
</tr>
<tr>
<td>Sporadic</td>
<td>AJ</td>
<td>c.801_803delGAC</td>
<td>p.Asp239del</td>
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<tr>
<td>Sporadic</td>
<td>SD</td>
<td>c.840T&gt;C</td>
<td>p.Phe282Leu</td>
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<tr>
<td>Sporadic</td>
<td>IP</td>
<td>c.4161C&gt;T</td>
<td>p.Arg1359Cys</td>
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</table>

**Accession Numbers (GenBank/FASTA)**

Accession numbers (from GenBank/FASTA) were as follows: Homo sapiens myosin, heavy polypeptide 7, cardiac muscle, beta (MYH7), NM_000257; Homo sapiens troponin T type 2 (cardiac; TNNT2), transcript variant 3, NM_001001431; human cardiac β-myosin heavy chain, NP_002048; rat cardiac α-myosin heavy chain, NP_058935; chicken fast skeletal myosin heavy chain, NP_001013414; Danio rerio ventricular myosin heavy chain, AAFO00096; Drosophilia melanogaster muscle myosin heavy chain NP_723999; Caenorhabditis elegans myosin heavy chain, NP_510092; human troponin T type 2, cardiac isoform 3, NP_001001431; rat cardiac troponin T2, NP_036808; mouse troponin T2, NP_035749; chicken cardiac troponin T type 2, NP_990780; Danio rerio cardiac troponin T2, NP_690825; Caenorhabditis elegans troponin T family member (nt-2), NP_000142703.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

A cohort of 63 unrelated white individuals of western European descent (43 men and 20 women; mean age 40 years, range 15 to 70 years) were diagnosed with LVNC. Heterozygous mutations were identified in 11 probands in 3 sarcomeric protein genes: MYH7, ACTC, and TNNT2. No mutations were found in TNNT3, MYL2, and MYL3. Clinical phenotypes were assessed in all available family members of the 11 probands with mutations, and familial disease was found in 6 of them. Two families with autosomal dominant inheritance of the disease have previously been published as kindreds INVM-101 and INVM-107. Table 1 shows the mutations of probands. The clinical characteristics of all affected family members at initial diagnosis are presented in Table 2. LVNC was diagnosed at an age range from 2 to 70 years. Younger affected individuals were diagnosed because of family screening and were usually clinically asymptomatic. The age range at onset of symptoms in the 11 probands with mutations in the present study was 15 to 65 years.
Mutations in \(\beta\)-Myosin Heavy Chain

Eight mutations in \(MYH7\) in 63 probands with LVNC were identified. Families LVNC-101 and LVNC-108 carry the same splice-site mutation (c.818\_G>\_A). The missense mutation of the proband of family LVNC-107 (Arg243His) has been reported in an individual with apical HCM.\(^{13}\) Therefore, 6 of the 8 detected mutations are novel \(MYH7\) mutations.

The mutation of families LVNC-101 and LVNC-108 (c.818\_G>\_A) is the first \(MYH7\) splice-site mutation in patients with cardiomyopathies or skeletal myopathies found to date (OMIM, http://www.ncbi.nlm.nih.gov/omim and CardioGenomics home page, http://www.cardiogenomics.org). It is located at the splice donor site of intron 8 and arose independently, because haplotype analyses (data not shown) ruled out a founding mutation in both families. The G\(\rightarrow\)A transition was present in all available affected family members and absent in family members with normal cardiac morphology and function. Linkage analysis in family LVNC-101 resulted in a maximal 2-point LOD score of 2.55 at D14S990.

To determine whether or how mRNA for the mutant \(MYH7\) gene allele is transcribed, RT-PCR was performed on mRNA from blood lymphocytes. Cardiac tissue was not available. Attempts to demonstrate transcription of the mutant allele with nested PCR consistently produced the normal allele and, in addition, inconsistently yielded several aberrant transcripts at very low levels (data not shown).

