A case of partial monosomy 21q22.2 associated with Rieger's syndrome

FRANK NIELSEN* AND LISBETH TRANEBJÆRG†

*Department of Pediatrics, Sønderborg Sygehus; and †Department of Medical Genetics, The J F Kennedy Institute, Glostrup, Copenhagen, Denmark.

SUMMARY A deleted chromosome 21 is reported in a mentally retarded girl with prominent occiput, high nasal bridge, downward slanting eyes, enophthalmus, atresia of the right lacrimal duct, displaced anal opening, and supernumerary ribs. Cytogenetic investigation of cultured lymphocytes and skin fibroblasts revealed a deletion of the long arm of chromosome 21 at sub-band q22.2 with satellites on both arms. Normal SOD-1 activity confirmed the breakpoint to be distal to band q22.1.

Partial monosomy of the long arm of chromosome 21 was first described by Lejeune *et al*¹ in a child with downward slanting eyes, prominent nasal bridge, and hypertonia; they named the condition antimongolism. The delineation of the clinical findings in cases of deletion 21q is complicated by the fact that at least 12 of the 23 previously reported patients were mosaics. We report another case with deletion of the long arm of chromosome 21 associated with the characteristic signs. In this patient the deletion was found in cultured lymphocytes and skin fibroblasts.

Family history

The mother has congenital stenosis of the lacrimal ducts. A sister of the maternal grandmother suffered neonatally from congenital corneal clouding and strabismus. Another sister had congenital dislocation of the hip. Neither of these relatives was mentally retarded.

Case report

The proband, the second of two sibs, was born in September 1980. The older brother born in 1979 is healthy. Both parents were 22 years old when the patient was born and they were non-consanguineous. A therapeutic abortion had been performed sometime before the birth of our patient.

Pregnancy was uncomplicated and the birth was uneventful after 39 weeks' gestation. Birth weight was 2400 g, length 46 cm, and head circumference

31 cm. Apgar score was 10 at 1 minute and 5 minutes. Fourteen hours after birth the child was admitted to the neonatal department because of cyanosis. During the following days there were further episodes of apnoea and convulsions, successfully treated with phenobarbital.

The infant presented hypertonia, a prominent occiput, retromicrognathia, a high nasal bridge, and rotated ears which were of normal size and location. There was a weak systolic murmur, and the anus was displaced anteriorly and separated from the vaginal orifice by a septum. The hips could be abducted only with difficulty, but there was no dislocation. When the child was 6 months old, computerised tomography of the brain showed cerebral atrophy. Radiography of the chest showed 13 ribs bilaterally, but the heart and lungs were normal.

At 15 months of age there were delayed milestones and growth retardation. The length was 75 cm and weight 7.6 kg (weight below the 95th centile). The girl could support her head, but was unable to turn from her back to her front or vice versa. She only sat with support. At 17 months of age she had mumps and convulsions reappeared.

The eyes were examined at birth and several times during the next 18 months. There was congenital corneal clouding involving the stroma. This gradually regressed and at the age of 4 months it was present only peripherally, apart from a small central opacity in the right eye. This opacity was associated with an anterior synechia. In the right eye a white membrane was observed lining the limbus at the inner side of the cornea, and at 16 months of age transillumination showed a right central lenticular opacity.

Both eyes were deeply set, the palpebral fissures showed antimongoloid slanting, and the distances between the inner and outer canthi were 29 and 67 mm respectively at 16 months. The corneae measured 9.5 mm each and there was a scar over the right inner canthus after dacryocystectomy. This was performed at the age of 4 months for repeated inflammations of the lacrimal sac, caused by congenital atresia of the right lacrimal duct.

The peculiar appearance of the child led to chromosome investigations shortly after birth.

Case reports

BIOCHEMISTRY

The activity of the enzyme superoxide dismutase-1 (SOD-1) in serum was examined with the method of Sun and Zigman² by inhibition of epinephrine auto-oxidation. The activity in the patient was identical with two controls matched for age and weight.

