Crouzon syndrome is not linked to craniosynostosis loci at 7p and 5qter

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Abstract

Evidence for linkage has been sought, in four pedigrees with Crouzon syndrome, between polymorphic markers known to be linked to the Saethre-Chotzen locus on 7p and another form of autosomal dominant craniosynostosis on 5q. The data we present exclude Crouzon syndrome as an allelic variant at either of these known craniosynostosis loci.

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The craniosynostoses comprise a clinically and genetically heterogeneous group of disorders characterised by premature fusion of the skull bone sutures. Several recognisable entities are identifiable within this broad group, among them Crouzon, Apert, Pfeiffer, and Jackson-Weiss syndromes.¹ Originally described by Crouzon in a mother and son in 1912,² the syndrome which bears his name (MIM No 123500) is principally characterised by craniosynostosis, shallow orbits, ocular proptosis, and maxillary hypoplasia, although a host of other clinical features have been identified.^{3,4} Although variability in gene expression within families is well documented, and indeed craniosynostosis has occasionally been absent in obligate gene carriers, the phenotype of the disorder is usually readily recognisable and the autosomal dominant mode of transmission is not in doubt.⁵⁻⁷

While Crouzon syndrome is clinically distinct from other autosomal dominant craniosynostosis syndromes, the aetiological relationship between these disorders remains unclear. Two such conditions have recently been mapped, the locus for Saethre-Chotzen syndrome being localised by mapping and cytogenetic evidence to 7p21⁸⁻¹⁰ and a family with autosomal dominant craniosynostosis of possibly undescribed type being assigned to 5qter using linked markers.^{11,12}

Among our population of patients with Crouzon syndrome, we have identified four pedigrees suitable for linkage studies. We have sought evidence for linkage of Crouzon syndrome to the known craniosynostosis loci on 7p and 5qter as described. The purpose of this report is to present these data and to emphasise the locus heterogeneity that is likely to underlie the autosomal dominant craniosynostosis syndromes.

Materials and methods

PATIENTS

The four pedigrees are shown in the figure. These were identified through the craniofacial

and reconstructive surgery department as well as through old records within the genetics department at the Hospital for Sick Children, Great Ormond Street, London. All four pedigrees were phenotypically characteristic of Crouzon syndrome, the predominant clinical features being marked proptosis and craniosynostosis. Blood was obtained from 24 affected and 28 normal subjects for the study.

LABORATORY STUDIES

DNA was extracted from lymphocytes using standard methods.¹³ This was amplified in the polymerase chain reaction (PCR) using primers flanking short tandem repeat polymorphisms, D5S211 on 5q and D7S488 on 7p. Details of primers are available elsewhere.^{9,11} Each PCR reaction contained 50 ng genomic DNA, 10 mmol/l Tris, pH 8.3, 1.5 mmol/l MgCl₂, 50 mmol/l KCl, 200 μmol/l each dGTP, dATP, dTTP, and 20 μmol/l dCTP, 0.7 μCi α ³²P-dCTP, 25 pmol of each primer, and 0.5 units *Taq* polymerase (Boehringer-Mannheim) in a final volume of 20 μl. The products of amplification were separated by denaturing polyacrylamide gel electrophoresis and autoradiographed. The data were analysed using the Linkage program, version 5.03.¹⁴

Results

The results of the analysis are presented in the table. Each pedigree showed at least one recombination between the disease and both test loci.

Discussion

The preliminary approach to mapping the locus for Saethre-Chotzen syndrome was greatly facilitated by an array of cytogenetic data from unrelated patients with craniosynostosis in whom 7p deletions were observed,¹⁵ thus identifying this region as a possible candidate for syndromic craniosynostosis. Confirmation of linkage between 7p markers and several families with the Saethre-Chotzen phenotype followed.⁸ This observation has subsequently been confirmed by more detailed mapping studies and, most recently, by the report of the Saethre-Chotzen phenotype in a patient with a de novo translocation involving 7p21.¹⁰ No such cytogenetic pointers have been reported for Crouzon syndrome and likely candidate loci for this form of craniosynostosis are not widely recognised. For this reason, and because it has been suggested that allelic mutations at the 5qter craniosynostosis locus might be the basis of

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The four pedigrees used in the study are detailed.

Lod scores for Crouzon syndrome against D5S211 and D7S488

Locus	$\theta = 0$	0.01	0.1	0.2	0.3	0.4
D5S211	$-\infty$	-11.86	-3.23	-1.09	-0.23	0.06
D7S488	$-\infty$	-14.61	-4.25	-1.69	-0.57	-0.08

other autosomal dominant craniosynostosis syndromes,¹¹ it is important to investigate the possibility of linkage between Crouzon syndrome and known craniosynostosis loci. D7S488 has been shown to be tightly linked to the Saethre-Chotzen gene with a maximum lod score of 5.574 at $\theta=0.05$.⁹ In these Crouzon pedigrees there is a lod score of -2 at 19 cM, excluding the possibility that Crouzon

and Saethre-Chotzen syndromes are allelic forms of craniosynostosis.

A further family with a previously undescribed form of craniosynostosis has shown tight linkage with the probe D5S211 on 5qter, with a maximum lod score of 4.82 at $\theta = 0$. The negative lod scores with this marker in the Crouzon families (-2 at $\theta = 0.15$) mean that Crouzon syndrome is not allelic with the 5q craniosynostosis locus.

The data we present conclusively exclude linkage of Crouzon syndrome within 10 cM on either side of the markers linked to the known craniosynostosis loci and dismiss the possibility of Crouzon syndrome representing an allelic variant of either of these forms of craniosynostosis. Further efforts to map Crouzon syndrome are under way.

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