The clinical evaluation of members of families LVNC-101 and LVNC-108 was remarkable for the very pronounced

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### Table 2. Clinical Characteristics of Affected Family Members at Initial Diagnosis

<table>
<thead>
<tr>
<th>Family ID</th>
<th>Age, y/Sex</th>
<th>NYHA Class</th>
<th>Site of LVNC*</th>
<th>RV†</th>
<th>LVED Z Score</th>
<th>EF/FS, %</th>
<th>ECG§</th>
<th>Cardiovascular Complications</th>
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<tr>
<td>LVNC-101</td>
<td>II-3</td>
<td>70/M</td>
<td>3</td>
<td>Yes</td>
<td>MD</td>
<td>20/NA</td>
<td>AF, AVB 1</td>
<td>CHF, PTE, PHT, CAD</td>
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<td></td>
<td>II-4</td>
<td>60/M</td>
<td>1</td>
<td>Yes</td>
<td>3.2</td>
<td>27/14</td>
<td>T ↓</td>
<td>NSVT, CVI, SPTE, CHF</td>
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<tr>
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<td>III-2</td>
<td>46/F</td>
<td>1</td>
<td>No</td>
<td>0</td>
<td>55/29</td>
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<td></td>
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<td>40/F</td>
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<td>0.6</td>
<td>65/31</td>
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<td>III-6</td>
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<td>60/NA</td>
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<td>III-11</td>
<td>24/F</td>
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<td>45/21</td>
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<td>I-2</td>
<td>68/F</td>
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<td>No</td>
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<td>43/40</td>
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<td>25/M</td>
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<td>50/30</td>
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<td>III-3</td>
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<td>0.5</td>
<td>76/34</td>
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<td>LVNC-108</td>
<td>II-2</td>
<td>36/M</td>
<td>1</td>
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<td>0.3</td>
<td>54/28</td>
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<td>III-1</td>
<td>8/M</td>
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<td>0.8</td>
<td>48/25</td>
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<td>16/F</td>
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<td>II-1</td>
<td>50/M</td>
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<td>45/32</td>
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<td>58/M</td>
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<td>4.2</td>
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<td>29/M</td>
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<td>CHF, CVI, AF at EPI, ICD</td>
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<td>MT</td>
<td>20/M</td>
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<td>50/17</td>
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<td>LJ</td>
<td>15/F</td>
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<td>20/F</td>
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<td>3.3</td>
<td>20/14</td>
<td>CHF, TIA</td>
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</tbody>
</table>

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**ID indicates identification; NYHA, New York Heart Association; LVED, left ventricular end-diastolic diameter; Z score, normal reference range −2 to 2; EF/FS, left ventricular ejection fraction/fractional shortening; MD, massive dilatation; NL, normal limits; NA, not available; AVB1, atrioventricular block grade 1; LBBB, left bundle-branch block; RBBB, right bundle-branch block; ST ↓, ST inversion; T ↓, T-wave inversion; AF, atrial fibrillation; SVT, sustained ventricular tachycardia; CHF, congestive heart failure; PHT, pulmonary hypertension; ICD, intracardiac defibrillator; NSVT, nonsustained ventricular tachycardia; HTX, heart transplantation; EPI, electrophysiological investigation; CVI, cerebrovascular insult; SPTE, systemic peripheral thromboemboli; PTE, pulmonic thromboemboli; CAD, coronary artery disease; PM, pacemaker; HBD, hypoxic brain damage; and TIA, transient ischemic attack.**

*Noncompacted segments: Apex=1; Apex, midventricular wall=2.*

†Right ventricular involvement.

§Normal ECG unless otherwise indicated.
morbidity of LVNC. The proband of LVNC-101 (II-4) was diagnosed because of T-wave inversions and later had a stroke and systemic peripheral emboli. His brother (II-3) initially presented with decompensated heart failure and pulmonary emboli. Both patients remained clinically stable during a follow-up period of 8 years. Other affected family members (III-2, III-5, III-6, and III-9) of family LVNC-101 fulfilled morphological LVNC criteria but were clinically asymptomatic. The proband of family LVNC-108 (II-2; Figures 1A, 2A, and 2B) was diagnosed because of atypical chest pain. He and his 8-year-old son (III-1; Figures 1A, 2C, and 2D) had no signs of heart failure.

In family LVNC-107, a missense mutation was identified at nucleotide 814 in exon 8, which replaces arginine with histidine at residue 243 (designated Arg243His), in the proband. He received a cardiac transplant at the age of 26 years after LVNC was first diagnosed when he was in cardiogenic shock and pulmonary and systemic peripheral emboli had occurred. The mutation was also present in his 32-year-old affected brother (II-5; Figure 1A). Their 65-year-old mother (I-2) with typical LVNC morphology remained clinically asymptomatic. Individual III-3 was suspected of having LVNC at birth, but diagnostic criteria were only fulfilled when he was 2 years old.

