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Deletion 14q(q24.3 to q32.1) syndrome: significance of peculiar facial appearance in its diagnosis, and deletion mapping of Pi(α_1-antitrypsin)

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Summary. A 10-month-old Japanese boy who had interstitial deletion of the long arm of chromosome No. 14; 46,XY, del(14)(pter→q24.3::q32.1→qter) is reported. A peculiar facial appearance, including round face, frontal hypertrichosis with thick eyebrows, horizontal narrow palpebral fissures, a short bulbous nose with a flat nasal root, and mild micrognathia, appeared to be common with the two previously reported cases. We stress the significance of this peculiar facial appearance in the diagnosis of 14q−(q24.3 to q32.1) syndrome. The level of α_1-antitrypsin in the patient was only about half of that of his parents and controls, and the Pi locus was tentatively assigned to band 14q32.1.

Introduction

Deletions of 14q are very rare and the reported cases include mainly r(14)s. Only five cases of de novo deletions without ring formation have been reported (Nielsen et al. 1978; Hreidarsson and Stamberg 1983; Turleau et al. 1984; Kawamura et al. 1985). We describe here another patient with de novo interstitial deletion, including band 14q31, and discuss the phenotype-karyotype correlation. The results of studies on some genetic markers especially for α_1-antitrypsin (α_1-AT) are also presented.

Case report

The patient, Y.I. JMS-2752277, was a 10-month-old Japanese boy. He was the first child of a 26-year-old mother and a 34-year-old father. Both parents were healthy and they were not related. The mother suffered from cholelithiasis and underwent surgery 6 months before the pregnancy, and at that time several abdominal X-ray films were taken. The boy was born after a 37-week uncomplicated pregnancy. His birth weight was 2350 g, length 47.0 cm, and head circumference 30.0 cm. The main problems in the neonatal period were mild neonatal jaundice and transient sucking difficulty. He smiled at 3 months and showed head control at 4 months old. At 6 months old, he caught a cold and visited Shimodate Citzen's Hospital. At that time, facial dysmorphism and microcephalus were detected and chromosome analysis was carried out. Following the detection of chromosomal abnormality, he was referred to our hospital for further examination.

At the time of investigation, the patient was 10 months old. He was 70.0 cm tall (−1.1 SD), weighed 10.0 kg (+0.8 SD), and had a head circumference of 43.5 cm (−1.7 SD). He had a peculiar facial appearance, including round face, frontal hypertrichosis with thick eyebrows, horizontal narrow palpebral fissures, a short bulbous nose with a flat nasal root, mild micrognathia, and carp mouth (Fig. 1). He also revealed brachycephalus, an excess of skin on the nape, and bilateral single palmar crease.

His motor and mental development were mildly retarded, and his developmental age was estimated as 6 months and 29 days for a chronological age of 10 months and 15 days (DQ = 66) by Tsumori and Inage's method. However his attitude was very friendly and cheerful.

Eye examinations were normal except for the narrow palpebral fissures. No heart or other inner organ defects were noted. Laboratory studies, including a complete blood count, urine analysis, liver function tests, renal function tests, and serum electrolytes, were all within normal limits. Screening tests on urine for inborn errors of metabolism, the Guthrie test, and screening tests for cretinism revealed no abnormalities. A brain computed tomography (CT) showed mild

