Segregating Reciprocal (4;21) (q21;q21) Translocation with Proposita Trisomic for Parts of 4q and 21

Summary. The segregation of a balanced reciprocal (4;21)(q21;q21) translocation is described. The family was ascertained through a clinically abnormal proposita with an unbalanced karyotype 47,XX,+der(21)t(4;21)(q21;q21)mat. The proposita was trisomic for regions 4q2, 4q3, 21p, and 21q1. Symptoms that might be attributed to the partial trisomy for parts of 4q were narrow bird face with slanting forehead, prominent nasal bridge and small mandible, downward pointing corners of the mouth, deformed ears, palpebral ptosis, and bushy eyebrows. Similar symptoms occur in other trisomy and deletion syndromes.

Several different procedures can be used to produce banding patterns in mammalian chromosomes (Paris Conference, 1971). The application of these methods often permits the precise identification and description of chromosomal rearrangements such as translocations. It thus becomes feasible, for example, to determine which segments occur in triplicate in unbalanced translocation heterozygotes. The object of the present report is to describe the segregation of a balanced human reciprocal translocation in a family. Clinical signs in the unbalanced proposita may be attributed to trisomy for parts of 4q and 21.

Case Report

The proposita was the parents' only child. She was born at term in August 1970 after an uncomplicated pregnancy and delivery. She weighed 2810 g and was 48 cm long. Her head circumference was 31 cm at birth. One day after birth she was admitted to a paediatric ward because of respiratory difficulties.

Physical examination revealed her to be a malformed microcephalic infant (Fig. 1). She had a bird face with slanting forehead, prominent nasal bridge, narrow and high palate, and micrognathia. Her face was narrow with narrow palpebral fissures. She had slight epicanthal folds and deformed ears. Her fingers and toes were short and square. The thumbs were small and widely separated from the second fingers, as were the first and second toes. She had transverse plantar creases. Her muscles were hypotonic. There was a large umbilical hernia, pectus excavatum, and slight pes equinovarus in both feet. The external genitalia were normal and no abnormalities were detected in the genito-urinary or cardiovascular systems.

She was examined at regular intervals and showed retarded somatic and psychomotor development. She rolled over at 8 months, crawled at 13 months, and sat at 16 months, but at 28 months she still could not stand or walk without support. At 28 months she weighed 7340 g.
and was 82 cm long (Fig. 2). She prattled and understood small requests but could not say any words. She was microcephalic with a head circumference of 43.5 cm. The skull was short. Bushy eyebrows crossed the nasal bridge in the midline. She had bilateral palpebral ptosis and the corners of the mouth pointed downward. She had marked generalized hypotonia and oedema in the hands and feet. The laxity of the ligaments was increased.

Laboratory tests, including a complete blood count, urinalysis, cerebrospinal fluid examination, serum electrolytes, acid base balance, and serum alkaline phosphatase tests were normal. Urine amino-acid chromatography and serum electrophoresis were also normal. The electroencephalogram was normal before the age of 1 year but later the basic activity was slower than normal.

**Family History**

The father was 22 and the mother 19 years old at the patient's birth. Both were healthy and phenotypically normal. The mother became pregnant one year after the birth of the proposita. She applied for therapeutic abortion and refused to have an amniocentesis. An abortion was performed but the fetal material was not available for cytogenetic investigation. The pedigree is shown in Fig. 3.
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**Fig. 3.** Pedigree of the family.

### Cytogenetical Findings

The karyotypes were studied from phytohaemagglutinin-stimulated mitoses from cultures of peripheral blood using standard methods. Quinacrine mustard (QM) fluorescence (Caspersson et al., 1970) and Giemsa staining after trypsin treatment (Seabright, 1971) were used to identify the rearrangements.

The proposita (IV.1) had 47 chromosomes. In conventionally stained cells the extra chromosome appeared to belong to group D. In the phenotypically normal mother (II.1) a balanced B-G translocation appeared likely since one B-group chromosome and one G-group chromosome were missing and had been replaced by a C- and D-group chromosome, respectively. This assumption was confirmed by the banding patterns that emerged after QM fluorescence staining and Giemsa staining following trypsin treatment.

A break had occurred in or near the negative or pale staining band 4q21, and the entire portion of 4q distal to this break had become attached to 21q. The break in chromosome 21 was within band q21, and the entire portion distal to the break was attached to the broken end of 4q. The break had probably occurred within band 21q21, because each translocation chromosome contained part of this darkly staining G-band (Figs. 4–5). The mother’s karyotype could hence be written 46,XX,t(4;21)(q21;q21).

The child had inherited the translocation chromosome carrying the centromere of chromosome 21 from her mother. Hence, the child’s karyotype could be written: 47,XX,+der(21),t(4;21) (q21;q21)mat. This implies that she was trisomic for the following chromosome segments: 21p, 21q1, part of 21q21, and all 4q regions distal to q21. Further evidence that the centromere of the translocation chromosome was derived from chromosome 21 was supplied by the frequent satellite associations of this chromosome with other acrocentric chromosomes, such as No. 13 (Fig. 6).