In family LVNC-109, a G→C transition at the third nucleotide position of intron 8 was detected in the proband and his 14-year-old asymptomatic affected son (III-1; Figure 1A). This nucleotide change was absent in the unaffected daughter of the proband (III-2) and is located in a highly conserved intronic sequence known to be important for correct splicing of the transcript.16 Analogous to the c.818+1G→A mutation, attempts to obtain consistent RT-PCR products from the transcript were unsuccessful (data not shown). The Ala13Thr variation was identified in the proband of LVNC-102 (II-1) and his sister (II-4). Both probands inherited the Glu101Lys mutation from their affected fathers, LN and VK, respectively (Table 2). Haplo-type analysis excluded a common ancestor in the 2 families (data not shown). This same mutation was described previously in patients with apical HCM.13,17 In a recent study by Monserrat et al,14 some family members of the families MH and MG originally described by Arad et al13 presented with LVNC rather than apical HCM. The probands in the present study clearly fulfilled standard criteria for LVNC (Figure 2E). Interestingly, the proband of LVNC-110 had initially been diagnosed with HCM (basal posterior left ventricular wall 16 mm, apical left ventricular wall 25 mm).

Mutations in α-Cardiac Actin and Cardiac Troponin T

α-Cardiac Actin

A Glu101Lys cardiac actin missense mutation was detected in the probands of LVNC-110 (LJ) and LVNC-111 (SA). Both probands inherited the Glu101Lys mutation from their affected fathers, LN and VK, respectively (Table 2). Haplo-type analysis excluded a common ancestor in the 2 families (data not shown). This same mutation was described previously in patients with apical HCM.13,17 In a recent study by Monserrat et al,14 some family members of the families MH and MG originally described by Arad et al13 presented with LVNC rather than apical HCM. The probands in the present study clearly fulfilled standard criteria for LVNC (Figure 2E). Interestingly, the proband of LVNC-110 had initially been diagnosed with HCM (basal posterior left ventricular wall 16 mm, apical left ventricular wall 25 mm).

Cardiac Troponin T

A de novo Arg131Trp missense mutation in exon 10 of cardiac troponin T (TNNT2) was detected in proband CR, who experienced cardiogenic shock at initial diagnosis. She presented with mainly midlateral and midinferior LVNC (Figure 2F), left ventricular dilatation, and impaired left ventricular systolic function (Table 2). The Arg131Trp mutation affects an arginine with a high degree of conservation throughout evolution, which suggests its functional importance (Figure 1D). The mutation was not present in 360 control chromosomes and had occurred de novo, because it was not present in the unaffected parents of the proband.

Sequence Variation in the Regulatory Myosin Light Chain

A regulatory myosin light chain (MYL2) sequence variation Ala13Thr was identified in the proband of LVNC-102 (II-1) and his sister (II-4). His nephew (III-2) with typical LVNC did not show the sequence variation. The Ala13Thr variation...
Figure 1. A, Pedigrees of kindreds LVNC-101, LVNC-102, LVNC-107, LVNC-108, and LVNC-109 with autosomal dominant LVNC. Filled symbols indicate individuals with LVNC; open symbols, unaffected status; and shaded symbols, unknown clinical status. Plus signs (+) indicate the presence of a mutation, and minus signs (−) the absence of a mutation. Sequence analysis of the proband is shown for each family. B, Alignment of the regions flanking the novel mutations in MYH7 showing evolutionary conservation of the mutated residues across species. The residues with the novel amino acid changes in LVNC are boxed. Dots identify amino acids identical to the one in the human sequence. Chicken f. skel. indicates chicken fast skeletal myosin heavy chain. C, Cluster of mutations (exon 8/9) in MYH7 that reside within a distance of 14 amino acids of the translated protein. D, Sequence analysis of individual CR showing the Arg131Trp missense mutation in exon 10 of TNNT2 and the evolutionary conservation of the mutated residue across species.
was localized on the haplotype segregating with the disease for microsatellite marker D12S1645 for individuals II-1 and II-4 but not for individual III-2 (data not shown). This same sequence variation, which lacks high conservation throughout evolution, has been reported as a disease-causing mutation in a single individual with pronounced midcavity obstruction in a rare subtype of HCM. The Ala13Thr variation was not present in 720 control chromosomes based on data of the present study and the work by Poetter et al. However, because of the lack of cosegregation in individual III-2, the sequence variation cannot be considered as disease-associated with LVNC.