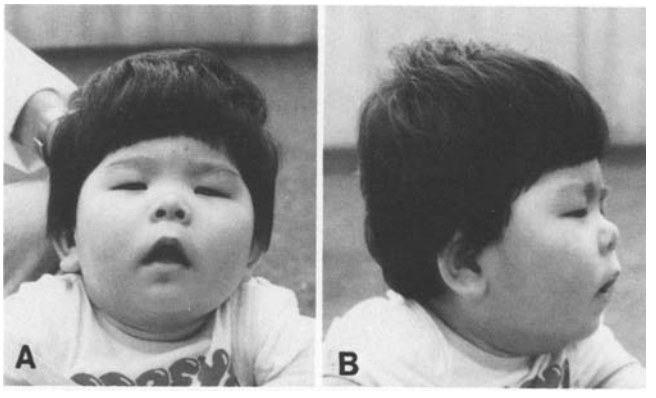

Fig. 1A, B. Frontal and lateral views of the patient

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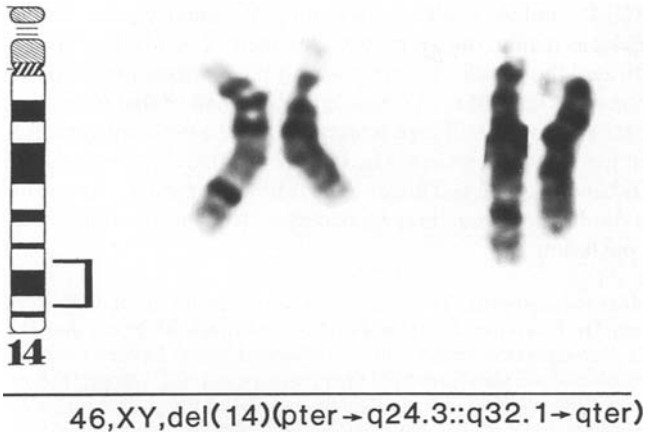


Fig. 2. Partial karyotype. No. 14 chromosome pair from the propositus. The chromosome situated on the right is shortened due to an interstitial deletion

Table 1. Serum concentration of α_1-AT and Pi phenotype in the patient and his parents

	α_1-AT (mg/dl)[a]	Pi type[b]
Patient	104	M1M1 (?)
Father	241	M1M1
Mother	231	M1M1

[a] Confidence interval: 148–317 mg/dl
[b] See text and Fig. 3

Fig. 3. Pi typing by isoelectric focusing in polyacrylamide gel. *Lanes A, B, C:* father, patient, and mother respectively. The phenotype of patient could not be distinguished from M1M1, but the reduced intensity of main bands indicate the hemizygosity at the Pi locus

generalized cortical atrophy. His electroencephalogram and acoustic brainstem response were normal. A bone survery and intravenous pyelogram demonstrated no particular change.

A dermatoglyphic investigation showed: finger (I to V) W.W.W.L.L. (left), W.W.U.U.U. (right), TFRC 182, palm 11.9.7.5.13.−t−0.0./0.0.L.0. (left), 9.9.5.5.13.−t−0.0./0.0.L.0 (right).

Cytogenetic studies

Chromosome analysis from a peripheral blood leucocyte culture of the patient revealed 46 chromosomes with deletion of the long arm of chromosome 14. Precise analysis by the ethidium bromide method (Ikeuchi and Sasaki 1979) showed a karyotype of 46,XY,del(14)(pter→q24.3::q32.1→qter) at the 550 bands level (Fig. 2). The parents had normal karyotypes. The origin of the deleted chromosome could not be determined by a study based on Q polymorphism.

Genetic markers

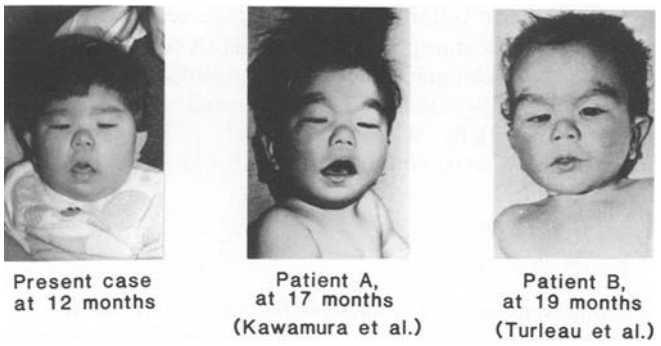
The levels of immunoglobulins showed normal values: IgG, 801 mg/dl; IgA, 144 mg/dl; IgM, 30 mg/dl; IgE, 27 U/ml. The level and isoenzymes of creatine phosphokinase revealed normal values: total activity, 95 IU (MM 93.9%, MB 2.6%, and BB 1.5%).

