Partial monosomy and partial trisomy 18 in two offspring of carrier of pericentric inversion of chromosome 18

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Summary. A pericentric inversion of chromosome 18 is described in the mother of a patient with clinical diagnosis of 18q— syndrome. The propositus' chromosome complement includes the recombinant 18 with deficiency of the distal one-third of the long arm and duplication of the terminal segment of the short arm. The propositus' sister carries the recombinant 18 with a duplication of the distal one-third of the long arm and a deficiency of the terminal segment of the short arm. The relative length of the inverted segment represents about 60% of the total chromosome 18 length. The probability of recombinant formation following the occurrence of a chiasma within the inverted segment is predicted to be high.

In humans, familial pericentric inversions of autosomes have been found both in patients with multiple congenital anomalies caused by chromosome deficiency and duplication (Wilson *et al*, 1970; Parrington and Edwards, 1971; Faed *et al*, 1972; Hauksdóttir *et al*, 1972; Morić Petrović, Laća, and Kalicanin, 1972; Surana and Conen, 1972; Warter, Ruch, and Lehmann, 1973) and through propositi whose phenotype did not bear a causal relation with the inversion (Jacobs *et al*, 1968; Weitkamp *et al*, 1969; Crandall and Sparkes, 1970; Wahrman *et al*, 1972; Soudek *et al*, 1974). The study of the banding patterns of the inverted chromosomes and their recombinants allows for the precise identification of the length of the inverted segment. Consequently a better evaluation of the relation between the length of the inverted segment and the meiotic behaviour of the abnormal chromosome can be achieved.

We describe here a carrier of a pericentric inversion of chromosome 18 and her two offspring, both carriers of chromosome 18 recombinants.

Case report

Propositus (Fig. 1). The second child was born to nonconsanguineous healthy parents, a 21-year-old mother and a 26-year-old father, in September 1971. The only sib was a mentally retarded girl with the multiple congenital anomalies which are described below. The mother had not had any spontaneous abortions. One of the mother's sisters was mentally retarded. The propositus was born after an uneventful pregnancy and delivery. Birthweight was 2840 g but the body length was not recorded. Evaluation at 18 months showed a hypotonic child with severe developmental retardation and multiple congenital anomalies. His length was 73 cm and head circumference was 41.2 cm (both much below the third centile). Other features included: brachycephaly, sparse, thin, and short hair, and evidence of previous midline scalp defect, which was ascertained because of a 1 cm scar in the vertex. There was pronounced hypoplasia of the mid-portion of the face, better noticed in profile. Consequently, the nasal bridge was flat, the forehead relatively prominent, and there was a forward projection of the inferior portion of the face. The supraorbital ridges were noticeably flat, and there were epicanthal folds in the inner canthi. Long and numerous eyelashes were observed. Hypertelorism was apparent. The philtrum was somewhat

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FIG. 1. Propositus at 18 months of age.

FIG. 2. The sister of the propositus at 3 years and 6 months.

elongated and its groove poorly defined. The mouth was carp-shaped with downward displacement of the lateral portions. The eight deciduous incisors were present in the mouth. The mandible could easily be displaced either actively or passively forward, leading to a transitory prognathism. The ears had a small tragus and an overfold of the upper helix. The only abnormal finding in the thorax was an increased distance between the nipples. There was a narrow pelvis, with limited hip abduction. The genitalia had a hypoplastic appearance: the scrotum was flat and smooth, testes were undescended, and the penis was very small and hidden in the suprapubic adipose tissue. A simian crease was present in both hands; all fingers except the first and second had a slight degree of camptodactyly. Swelling was noted in the dorsum of both feet. The bone age was

6 months (Greulich-Pyle) and an electroencephalogram showed asynchronous activity.

Sister of propositus (Fig. 2). The elder sister was born in February 1970. Normal delivery followed an uneventful pregnancy. The birthweight was 2150 g. Examination at 3 years and 6 months showed a mentally retarded girl. Multiple haemangiomas were present on the nape at the neck, above the left elbow, on the lumbar region, and on the left thigh, just above the knee. Her height was 89 cm (below the third centile) and her head circumference was 48.3 cm (about the 50th centile). She had a protruding sagittal suture, flat supraorbital ridges, and an asymmetrical face. Ptosis and small palpebral fissures were noted. The ears had somewhat simplified helix and antihelix. Slight micrognathia was

TABLE
DERMATOGLYPHIC PATTERNS

	I	II	III	IV	V	TRC	a-b ridge count	ad angle	Palmar formula	Hallucal Areas
Propositus										
Right	W	U	W	W	W	138	58	34.5°	9(10).9.7(6).5'-t-Ar.O.O.L.O	L ^d
Left	U	U	W	W	W			44°	9.X.5"11-t-Lr.Lc/V.O.O.O	W
Sister										
Right	A	A	A	A	A	0	65	47.5°	11.9.7.5"-r'-O.O.O.L.O	L ^d
Left	A	A	A	A	A			56°	10.0.6.5'-r'-O.V/O.O.O.O	L ^d

present. The anterior thoracic diameter was increased, with no identifiable cardiopathy or pneumopathy. The sternum was short. Hypoplastic labia majora were observed. Camptodactyly of the fifth digit was present on both hands. The feet were flat, with slightly prominent heels. On the right foot there was a severe hypoplasia of the third toe and in its place only a vestigial rudiment was noticed. There was also an abnormal diastasis between the first and second toes. On the left foot there was complete soft tissue syndactyly between the third and fourth toes, without nail fusion.

Dermatoglyphs. Dermatoglyphs are summarized in the Table. The high frequency of whorls (7/10) on the digital areas in the propositus, and the presence of simple arches on all digits of his sister constitute the remarkable features.

