tively assigned to the 2q32→qter region.⁸ The results of the assays in our proband and in the patient of Turleau *et al*² confirm this localisation. In the latter, no position effect, which would tend to give an activity level lower than expected for a trisomic subject, could be shown. This was also the case for esterase D in a patient of Mohandas *et al*,⁹ who was the carrier of a de novo unbalanced t(X;13)(q27;q12).

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Partial trisomy 12q24.31→qter

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SUMMARY Clinical details of a male child with the karyotype 46,XY,-4,+der(4),t(4;12)(p16;q24.31)mat are reported and compared with those of other known cases of partial trisomy of the distal region of 12q. This condition is apparently associated with mental and psychomotor retardation, widely spaced eyes, flat nasal bridge, low set ears, downturned mouth, micrognathia, loose skin at the nape, widely spaced nipples, simian creases, clinodactyly, abnormalities of the genitourinary system, alterations in the sacrococcygeal region, and deformities of the lower limbs. In the majority of the reported cases, the breakpoint was in the 12q24 region and resulted from adjacent 1 segregation of a maternal balanced translocation.

Case report

The proband was the second child of a 27 year old mother and a 45 year old father, both in good health and unrelated. The mother had no difficulty conceiving and had never miscarried. Pregnancy and delivery were uneventful at term and the birth weight was 1670 g.

At birth the infant was noted to have multiple congenital anomalies and was referred for clinical and cytogenetical evaluation. Clinical examination revealed dolichocephaly and peculiar facial features (fig 1), including prominent forehead, upward slanting palpebral fissures, convergent strabismus, hypertelorism, large and low set ears with poorly formed external lobules, high arched palate, wide mouth with downturned corners, beaked nose with a broad base, and micrognathia. No epicanthic folds were seen and the neck appeared long. Other abnormalities included a narrow chest with hypoplastic nipples, bilateral palmar simian creases, clinodactyly, large, proximally

FIG 1 Proband at the age of 15 months.

placed thumbs, relatively long and hyperextensible fingers, right lower limb shorter than the left, right inguinal hernia, valgus deformity of the feet, cryptorchidism, small penis with glandular hypospadias, and deep coccygeal dimple. Abnormal hand position, limited elbow movement, and hip dislocation were not present.

At 15 months the patient was microcephalic (head circumference 43 cm), showed marked growth retardation (weight 5400 g and height 74 cm), severe muscular hypotonia, and retarded psychomotor development. Cardiopathy was not present. He also had very sweaty forehead and hands and decreased cutaneous pigmentation. During the first months of life the patient had recurrent urinary tract and ear infections and rickets controlled by vitamin D; he was a marasmus-type malnourished child. Generalised convulsions developed and were adequately controlled with phenobarbital and clonazepam. Excretory urography was normal and the voiding cystourethrogram showed unilateral vesicoureteric reflux.

Dermatoglyphic studies of the proband showed eight whorls and two large ulnar loops on the fingers with a high TRC, bilateral absence of *b* and *c* triradii, distal dislocation of *t* triradii, tibial loop in the hallux areas, and deep palmar and plantar skin creases. Ridge dissociation occurred on palms and soles.

FIG 2 (A) *G* banded chromosomes 4 and 12 from three cells of the proband's mother. (B) Schematic illustrations of the balanced translocation. (C) Partial karyotypes of the proband.

The mother was phenotypically normal and the older brother, a 7 year old boy, underwent surgical correction of left cryptorchidism. Dermatoglyphic patterns of the proband's mother and brother were normal and there was no ridge dissociation.

CYTOGENETIC STUDIES

G banding of peripheral blood lymphocytes of the proband revealed extra pale-staining material on the short arm of chromosome 4. The father's chromosomes were normal. The mother carried a balanced reciprocal translocation: t(4;12)(p16;q24.31) (fig 2). The patient inherited the 4p+ chromosome, resulting in monosomy of the terminal segment of 4p and trisomy 12q24.31→qter. His karyotype was 46,XY,-4,-der(4),t(4;12)(p16;q24.31)mat (fig 2). The proband's older brother was found to have the same balanced chromosomal rearrangement as his mother.

Discussion

Trisomy for the distal region of the long arm of chromosome 12 is an infrequent condition and only 13 patients with this anomaly have been reported so far (table 1), two of these in a single sibship. Eleven patients, including the one presented here, were the unbalanced products of a parental translocation involving the long arm of chromosome 12 and a second chromosome, the translocation carrier being the mother in seven families and the father in three. The two remaining cases were described as pure duplications of 12q24.1→q24.5⁵ (q24.1→q24.33 according to ISCN¹¹).

In the patients described by Hirschhorn *et al*¹ and Aurias *et al*³ there were significant deletions of other autosomes and the clinical features may also be attributed to 4q monosomy in the first case and 9q monosomy in the second. In the 11 patients manifesting the phenotype of distal 12q trisomy an association of some signs is evident (table 2).

TABLE 1 Patients trisomic for a distal region of the long arm of chromosome 12.

