A Family Showing Transmission of a Translocation Between a 6-12 Chromosome and a 21-22 Chromosome

J. E. GRAY, J. A. DARTNALL, and B. G. P. MACNAMARA

From the Department of Anatomy, Medical School, University of Newcastle upon Tyne, and the Department of Paediatrics, Newcastle upon Tyne Regional Hospital Board

A family transmitting a reciprocal chromosome translocation through three generations is reported. The chromosomes involved are one from group 6-12, the other from group 21-22. The family tree is given in Fig. 1. The propositus, III.12, was admitted to the Fleming Memorial Hospital, Newcastle upon Tyne, when 2½ hours old, because of multiple congenital anomalies. His mother was 26 years, his father 36; there were two living sibs, a girl aged 5 (III.10) and a boy aged 3 (III.11). All were well. The mother had tuberculous pleural effusion two years previously but was fully recovered before the pregnancy started. The father had a severe kyphoscoliosis and had received many x-ray examinations in childhood.

Case Report

Clinical Description. The affected child was born after a 38-week pregnancy. His birth weight was 4 lb.

5 oz. (1660 g.). He was a small baby of good colour with bilateral low-set 'bat ears', bilateral cleft-lip and palate, moderate hypertelorism, and bilateral talipes equinovarus (Fig. 2). The fingers were flexed and bunched with crossing of index over middle finger (Fig. 3). A cyanotic episode at 3 days responded to oxygen. Two days later he developed left basal pneumonia. He fed well but did not gain weight. At 8 days he developed a systolic murmur at the left sternal edge. It later became continuous, and patent ductus arteriosus was diagnosed. The blood pressure was 80/40 mm. Hg. At 2 weeks he developed projectile vomiting and a pyloric tumour was palpated. Rastaldi's operation was performed, and he made a good recovery. Subsequently he fed well from a spoon but failed to gain weight. Episodes of respiratory infection and of mild gastro-enteritis occurred. He died at 3 months of age when his height was only 20 in. (51 cm) and his weight was 4 lb. 6 oz. (1690 g.). Necropsy (Dr. T. Bird) disclosed no further anomalies and confirmed the persistent ductus arteriosus which was not widely patent and had produced only slight ventricular hypertrophy. The pylorus and stomach were the

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FIG. 1. Pedigree of the family.

FIG. 2. The proband at 1 month.

normal in appearance. The infant had spent all but a few days of his life in hospital.

Chromosome Analyses. Chromosome analysis was performed on a culture of peripheral blood lympho-

FIG. 3. Left hand of proband.

cytes using standard techniques (Moorhead, Nowell, Mellman, Battips, and Hungerford, 1960). There were 46 chromosomes, and the Y chromosome could be identified. There were apparently 16 in group 6-12 including X, and 3 in group 21-22 and a Y chromosome (Fig. 4). The buccal smear was chromatin negative.

Other members of the family were examined with the

FIG. 4. Karyotype of proband. The Y, 21st, and 22nd chromosomes have been placed in the same group.

FIG. 5. Karyotype of mother, II.7.

following results: the grandfather I.1, the father II.7, and the female sib III.10 were normal. Anomaly was present in the others, the grandmother I.2, the maternal aunt II.2, the mother II.6, and the male sib III.11. The anomalous karyotypes presented an apparent extra chromosome in group 13-15, and one missing from group 21-22 (Fig. 5).

Discussion

Interpretation of Abnormal Karyotypes.

The most economical explanation is to assume that a translocation between a 6-12 and 21-22 group chromosome occurred in an ancestor of the family. We suggest that the breaks leading to the translocation were near the centromere in both chromosomes. Our interpretation implies that the extra 13-15 chromosome is actually the short arms of a 6-12 joined to the short arms and satellites of a 21-22. We reached this conclusion because in many cells in the phenotypically normal carriers there was a rather short 13-15 chromosome bearing satellites. The interpretation implies also that the group 6-12 in carriers actually contained an abnormal chromosome formed by the long arms of a 6-12 and the long arms of a 21-22. The carrier relatives must carry both abnormal chromosomes. The propositus has

only one abnormal namely the novel 6-12. He has 15 normal chromosomes in group 6-12 in addition to the abnormal, and is therefore trisomic for the long arms of a 6-12.

Prognosis for Further Children. The prognosis for further children is suggested by the family history and may be estimated from the results of meiotic studies in other forms where translocation is present. The grandmother lost her first-born a few days after birth (II.1). This infant was underweight at birth, and prematurity was diagnosed. II.2 also lost her first-born, a boy who died at 5 days of age. Talipes and cleft-palate were not present. He weighed under 2000 g., though born at full-term, and died after repeated cyanotic attacks. II.3 has not been examined: he also lost a child (III.6) at 5 days of age: this infant had talipes and spina bifida. It is possible that all these children were affected by an unbalanced form of the translocation. The implication from the family history is that there is a serious risk of further children being affected (perhaps 1 in 4 is a fair estimate). It is evident, also, that carriers of the translocation are likely to occur.

The events of meiosis lead to the production of pairs of gametes, depending on the position and frequency of chiasmata that have been formed in the translocation cross produced by the translocated chromosomes and their normal homologues during 'pairing' of the chromosomes (Burnham, 1956; Lewis and John, 1963; John and Hewitt, 1963). We have not studied meiotic chromosomes in this family and can only guess at the arrangement of the chromosomes. It is probable that normal and balanced gametes would be produced in equal numbers and that the sum of these would be approximately equal to the sum of a pair of unbalanced gametes. We suggest that half the unbalanced gametes would be trisomic for a 6-12 and the other half partially monosomic for this 6-12. If we assume that the partially monosomic chromosome would lead to early embryonic death, the

proportions of normal, balanced translocation carriers and abnormal would occur in approximately equal numbers. A prognosis to this effect has been given to the carrier parents who have accepted it well.

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