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

Katri Vuopala, Päivi 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.

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, D5S242) 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 Généthon (The Généthon 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.

Figure 1 The pedigrees of the families studied. Filled symbols denote affected members, open symbols denote unaffected spouses. One star indicates subjects from whom fibroblasts were available for DNA isolation, two stars those from whom placenta was collected, and three stars those from whom laser biopsy was available for DNA isolation. Peripheral blood samples were available from all unaffected family members.

Department of Pathology, University of Oulu, Kajaanintie 52D, FIN-90220 Oulu, Finland
K Vuopala R Herva

Department of Clinical Genetics, University of Oulu, Kajaanintie 52D, FIN-90220 Oulu, Finland
J Leisti

Department of Human Molecular Genetics, National Public Health Institute, Mannerheimintie 166, FIN-00385 Helsinki, Finland
P Mäkelä-Bengs A Suomalainen L Peltonen

Correspondence to:
Dr Vuopala.
Received 14 June 1994 Revised version accepted for publication 24 August 1994
in the parents to analyse the informativeness of our family material. The MSIM option of the SLINK computer program was used with 2000 replicates (one replicate equals one round of generating marker genotype for each subject) to obtain the elod values (expected logarithm of odds score). This simulation analysis showed an average elod of 1-4 at the recombination fraction (0) 0-07, SD 0-5. The elod values remained over 1-0 at 0-0-13 with 85% of replicates.

Linkage analyses between the disease locus of LCSS and the polymorphic marker loci were carried by using the MLINK and LINKMAP options of the LINKAGE package computer program (version 5.1). The frequency applied for the disease allele was 0-016 with complete penetrance. Locus homogeneity was assumed owing to the enrichment of the diseases in the genetically isolated Finnish population and the homogeneity of the clinical presentation.

The marker DSS359 was reported to be the closest marker to the SMA locus with DSS359 and DSS435 being distal and proximal flanking markers, respectively. The results of the two point analyses are summarised in the table. No evidence of linkage between any of the markers and the LCSS locus was found, and only negative lod scores were obtained at the recombination fractions 0-0-1. Also the multipoint linkage analyses with the markers resulted in negative lod scores excluding a continuous area 13-7 cM proximal to DSS351, the closest marker to the SMA locus, and 11 cM distal to it (fig 2). These data show that the LCSS locus is not allelic with SMA.

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 LCSS: 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 linkage 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 LCSS gene locus show that LCSS does not represent a subtype of SMA, but is a genetically distinct syndrome.

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

We would like to thank Pekka Laurila and Riitta Salonen for identifying the LCSS fetuses and sending us the tissue samples. Jaakko Ignatius is thanked for valuable comments on current knowledge of SMA. This study was supported by Emil Aaltonen Foundation, Finland.

References

10. Soares VM, Brzustowicz LM, Klayen PW, et al. Refinement of the spinal muscular atrophy locus to the interval between...