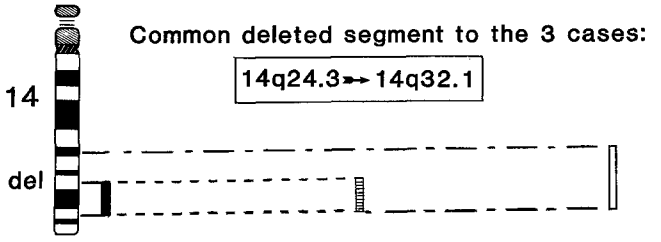
Table 1 and Fig. 3 show the level of α_1-antitrypsin and Pi (genetic locus for α_1-AT) phenotypes of the patient and his parents. α_1-AT was quantitated by turbidimetric immunoassay (Hirabayashi et al. 1986), and Pi typing was carried out by isoelectric focusing in polyacrylamide gels (van den Broek et al. 1976).

Discussion

Among four reported cases of de novo deletions of chromosome 14, two cases revealed interstitial deletions, including 14q31 (case 1 of Turleau et al. 1984; and Kawamura et al. 1985). The patient reported by Kawamura et al. (1985) had the same breakpoints as the present patient. As shown in Fig. 4, the only features common to these cases appeared to be their peculiar facial appearance and mental retardation. In particular, our patient had no other definite anomalies involving other organs. It is concluded therefore that the key phenotypes for the diagnosis of the 14q− (q24.3 to q32.1) syndrome are a peculiar facial appearance and mental retardation of variable degree.

Recently, Couturier et al. (1985) reported interesting patients having deletions of 13q21 with a normal phenotype. They suggested that the normal phenotype of their patients reflected the fact that the deletion concerned a very late replicating G-band, transcriptionally non-active. According to the ISCN (1981), 13q21 is divided into three bands at the 550-band level (including one R-band, 13q21.2). The band 14q31 is also one of the latest replicating segments (Camargo and Cervenka 1982) and is divided into three bands at the 850-band level, including one R-band 14q31.2 (ISCN 1981). If the segment 14q31.2 is not related to the abnormal phenotype as in the cases of Couturier et al. (1985), the critical segment to the abnormal phenotype in our case should be in the part 14q24.3 or 14q32.1 around the band 14q31. Deletion of 14q31 is readily detected by routine G-banding analysis, but 14q24.3





Simian line	Simian line	Simian line
Brachycephalus	Pes varus	Atrial septal defect, etc.
DQ 66 (at 10 months)	Cleft uvula	Horse-shoe kidney with left VUR
	High arched palate	Left inguinal hernia
	Diathesis recti	Micropenis and cryptorchidism
	Abnormal dermatoglyphics (10 L and bilateral hypothenar pattern)	Dolichocephalus
	DQ 39 (at 17 months)	Frequent respiratory infections
		Died at 2 years

Fig. 4. Comparison of the facial appearances of the reported cases. *Patient A*, by courtesy of Dr. G. Kawamura, and *patient B*, by courtesy of Dr. C. Turleau and Dr. J. de Grouchy. Note the common peculiar facial appearance

and 14q32.1 are not. At present, precise analysis of these negative G-bands is thus also necessary for the diagnosis and genetic counselling of patients with the above mentioned phenotypes.

Generally speaking, considering de novo rearrangements which do not involve a Robertsonian translocation or segregation error, there is a marked excess of paternal errors (Chamberlin and Magenis 1980). The maternal origin of the deleted chromosome could not be revealed in our patient and the possibility of an effect of her X-ray exposure to the deletion was obscure.

The Pi (α_1-AT) gene is currently assigned to 14q24.3 to q32.2 (Cox et al. 1982) and more recently to 14q31–32 (Schroeder et al. 1985). Turleau et al. (1984) further assigned the tentative locus to band 14q32.1 by exclusion mapping in view of the fact that their patient 1 was heterozygous for the Pi locus. Pi types of our patient and his parents were all M1M1, and we could not determine the hemizygosity for the Pi locus in him, but his reduced intensity of bands (Fig. 3B) indicated the possible hemizygosity at the Pi locus. On the other hand, his level of α_1-AT was only about half of that of his parents and controls. These findings indicate a gene dosage effect of the deleted segment. The Pi gene can therefore be assigned to band 14q32.1 as Turleau et al. (1984) suggested. An in situ hybridization study may be necessary for confirmation of this conclusion.

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