Reference	Karyotype
Hirschhorn <i>et al</i> ¹	46,XY,-4,+der(4).t(4;12)(q26;q12)pat
Hobolth <i>et al</i> ²	46,XY,-21,+der(21).t(12;21)(q24;p11)mat
Aurias <i>et al</i> ³	46,XY,-9,+der(9).t(9;12)(p23;q24.3)mat
Hemming and Brown ⁴	46,XX,-18,+der(18).t(12;18)(q24;qter)pat
Harrod <i>et al</i> ⁵	46,XX/46,XX,dup(12)(q24.1→q24.5) 46,XY/46,XY,dup(12)(q24.1→q24.5)
de Muelenaere <i>et al</i> ⁶	46,XX,-17,+der(17).t(12;17)(q24;q25)mat 46,XX,-17,+der(17).t(12;17)(q24;q25)mat
Melnick <i>et al</i> ⁷	46,XY,-4,+der(4).t(4;12)(p16;q24.1)mat
Roberts <i>et al</i> ⁸	46,XY,-2,+der(2).t(2;12)(q37;q24.1)pat
Zabel and Baumann ⁹	46,XY,-9,+der(9).t(9;12)(p24.3;q24.3)mat
Pratt and Bulughapitiya ¹⁰	46,XX,-9,+der(9).t(9;12)(p24;q21.2)mat
Present case	46,XY,-4,+der(4).t(4;12)(p16;q24.31)mat

TABLE 2 Clinical features of our proband and other patients with trisomy for a distal region of 12q.

Clinical features	Present case	Other cases
		Positive/informative*
Normal weight for gestational age	-	9/10 ² 4-10
Microcephaly	+	0/7 ⁴ 5 7-10
Ocular hypertelorism	+	6/6 ⁴ 5 7 9 10
Flat nasal bridge	+	7/9 ² 5-10
Low set and/or malformed ears	+	8/8 ² 4 5 7-10
Downturned mouth	+	6/7 ² 4 5 7 9 10
Micrognathia	+	6/8 ² 4 5 7-10
Loose skin at nape	-	8/8 ² 4 5 7-10
Widely spaced nipples	-	6/6 ⁴ 5 7 9 10
Cardiovascular anomalies	-	6/8 ² 4 5 7-10
Simian palmar creases	+	8/10 ² 4 5-10
Clinodactyly	+	6/7 ⁴⁻⁸
Planovalgus feet	+	4/10 ² 4-10
Subluxation of hips	-	4/6 ⁴ 5 7 9 10
Genitourinary anomalies	+	7/7 ² 4 5 7-9
Sacroccocygeal anomalies	+	7/8 ² 4 5 7-10
Mental and psychomotor retardation	+	7/7 ² 5-8

*Number of cases in which the feature is present.

Our patient seems to be more severely affected than those described by Harrod *et al*⁵ and Melnick *et al*⁷ who were trisomic for a larger segment. Although we cannot reach a definite conclusion, it is possible that these findings resulted from the particular genic content or from a position effect of the material involved. Additionally, the less severe characteristics observed in the patients described by Harrod *et al*⁵ might be related to the presence of a normal cell line. Several clinical features of the present case are also frequently observed in patients with monosomy 4p.¹²

The short arm of the chromosome 4 participates in two break rearrangements, resulting in reciprocal translocations, more frequently than expected on the basis of its length.^{3 13} In cases with an affected chromosome 12 the long arm is more commonly involved in balanced reciprocal translocations¹⁴ and some carriers show mental retardation and other malformations,¹⁵ sterility, or miscarriage.^{7 13 14}

Ford *et al*¹⁴ reported 31 subjects with breaks in chromosome 12. In 10 of these the breakpoints were located in band q24, showing that this breakpoint has frequencies in vivo which differ significantly from random expectation. In 11 of the 13 cases considered in table 1 the breakpoint is at q24. In four of these (published before the ISCN¹¹) there is no reference to the subband, in four others the break is at q24.1, in two it is at q24.3, and in one at q24.31. In the remaining two patients the breaks are at q21.2¹⁰ and q12.¹ The preferential breakage at some bands, including 12q24, seems to be influenced by the genetic composition of these regions rather than by their structure.¹⁶

An important question in familial translocations is the mode of segregation and its implications for genetic counselling. The relative frequency of unbalanced gametes depends both on the type of the multivalent formed and its orientation on the metaphase plate, but the more important factor for predicting the prospective risk for carriers of a reciprocal translocation is the degree of possible resulting chromosomal imbalance. In reciprocal translocations causing trisomy for distal 12q, the centric segments are larger than the translocated ones and all the probands result from adjacent 1 segregation, which, in such a situation, would cause the least imbalanced karyotypes at birth. Another factor to be considered is the sex of the carrier parent. In seven of the 10 affected families trisomy for the distal region of 12q was the consequence of a maternal translocation. This preponderance of maternal origin has also been noted for other trisomies due to malsegregation of the 3:1 type, but is not common among translocations of the 2:2 type.³ As mean maternal age is not increased and there is no obvious bias of ascertainment, the more probable determining factor is the difference between male and female meiosis which results in decreased fertility or even sterility among men carrying these rearrangements. This was noted in the family history of some probands.^{7 10}

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Fraser syndrome presenting as monozygotic twins with bilateral renal agenesis

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SUMMARY Fraser syndrome without cryptophthalmos is described in monozygotic twins concordant for bilateral renal agenesis.

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The cryptophthalmos syndrome is an autosomal recessive condition,¹ the main features of which are cryptophthalmos, ear and nose anomalies, cutaneous syndactyly, genital malformations, laryngeal stenosis, and renal anomaly.²⁻⁴ Because