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Translocation, t(4q−;13q+), in three generations resulting in partial trisomy of the long arm of chromosome 4 in the fourth generation

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Summary. The karyotype of a child with severe mental retardation, microcephaly, minor facial anomalies, and urinary tract outflow obstruction was found to be 46,XY,13q+mat. Trypsin-Giemsa banding studies showed an inherited translocation, t(4q−;13q+), in several asymptomatic members of the family including the propositus' mother. This indicates that the propositus had partial trisomy for the distal one-third of the long arm of chromosome 4. Review of the literature suggests that urinary tract and genital anomalies may be a consistent feature of this partial trisomy.

Chromosomal translocations are found in approximately 0·14% (1/700) of all newborn babies (Sergovich *et al*, 1969, Walzer, Breau, and Gerald, 1969; Lubs and Ruddle, 1970; Ratcliffe *et al*, 1970; Turner and Wald, 1970). Of these, one-third are reciprocal translocations resulting from the mutual exchange of chromosome segments between two non-homologous chromosomes. Individuals bearing both products of the exchange ('balanced translocation carriers') are generally normal phenotypically because they have lost little or no genetic material. However, such translocation heterozygotes may transmit to their offspring only one of the two translocation chromosomes, and this results in a child with chromosomal deficiency or duplication. It is the consequent congenital anomalies that bring the family to the attention of a physician. We report here a family in which a balanced translocation, presumably reciprocal, was transmitted through three generations and was then unmasked in the fourth generation by the birth of a child with multiple congenital defects. The child had partial trisomy of the distal long arm of chromosome 4.

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Case Report

The propositus was admitted to Stanford University Hospital at 3 months of age because of multiple congenital defects and failure to thrive. He was the second child of unrelated parents, a 25-year-old mother and 26-year-old father. A 4-year-old brother was normal and there was no history of previous spontaneous abortions. Delivery allegedly occurred 1 month early; birth weight was 1986 g. Shortly after birth, the patient was noted to urinate only by dribbling. Intravenous pyelogram showed absence of renal function on the left and moderate hydronephrosis and hydroureter on the right side. Voiding cystourethrogram showed a small, thickened bladder with bilateral ureteral reflux. The obstruction was relieved by a suprapubic cystostomy. Follow-up pyelogram showed a normally functioning right kidney and a hydronephrotic left kidney. At 2 months of age, the patient had aspiration pneumonia. Weight was 2560 g, length was 48·7 cm, and head circumference was 32·6 cm. He had a good cry, although muscle tone was poor. The head was normal in shape and the anterior fontanelle was closed. The nose was prominent and the

right ear showed mild peaking of the antihelix. Mild micrognathia was present. The eyes, palate, and extremities were normal. Heart evaluation revealed no abnormalities. The right testis was undescended. The skin was mottled and hands showed bilateral simian creases with *Atd* angles in the t' position bilaterally. A urinary tract infection (*Proteus* sp.) was detected.

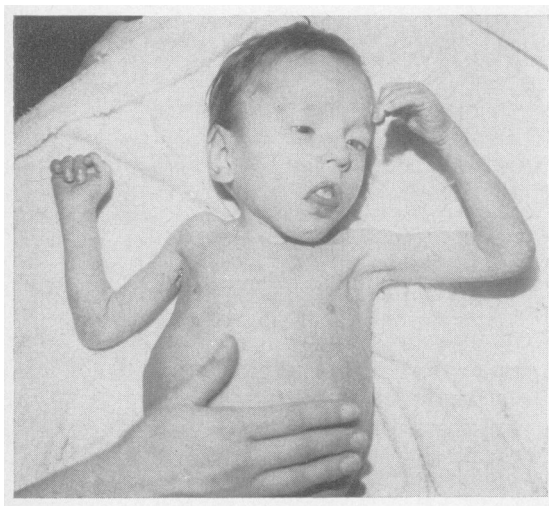

FIG. 1. Appearance of the propositus, IV.4, at 43 months of age.

The subsequent course was marked by recurrent urinary tract infections which necessitated a bilateral nephrostomy at 1 year of age. Growth continued to be markedly retarded: height 60·5 cm and weight 5 kg at 14 months of age, and height 63·5 cm and weight 4·84 kg at 27 months of age. At 30 months, he appeared severely malnourished, showed no interest in his surroundings, and was unable to turn over. Head circumference was 38·5 cm. The teeth were abnormally shaped and positioned. The nose beaked with a long narrow saddle, and the mouth had a downward slant at the corners. Serum creatinine was 0·8 mg/dl. His weight, height, and head circumference had not changed appreciably on his last visit at age 43 months (Fig. 1).

