The acrocallosal syndrome and Greig syndrome are not allelic disorders

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Abstract

Acrocallosal syndrome is an autosomal recessive form of polysyndactyly associated with mental retardation and agenesis of the corpus callosum. There have been suggestions that it is allelic to the Greig cephalopolysyndactyly syndrome. Linkage analysis, using flanking markers, shows this suggestion is unlikely to be correct.

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The acrocallosal syndrome, first described by Schinzel,1 is characterised by the combination of pre- and postaxial polydactyly, syndactyly, severe mental retardation, agenesis or hypoplasia of the corpus callosum, hypertelorism, a prominent forehead, and macrocephaly.

Fewer than 20 cases have been reported1-7 and several of the cases described have originated from a small area of Switzerland.8-13 Reports of parental consanguinity,11,18,17 affected sibs,14 and affected first cousins13 provide evidence for autosomal recessive inheritance.

The digital changes and dysmorphic features observed in the acrocallosal syndrome are similar to those of Greig cephalopolysyndactyly (GCPS) and in view of the considerable phenotypic overlap between the two disorders several authors have considered the possibility that the Greig and acrocallosal syndromes could affect the same developmental gene14-18 and represent either allelic mutations or different sized contiguous deletions of the same area. The finding of an extra bone within the anterior fontanelle in a patient with the acrocallosal syndrome1 suggested similarity to the Xt mouse mutant which is considered homologous to GCPS in man,19 further supporting the hypothesis that the Greig and acrocallosal syndromes may be allelic disorders. The knowledge that GCPS maps to 7p20-23 allows testing of this hypothesis. Three balanced translocations involving 7p13 and associated with GCPS in different families have been reported21,22,24 and two of the three have recently been shown to interrupt the GLI3 gene,25 a zinc finger gene previously localized to 7p13.24 We have undertaken a study to look for linkage to and microdeletions of the region of the GCPS locus on chromosome 7p in patients with the acrocallosal syndrome.

DNA ANALYSIS

Several chromosome 7p probes, R-944, P137, EGFR, and TCRG, all known to be in the close vicinity of the GCPS locus, were used to detect restriction fragment length polymorphisms, together with Ef', an 942 base pair fragment from the 3' end of the GLI3 gene, which has been found to detect a rare TaqI polymorphism (M Farrall, personal communication). The probe R-944 contains highly repetitive human sequences and so to facilitate studies using this probe, a 2-4 kb EcoRI fragment was subcloned into the plasmid pUC13. Standard protocols were used for isolation of genomic DNA from lymphocytes, restriction enzyme digestion of DNA, agarose gel electrophoresis, and Southern transfer to nylon membranes (Hybond-N, Amersham plc).27 The probes were 32P labelled by random oligonucleotide primed synthesis of the probe insert.28 After hybridisation, filters were washed at a final stringency of 0-5 x SSC/0-1% SDS at 65°C and exposed to x ray film for two to seven days.

LINKAGE

Linkage analysis between the acrocallosal syndrome and marker loci on the short arm of chromosome 7 was undertaken using the programme LIPED.29 A lod score of at least 3 was considered evidence of genetic linkage and the lod score of -2-0 taken as an exclusion boundary.

Results

SOUTHERN BLOT ANALYSIS

DNA samples from four subjects with the acrocallosal syndrome were digested with several different restriction enzymes and hybridised to DNA probes known to flank or be close to the GCPS locus on chromosome 7p. Using conventional methods of electrophoresis no microdeletions or rearrangements were detected in these cases with R944, P137, EGFR, GLI3, and TCRG probes. The polymorphic characteristics and regional assignments of these probes are given in the table.

LINKAGE STUDY

Linkage analysis of the data obtained on the family with the affected first cousins generated a lod score of -2-7 (8 = 0-01) with probe P137...
and \(-3:1 (\theta = 0.01)\) with \(EGRF\). \(EGRF\) is proximal to the GCPS translocation breakpoint and \(P137\) flanks it distally. The affected children have inherited different \(P137\) and \(EGRF\) alleles from their mothers who are sisters (figure). The results indicate a double crossover in this family with these two flanking probes and provide evidence that the acrocallosal syndrome does not map in the same region as GCPS. The \(R944, GLI3\), and \(TCRG\) probes were largely uninformative.

**Discussion**

The data presented here give no support to the suggestion that GCPS and the acrocallosal syndromes are allelic disorders. The probes \(CRI-R944\) and \(P137\) have been shown to flank the Greig 3;7 translocation breakpoint\(^{20}\) and \(R944\) is deleted in a patient with GCPS and an interstitial deletion of chromosome \(7p13\).\(^{14,21}\) No microdeletions or rearrangements of DNA sequences were recognised by these probes in four patients with the acrocallosal syndrome. \(P137\) is proximal to \(TCRG\).\(^{20}\) Although there are no detailed linkage data between GCPS and \(P137\), \(TCRG\) maps about 5 cm from \(GROV\) (Brue, Q et al., unpublished observation). Close linkage of \(EGRF\), localised to \(7p12-13\), to GCPS has been shown.\(^{20}\) In addition, Rosenkranz et al\(^{a}\) studied two patients with GCPS resulting from cytogenetically visible deletions of the short arm of chromosome \(7\). There was a deletion of the \(EGRF\) gene in one of them and hemizygosity for the \(TCRG\) gene shown by dosage analysis in the other.\(^{23}\) Recent studies suggest that \(GLI3\), a zinc finger gene mapping to \(7p13\), is likely to be the gene responsible for GCPS.\(^{20}\) However, no deletions or rearrangements were detected with \(EGRF\), \(GLI3\), or \(TCRG\) probes in the acrocallosal cases under investigation. The results of linkage analysis suggest that the acrocallosal syndrome does not map to the same region as GCPS. Even on the most conservative estimates the chance of a double crossover between \(P137\) and \(EGRF\) is less than 1 in 100. This provides evidence that the acrocallosal and Greig syndromes are neither allelic mutations nor represent different sized contiguous deletions of the same area.

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