Cytogenetic findings

After routine chromosome analysis on peripheral blood leucocytes the procedure of Caspersson, Lomakka, and Zech (1971) was employed to obtain Q-band patterns.

The propositus had 46 chromosomes including a number 18, with a deleted long arm; only the proximal bright band typical of the long arm of number 18 was seen (Fig. 3 B and 4 B). In his mother's karyotype, a number 18 was replaced by an almost metacentric chromosome. This chromosome was the size of a normal 18; one arm showed the bright proximal band and the other, the bright distal band of the long arm of number 18 (Fig. 3 A and 4 A). The sister of the propositus had 46 chromosomes including a submetacentric longer than a number 16; the fluorescence patterns of its long arm were similar to those on the long arm of a normal 18; on its short arm, a bright fluorescent band corresponding to the bright distal band of the long arm of number 18 was seen (Fig. 3 C and 4 C).

FIG. 3. Chromosome pair number 18 of (A) the propositus' mother (B) the propositus, and (C) his sister.

FIG. 4. Q-bands of chromosome pair number 18 of (A) the propositus' mother, (B) the propositus, and (C) his sister.

The metacentric chromosome seen in the mother of the propositus was thought to result from a pericentric inversion of chromosome 18. This inversion probably took place in one of her parents during gamete formation. The breakpoints were probably located on band 1 of region 1 of the short arm and on band 1 of region 2 of the long arm (Fig. 5). Her chromosome constitution may be written: 46,XX,inv(18)(p11q21), or 46,XX,inv(18)(pter→p11::q21→p11::q21→qter). The inverted segment represents about 60% of the total length of chromosome 18.

The abnormal chromosomes found in the propositus and his sister may be interpreted as recombinants which resulted from a chiasma occurring within the inverted segment (Fig. 5). The propositus received a number 18 with a deletion of the distal one-third of the long arm and a duplication of the terminal segment of the short arm. The propositus' sister received a number 18 with a duplication of one-third of the long arm and deletion of the terminal segment of the short arm. Thus the propositus is monosomic for the distal one-third of the long arm and trisomic for the terminal segment of the short arm: 46,XY,-18,+rec(18)dup p,inv(18),(pter→q21::p11→pter) mat. His sister is trisomic for the distal one-third of the long arm and monosomic for the terminal segment of the short arm of chromosome 18: 46,XX,-18,+rec(18)dup p,inv(18),(qter→q21::p11→qter) mat. The phenotypic features of the propositus are consistent with the diagnosis of 18q- syndrome. His sister presents clinical signs compatible with a partial 18 trisomy.

FIG. 5. Diagram showing the recombinant formation following a chiasma within the inverted segment of the maternal chromosome 18.

The propositus' father, maternal grandparents, and two maternal aunts, one of whom was mentally retarded, showed normal karyotypes.

Discussion

The length of the inverted segment is a factor to be considered when evaluating the meiotic behaviour of inverted chromosomes. This has been recognized since the first studies on the meiotic pairing in heterozygotes for inversions were performed (McClintock, 1931; 1933). Sjödin (1971), studying induced inversions in *Vicia faba*, pointed out the importance of considering the *relative length* of the inverted segment.

In humans, chromosomally deficient and dupli-

cated individuals born to normal parents one of whom is heterozygous for a pericentric inversion of an autosome have been described (Wilson *et al*, 1970; Parrington and Edwards, 1971; Faed *et al*, 1972; Hauksdóttir *et al*, 1972; Morić-Petrović *et al*, 1972; Surana and Conen, 1972; Warter *et al*, 1973; Jacobs, Melville, and Ratcliffe, 1974). Reduced fertility and an increase in neonatal death in the offspring of heterozygous inversion carriers have been reported in some of these families (Parrington and Edwards, 1971; Faed *et al*, 1972; Hauksdóttir *et al*, 1972). In only one instance have both possible recombinants from an inverted chromosome been described in the same sibship (Warter *et al*, 1973): an inverted number 5 chromosome was

present in the normal carrier father of two girls affected by the 'cri-du-chat' syndrome and its counterpart, respectively. An inversion of chromosome 18 with breakpoints sited in the same regions as in the one here reported was described by Jacobs *et al* (1974): the patient inherited from her mother both the original inverted chromosome and the recombinant, being trisomic for much of chromosome 18 and tetrasomic for a part of its short arm. The banding patterns and/or the morphology of the inverted and recombinant chromosomes allowed in each of the above cases the estimation of the inverted segment which ranged from 50% to 80% of the total chromosome length.

Inversions have also been reported in propositi whose phenotypic features were not causally related to the presence of the inversion and in their normal relatives. An increase of fetal losses or neonatal deaths was not observed in these families (Jacobs *et al*, 1968; Weitkamp *et al*, 1969; Crandall and Sparkes, 1970; Wahrman *et al*, 1972; Soudek *et al*, 1974). In each such case the probable position of the breakpoints assigns to the inverted segment a probable length of not more than 50% of the total chromosome length. Thus, at meiotic synapsis, the relatively short inverted segment probably would lead to nonhomologous pairing or asynapsis, preventing crossing over from occurring. These inversions could, therefore, be maintained in a polymorphic state in the population. This, at least, seems to be the case with those inversions involving the pericentromeric segment of chromosomes number 3 (Soudek *et al*, 1974), and number 9 (Jacobs *et al*, 1974).

In the present report, the mother of the propositus carried an inversion of a relatively long segment (about 60% of the total chromosome length). The probability of recombinant formation following the occurrence of a chiasma within the inverted segment appears high. The carrier of the inversion is, therefore, at high risk for unbalanced progeny.

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