Discussion

Comprehensive genetic analyses of 63 unrelated probands with LVNC identified 9 distinct disease-associated mutations in genes encoding β-myosin heavy chain, α-cardiac actin, and cardiac troponin T. The identification of mutations in 11 samples of 63 probands presenting with LVNC broadens the spectrum of cardiomyopathy syndromes associated with sarcomere gene defects. Mutations in MYH7 are among the most common gene defects that produce HCM and DCM, and MYH7 mutations were detected in the present cohort of patients with LVNC. The MYH7 Arg243His and ACTC Glu101Lys mutations associated with LVNC have been described previously in apical HCM. With the present study, a direct relationship between specific gene mutations and specific cardiomyopathic phenotypes was not established. Allelic mutations in sarcomere protein genes affect a diverse phenotypic spectrum of cardiomyopathies.

Structural Interpretation of the Mutations in LVNC

The subfragment-1 (S1) of β-cardiac myosin contains the ATPase site and an actin binding region. The MYH7 amino acid positions that are mutated in patients with LVNC are highly conserved in myosins throughout evolution (Figure 1B). Therefore, the 3D structure of the chicken skeletal myosin S1 fragment can be used to discuss the functional consequences of the amino acid changes. The Arg243His, Asp239del, and Phe252Leu amino acid changes in MYH7 are located in the head region that contains all the necessary elements to generate movement of actin relative to the myosin during ATP hydrolysis. These 3 modified residues are located directly in or at the outer surface of the nucleotide binding pocket and are important for proper ATP hydrolysis (Figure 3): At position Asp239, a salt bridge with Lys679 is formed that stabilizes the surface of the ATP binding site. Absence of Asp239 could change the steric structure of the binding site and interfere with ATP binding. The positively charged residue Arg243 is involved in phosphate binding, and ATP binding may be diminished if the residue is changed for a histidine. Phe252 is located in a loop that is part of a hydrophobic cluster at the outer surface of the ATP binding cleft. The leucine substitution could shift the loop and the adjacent α-helix (residues Lys184-Ala201) and thereby interfere with ATP binding. We therefore propose that these MYH7 mutations are likely to diminish force generation of cardiac myocytes.

The functional consequences of the Arg1359Cys substitution in exon 30 of MYH7 and the Ala1766Thr substitution in

Figure 2. Echocardiographic images of affected individuals with LVNC. A, Apical 4-chamber view of proband II-2 of family LVNC-108; color Doppler image showing deep recesses filled with blood from the left ventricular cavity at end diastole. B, The same patient as in A; this apical 4-chamber view (at end diastole) demonstrates markedly pronounced trabeculations of the right ventricular apex, which also suggests right ventricular involvement. Patient III-1 of family LVNC-108: End-diastolic (C) and end-systolic (D) still frame in the parasternal short-axis view with prominent trabeculations. E, Apical 2-chamber view of the proband of LVNC-110 with prominent apical and midventricular trabeculations (diastolic color Doppler view). F, End-diastolic 4-chamber view of proband CR with mainly midventricular LVNC.
exon 37 of MYH7, located in the rod domain of the β-myosin heavy chain molecule, are uncertain. The Glu101Lys substitution in α-cardiac actin resides in a region of the actin filament in close apposition to the myosin head and forms a weak actomyosin binding site.17 In a cell-expression system, the primary defects of Glu101Lys actin were slower motility, reduced average force, and a weakened interaction with cardiac myosin in the presence of ATP. These deficits at the molecular level appear to be sufficient to trigger the disease phenotype.23 Troponin T transmits calcium signals that regulate actin-myosin interactions and ATPase activity. The Arg131Trp mutation is located in the tail domain (residues 112 to 136), which is responsible for critical interactions between tropomyosin and troponin T.24

