Lethal congenital contracture syndrome (LCCS), a fetal anterior horn cell disease, is not linked to the SMA 5q locus

Katri Vuopala, Paivi Mäkelä-Bengs, Anu Suomalainen, Riitta Herva, Jaakko Leisti, Leena Peltonen

Abstract
The lethal congenital contracture syndrome (LCCS) is an autosomal recessive syndrome (McKusick 253310) leading to perinatal death owing to early onset degeneration of the anterior horn motor neurones of the spinal cord. The neuropathological findings in the LCCS closely resemble those of spinal muscular atrophy (SMA). Since all the three types of SMA have been localised to the same gene locus on the long arm of chromosome 5, we analysed samples from seven families with 10 LCCS fetuses with the microsatellite markers assigned to the SMA 5q region. Linkage analyses between the SMA linked DNA markers and the disease allele in the LCCS families excluded the critical chromosomal region around the SMA locus as the critical chromosomal region for the LCCS locus.

The lethal congenital contracture syndrome (LCCS) is an autosomal recessive syndrome (McKusick 253310), so far reported mostly in Finland. It leads to perinatal death and the fetuses typically have hypoplastic lungs, marked skeletal muscle hypoplasia, and contractures of the extremities. The pathological mechanism of LCCS, the early onset degeneration of the anterior horn motor neurones of the spinal cord, has been well documented.

The neuropathological findings in LCCS closely resemble those of spinal muscular atrophy (SMA). Three different forms of SMA can be distinguished by the age of onset and the course of the disease. Since all three types share a gene locus at 5q13.3, between the polymorphic DNA markers D5S435 and D5S39, the question arises whether LCCS might represent an extreme form of SMA. To study this hypothesis, we performed linkage analysis using samples from seven Finnish families with 10 LCCS fetuses and the markers closely linked to or flanking the SMA locus on 5q.

Methods and results
Fig 1 shows the LCCS pedigrees used in this study. Peripheral blood samples were stored at −20°C and were available from 14 parents and seven healthy children. Total DNA was isolated according to standard procedures.

The polymorphic microsatellite markers (D5S407, D5S435, D5S351, D5S39, D5S424) assigned to the SMA 5q region were amplified using polymerase chain reaction (PCR). PCR was performed in a microtitre well format as described previously. All the primer sequences of the markers originated from the amplifiable marker collection of Genethon (The Genethon Microsatellite Map Catalogue 1993) or that of the Nordic Human Genome Organisation.

We carried out data simulation for the LCCS family material in the linkage analyses assuming a single marker locus and double heterozygosity
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Marker Recombination fraction

<table>
<thead>
<tr>
<th>Marker</th>
<th>0.00</th>
<th>0.01</th>
<th>0.05</th>
<th>0.07</th>
<th>0.1</th>
</tr>
</thead>
<tbody>
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<td>-</td>
<td>-2</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>DSS435</td>
<td>-</td>
<td>-2</td>
<td>-1.5</td>
<td>-1.2</td>
<td>-1</td>
</tr>
<tr>
<td>DSS351</td>
<td>-</td>
<td>-2</td>
<td>-2.2</td>
<td>-1.8</td>
<td>-1</td>
</tr>
<tr>
<td>DSS39</td>
<td>-</td>
<td>-4</td>
<td>-2.2</td>
<td>-1.8</td>
<td>-1</td>
</tr>
<tr>
<td>DSS424</td>
<td>-</td>
<td>-5</td>
<td>-2.4</td>
<td>-1.9</td>
<td>-1</td>
</tr>
</tbody>
</table>

Pairwise linkage data between LCCS and markers flanking the SMA locus

Figure 2  The result of multipoint linkage analyses of LCCS and SMA. The critical chromosomal region was considered excluded with lod score values below -1.5 of flanking or closely linked markers. The markers are shown above the horizontal axis and genetic distances between markers are expressed in centiMorgans (cM).

Discussion

Diseases affecting anterior horn cells are a heterogeneous group of neurodegenerative disorders which may become manifest at any time of life. The most common of these disorders is spinal muscular atrophy. The assignment of the SMA loci to chromosome 5q has made prenatal diagnosis possible for SMA families. However, it has led to confusion in the families with so-called variants of SMA, that is, diseases with anterior horn cell involvement and a phenotype atypical of SMA. The group of “variants” of infantile SMA, or more precisely anterior horn cell disease (AHD), includes two subgroups that resemble LCCS: cases with AHD and multiple congenital fractures and cases with AHD and early respiratory insufficiency.

It has been suggested that the SMA variants differ genetically from SMA 5q. The reported pedigrees with AHD and arthrogryposis suggest autosomal recessive transmission, but X-linked inheritance cannot be excluded. A link study in a consanguineous family with two affected males out of five sibs was performed resulting in exclusion of 5q. Our results excluding the SMA 5q locus as the LCCS gene locus show that LCCS does not represent a subtype of SMA, but is a genetically distinct syndrome.

At present, the prenatal diagnosis of LCCS is based on sonographic findings of fetal akinesia and hydrops. The localisation of the LCCS gene would make specific prenatal diagnosis available for LCCS families. In addition to the clinical advantage, the further characterisation of LCCS would provide data on the molecular pathomechanism of motor neurone disease.

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10 Soares VM, Brustowicz LM, Kley B, et al. Refinement of the spinal muscular atrophy locus to the interval between
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