CYTOGENETIC INVESTIGATION

Cultured lymphocytes and skin fibroblasts from the proband were examined. Cultured lymphocytes from the parents were also investigated. Slides were stained with QM, C, and Ag staining. R banding

FIG 1(A) Partial karyotypes from the patient showing the two chromosomes 21. The deleted one is indicated by an arrow. (a) QM staining (left) and destaining of the same cell followed by silver staining (right). (b) QM staining (left) and C banding (right) of the same cell. (c) Chromosomes 21 from a BudR culture (RBA staining). (d) Methotrexate synchronised prometaphase chromosomes 21. (B) Satellite association between (a) normal chromosomes 22 and 21, the bisatellited 21, and a chromosome 13, QM staining on the left, silver staining on the right (of the same cell). The deleted chromosome 21 is indicated by an arrow. (b) The deleted chromosome 21 is in satellite association with the normal 21 and one chromosome 22, QM staining on the left and silver staining on the right.

FIG 2 The patient at the age of 18 months.

was carried out after BudR incorporation and subsequently acridine orange staining (RBA). Furthermore, prometaphase chromosome analysis (after synchronisation with MTX) was done on cells from the patient (fig 1A). The karyotype was 46,XX,del (21)(pter→q22·2:: (?)p12→pter) in lymphocytes and skin fibroblasts. Altogether 50 metaphases were examined. Both parents had normal karyotypes. The older, clinically normal brother was not investigated. The deleted chromosome 21 was suspected to be paternally derived because of similarity between the chromosomal QFQ and Ag NOR markers on the deleted chromosome and one chromosome 21 from the father. Comparison of the acrocentric chromosomes of the proband and her parents with different staining methods did not definitely disclose the origin of the translocated satellite material. Satellite association of both the satellites of the short arm and the long arm was frequently observed (fig 1B).

Discussion

Since the availability of banding techniques, at least 19 reports of 23 cases of partial monosomy 21 have been published. Most of these dealt with mosaics or ring chromosomes and often the break-point could not be determined.

In at least five previous cases the authors have succeeded in establishing the breakpoint. Earlier reports have shown that trisomy for band 21q22 is responsible for the Down's syndrome phenotype.³ Habedank and Rodewald⁴ reported three sibs with partial trisomy 21 (q22·2→pter) who showed the typical Down's phenotype, apart from the dermatoglyphs. This was probably because of the absence of a triplicate 21q22·1 band. Cantu *et al*⁵ described a boy with partial trisomy 21q22·1 and 21q22·2 and concomitant monosomy of 21q22·3 owing to presumptive complex breaks and rearrangements in chromosome 21. The signs included some characteristics of Down's syndrome, probably due to trisomy 21 (q22·1→q22·2), and also some antimongoloid features, such as large ears, micrognathia, and prominent nasal bridge, probably due to monosomy 21q22·3. In the present case, the demonstration of normal activity of SOD-1 confirms that the breakpoint is distal to 21q22·1.⁶ Our patient resembles the case of G deletion I syndrome reported by Mikkelsen and Vestermark⁷ with the karyotype 45,XX,-21/46,XX,del(21)(q22). Similarity is also present between the present case and that of Yamamoto *et al*,⁸ where the karyotype was 46,XX,del(21)(q22·1 or 22·2). The case reported by Mikkelsen and Vestermark⁷ was a mosaic, and in the case of Yamamoto *et al*⁸ mosaicism could not be ruled out since only peripheral lymphocytes were examined.

The presence of the chromosomal abnormality in both lymphocytes and skin fibroblasts makes it unlikely that the present case is a mosaic.

We also noticed clinical similarities between reported cases of r(21)⁹ and the present case. Regrettably the breakpoints of the other cases could not be determined, but the presence of large ears, micrognathia, and prominent nasal bridge suggests monosomy of 21q22·3. A variety of ocular malformations are often found in cases of partial monosomy 21, but the criteria of Rieger's syndrome were not fulfilled in previously reported cases and Rieger's syndrome should be regarded in principle as being unrelated to deletion 21 syndrome. Corneal clouding can be present in cases with a r21.⁹ Our patient had malformations similar to those of Rieger's syndrome, which shows dominant inheritance¹⁰ and a great variability of clinical expression. A variety of associated malformations including congenital dislocation of the hip and anal malformations have been reported in isolated cases.¹¹ Chromosomal investigations have been reported in very few cases (table).

