Saethre-Chotzen syndrome associated with balanced translocations involving 7p21: three further families

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Abstract

We describe three families segregating different reciprocal chromosome translocations, t(7;18)(p21.2;q23), t(2;7)(q21.1;p21.2), and t(5;7)(p15.3;p21.2). A total of seven apparently balanced carriers have been identified and all manifest features of the Saethre-Chotzen syndrome, although only two have overt craniosynostosis. In one family the carriers are immediately recognisable by their unusual ears, and clefts of the hard or soft palate are present in all three families. These observations extend previous linkage and cytogenetic evidence that a locus for Saethre-Chotzen syndrome resides in band 7p21.2.

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Saethre-Chotzen syndrome (SCS, also referred to as acrocephalosyndactyly type III/ACS3, MIM 101400) is a very variable, and probably underascertained, autosomal dominant disorder. Classically it comprises craniosynostosis (CRS, usually involving one or both coronal sutures), low frontal hairline, facial asymmetry, ptosis, small ears with prominent crura, mild cutaneous digital syndactyly, and broad haluces in a valgus position.¹⁻⁴ However, most or all of these features may be subtle or absent, and non-penetrance has been described on several occasions.^{5,6} Saethre-Chotzen syndrome is the commonest syndromal cause of CRS, and it may be speculated that mutation of the Saethre-Chotzen gene(s) also contributes substantially to non-syndromal coronal synostosis. However, confirmation of this possibility awaits identification of the causative gene(s).

Progress towards this goal has advanced rapidly over the past three years. In 1992 Brueton *et al*⁷ reported genetic linkage of SCS to markers on the short arm of chromosome 7, and the localisation of the major SCS gene to this region by linkage analysis has since been confirmed and refined.^{8,9} Further confirmation, and a resource for positional cloning of the gene(s), is provided by three reciprocal chromosome translocations associated with CRS, each with one breakpoint in 7p.¹⁰⁻¹² However, a complicating factor is that slightly different 7p breakpoints were assigned for each translocation. Reardon *et al*¹⁰ described a father and daughter with a classical SCS phenotype, and

a breakpoint in 7p21.2; the mother and son reported by Reid *et al*,¹¹ also considered to have SCS, had a breakpoint in 7p22; and the case of Tsuji *et al*,¹² described as non-syndromal CRS but with some dysmorphic features suggestive of SCS, had a breakpoint in 7p15.3. The three most likely interpretations for these discrepancies are that one or more band assignments are mistaken, that more complex rearrangements have occurred, or that two or three separate CRS loci are involved. Some evidence for the last possibility has been adduced from the phenotypic analysis of 7p deletions.^{13,14}

Here we describe three further families with independent chromosomal translocations segregating for SCS. In all three the 7p breakpoint involves the band 7p21.2, strengthening the evidence that a major SCS locus lies in this band. In one family, carriers could be readily identified by their unusual ears. The association with the 7p21.2 translocation confirms that this phenotype, previously labelled as "aural-cephalosyndactyly",¹⁵ represents part of the phenotypic spectrum of SCS.¹⁶

Case reports

FAMILY 1

Pedigree

The pedigree of the family is shown in fig 1A. The translocation was ascertained in 1981 when subject II·3 had an amniocentesis because of raised maternal age in her second pregnancy. This prompted further workup of the family, and the same translocation was found in her husband (II·2) and daughter (III·2) affected with CRS. The translocation was thought to be coincidental to the CRS, the pregnancy continued, and an apparently healthy girl (III·4) was born. More recently III·2 has had two children, one of whom (IV·1) also carries the translocation. The mother of II·2 (I·2) has normal chromosomes, the father is dead, and the brother of II·2 refused testing. II·2 is the first member of his family with distinctive ears, so the translocation probably arose *de novo* in him.

Cytogenetic analysis

A G banded karyotype from III·2, prepared using routine methods, is shown in fig 2A. The karyotype was interpreted as 46,XX,t(7;18)(p21.2;q23). An identical appearance of the translocation chromosomes was observed in

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Figure 1 Pedigrees of (A) family 1, (B) family 2, (C) family 3.

the three other carriers (II·2, III·4, IV·1). The karyotypes of I·2, II·3, and IV·2 were normal.

Clinical features

Case III·2. Following delivery by caesarean section, she was noted to have an abnormal skull shape. Craniosynostosis was confirmed shortly after birth on skull radiographs; she has never had any surgery. She was educated at special schools (full scale IQ of 59 aged 10½ years). At the age of 22 years (fig 3A,B), she has very marked brachycephaly, a high forehead, mild proptosis, a prominent nose, a short philtrum, a tented upper lip, unusual ears, and a very high arched palate with a bifid uvula. Her hands and feet are normal both clinically and radiologically. The skull radiograph confirms coronal synostosis (fig 4A) with hypoplasia of the frontal bone and patent sagittal and lambdoid sutures.

