Novel Gene Locus for Autosomal Dominant Left Ventricular Noncompaction Maps to Chromosome 11p15

Sabine Sasse-Klaassen, MD; Susanne Probst, MSc; Brenda Gerull, MD; Erwin Oechslin, MD; Peter Nürnberg, PhD; Arnd Heuser, MD; Rolf Jenni, MD; Hans Christian Hennies, PhD; Ludwig Thierfelder, MD

Background—Left ventricular noncompaction (LVNC) is a congenital unclassified cardiomyopathy with numerous prominent trabeculations and deep intertrabecular recesses in a hypertrophied and hypokinetic myocardium. It has been reported to occur in isolation or in association with congenital heart disease. Mutations in the X-linked G4.5 gene are responsible for cases of isolated LVNC in male infants, but G4.5 mutations were not found in patients with clinical onset of disease in adulthood. In addition, several families with LVNC and an autosomal dominant pattern of inheritance suggest genetic heterogeneity.

Methods and Results—We performed a genome-wide linkage analysis in a family with autosomal dominant LVNC and show that a locus containing the LVNC disease gene maps to chromosome 11p15. A peak 2-point logarithm of odds score of 5.06 was obtained with marker D11S902 at θ=0. Haplotype analysis defined a critical interval of 6.4 centimorgan between D11S1794 and D11S928 corresponding to a physical distance of 6.8 megabases. No disease-causing mutation was identified in 2 prime positional candidate genes, muscle LIM protein (MLP) and SOX6.

Conclusions—We have mapped a locus for autosomal dominant LVNC to a 6.8-megabase region on human chromosome 11p15. Identification of the disease gene will allow genetic screening and provide fundamental insight into the understanding of myocardial morphogenesis. (Circulation. 2004;109:2720-2723.)

Key Words: cardiomyopathy ■ genetics ■ mapping ■ noncompaction
echocardiographic analyses was performed at the University Hospital Zürich before the genetic analyses. Echocardiographic criteria for LVNC were as follows: The noncompacted endocardial layer is at least twice as thick as the compacted epicardial layer (ratio ≥2) and consists of prominent and excessive trabeculations and deep recesses filled with blood from the ventricular cavity as visualized by color Doppler imaging. In partially penetrant cases of LVNC, the ratio of noncompacted to compacted myocardium is <2.

**Linkage Analysis**

A genome-wide linkage analysis was conducted using microsatellite markers spaced at a maximum of 10 centimorgan (cM) apart according to the Marshfield Genetic Map. Two-point logarithm of odds (LOD) score calculations were performed by the LINKAGE 5.20 package, and multipoint LOD scores were calculated with the SIMWALK 2.82 program. Autosomal dominant inheritance was assumed, and LOD score calculations were performed with disease penetrance values between 0.75 and 0.90; for partially penetrant phenotypes, disease penetrance was set at 0.50.

**Candidate Gene Analysis**

Mutation screening of candidate genes was performed as described previously. Oligonucleotide primers for polymerase chain reaction amplification of MLP, SOX6, and ZASP were designed according to sequences from a public database. Southern blot experiments of MLP exons 1 to 6 were performed according to standard protocols.

**Results**

**Patient Characteristics**

Kindred LVNC-105 has previously been described (INVM-105) and was reevaluated for this study (33 subjects; 14 males, 19 females). Nine individuals were diagnosed with LVNC; 3 were found to have a partially penetrant LVNC phenotype (III-7, III-12, and IV-12); and the remaining 21 family members were classified as unaffected (see the Data Supplement for details). Reevaluation resulted in the following changes compared with the original pedigree: Individual IV-7 developed LVNC since she was last seen 3 years ago; individual III-12 was diagnosed with partially penetrant LVNC; and another parent (III-11a) was introduced. On echocardiography, 2 patients (III-7 and III-12) showed mild valvular pulmonary stenosis with mean pressure gradients of 12 and 16 mm Hg, respectively, and another 5 patients had a mild mitral valve prolapse. Patient IV-16 without LVNC had a small secundum atrial septal defect and a mild pulmonary stenosis with a mean pressure gradient of 11 mm Hg.