In summary, this child has severe mental and growth retardation with microcephaly, minor facial anomalies, and urinary tract outflow obstruction.

Cytogenetic Studies

Chromosome preparations were done on peripheral leucocytes from the propositus (IV.4) and from all potentially affected living relatives (Fig. 2) by using a modification of the technique of Moorhead *et al* (1960). For determination of the breakpoints, chromosome preparations from the propositus' aunt (III.1) were studied with trypsyn-

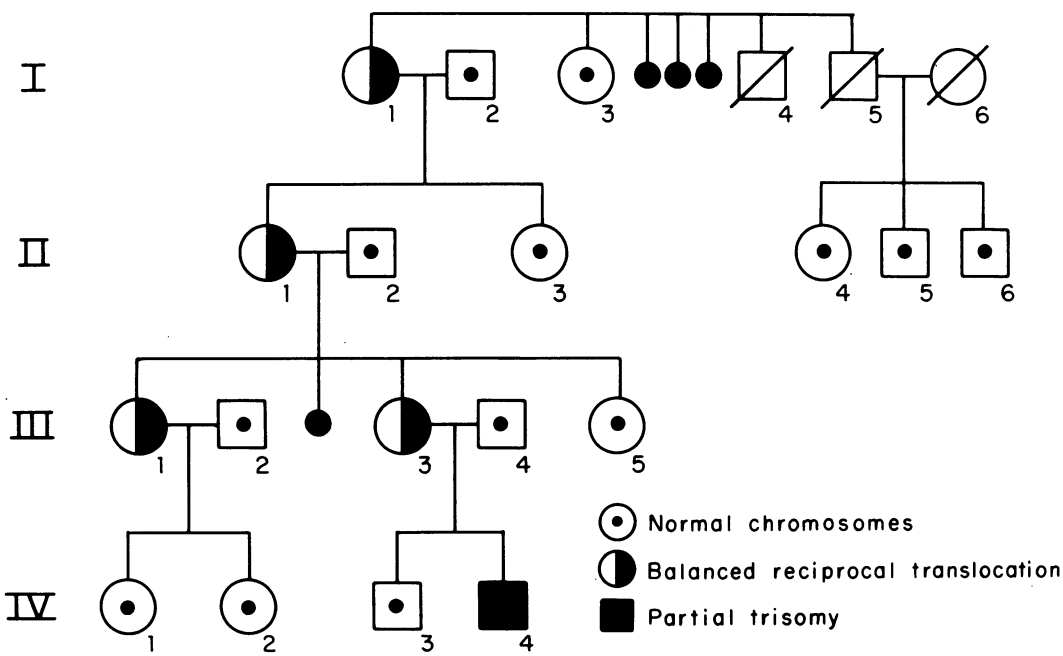

FIG. 2. Pedigree of family. I.1, II.1, III.1, and III.3 are carriers of a balanced translocation, t(4q−;13q+). IV.4 is the propositus who has a partial trisomy of the distal long arm of chromosome 4(46,XY, 13q+mat).