Case II·2. His facial appearance and skull shape are normal (fig 3C). However, his ears are unusual (fig 3D), with a very short crus helicis and absence of the normal furrow (scapha) between the antihelix and helix at the posterior margin of the ear. He has a very high arched palate with a central groove along the soft palate. His hands, feet, and skull radiographs are normal. He works as a bricklayer.

Case III·4. She has a high forehead, prominent nose, and tented upper lip, although these features are less marked than in her sister (fig 3E). Her palate is high arched and the uvula bifid, and she has unusual ears similar to other affected family members. Her hands and feet are normal. Her skull radiograph (fig 4B) shows parietal foramina bilaterally, and the coronal and sagittal sutures, although patent, have rather sclerotic margins. She attends a normal school but requires remedial help.

Case IV·1. Her skull shape is normal and skull radiographs confirm patency of the major cranial sutures. She has a similar facial appearance to III·2 and III·4 and also has a bifid uvula. Her ears are low set and similar in morphology to other translocation carriers (fig 3F). Her milestones are mildly delayed.

FAMILY 2

Pedigree

The pedigree is shown in fig 1B. The translocation was detected when III·2 presented with dysmorphic features. Her father, II·2, is also a carrier, but her brother, III·1, has a normal karyotype. The father of II·2 is dead and the mother (I·2) has not been examined or karyotyped, so it is unclear whether or not the translocation arose de novo in II·2.

Cytogenetic analysis

A G banded karyotype from II·2 is shown in fig 2B. This was interpreted as 46,XY,t(2;7)(q21.1;p21.2). His daughter has apparently identical translocation chromosomes.

Clinical features

Case III·2. She was born at 38 weeks' gestation weighing 2420 g (−1.2 SD), and was noted to have a large central cleft palate and mild dysmorphism, including wide separation of the sagittal suture, short, slightly upward slanting palpebral fissures, and bilateral transverse palmar creases. The palate was repaired at the age of 9 months. At 3 years 3 months she has persistent brachycephaly, a high flat forehead, mild facial asymmetry, midface hypoplasia, a depressed nasal bridge, and small ears with prominent crura and helical overfolding (fig 5A,B). Other features are mild 2/3 cutaneous syndactyly of the hands, and broad halluces with a slight midline furrow bilaterally. The skull radiograph showed widespread digital markings and patent, but dysplastic coronal sutures. CT brain scan showed asymmetry of the calvarium, but was otherwise normal. She has not required any cranial surgery.

Case II·2. He is relatively short (167.5 cm, −1.1 SD) but has a normal appearance; in particular there is no significant abnormality of skull shape or digits. He has a deviated nasal septum, possibly resulting from trauma, small ears similar in appearance to III·2, and bilateral transverse palmar creases.

Figure 2 Partial G banded karyotypes and ideograms of (A) III-2 from family 1, (B) II-2 from family 2, (C) the proband II-1 in family 3. The positions of the breakpoints on the derivative chromosomes are indicated by unfilled arrows; the equivalent positions on the normal homologues are shown as filled arrows.

Figure 3 Clinical features of translocation carriers in family 1. (A,B) III-2 aged 22 years; (C,D) II-2 aged 36 years; (E) III-4 aged 11 years; (F) IV-1 aged 3 years 3 months.

FAMILY 3

Pedigree

The family is of Hispanic origin and the pedigree is shown in fig 1C. The proband is the only affected family member and the translocation was detected in 1983 during the neonatal period. Both parents have normal karyotypes, so the translocation arose de novo in the proband.

Cytogenetic analysis

A G banded karyotype from the proband is shown in fig 2C. This was interpreted as 46, XX,t(5;7)(p15.3;p21.2).

Clinical features

She was born at 34 weeks' gestation by dates, weighing 1480 g (−1.6 SD). Frontal bossing,

with a very large anterior fontanelle, hypertelorism and brachydactyly with mild cutaneous syndactyly were apparent. Cytomegalovirus (CMV) was cultured from the urine and the CMV-IgM was positive. Skull radiographs confirmed bilateral coronal craniosynostosis, and there was "copper beating" suggestive of raised intracranial pressure. A frontal advancement was initially performed aged 7 months, with a revision at 5 years; several additional operations have been required to ameliorate the craniofacial deformity, including reconstructions of the supraorbital ridges, facial bipartition for hypertelorism, and ptosis repair.

Her motor development was normal but there was marked speech delay. This was thought to be related to a combination of reduced hearing owing to middle ear disease, a high arched palate, and absence of the musculus

Figure 4 Skull radiographs of patients in family 1. (A) III-2, lateral view; (B) III-4, posteroanterior view.

