Two balanced translocations in three generations of a pedigree: t(7;10) (q11;q22) and t(14;21) (14qter→cen→21qter)¹

HAROLD N. BASS AND ROBERT S. SPARKES

From the Department of Pediatrics (Genetics), Kaiser-Permanente Medical Center, Panorama City, California; and Division of Medical Genetics, Departments of Medicine, Pediatrics, and Psychiatry, UCLA Center for the Health Sciences, Los Angeles, California, USA

SUMMARY A reciprocal chromosome translocation between 7q and 10q and an unrelated Robertsonian translocation involving 14q and 21q were found in a healthy 44-year-old man, in his normal 18-year-old son, and in his mother. They were ascertained through the man's brother, whose grandson has Down's syndrome as a result of an inherited 14q21q translocation. To our knowledge, this is the second report of a karyotype with both reciprocal and Robertsonian translocations in a single subject, and only the fourth report of independently segregating double translocations occurring in more than one generation.

While evaluating relatives of a child with Down's syndrome resulting from an inherited D/G translocation, we discovered three subjects in three generations who have independently segregating double translocations. One is a reciprocal rearrangement between chromosomes 7 and 10, and the other is a Robertsonian translocation between chromosomes 14 and 21.

Case report and cytogenetic studies

The consultand (II.1) was a 44-year-old Caucasian man who sought genetic counselling because one of

his two brothers (II.4) had recently been identified as the carrier of a Robertsonian translocation between 14q and 21q (Fig. 1).

The brother's grandson (IV.3) was a 3-year-old boy with Down's syndrome whose karyotype was prepared at the University of California in San Francisco. When it was discovered that he was 46,XY,t(14;21) (14qter→cen→21qter), +21, chromosome studies were performed on his mother (III.5). The mother carried the same translocation in a balanced form: 45,XX,-14,-21,+t(14;21) (14qter→cen→21qter). She shared this translocation with her father (II.4) and one of her two sisters (III.4). The consultand and his other brother (II.3) also underwent karyotyping. The latter's karyotype was 46,XY. Trypsin-Giemsa banding analysis of the consultand's peripheral blood lymphocytes and skin

Fig. 1 Pedigree of family with independently segregating reciprocal and Robertsonian translocations in 3 generations.

fibroblasts showed two unrelated translocations. One of the translocations involved a portion of the long arm of a number 7 and number 10 chromosome in a reciprocal rearrangement; in the other translocation, the long arm of a number 14 chromosome was fused with the long arm of a number 21 in Robertsonian fashion: 45,XY,-14,-21,t(7;10)(q11;q22),+t(14;21)(14qter→cen→21qter).

The parents of the consultand and his three children were similarly studied. His mother (I.2), who had no sibs and whose own parents apparently had no other children or miscarriages, had had seven spontaneous abortions, all but one of which occurred in the first trimester. Her karyotype showed a double translocation: 45,XX,-14,-21,t(7;10)(q11;q22),+t(14;21)(14qter→cen→21qter) (Fig. 2). Her husband (I.1) was 46,XY.

Among the consultand's three children (his wife has had no miscarriages), only his son (III.3) inherited the two translocations. One daughter (III.2) was 46,XX and the other (III.1) was 45,XX,-14,-21,+t(14;21)(14qter→cen→21qter)pat.

Discussion

In the pedigree just described there are two independently segregating translocations in three generations. One is a balanced rearrangement between 7q and 10q, while the other is a Robertsonian translocation between 14 and 21.

Two independent translocations in a subject were first reported by de Grouchy and Lautmann (1968). Their patient was a 2-year-old girl with micrognathia, downward slanting palpebral fissures, abnormal ears, and overlapping fingers and toes. Her karyotype was interpreted as 46,XX,t(1q-;Dq+),t(2q-;16q+), while those of her parents and sister were normal.

Studies on a large kindred with three cytogenetic markers were described by Jacobs *et al.* (1970). The healthy proband, ascertained through a cytogenetic survey, was found to have a balanced translocation between a number 1 chromosome and a chromosome in group C. He also had a prominent secondary constriction in the proximal portion of the same arm of the number 1 chromosome as that involved in the translocation, thus making him 46,XY,t(1qh+q+;Cq-). The boy's sister showed similar changes in one of her number 1 chromosomes.

