A family with an inherited translocation involving the No. 4/No. 21 chromosomes

This report describes the clinical and cytogenetic findings of an English family (Fig. 1) with an unusual chromosomal translocation. The proband (III.3) had an unbalanced translocation 4;21(p11;p12) and had multiple congenital abnormalities. His brother (III.2) had similar features and is presumed to have had the same chromosomal abnormalities. Both his mother (II.2) and sister (III.1) have a balanced translocation involving the same chromosomes. His maternal grandmother (I.6), although having a normal karyotype, shows an increased number of spontaneous chromosome breaks.

Case reports

Case III.3. The proband (Fig. 2) was admitted for repair of a paraoesophageal hernia.

The pregnancy had been uneventful except for poor maternal weight gain. He was delivered by elective Caesarean section in November 1971 at 38 weeks' gestation and weighed 2 440 g.

He had abnormal facies with low-set ears, short neck

FIG. 1. Pedigree of the family.

with low hairline, deep-set small eyes, and a retroussé nose. Head circumference was 34 cm and the skull scaphocephalic. His hands had single palmar creases, flexed metacarpophalangeal joints, extended interphalangeal joints, a trigger thumb, and an ulnar deviation. There was marked limitation of abduction of both hips and the right hip was dislocated. The left knee could not be fully extended and there was bilateral talipes equinovarus. He had small male genitalia with a glandular hypospadias and the testes were high in the inguinal canal. A large paraoesophageal hernia was demonstrated radiologically.

Initially tube feeding was necessary and weight gain was slow. There was some subsequent improvement, but considerable feeding difficulties recurred from about 7 months and frequent severe vomiting often followed bouts of crying.

On admission at 11 months he weighed 5 500 g and was mentally and physically retarded. He had microcephaly (head circumference 41 cm), marked kyphoscoliosis, and small eyes with a persistent nystagmus and a variable convergent squint. No renal or cardiac

FIG. 2. The proband aged 11 months.

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abnormalities were detected. His cry was a distinctive, rather high-pitched whine.

At laparotomy a large paraesophageal hernia containing the fundus and most of the stomach was found. This was reduced and the sac excised. Other structures appeared normal except the aorta which was hypoplastic.

Post-operatively, the symptoms of crying and vomiting ceased and he gained a little weight, but his physical and mental progress remained very slow. He died at home at the age of 15 months; there was no post-mortem examination.

Case III.2 was born in March 1970. He was delivered by Caesarean section for fetal distress at 42 weeks' gestation. Birth weight was 2380 g; he required resuscitation and had mild respiratory distress.

He had facial characteristics and skull shape identical to those of his brother, the propositus. His hands

showed similar joint deformities and he had an accessory digit of the right hand. The hips had limited abduction with a dislocation on the right and there was a right talipes equino-varus deformity. There was also a large paraesophageal hernia. The respiratory distress increased and he died at 13 days.

Necropsy showed some areas of haemorrhage in the basal ganglia of the brain, paraesophageal sliding hernia and areas of infarction of the liver and lungs. The other organs were essentially normal.

Case III.1 was born in 1968 after a normal pregnancy; she is a healthy, normal child of good intelligence.

Case II.2. The mother was aged 28 years at the propositus' birth. She is phenotypically normal, of good health, and has no history of abortions or of illness during her pregnancies.

FIG. 3. Trypsin-banded karyotype from the propositus; 46,XY,der(21),t(4;21)(p11;p12).

FIG. 4. Trypsin-banded karyotype from the mother (II.2);46,XX,t(4;21)(p11;p12).

Cytogenetic studies

Chromosome preparations were made from two separate cultures of peripheral blood lymphocytes (Moorhead *et al.*, 1960) and from skin fibroblasts (Harnden, 1960) of the *propositus*. In both tissues the modal chromosome number was 46 and all cells analysed showed that a member of the G group had been replaced by a metacentric chromosome similar in size and morphology to a No. 16. Trypsin banding (Seabright, 1971) showed that this chromosome was the product of a translocation of most of the short arm of a No. 4 chromosome (the break having occurred close to the centromere) to the short arm of a No. 21 (Fig. 3), and there was therefore a trisomy for the short arm of No. 4. Chromosome studies from both II.2 and III.1 showed the presence of a balanced translocation, 46,XX,t(4;21)(p11;p12) (Fig. 4).

Cells from skin and two blood cultures, taken on separate occasions, from the maternal grandmother (I.6) had a normal chromosome complement but

15% of the cells showed spontaneous breaks and exchanges, including abnormalities and errors of centromeric behaviour in one or more chromosomes of the C group. Acentric fragments, rings, dicentrics, and chromatid breaks were observed. She had no history of drugs, radium therapy, or viral infection. A full report of these findings is to be published shortly.

The chromosomes of eight other relatives were examined and found to be normal (see Fig. 1).

Unfortunately the chromosome complement of III.2 was not established, but as his clinical features were very similar to those of his brother III.3 it is reasonable to assume that he also carried the unbalanced form of the translocation.

Discussion

Until recently, identification of chromosomes was performed by methods dependent on either measurements of length, position of the centromere, autoradiography or, in the case of B-group abnormalities,

by using their different replication patterns. The banding techniques, have now made possible not only the identification of each chromosome, but also the accurate detection of the sites of breaks and exchanges along the chromosome arms.

Gustavson *et al* (1964) described a child with multiple congenital abnormalities whose karyotype showed an unbalanced translocation between a B-group chromosome, tentatively identified as No. 5, and a chromosome of the G group. The mother and the grandfather carried the balanced form of the translocation. De la Chapelle *et al* (1973) have described a balanced 4;21 translocation in a family and an unbalanced form in the clinically affected proposita. The break-points of this translocation, when determined by banding techniques, occurred in the long arm of No. 4 (q4) and in the long arm of No. 21 (q21) chromosome. The proposita had inherited from her mother the chromosome carrying the centromere of 21, therefore she was trisomic for the short arm and part of the long arm of chromosome 21 and, in addition, she was trisomic for the main part of the long arm of No. 4.

Other reports have shown that subjects with balanced translocation involving the B group may also result either in children with a balanced translocation but phenotypically normal (White *et al*, 1971) or offspring with a partial deletion associated with the cri-du-chat syndrome (de Grouchy and Gabilan, 1965). In some families more than one gamete type may be represented (de Capoa *et al*, 1967). In the present family, the mother and the daughter showed the balanced translocation, whereas the two sons were clinically affected and both probably had the unbalanced translocation.

Though the exact mechanism of the production of translocation is not completely understood, it is likely that with different distribution of number and

position of crossover, each individual translocation is unique (Ford and Clegg, 1969).

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