Figure 5 (A,B) Facial features of III-2 in family 2 aged 3 years 3 months.

uvulae causing velopharyngeal incompetence. Pharyngeal flap surgery was carried out at the age of 6 years.

During early childhood her height was persistently below the 3rd centile and her bone age was moderately delayed (2.5 years at a chronological age of 3.25 years). A growth hormone stimulation test at the age of 3 years showed a low-normal response. However, at 7 years she developed precocious puberty. A gonadotrophin releasing hormone (GnRH) test gave an adult type response, and a growth hormone stimulation test showed a subnormal response. Levels of cortisol and thyroid hormone were normal. She was treated with a GnRH analogue to suppress menstruation, to-

gether with growth hormone. At the age of 10.75 years, her bone age had advanced to 13.5 years.

The diagnosis of SCS was confirmed at the age of 4 years. Currently aged 11 years, her facial features (fig 6A) include a high forehead, brachycephaly, marked ptosis, epicanthic folds, and small posteriorly rotated ears with prominent helical crura. She is short (height 122 cm, -3.4 SD) and obese (weight 47.4 kg, $+1.1$ SD), with bilateral accessory nipples, multiple cutaneous striae, a buffalo hump on her neck, and is in advanced puberty. She has cutaneous syndactyly of the hands involving the second and third web spaces (fig 6B), with brachydactyly and marked fifth finger clino-

Figure 6 Clinical features of the proband II-1 in family 3. (A) facial appearance aged 11 years; (B) left hand aged 10 years 7 months.

dactyly. In the feet, the fourth metatarsals are shortened bilaterally.

Discussion

The constellation of clinical features present in the three families both confirms the diagnosis of Saethre-Chotzen syndrome and emphasises the variability of the phenotype. Only the affected subject in family 3 had both of the "hallmark" features of SCS, namely craniosynostosis and digital syndactyly. In the other two families, the proband showed just one of these features (craniosynostosis in III-2, family 1; syndactyly in III-2, family 2), whereas the other four translocation carriers had neither. Nevertheless, the combination of high forehead, ptosis, facial asymmetry, and unusual ears, present in most or all of the carriers, confirms the diagnosis in the clinical context.

Four phenotypic features are particularly noteworthy in relation to SCS. The bilateral parietal foramina present in III-4 from family 1 (fig 4B) represent an infrequent, but well recognised association.^{2,17,18} Similarly the bifid halluces observed in III-2 from family 2 are characteristic: although initially classified as a separate entity,^{5,19,20} recent genetic evidence indicates that this sign is part of the SCS phenotype.^{9,10} Unusual ears are common in SCS, and are often described as small, low set, with a prominent crus or overfolded helix or both. A more extreme abnormality of ear morphology associated with CRS has been named "auralcephalosyndactyly",¹⁵ although Legius *et al*¹⁶ questioned whether this was distinct from SCS. Family 1 has strikingly unusual ears characterised by a flat or even convex scapha, which allows translocation carriers to be picked out easily. This suggests that auralcephalosyndactyly represents a subgroup of SCS, and the tendency for the unusual ears to breed true within families indicates that the phenotype is attributable to certain mutant alleles of the SCS gene. The presence of palatal

anomalies in all three families is interesting. Although high arched palate is frequently observed in SCS, overt clefts are relatively unusual.^{1,11,16,17} The tenting of the mouth present in several members of family 1 is probably related to the palatal abnormality.

The proband in family 3, as well as having the most severe craniofacial deformity, also developed precocious puberty and had persistent short stature with evidence of growth hormone deficiency. These problems have been attributed to a disturbance of hypothalamic function, but its relationship to the other craniofacial problems, the chromosome translocation, or the possible congenital CMV infection is unclear. Although it has been speculated that disorders of the hypothalamic-pituitary axis may be more common in patients with craniosynostosis,²¹ this association has not, to our knowledge, previously been described in SCS.

In summary, the observation in all three families that the SCS phenotype is associated with a translocation breakpoint in band 7p21.2 is in accordance with the previous report of Reardon *et al*¹⁰ and suggests that a major locus for SCS is present in this band. This cytogenetic assignment is based on the observation that in each case the derivative chromosome 7 retains a dark band in the position corresponding to 7p21.1, indicating that part or all of this band lies proximal to the translocation breakpoint. Independent confirmation that these three families, and that of Reardon *et al*,¹⁰ have similar 7p breakpoints has recently been obtained by fluorescence in situ hybridisation. All four breakpoints are flanked by the same pair of yeast artificial chromosomes corresponding to genetic markers D7S493 (proximal) and D7S488 (distal),²² which are separated by 6 cM and map physically within the region 7p15.3-p21.2.²³ The clustering of these breakpoints within a relatively small region suggests that they will provide a valuable resource in the positional cloning of the SCS gene or genes.

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