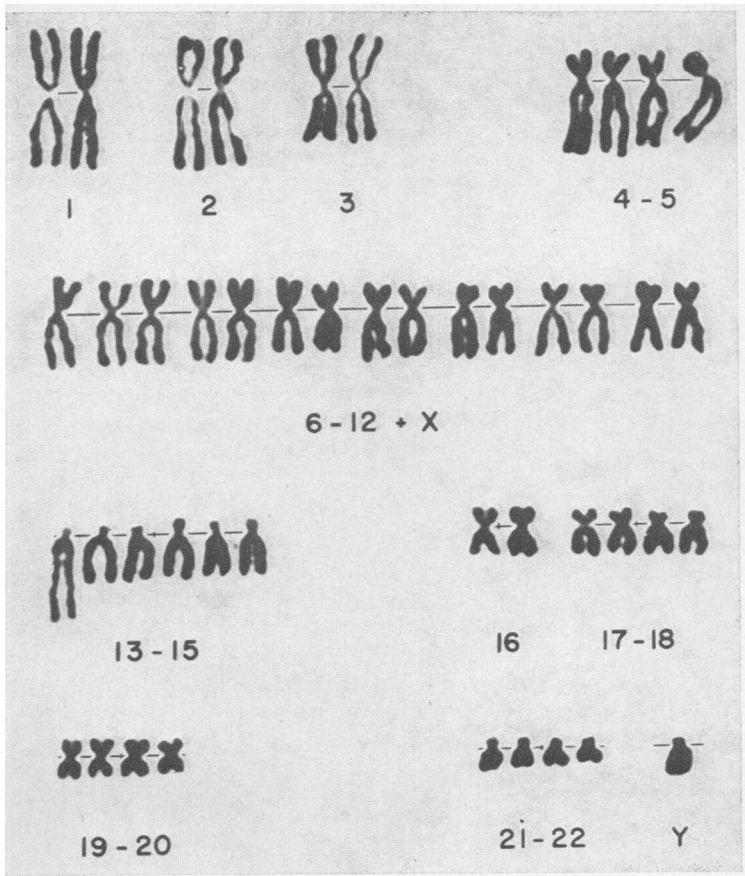

FIG. 3. Karyotype of the propositus, IV.4, showing an extra long group D chromosome.

Giemsa banding techniques (Francke, Hammond, and Schneider, 1973).

All karyotypes of the propositus showed the long arms of one group D chromosome to be almost doubled in length (Fig. 3). This enlarged group D chromosome was present in four relatives in three generations (see Fig. 2). The breakpoint on the long arm of chromosome 4 (Fig. 4) appears to have occurred in band 4q26 or 4q27 (Paris Conference, 1971). Since this presumably is a reciprocal translocation, another break must have occurred in the distal region of the long arms of chromosome 13. Most of the weakly-staining distal bands 13q32 to 13q24 seem to be retained in the rearranged chromosome 13q+. The presumed break in chromosome 13 therefore might have taken place in the terminal band, 13q34. The recommended designation of this translocation would be 46,XY,t(4;13) (q26 or 27, q34) in the short system and 46,XY, t(4;13) (4pter−4q26 or 27::13q34−13qter;13pter −13q34::4q26 or 27−4qter) in the detailed system.

Genetic Markers*

Erythrocyte Enzymes: acid phosphatase (AP), phosphoglucomutases (PGM_1, PGM_2, PGM_3), adenosine deaminase, 6-phosphogluconate dehydrogenase, adenylate kinase, peptidases (A, B, and C), aldolase, NADP-isocitrate dehydrogenase, lactate dehydrogenase, phosphohexose isomerase, hexokinase, phosphofructokinase, phosphoglycerate kinase, and glutamic-oxalacetic transaminase.

Blood Groups: ABO, Rh, MNS, Duffy, Kidd, Kell, Lutheran, P, and Xg^a. The informative markers in this family are ABO, Rh, Duffy, Kidd,

* The tests were performed by E. R. Giblett, MD (King County Central Blood Bank, Seattle) on each of the family members.

