Chromosome 2 interstitial deletion (del(2)(q14.1q21)) associated with connective tissue laxity and an attention deficit disorder

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EDITOR—Reports of interstitial deletions involving the long arm of chromosome 2 are uncommon.[1–10] Among these, there are only four which involve the region q14q21. We report a further case with a paternally derived de novo interstitial deletion of chromosome 2q14.1q21.

Case report

The proband was a male born by spontaneous vaginal delivery at term following an uneventful pregnancy. The parents are healthy, unrelated, and white. Birth weight was 4140 g (97th centile). Early childhood was complicated by hypotonia and recurrent sleep apnoea which resolved following adenoidectomy at 2 years of age. Otherwise, his medical history showed the normal range of intercurrent childhood viral illnesses. While childhood linear growth was rapid, during the second year there was considerable concern about poor weight gain. At 6 years of age he was noted to have a high, bossed forehead with a large head circumference (90-97th centile). A thoracolumbar kyphoscoliosis and a mild sternal depression was noted. He attended normal school although moderate learning difficulties were experienced. An attention deficit defect was identified and managed with the aid of methylphenidate hydrochloride. At 15 years of age, he was tall and thin (height 176 cm, 80th centile; weight 43.3 kg, 5th centile) with an associated moderate thoracolumbar kyphoscoliosis and pectus carinatum deformity. While the upper segment:lower segment ratio was 0.804, it was apparent that spinal height was somewhat reduced by the curvature of the scoliosis. The span measurement was 175 cm and head circumference was 56.0 cm (60th centile). He was a generally thinly muscled adolescent with little subcutaneous tissue. Some mild proximal upper limb weakness was detected and winging of the scapulae was evident, particularly on the right side. Examination of the musculature around the scapulae showed that the trapezius muscles were absent or possibly extremely hypoplastic. Ophthalmic examination showed normal fundi with no evidence of corneal or anterior chamber abnormalities, lens opacities, or dislocation. Other than findings of brisk lower limb reflexes, no other neuromuscular signs were present. No striae were evident. The forehead was high and the mandible was prominent owing to obtuse angulation. The ears were low set and dysplastic with some overfolding of the pinnae. The palate was high arched. Puberty had started, with stage 4 pubic hair development and a testicular volume of 25 ml. Cardiac echocardiography showed a mild degree of aortic root dilatation (aortic diameter 2.9 cm, calculated body surface area of 1.5 m^2) but otherwise normal cardiac anatomy. Cytogenetic studies showed a small proximal interstitial deletion on the long arm of chromosome 2 (46,XY,del(2)(q14.1-21)). Before this result, no syndromic diagnosis was immediately apparent, although the occurrence of a high birth weight, a markedly prominent forehead in early childhood (fig 1A, B), and later development of mandibular prominence, hypotonia, and disproportionately long limbs had raised the question of Sotos syndrome.[11] No bone age assessments were performed earlier in childhood and it was concluded that there were insufficient features present to confirm this diagnosis. Later photographs taken in mid childhood (fig 1C-F) were not supportive of the diagnosis.

In view of the phenotype observed in this child and the rarity of interstitial deletions within this region of chromosome 2, it was decided to delineate the breakpoints of the deletion further by both fluorescence in situ hybridisation and microsatellite analysis. FISH analysis with three YACS identified a region of deletion defined by YAC694-d-4. The deleted YAC contains marker D2S110 which provided an anchor point for the microsatellite work. Microsatellite markers (Genethon map) were selected and loss of heterozygosity analysis further defined the deletion within a genetic distance of approximately 10-12 cM and involves markers ranging from 2q14.1 to 2q21.1 (fig 2). The loss of alleles was paternal for all markers and the patient displayed only the maternal alleles for the deleted region.

Discussion

Common clinical features among the few reports of proximal interstitial deletions of chromosome 2 involving the region q14.1q21 include developmental delay, microcephaly, defects of the corpus callosum, prominence of the forehead, low set and malformed ears, cardiac anomalies, and a tendency to recurrent, severe infections (table 1). Our case has some

of the characteristics reported in these earlier cases, including a prominent forehead and low set and malformed ears. Like the case reported by Frydman et *al*,[6] the birth weight of our case was unusually high. The older age of our patient, compared with those in earlier reports, provided an opportunity to document a more extensive medical history than has been recorded previously.