Family studies showed the proposita’s maternal grandfather (II.1) and three of the sibs of the proposita’s mother (III.3, III.6, and III.7) to be balanced translocation carriers. It was not possible to ascertain whether II.1 had inherited the translocation, because his father (I.1) was dead and his mother (I.2) had a normal karyotype. It is possible that this translocation had arisen de novo at gametogenesis in I.1 or I.2, since none of the five sibs of II.1 had the translocation. This view is strengthened by the fact that the balanced translocation present in II.1 had been passed on to four of his children.
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FIG. 4. Quinacrine mustard stained karyotype from the mother (III.2). There is a balanced reciprocal translocation 46,XX,t(4;21) (q21;q21). The translocation chromosomes are arrowed.

FIG. 5. Chromosomes from a trypsin-Giemsa treated cell of the mother (III.2). Upper line: (a) normal chromosome 21; (b) translocation chromosome der(4),t(4;21)(q21;q21); (c) normal chromosome 4; (d) translocation chromosome der(21),t(4;21)(q21;q21). Lower line: normal homologues 5, 13, 14, 15, and 22.
Discussion

Since the proposita was trisomic for the entire short arm and part of the long arm of chromosome 21, features of Down's syndrome might have been expected. Apart from psychomotor retardation, features compatible with 21 trisomy were muscular hypotonia, laxity of ligaments, umbilical hernia, and hands and feet characteristic of 21 trisomy.

On the other hand, more than half of 21q (the greatest part of region 21q2) were not present in triplicate. It is therefore not surprising that the proposita did not show more clear-cut features resembling those seen in Down's syndrome. Since she was, in addition, trisomic for regions 4q2 and 4q3 (the main part of the long arm of chromosome 4), many of her symptoms could be attributed to this partial trisomy. Owing to the absence of definite evidence of trisomy for 4q in the literature, it is not known what phenotypic effects should be expected. We propose that some of the more obvious non-Down's syndrome features of our proposita, such as the bird face (with slanting forehead, prominent nasal bridge and small mandible), deformed ears, bilateral palpebral ptosis, narrow face, and bushy eyebrows could be due to trisomy for 4q2 and 4q3. Shaw, Cohen, and Hildebrandt (1965) described a patient with possible partial trisomy B, but precise identification of the cytogenetical abnormality was not possible. Some of the features of their patient resembled those of our patient. The phenotypic effects of trisomy for parts of 4q can probably be definitely determined only after several informative patients have been studied. It should be noted that some of the symptoms enumerated above occur in other trisomy and deletion syndromes as well.

A point worth discussing is the fact that the first and so far only child (IV.1) of the mother (III.2) had an unbalanced karyotype while no unbalanced karyotypes were known to have occurred in generation III. It is especially noteworthy that the proposita's maternal grandfather (II.1) had fathered six children of whom four were balanced carriers and two were cytogenetically normal. His wife (II.2) had not had
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any recognized abortions. From the point of view of genetic counselling, it is desirable that the proportion of conceptions which will have unbalanced karyotypes be established. Before the birth of the proposita it would have been reasonable to suppose, from the evidence in generation III, that unbalanced karyotypes were likely to occur with low incidence or not at all. It should be remembered that Jacobs (1972) has shown that the incidence of unbalanced karyotypes is low or nil in families in which the reciprocal translocation has not been ascertained through an abnormal individual. The present family, ascertained through the chromosomally abnormal proposita, provides an example of a translocation in which unbalanced zygotes are produced, but the incidence cannot be calculated. Therefore, prenatal chromosome diagnostics through amniocentesis should probably be advocated in future pregnancies of the translocation carriers or their spouses.

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REFERENCES


Cryptophthalmos in Two Families from Bahia, Brazil

Summary. Two families with cryptophthalmos are reported. Both families came from the same town in Bahia State, Brazil. Consanguinity was known between the parents themselves, but not between the individual families reported here. However, a common ancestor for both families is very likely because the four parents were born in the same 'municipio'. There was one affected girl in family 1 and four affected sibs in family 2. A pair of affected monozygotic twins and a case of possible low expressivity of the syndrome are described in family 2.

Congenital fusion of eyelids was described by Zehender and Manz (1872) as an isolated anomaly.

In 1969, François made an extensive review of the subject showing that cryptophthalmos is not a localized malformation but a syndrome characterized by cryptophthalmos, anomalies of the head, ears, nose, syndactyly, and genital abnormalities. Up to 1969 there were 43 cases reported in the world literature (Ide and Wollschläger, 1969). No chromosomal anomalies have been demonstrated, but parental consanguinity has been observed in 15% of the cases and it has therefore been suggested that autosomal recessive inheritance is likely (François, 1969). In the present paper we report two affected families from Bahia State in Brazil.

Fig. 1. Pedigree of family 1.

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