Confirmation of linkage of Sjögren-Larsson syndrome to chromosome 17 in families of different ethnic origins

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Abstract

Linkage analysis in two consanguineous pedigrees of Pakistani and English origin and one further Indian family in which affected subjects have Sjögren-Larsson syndrome (SLS) showed linkage to chromosome 17. Linkage of SLS to D17S783 and D17S805 has been reported in Swedish pedigrees, but since those data were generated from a single ethnic group originating from a common ancestor, there remained the question of whether this disease is genetically heterogeneous. This report confirms the linkage in non-Swedish pedigrees and, therefore, provides evidence to support a single locus for SLS. (J Med Genet 1996;33:258–259)

Key words: Sjögren-Larsson syndrome; chromosome 17; linkage analysis.

Sjögren-Larsson syndrome (SLS) (MIM 270200) is a rare, autosomal recessive, neurocutaneous disorder characterised by the association of congenital ichthyosisis, spastic di- or quadriplegia, and mental retardation. Patients present at birth with generalised skin thickening and brown, fine scaling which is particularly pronounced around the umbilicus, the neck, and flexures. Glistening white dots in the fundus of the eye are sometimes present. Mental retardation is severe in most patients, who usually become confined to a wheelchair during later childhood owing to progressive spasticity.

SLS is caused by a deficiency in the fatty aldehyde dehydrogenase component of a complex enzyme, the fatty alcohol NAD + oxidoreductase (FAO). The disorder has a worldwide distribution, although most of the published cases are from the northern part of Sweden. Most of the Swedish patients can be traced to a specific region in Sweden, known as the SLS area, where a mutation was introduced in around the 13th century. Using linkage analysis in 24 families from this area, Pigg et al recently found that the SLS gene is located on chromosome 17 flanked by D17S805 and D17S783.

In order to confirm linkage of Sjögren-Larsson syndrome to the same region in non-Swedish pedigrees, blood for DNA was taken from a large consanguineous Pakistani pedigree with affected first cousins, a further consanguineous pedigree of English origin, and a small Indian family. At least one affected subject in each family was previously reported to have deficient FAO activity in cultured fibroblasts, leucocytes, and skin. To analyse microsatellite polymorphisms PCR was performed in 25 µl using 250 ng DNA, 25 pmol either D17S805 or D17S783 5’-digoxigenin labelled primers, and 1 U of Taq polymerase in 1 x KCl buffer. PCR cycles were as follows: 10 minutes at 94°C, 30 x (one minute at 94°C (D17S805) or 65°C (D17S783), 30 seconds at 72°C, 30 seconds at 94°C), 10 minutes at 72°C. A total of 3 µl

Alleles found in SLS families for microsatellite markers at D17S805 (above) and D17S783 (below). Origins of the pedigrees are as follows: pedigree 1 Pakistan, pedigree 2 England, pedigree 3 India.
Two point lod scores between SLS and D17S783 and D17S805

<table>
<thead>
<tr>
<th></th>
<th>0.00</th>
<th>0.01</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
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</thead>
<tbody>
<tr>
<td>SLS-D17S783</td>
<td>2.85</td>
<td>2.77</td>
<td>2.01</td>
<td>1.20</td>
<td>0.57</td>
<td>0.20</td>
</tr>
<tr>
<td>SLS-D17S805</td>
<td>2.29</td>
<td>2.24</td>
<td>1.74</td>
<td>1.22</td>
<td>0.74</td>
<td>0.32</td>
</tr>
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of the PCR products were run on a 6% sequencing gel and blotted for one hour on a nylon membrane (Hybond-N+, Amersham). Alleles were then detected with a DIG luminescent Kit (Boehringer Mannheim).

The alleles found in SLS families for microsatellite markers at D17S783 and D17S805 were sized by comparing those of CEPH reference subject 1347-02. Linkage analysis was carried out using the MLINK and LINKMAP sections of the LINKAGE program package. The distance between D17S783 and S17S805 was fixed at 2 cM. The gene frequency was set at 0.0005. Allele frequencies for the markers were as published by Genethon.

The results are shown in the figure. Two point lod scores are shown in the table. Multipoint linkage analysis gave a maximum multipoint lod score of 5.25 at D17S783 and 5.19 at D17S805. Pedigree 1 gave a significant maximum multipoint lod score of 3.53 at D17S783.

The gene for SLS was mapped to proximal 17q in 24 Swedish families but the possibility of genetic heterogeneity could not be ruled out since these data were produced in a distinct population where affected subjects are thought to originate from a common ancestor. We have provided evidence which shows linkage of SLS to chromosome 17 in pedigrees from different ethnic groups which, therefore, supports the localisation and the hypothesis of a single locus for SLS. This information will allow carrier detection and prenatal diagnosis and will be useful in the counselling of families with SLS.

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