Weight gain was disproportionately poor from early childhood onwards, despite linear growth remaining above the 50th centile. In contrast to the earlier reports of marked microcephaly,[1 6] head growth in the case reported here was proportionate to linear growth. Similarly, the occurrence of moderate learning difficulties is in contrast to the severe developmental delay reported in the case of Frydman *et al*.[6]

The presence of kyphoscoliosis with pectus carinatum deformity and mild aortic root dilatation suggests an abnormality involving connective tissue. Although these features occur commonly in Marfan syndrome, there

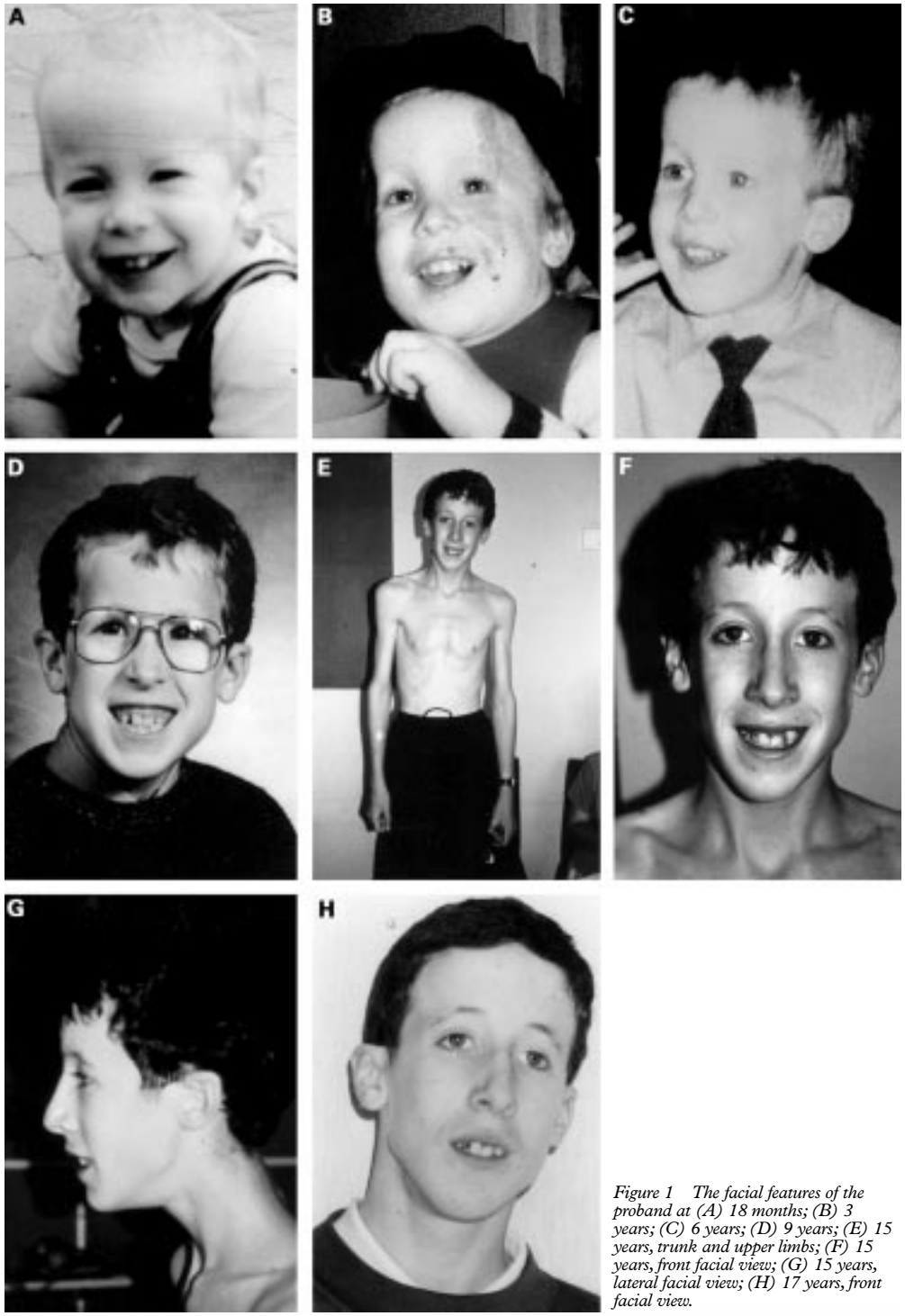

Figure 1 The facial features of the proband at (A) 18 months; (B) 3 years; (C) 6 years; (D) 9 years; (E) 15 years, trunk and upper limbs; (F) 15 years, front facial view; (G) 15 years, lateral facial view; (H) 17 years, front facial view.