However, the majority of patients with Rieger's syndrome are presumably chromosomally normal, and the presence of congenital corneal clouding in the sister of the maternal grandmother might

TABLE Chromosomal aberrations associated with Rieger's syndrome.

Chromosomal aberration	No of cases reported	Authors
6p+q—	2	Heinemann <i>et al</i> ¹⁴
Presumptive isochromosome of the long arm of chromosome 6	1	Tabbara <i>et al</i> ¹⁵
Trisomy 13	4	Reese and Ellsworth ¹⁶
Trisomy 18	3	Huggert ¹⁷
Trisomy 9 (mosaic)	1	Ginsberg <i>et al</i> ¹⁸
Partial monosomy 4p (Wolf-Hirschhorn syndrome)	1	Francois <i>et al</i> ¹⁹
Interstitial deletion 4q	1	Ligutic <i>et al</i> ²⁰
46,XX,del(21)(pter→q22·2:: (7)p12→pter)	1	Present case

indicate that she had malformations of the eyes consistent with Rieger's syndrome. Unfortunately only the proband was examined ophthalmologically. Anal malformations have been reported in two cases of true monosomy 21,^{12 13} but have not been reported in cases of partial monosomy 21.

Our patient had a coincidental chromosomal aberration and a malformation of the anterior eye chamber, morphologically identical to that found in Rieger's syndrome.

A thorough examination, cytogenetic investigation, and biochemical analysis are important in establishing the connection between clinical findings and chromosomal abnormalities.

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Correspondence and requests for reprints to Dr L Tranebjærg, Department of Medical Genetics, The John F Kennedy Institute, Gl Landevej 7, DK 2600 Glostrup, Denmark.

Inv dup (15) with mental retardation but few dysmorphic features

D H GILMORE, E BOYD, J P McCLURE*, P BATSTONE, AND J M CONNOR

*Duncan Guthrie Institute of Medical Genetics, Yorkhill, Glasgow G3 8SJ; and
Ayrshire Central Hospital, Kilwinning Road, Irvine, Scotland.

SUMMARY We report a Scottish child with inv dup (15) and compare the clinical features with those of previously reported cases.

Since the first report by Parker and Alfi in 1972,¹ there have been 44 reports of patients with confirmed or suspected inv dup (15). The extra chromosomal material has been variously described, but in all cases there appears to be an additional G group sized chromosome in which both ends are derived from the short arm, centromere, and proximal long arm of chromosome 15. In most cases there are satellites at both ends of this extra chromosome.

We report the first patient from Scotland with similar cytogenetic findings.

Case report

The proband was referred for assessment of developmental delay. He was the third child of non-consanguineous Scottish parents. His father was 44 years old and his mother was 30 years old at the time of his birth. The pregnancy was uneventful

and spontaneous vertex delivery occurred at term. His birth weight was 3.43 kg.

All developmental milestones were delayed. He sat unsupported and crawled at the age of 10 months. He walked with support at 22 months. Speech development has also been delayed.

He underwent a right inguinal hernia repair at 12 months but otherwise has had good general health.

At 2.5 years of age examination revealed height, weight, and head circumference all on the 50th centile. His eyes had an antimongoloid slant and he tended to hold his head in dorsiflexion. Interpupillary distance was 4.8 cm (50th centile) and inner intercanthal distance was 2.6 cm (50th centile). Dermatoglyphs were abnormal with arches on five fingers. Apart from developmental delay, the remainder of his clinical examination was unremarkable.

CYTOGENETICS

Chromosome analysis of cultured lymphocytes by Giemsa banding, C banding, and DAPI/Distamycin A staining revealed a 47,XY chromosome constitution, with a small additional chromosome derived