LVNC Phenotype
Patients with the MYH7 mutations show an LVNC phenotype with variable adult onset of symptoms such as heart failure and systemic emboli. Life-threatening arrhythmias and sudden cardiac deaths were not reported. Autosomal dominant inheritance with complete penetrance is suggested for the manifestation of LVNC because there was no mutation carrier without the typical echocardiographic morphology of LVNC. We could not establish whether LVNC was already present at birth, but asymptomatic familial disease was observed in a subset of patients. Clinically asymptomatic LVNC may be present at an early age, as demonstrated by the diagnosis in a 2-year-old boy, individual LVNC-107, III-3, and an 8-year-old boy, LVNC-108, III-1 (Figure 2C and 2D). LVNC was also found in patients without functional impairment at older age (LVNC-107, I-2). Nevertheless, the proposed changes in myosin conformation may lead to functional myocardial impairment later in life in a certain proportion of patients, very much like the pathogenesis observed in most cases of HCM and DCM. The functional impairment results in a failing left ventricle that remodels and dilates, as shown in some of the patients (Table 2). The current definitions and classifications of cardiomyopathies acknowledge that impairment of systolic function, left ventricular dilatation, and heart failure are nonspecific, often late findings in many conditions, including LVNC.1,25 Nonavailability of family members limited the detailed interpretation of the expression of the phenotype. Also, because we were not able to explore all families in detail, we cannot rule out that some of our “sporadic” LVNC cases were familial cases. Comprehensive studies for the prognosis of mutations in distinct functional domains of MYH7 are missing. From our data, we are unable to predict whether the mutations in the nucleotide binding site of MYH7 are associated with a certain phenotype or prognosis in LVNC patients.

Myocardial Remodeling Triggered by Sarcomere Gene Mutations
More than 200 mutations have been described for MYH7; the majority of them cause HCM, and several lead to DCM (Figure 4). Mutations that cause HCM and DCM are distributed throughout the molecule but are clustered around...
specific locations in the myosin head, ie, the actin myosin interface, around the nucleotide binding site, and the ELC (essential light chain) and RLC (regulatory light chain) binding interface. The rod of the molecule appears to be the primary location for mutations responsible for a distal myopathy, but several mutations for HCM and DCM were also detected in the rod. Mutations in the myosin rod are not expected to directly affect motor function but rather myosin filament assembly or interaction with thick-filament binding proteins. Blair et al. conclude that if the rod mutations initiate the disease by a different pathogenic mechanism, the phenotype of a distinct cardiomyopathy likely results from a final common pathway. Alternatively, the type of remodeling in HCM, DCM, or LVNC patients with specific sarcomere gene mutations could be due to the influence of modifying genes that affect cardiac remodeling. One example is the MYH7 Arg243His substitution reported in a proband with apical HCM and found in 1 of the families with LVNC in the present study (LVNC-107). As in this case, 1 sarcomere gene mutation may trigger different pathological patterns of remodeling of the myocardium. Indeed, this discordance between the etiology of the disease and the “clinical syndrome” is one of the main findings of the present study. It is increasingly realized that the current nomenclature fails to adequately describe the substantial overlap between the classic cardiomyopathy syndromes. The molecular etiology of different cardiomyopathic phenotypes most likely reflects the interactions of genetic etiology, background modifier genes, and hemodynamic factors for the development of the phenotype.

Conclusions

We conclude that LVNC is within the diverse spectrum of cardiac morphologies triggered by sarcomere protein gene defects. Our findings support the hypothesis that there is a shared molecular etiology of different cardiomyopathic phenotypes. The role of sarcomere proteins in myocardial morphogenesis should be subject to further investigation.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Left ventricular noncompaction has recently been classified as a primary cardiomyopathy. The echocardiographic characteristics in affected individuals include a severely thickened, 2-layered myocardium, numerous prominent trabeculations, and deep intertrabecular recesses. The clinical features consist of both asymptomatic and symptomatic patients with progressive deterioration of cardiac function. Major complications are congestive heart failure, arrhythmias, thromboembolic events, and sudden cardiac death. The genetic basis of the disease is still unresolved in a large proportion of patients. Both familial and sporadic cases have been described. For familial cases, the predominant mode of transmission is autosomal dominant. Detailed pedigree analysis and cardiac evaluation of first-degree family members of affected individuals is recommended. In this study, we describe that left ventricular noncompaction is within the diverse spectrum of cardiac morphologies triggered by sarcomere protein gene defects. Heterozygous mutations in left ventricular noncompaction were found in 3 genes: β-myosin heavy chain (*MYH7*), α-cardiac actin (*ACTC*), and cardiac troponin T (*TNNT2*). Mutations in several sarcomeric protein genes have previously been implicated in familial hypertrophic cardiomyopathy and in dilated cardiomyopathy. Our findings support the hypothesis that there is a shared molecular etiology of different cardiomyopathic phenotypes. It is increasingly realized that the current nomenclature fails to adequately describe the substantial overlap between the classic cardiomyopathy syndromes. Indeed, this discordance between the etiology and the “clinical syndrome” is one of the main messages of our study.
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