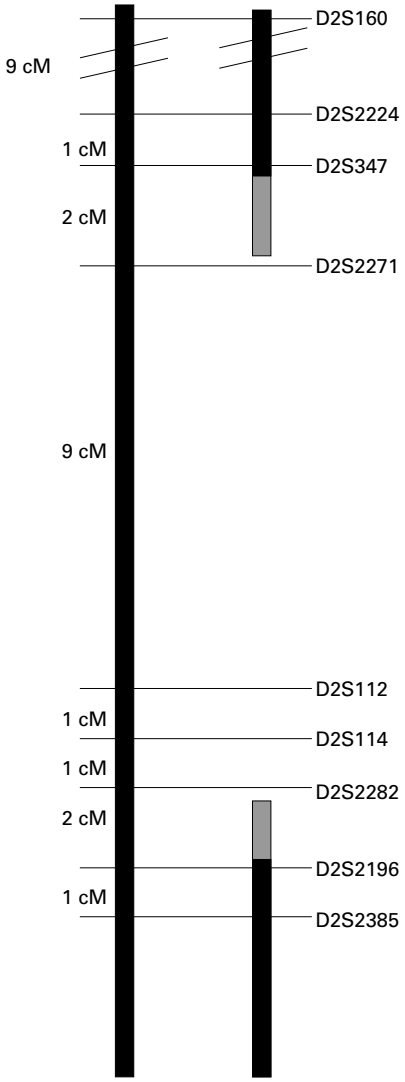

Figure 2 Deleted region at 2q14.1-q21. Markers proximal to D2S2224 and distal to D2S2385 were consistently biallelic. Grey portions of the del(2) chromosome represents the areas on which the deletion breakpoints can be localised.

were insufficient other physical features present to support this diagnosis. Nevertheless, there are some similarities, which raise the interesting possibility of another potential FBN gene within the chromosome 2 deleted region. Similarly, the associated occurrence of a moderate learning disability, together with an attention deficit defect, suggests that genes involved with higher level cerebral function are located within the deleted region. Occurrence of callosal defects among the other cases with interstitial deletions of this chromosomal region points to an abnormality of neuronal migration. Unfortunately, it was not possible to arrange neuroimaging in our own case. Nevertheless, the more moderate neurodeficit in our case contrasted with the earlier case reports of proximal 2q deletions and indicates that a variable CNS phenotype is associated with interstitial deletions in this region.

Haploinsufficiency involving one or more genes is a likely explanation for the observed phenotype. There are a number of genes within or close to the deleted region that are determinants for growth and development. Genes that could contribute to the phenotypes observed among those with interstitial deletions in this region include *GLI2* and the interleukin 1 genes and their receptors (*IL1A, IL1B, IL1RN*, and *IL1R2*). Gli2, a zinc finger transcription factor whose human homologue *GLI2* is positioned at 2q14, has been shown to have overlapping functions with Gli3 in Shh signalling.[12] It is of interest that the most proximal 2q interstitial deletion (q12-q14) has lower limb postaxial hexadactyly[4] in keeping with the polydactyly observed with *GLI3* mutations in Greig cephalopolysyndactyly syndrome, Pallister-Hall syndrome, and postaxial polydactyly type A syndrome.[13] The occurrence of severe childhood infections, and unexplained febrile episodes as well as leukaemoid reactions among many of these cases with interstitial deletions in this proximal region of 2q is of interest. In this context, it is notable that our case did not have such a history. Candidate genes for these features include the interleukin-1 (IL-1) gene cluster and the IL-1 receptor gene cluster which map in the region of chromosome 2q12 to 2q13.[14 15]

