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Further Evidence of Genetic Homogeneity in Sjögren-Larsson Syndrome

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Sjögren-Larsson syndrome is an autosomal recessive disorder characterized by congenital ichthyosis, spastic di- or tetraplegia and mental retardation. In 1994 Sjögren-Larsson syndrome was mapped to chromosome 17, close to the genetic marker D17S805 in a study of 24 Swedish families. We have analysed 12 microsatellite markers in 10 additional non-Swedish families with Sjögren-Larsson syndrome originating from Germany, Lebanon, Spain and Canada. The results are consistent with earlier data and give further evidence of Sjögren-Larsson syndrome being a homogeneous disorder. Swedish soldiers were bivouacking in Germany during the 30-year war in the 17th century and it has been suggested that they could have introduced the Sjögren-Larsson syndrome gene to the German population. Haplotypes from 7 German families with Sjögren-Larsson syndrome were compared with earlier analysed Swedish haplotypes. No evidence of all German patients carrying the same mutation or the major "Swedish Sjögren-Larsson syndrome gene" was found. ***Key words: linkage analysis; allele association; German families.***

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Sjögren-Larsson syndrome (SLS) (MIM 270 200) is an autosomal recessive disorder with complete penetrance. SLS is characterized by congenital ichthyosis, spastic di- or tetraplegia, mental retardation (1) and glistening white dots in the fundus of the eye (2, 3). Many SLS patients also exhibit other features, such as epilepsy, kyphoscoliosis, short stature, speech defects and defective development of the dental enamel (4). SLS has been reported worldwide (5–7) but is of an unusually high incidence in the Northern part of Sweden, in the counties of Västerbotten and Norrbotten. The majority of the Swedish patients can be traced to three large pedigrees dating back to the 17th century (8).

Previously the SLS gene was mapped to chromosome 17 using 24 Swedish SLS families. Several microsatellite markers located pericentromerically on chromosome 17p showed linkage to the disease gene. Meiotic recombinations showed that the gene is flanked by the markers D17S805 and D17S783 (9). Strong allelic association was found to allele 3 of the marker D17S805. This indicated that the SLS mutation was introduced into the population on a chromosome carrying allele 3 at D17S805 and this relationship has been maintained since the founding in the 13th century. It has also been suggested (10) that SLS patients from the North of Bavaria in Germany could carry the "Swedish SLS mutation". Swedish soldiers were bivouacking in Germany during the 30-year war in the 17th century and could have introduced the SLS gene to the German population. Previously linkage to the same locus on chromosome 17 was shown in non-Swedish SLS families (11, 12) indicating genetic homogeneity.

Earlier fatty aldehyde dehydrogenase (FALDH) has been suggested as the defective enzyme causing SLS, based on enzyme measurements in cultured skin fibroblasts from SLS patients (13). Recently the FALDH cDNA was cloned and mapped to the SLS locus on chromosome 17 and mutations in 3 unrelated patients were shown (14).

In order to confirm previous evidence of SLS being a genetically homogeneous disorder and to test the hypothesis of a common origin of Swedish and German SLS families, we performed linkage analysis and haplotype analysis in 10 non-Swedish SLS families.

Allele association was determined in the German families for all markers tested.

MATERIALS AND METHODS

Subjects

The subjects comprised 10 families, 35 individuals of whom 15 were affected with SLS. One family originated from Canada, 1 from Spain, 1 from Lebanon and 7 from Germany. Five families had 2 affected individuals and the other 5 families had 1 affected person. In 1 of the German families the 2 affected persons were first cousins. In the remaining families of German origin there was no proof of consanguinity. All patients included in the study showed the typical symptoms of SLS: mental retardation, spastic di- or tetraplegia and congenital ichthyosis. Some of them also exhibited kyphoscoliosis and short stature. One of the German families has been reported earlier (5).

The study was approved by the Ethics committee of Uppsala University, Sweden.

DNA analysis

DNA was extracted from white blood cells using standard procedures. Microsatellite markers were analysed as described (9). All primers were purchased from Genset (Paris, France) and the primer sequences were as published previously (15, 16).

Linkage and haplotype analysis

Family members were typed with microsatellite markers which were previously shown linked to the SLS locus: D17S805, D17S959, D17S842 and D17S689 (9, 11). Eight additional markers close to the previous linked markers were also tested: D17S1871, D17S1824, D17S1873, D17S1878, D17S1863, D17S1880, D17S696 and D17S620 (15, 16). The marker alleles were compared with reference alleles when possible. Linkage analysis was calculated using the Linkage package (17) on a SUN Spark station 5 and the gene frequency was set at 0.001. Allele frequencies for the markers were as published.

Homogeneity was tested using the HOMOG programs (18) and allele associations were determined by the chi-square method.

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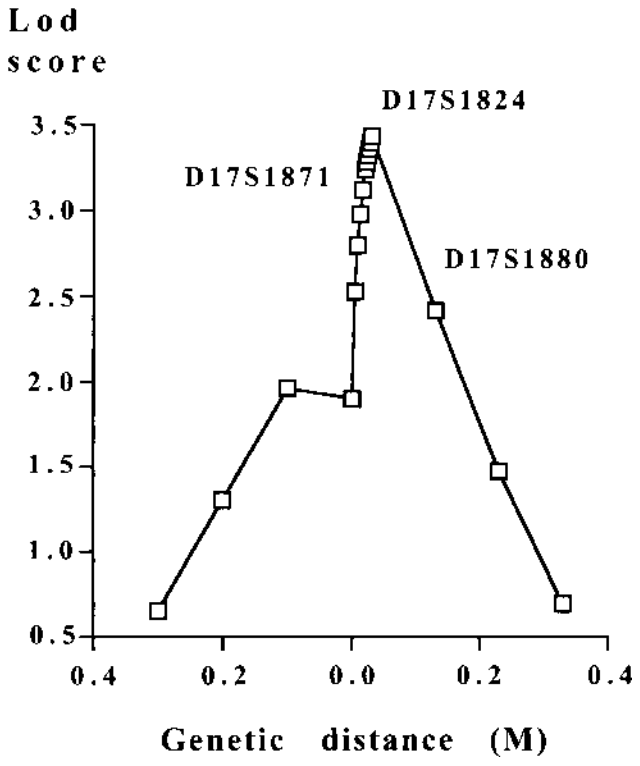


Fig. 1. Four-point analysis around the SLS locus in 10 non-Swedish families.