**Linkage Results**

In a genome-wide linkage analysis of LVNC in kindred LVNC-105 that used 447 highly polymorphic microsatellite markers, significant 2-point LOD scores were obtained only for markers at chromosome 11p15 (Table). The multipoint LOD score peaked at D11S902 (Z = 5.15). LOD scores at chromosome 11p15 were robust for different values of penetrance. Haplotype analysis identified segregation of an affected haplotype in family LVNC-105 (Figure). Individual IV-16, a 14-year-old girl, carries the affected haplotype but
Two-Point LOD Scores of Chromosome 11p15 Microsatellite Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>cM</th>
<th>Mb</th>
<th>0.00</th>
<th>0.01</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>D11S2362</td>
<td>8.9</td>
<td>4.9</td>
<td>-4.49</td>
<td>-3.00</td>
<td>-0.89</td>
<td>0.02</td>
<td>0.63</td>
<td>0.67</td>
<td>0.43</td>
</tr>
<tr>
<td>D11S1999</td>
<td>17.2</td>
<td>10.7</td>
<td>0.20</td>
<td>1.30</td>
<td>2.09</td>
<td>2.28</td>
<td>2.02</td>
<td>1.41</td>
<td>0.68</td>
</tr>
<tr>
<td>D11S1794</td>
<td>19.9</td>
<td>13.3</td>
<td>0.42</td>
<td>1.40</td>
<td>1.95</td>
<td>2.05</td>
<td>1.82</td>
<td>1.33</td>
<td>0.71</td>
</tr>
<tr>
<td>D11S4170</td>
<td>20.9</td>
<td>14.4</td>
<td>2.83</td>
<td>2.78</td>
<td>2.57</td>
<td>2.30</td>
<td>1.72</td>
<td>1.09</td>
<td>0.44</td>
</tr>
<tr>
<td>D11S1981</td>
<td>21.4</td>
<td>17.1</td>
<td>3.39</td>
<td>3.36</td>
<td>3.22</td>
<td>2.99</td>
<td>2.40</td>
<td>1.68</td>
<td>0.88</td>
</tr>
<tr>
<td>D11S902</td>
<td>21.4</td>
<td>17.5</td>
<td>5.06</td>
<td>5.00</td>
<td>4.73</td>
<td>4.34</td>
<td>3.41</td>
<td>2.31</td>
<td>1.10</td>
</tr>
<tr>
<td>D11S4138</td>
<td>21.4</td>
<td>17.7</td>
<td>3.17</td>
<td>3.14</td>
<td>2.99</td>
<td>2.76</td>
<td>2.20</td>
<td>1.53</td>
<td>0.75</td>
</tr>
<tr>
<td>D11S899</td>
<td>23.1</td>
<td>19.4</td>
<td>2.01</td>
<td>1.97</td>
<td>1.81</td>
<td>1.62</td>
<td>1.21</td>
<td>0.79</td>
<td>0.38</td>
</tr>
<tr>
<td>D11S928</td>
<td>26.3</td>
<td>20.1</td>
<td>-1.01</td>
<td>0.03</td>
<td>0.78</td>
<td>1.05</td>
<td>1.05</td>
<td>0.74</td>
<td>0.31</td>
</tr>
<tr>
<td>ATA34E08</td>
<td>33.0</td>
<td>25.9</td>
<td>-0.65</td>
<td>0.31</td>
<td>0.82</td>
<td>0.93</td>
<td>0.84</td>
<td>0.61</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Microsatellite marker location (in cM) on the Marshfield sex-averaged linkage map; distances (in Mb) as shown in the Ensembl Genome Browser. Locations for multipoint calculations were adjusted according to the physical order. Disease penetrance was set at 0.90.

Currently does not express the phenotype. A recombination event in affected individual IV-6 defines D11S1794 as the distal flanking marker. The proximal flanking marker, D11S928, is defined by 2 recombination events in affected individuals IV-3 and IV-8. This 6.4-cM critical interval corresponds physically to 6.8 megabases (Mb).

Candidate Gene Analysis

Within the 6.8-Mb LVNC disease gene region, 51 putative genes are contained according to the Ensembl Genome Browser and 68 genes according to the National Center for Biotechnology Information (NCBI) human genome assembly. The products of most these genes are known. MLP is an important component of the cytoskeleton of cardiac and skeletal myocytes, and mutations in MLP cause hypertrophic or dilated cardiomyopathy.13,14 Sequence analysis and Southern blot hybridizations of MLP from individuals of kindred LVNC-105 (2 affected, 1 unaffected) did not reveal any alterations. In addition, in another 38 unrelated isolated LVNC index patients, no mutations in MLP were detected. Another intriguing candidate gene for LVNC at chromosome 11p15 is SOX6, coding for a member of the SOX DNA binding protein family. SOX6 is a candidate gene for p100H myopathy, heart block, and sudden neonatal death,15 but no mutations were detected in kindred LVNC-105.

Like in other heart muscle disorders,12 LVNC shows genetic heterogeneity, and mutations in G4.5, ZASP, and α-dystrobrevin have been reported.6,7,11,18 Linkage analysis in LVNC-105 provides a novel locus for LVNC and serves as an example for the autosomal dominant form of LVNC (OMIM, No. 604169). Most patients presented with isolated LVNC, meaning the absence of any associated congenital heart anomalies. However, 2 patients with partially penetrant LVNC and mild congenital heart disease (pulmonary stenosis) were identified to carry the disease locus for autosomal dominant LVNC (III-7, III-12). These patients did not fulfill all the diagnostic criteria established for isolated LVNC because the ratio of noncompacted to compacted myocardium was <2.2,3 However, the development of LVNC in these patients has a genetic cause and cannot be explained by the impact of a hemodynamic burden in the absence of any left ventricular inflow and outflow tract abnormalities. The autosomal dominant form of LVNC seems to comprise isolated LVNC and LVNC associated with congenital heart defects and underscores the clinical heterogeneity of this disease.

In conclusion, we have mapped a locus for autosomal dominant LVNC to chromosome 11p15 and narrowed the critical region to 6.4 Mb. These findings confirm the genetic heterogeneity of this disorder. Identification of the disease-causing gene will allow genetic screening and provide fundamental insight to the understanding of myocardial morphogenesis.

Acknowledgments

We are grateful to the family members for their participation in this study.

References


Novel Gene Locus for Autosomal Dominant Left Ventricular Noncompaction Maps to Chromosome 11p15

Sabine Sasse-Klaassen, Susanne Probst, Brenda Gerull, Erwin Oechslin, Peter Nürnberg, Arnd Heuser, Rolf Jenni, Hans Christian Hennies and Ludwig Thierfelder

_Circulation_. 2004;109:2720-2723; originally published online June 1, 2004;
doi: 10.1161/01.CIR.0000131865.21260.56

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/22/2720

Data Supplement (unedited) at:
http://circ.ahajournals.org//subscriptions/

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/