Other genetic explanations for the observed phenotype include the unmasking of autosomal recessive disease owing to hemizygosity, or a parent of origin, or imprinting, effect contributing in part or in whole to the observed differences. While microsatellite analysis showed that the deletion in this case was of paternal origin, the parental origins of the previously reported deletions were not determined. Interestingly, the father of the case with an interstitial deletion of the region q13q21, reported by Davis et *al*,[8] had a balanced translocation involving chromosome 2 as well as a pericentric inversion of chromosome 9 (46,XY,inv(9),t(2,7)(q32.2;p11). Other than this unusual report of co-occurrence of two chromosomal rearrangements involving the long arm of chromosome 2 in parent and child, there is insufficient evidence arising from earlier reports to determine whether a parent of origin effect occurs in this chromosomal region. Should such an effect occur, the paternal origin of the deletion reported here makes it possible to predict that maternal imprinting is involved. While reports of maternal disomy of chromosome 2 associated with phenotypic abnormalities is supportive of this concept,[16] a report of maternal isodisomy 2 owing to the de novo inheritance of two isochromosomes for chromosome 2 in a normal healthy female, karyotyped because of recurrent spontaneous abortions,[17] is strong evidence against.

To conclude, this case provides some additional insights into the effects of haploinsufficiency arising from a deletion of paternal origin in the proximal region of the long arm of chromosome 2.

Table 1 Reports of proximal deletions of chromosome 2

	Antich et al[4]	*German et al*[5]*	*Davis et al*[6]*	*Present case*	*Lucas et al*[7]*	*Frydman et al*[8]*	*Fryns et al*[2]	*McConnell et al*[3]
Deletion	q12-q14	q13-q21	q13-q21	q14.1-q21	q14-q21	q14-q21	q21-q24	q22-q31
Parental origin of deletion	Unknown	Unknown	Paternal karyotype 46,XY, inv (9), t(2,7)(q32.2;p11)	Paternal	Unknown	Unknown	Unknown	Unknown
Sex	M	M	F	M	F	F	F	F
Age	8 mth†	30 mth	29 mth†	17 y	11 mth	2 y	2 mth†	Newborn†
Birth weight (g)	2400		2790	4140 (97th centile)	3060	4900	2500	1500
Growth	Failure to thrive		Failure to thrive	Poor weight gain (5th centile) Linear growth normal (80th centile)		Weight 40th centile; Length 10th centile	Failure to thrive	Not applicable
Developmental delay/ learning difficulties	+ (Severe)		+ (Severe)	Mod learning difficulties Attention deficit disorder		Severe dev delay	+ (Severe)	Not applicable
OFC	Microcephaly Head circumference at birth 32 cm	Microcephaly	Macrocephaly Head circumference at birth: 36 cm (>95th centile)	Macrocephaly Head circumference 90–97th centile		Microcephaly	Microcephaly Head circumference at birth 32.5 cm (<3rd centile)	Hydrocephalus
Callosal defect	+		+	Unknown	+	+		+
Sutural irregularities	+			No	+	No		+
Prominent forehead	+			+	+	+	+	
Ocular anomalies				Normal ophthalmic examination		Corneal opacity Peter's anomaly	Cataract Microphthalmia	
Low set ears	+			+	+	+	+	+
Malformed ears	+		+	+		+		
Mandible	Micrognathia			Prominent, obtuse angulation		Micrognathia	Micrognathia	Micrognathia
Cleft lip/palate	+			No		No	+	+
Cardiac malformation	Ventriculoseptal defect		Atrial septal defect	Aortic root dilatation	No	Patent ductus arteriosus	Patent ductus arteriosus	Truncus arteriosus
Recurrent infections/ unusual immune responses	+		+ (Recurrent unexplained febrile episodes)	No	+	+ Leukaemoid reactions	+	
Other anomalies	Hydronephrosis Postaxial hexadactyly of toes	Abnormal gait Hemizygosity at the MN locus	Loose skin Generalised hyperextensibility Dandy-Walker malformation	Hypotonia in infancy Pectus carinatum Kyphoscoliosis	Hypotonia in infancy	Cortical blindness Seizures Renal malrotation and ectopia	Polycystic ovaries	Encephalocele
	Imperforate anus		Hydrocephalus Partial agenesis of the cerebellar vermis Ovarian dysgenesis Clinodactyly	Proximal upper limb weakness Winging of scapulae		Anteriorly placed anus		

*Cases with deleted regions which overlap that of the present case.
†Dead.

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