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.¹⁻³ Fewer than 20 cases have been reported¹⁻¹⁷ and several of the cases described have originated from a small area of Switzerland.^{2,13,14} Reports of parental consanguinity,^{11,16,17} 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 gene^{3,6,10,18} 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 syndrome⁵ 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 reported^{21,22,24} and two of the three have recently been shown to interrupt the GLI3 gene,²⁵ a zinc finger gene previously localised to 7p13.²⁶ 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.

Materials and methods

Four patients with the acrocallosal syndrome and their families participated in the study. Two cases were sporadic and two familial

(male and female first cousins whose mothers were sisters).

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 842 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 pUC 13. 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 × 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 performed 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 ($\theta = 0.01$) with probe P137

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Details of probes used in this study.

DNA probe	HGM symbol	Cytogenetic location	Enzyme	RFLP size (kb)
pHER-A64	<i>EGFR</i>	7p12-p13	<i>StuI/XbaI</i>	20/13.7; 12/10
CRI-R944	<i>D7S69</i>	7p13	<i>MspI</i>	4.0/3.0
CRI-P137	<i>D7S65</i>	7p13	<i>TaqI</i>	3.7/2.7; 1.0
Ef'	<i>GLI3</i>	7p13	<i>TaqI</i>	+/-3
pTgamma-1	<i>TCRG</i>	7p14-p15	<i>XbaI</i>	28/23/5.4/3.6
pV11SPRS	<i>TCRG</i>	7p14-p15	<i>TaqI</i>	4.1/3.7

and -3.1 ($\theta=0.01$) with *EGFR*. *EGFR* is proximal to the GCPS translocation breakpoint and P137 flanks it distally. The affected children have inherited different P137 and *EGFR* 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 breakpoint³⁰ and R944 is deleted in a patient with GCPS and an interstitial deletion of chromosome 7p13-14.³¹ No microdeletions or rearrangements of DNA sequences were recognised by these probes in four patients with the acrocallosal syndrome. P137 is proximal to *TCRG*.³⁰ Although there are no detailed linkage data between GCPS and P137, *TCRG* maps about 5 cm from GCPS (Brueton *et al*, unpublished observation). Close linkage of *EGFR*, localised to 7p12-13, to GCPS has been shown.²⁰ In addition Rosenkranz *et al*⁹ studied two patients with GCPS resulting from cytogenetically visible deletions of the short arm of chromosome 7. There was a deletion of the *EGFR* 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.³⁰ However, no deletions or rearrangements were detected with *EGFR*, *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 *EGFR* 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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Pedigree of informative family.

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