Their father, on the other hand, had changes in both of his number 1 chromosomes. The secondary constriction in the father was inherited from his mother, while the translocated chromosome was paternally derived. This difference between the father and two of his children was felt by Jacobs and her co-workers to be the first demonstration of meiotic crossing-over in man. In addition to the (1q+;Cq-) translocation, which has occurred in at least five generations of this family, the husband of an affected paternal great aunt of the proband was noted to

Fig. 2 Karyotype of maternal great grandmother (I.2) of proband showing double translocation 45,XX,-14,-21,t(7;10)(q11;q22),+t(14;21)(14qter→cen→21qter).

have a Robertsonian translocation between two D group chromosomes: 45,XY,-D,-D,+t(DqDq). The marriage of these two people resulted in the birth of two daughters each having both translocations: 45,XX,-D,-D,+t(DqDq),t(1q+;Cq-). One daughter had seven miscarriages and the other had three, but none of the abortuses was studied. Of the daughters' three living offspring, all males, only one inherited both translocations, but he had not yet reproduced at the time of Jacobs's report.

A double translocation segregating independently in each of two sisters was reported by de Grouchy *et al.* (1972). Their father's karyotype was 46,XY,t(10q-;12p+), and their mother's 46,XX,t(3p+;12q-). One of the sisters had two balanced translocations: 46,XX,t(3p+12q-),t(10q-;12p+). The other sister had the trisomy 10q syndrome: 46,XX,-12,+t(10q-;12p+),t(3p+;12q-).

A complex familial translocation was found by Dallapiccola *et al.* (1976) in a child with the 9p trisomy syndrome. The mother and healthy sister of the patient were 45,XX,-9,-21,-22,+der(9),+der(22),t(9;21)(9;22)(q21;p13)(q12;q11). The patient, who had 46 chromosomes, was trisomic for 9pter→9q12.

Bell and Warburton (1977) described another patient with two unrelated translocations. Their patient was a 2-year-old boy with microcephaly and psychomotor retardation whose karyotype was 46,XY,t(1;2)(1p2p;1q2q),t(5;7)(q21;q31) and occurred *de novo*. An additional patient possibly having a double translocation was studied by Biederman and Bowen (1978). That case was a girl with growth and developmental retardation, microcephaly, bulbous nose, prominent lips and philtrum, esotropia, and hypertonicity. Chromosome analysis showed a balanced t(8;9)(q12;q33)pat translocation. She also had a *de novo* del(7)(q32).

More recently, Bijlsma *et al.* (1978) described double translocation heterozygosity in three generations. Their proband was a 16-year-old mentally retarded boy with partial trisomy 12p as a result of a balanced maternal translocation t(7;12)(p22;q11). Family studies revealed that the proband's maternal grandmother, his maternal aunt, and a male first cousin had, in addition to the t(7;12), a reciprocal translocation t(2;6)(q35;q23).

Our family thus becomes the fourth kindred in published reports to have independently segregating double translocations in more than one generation. We also believe that ours is only the second report of reciprocal and Robertsonian translocations occurring in the same subject.

Another issue raised by this case is that of reproductive failure in people with a balanced translocation. In the extensive pedigree studied by Jacobs

et al. (1970), it was shown that the subjects with only a DqDq translocation did not experience increased fetal loss, and that those with the (1q+;Cq-) translocation had only a very slight increase in fetal wastage, if at all. Jacobs *et al.* (1970) suggested that the favourable outcome in the great majority of these pregnancies could be attributed either to the absence of gametes carrying unbalanced forms of the translocations, or to selection against gametes carrying an unbalanced chromosome complement, or to the very early loss of unbalanced zygotes.

However, the outcome of pregnancies in the two women carrying both translocations was not so favourable. Of their thirteen recorded pregnancies, ten ended in spontaneous abortions, while the other three resulted in phenotypically normal males, one of whom shares the double balanced translocations with his mother. Jacobs *et al.* (1970) suggested that there might be some mechanism operating at meiosis in both the DqDq and (1q+;Cq-) translocations that favours alternate segregation giving rise to normal or balanced gametes, and that this mechanism, at least in the female, breaks down when both translocations are present in the same germ cell. This may be the case in our family as well, where the consultand (II.1) and his mother (I.2) share the two translocations, but only his mother suffered numerous miscarriages. The consultand's wife (II.2) has had three known pregnancies, all of which resulted in living, healthy children, and there has been no history of menstrual irregularity to suggest early spontaneous abortions. It is possible that in this kindred, as in that of Jacobs, the men with a double translocation are less likely than the women to reproduce offspring that are either non-viable or unbalanced at birth. Though there is such a favourable advantage for males carrying a balanced Robertsonian translocation, this is not generally held to be true with regard to reciprocal translocations. Whether our family will prove an exception to this must await the passage of several additional generations.

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Requests for reprints to Dr Harold N. Bass, Department of Pediatrics (Genetics), Kaiser-Permanente Medical Center, Panorama City, California 91402, USA.