RESULTS

Linkage analysis

Two-point linkage analysis showed a significant linkage between two of the tested markers, D17S1871 ($Z=3.01$, $\Theta=0.00$) and D17S1824 ($Z=3.08$, $\Theta=0.00$) vs. SLS. The other 10 markers showed positive Lod scores ($Z=0.76-2.68$, $\Theta=0.00$) but not at a significant level, probably due to less genetic information in the tested families. Multi-point linkage analysis was limited to 4-point analysis by the computing capacity. Maximum Lod score in the multi-point analysis was 3.44 with the markers D17S1871, D17S1824 and D17S1880 (Fig. 1). HOMOG gave no evidence of locus heterogeneity. In the German families a significant allele association was found only to the marker D17S1878, allele 3 ($p=0.009$).

Haplotype analysis

When combining our data with previously published data (9, 11, 15, 16), the most probable haplotypes were constructed: *p*-tel D17S689, D17S696, D17S1871, D17S805/D17S842/D17S959, D17S1824, D17S1878, D17S1873, D17S1863, D17S1880 and D17S620 *p*-cen. None of the markers tested showed recombinations, except for D17S689.

German families

Four parents in 3 families shared the same SLS haplotype in all markers tested, a fifth parent shared a part of the same haplotype (D17S689, D17S696, D17S1871, D17S805, D17S842, D17S959) but more centromeric markers were different. Two parents from 2 other families shared a different SLS haplotype.

Table I. *Haplotypes in the Sjögren-Larsson syndrome locus of Swedish families investigated in earlier studies and of non-Swedish families investigated in the present study*

	Swedish haplotypes						Non-Swedish haplotypes								
Marker							C	G	G	G	G	G	G	L	S
D17S805	3	1	5	7	6	5	5	5	1	1	1	1	1	5	5
D17S842	3	3	3	3	3	6	3	3	1	1	3	3	3	1	3
D17S959	4	4	4	4	4	4	4	4	5	6	4	5	6	5	1
Total	39	3	3	1	1	1	2	4	5	2	1	1	1	2	2

G = German families, C = Canadian family, L = Lebanese family, S = Spanish family.

In 1 family, the 2 affected individuals were first cousins and they shared exactly the same homozygous haplotype except for the marker D17S620. Four German haplotypes for the previously closest linked markers D17S805, D17S842, D17S959 were the same (Table I) as seen in 6% of the previously tested Swedish SLS families (9). One additional German haplotype was shared with another 6% of previously tested Swedish families. The remaining German haplotypes were not seen in the Swedish SLS population (Table I).

Other families

In the Lebanese family both affected individuals shared identical haplotypes and were homozygous for 7 of the 12 markers tested. In the Spanish family both affected individuals shared identical haplotypes and were homozygous for all of the markers tested except 2. In the Canadian family both affected individuals shared identical haplotypes and were homozygous for 11 of 12 markers tested. However, the Canadian family shared a common haplotype with 2 of the German families and with 6% of the earlier tested Swedish SLS population (Table I).

DISCUSSION

After the initial study showing linkage to chromosome 17 markers vs. SLS in 24 Swedish families (9), linkage to the same markers in non-Swedish families has been shown (11, 12). In this study we provide further evidence of SLS being a genetically homogeneous disorder by linkage analysis in 10 non-Swedish families not earlier investigated. Haplotype analysis showed that all patients were homozygous for the closest linked markers and many patients showed homozygosity for almost the complete haplotype. The results indicate a high degree of consanguinity, that the patients are homozygous for one mutation and that there are different mutations in different families. Genetic heterogeneity was not seen with the HOMOG program.

The hypothesis that German SLS patients from the north of Bavaria could be caused by a "Swedish SLS mutation" was tested by comparing the haplotypes in all German families with earlier investigated Swedish families (9). There were no indications for the German SLS families carrying the major "Swedish SLS gene" (Table I).

Allele 3 for the marker D17S805 did not co-segregate with SLS in the German families, but showed a very strong allele association with SLS in the Swedish families (9). However, 2 of the German families and the Canadian family, shared a

haplotype with that seen in 6% of the Swedish SLS population. One additional German haplotype was shared with another 6% of previously tested Swedish families and a common origin could not be excluded in these families. Since these haplotypes occur fairly frequently in the normal population, the assumption of identical mutations has not been proven. The most common Swedish SLS mutation has been characterized (19, 20) and it was found also on chromosomes from 2 German cases. The present study, however, indicates that this mutation is not a common cause of the disease in the German population. Rather the study suggests a few different mutations in the German population. Even though the FALDH gene that causes SLS has been mapped (9, 14) and mutations have been reported (14, 19, 20), the benefit of linkage analysis is still obvious for detection of carriers of the gene, and for prenatal diagnosis in SLS families where the mutation is not yet known.

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