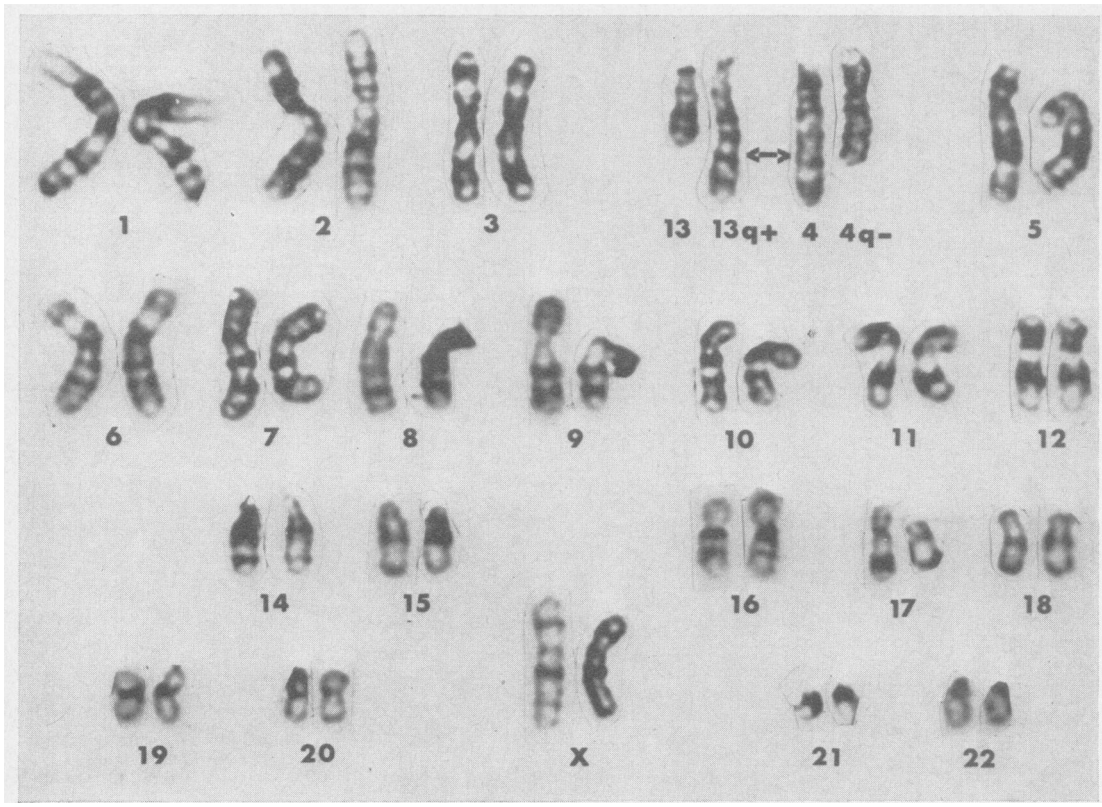

FIG. 4. Trypsin-Giemsa banded karyotype of the propositus' aunt, III.1. Arrows indicate the presumed locations of breakpoints.

TABLE I

LINKAGE DATA

	Age (yr)	ABO	Rhesus	Duffy	Kidd	P	MNS	AP	PGM-1
I.1	77	A_1	R_2r	a+b+	a+b+	+	MNSs	B	1
I.2	78	O	R_2R_2	a+b−	a−b+	−	NSs	A	1
I.3	75	A_2B	R_2r	a−b+	a+b+	+	Ns	B	2
II.1	52	A_1	R_2r	a+b+	a+b+	−	NSs	BA	1
II.2	59	A_2	rr	a+b−	a−b+	−	Ns	B	2–1
II.3	55	A_1	R_2R_2	a+b+	a+b+	+	MNS	BA	1
III.1	30	A_1	R_2r	a+b−	a−b+	−	NSs	BA	2–1
III.2	30	A_1	R_1r	a+b+	a+b+	+	MSs	BA	1
III.3	27	A_1	rr	a+b+	a−b+	−	NSs	BA	1
III.4	28	O	R_1r''	a+b+	a+b−	+	MSs	B	1
III.5	18	A_2	rr	a+b+	a+b−	−	NSs	B	2–1
IV.1	3	A_1	R_1r	a+b−	a+b+	−	MNs	B	2–1
IV.2	2	A_1	rr	a+b+	a−b+	+	MNSs	BA	2–1
IV.3	6	A_1	r″r	a+b+	a+b+	+	MNSs	B	1
IV.4	2	O	R_1r	a−	a+b−	−	MNS	BA	1

P, MNS, AP, and PGM_1 (Table 1). There was no suggestion of close linkage of any of these loci with the translocation chromosomes.

Discussion

Partial trisomy for the long arms of chromosome 4 has been reported previously in only two patients (Francke, 1972; Surana and Conen, 1972). In a third case it is not certain whether the partial trisomy involves the long arms of chromosome 4 or 5 (Shaw, Cohen, and Hildebrandt, 1965). This paucity of case reports may be ascribable at least in part to difficulties in identifying the chromosomal source in patients with this duplication. This can best be done by studying the carrier parent. Application of quinacrine fluorescence (Caspersson *et al*, 1970) or Giemsa (Schnedl, 1971) banding techniques may lead to unequivocal identification of the chromosomes involved in the translocation.

There are certain features common to the three cases described in the literature and the case presented here. Three of the four had renal abnormalities; two cases of hydroureter and hydronephrosis and one case with a single kidney, while in one case, the renal findings were not reported. All four had either ambiguous genitalia or undescended testes. Three of the four had low birth weight. Three of the four had muscular hypotonia. Two of the four had early closure of the fontanelles. All four had mental retardation. These findings are not distinctive enough to allow clinical diagnosis of this partial trisomy.

Whenever an inherited translocation is uncovered, it is essential to study asymptomatic relatives to determine if they are balanced translocation carriers. For example, the chance that a phenotypically normal sib of a propositus with an inherited translocation has a balanced reciprocal translocation may be as high as 50% (Jacobs *et al*, 1970). Once identified, such carriers should be offered amniocentesis during each pregnancy so that fetuses destined to have duplications or deficiencies can be aborted.

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