Familial balanced translocation 4p+/17q- as a suggested cause of primary trisomy-21 Down's syndrome

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SUMMARY A case is presented in which a 4p+/17q- familial balanced reciprocal translocation in the mother produced a son with primary trisomy-21, as well as the structural chromosomal anomaly. A number of similar situations have been reported, suggesting that the two events are related. In practice, this (as well as other direct risks) should be taken into account when counselling those families in which one parent carries a balanced translocation. A hypothesis, based on experiments in *Drosophila*, has been put forward by Grell to explain the mechanism which links the balanced structural abnormality to an aneuploidy of chromosomes not taking part in the structural change, and this has been extended to similar human situations.

Down's syndrome results from meiotic or mitotic nondisjunction or, rarely, from centric fusions (translocations) either originating *de novo*, or less often inherited from a parent who is a phenotypically normal centric-fusion carrier. Less accepted is the idea that primary trisomy-21 may occur when familial balanced translocation, not involving number 21 chromosomes, influences nondisjunction.

Examples have been reported of Down's syndrome coexisting with a familial translocation involving chromosomes other than number 21. Hamerton *et al.* (1963) discussed one of the earliest published histories of this association. They described a family with a D/D centric fusion and a primary trisomy-21 offspring with Down's syndrome who also inherited the D/D anomaly. Since then workers have speculated about the relation between the two anomalies: can the altered structure of a chromosome influence disjunction of chromosomes of another group? We suggest an affirmative answer and accept a mechanism for this relationship first suggested for the fruitfly and later extended to man (Grell and Valencia, 1964; Grell, 1971).

Case report

Our patient, a boy, is the only child born to a 37-year-old primipara who had a normal pregnancy

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and delivery. His birthweight was 3135 g and head circumference 33 cm. He has the classical features of Down's syndrome with typical dermatoglyphics. Early developmental milestones were greatly delayed, and he is now considered profoundly retarded. Seizures were first noticed by his mother at the age of 8 months, and from the age of 2 years he has received a number of anticonvulsants. Two second cousins, maternal and paternal, are reported to be mentally retarded.

Chromosome analysis was done on the peripheral blood leucocytes and skin fibroblasts, and the chromosomes were G-banded (Seabright, 1971). More than 100 metaphases were examined from both the propositus and parents. Ten selected banded spreads were karyotyped. The karyotype of the propositus is 47,XY,+21,t(4;17)(p16;q21)mat (Fig. 1); and that of the mother 46,XX,t(4;17)(p16;q21). Fibroblast cultures confirmed these findings. Father has a normal male karyotype. Other relatives were not available.

Discussion

The propositus has classical Down's syndrome. He has inherited from his mother the two balanced translocation chromosomes numbers 4 and 17, and in addition he is trisomic-21.

Hamerton *et al.* (1963) suggested that there may be

Fig. 1 Banded mitotic figure from peripheral blood of propositus.

a relation between the two anomalies and other authors have raised this issue (e.g. Tenconi *et al.*, 1974). While in the other reports other chromosomes are involved in the unrelated translocations, our patient and his mother possess a 4p+|17q- translocation, but we too believe that the primary trisomy is causally related to the structural aberration.

Four major cytogenetic types of Down's syndrome are recognized (Ford, 1973). (1) Primary trisomy-21 with 47 chromosomes accounting for 95% of the cases. This originates from meiotic nondisjunction during parental gametogenesis. (2) Centric-fusion trisomy of D/21 with 46 chromosomes, which occurs in less than 2% of the cases and may be inherited from a phenotypically normal D/21 carrier. (3) Translocation trisomy of the G/G type (22/21 or 21/21) which accounts for less than 1% of Down's syndrome. (4) Mosaicism, usually of normal and trisomic 21 cells in a small percentage of cases. We suggest that a fifth type should be added: primary trisomy 21 and 'unrelated' translocations. Here the

parental reciprocal translocation is responsible for the meiotic nondisjunction.

The exact type of translocation that causes and accompanies the trisomy does not appear to be critical. A t(DqDq) centric fusion has been observed by a number of authors (Hamerton *et al.*, 1963; Yunis *et al.*, 1964; Brown *et al.*, 1967; Atkins *et al.*, 1968; Palmer *et al.*, 1969; Borsgard *et al.*, 1974). Hahnemann and Eiberg (1973) reported a kindred with a D-group marker chromosome with Down's syndrome. Banding has suggested a D/Y translocation. In addition, a case with a D/G translocation involving chromosomes 14 and 22 in addition to the trisomy 21 has been recorded (Forabosco *et al.*, 1973). The Table summarizes the familial balanced reciprocal translocations.

Grell and Valencia (1964) discussed Grell's 'distributive pairing' hypothesis of female gametogenesis of *Drosophila melanogaster* to account for the appearance of rare karyotypic abnormalities. According to this explanation, two pairing events

Table Familial translocations not involving chromosome no. 21

Familial reciprocal translocation	Karyotype of propositus	Reference
t(Ap-; Bq+)	47, XY, Dp+, t(2p-; 5q+) mat, +21	Lundsteen <i>et al.</i> (1974)
t(Aq-; Dq+)	47, XX, t(2q-; 15q+) mat, +21	Stoll <i>et al.</i> (1976)
t(Ap-; Eq+)	47, XX, t(2p-; 16q+) pat, +G	Robson <i>et al.</i> (1969)
t(Ap-; Eq+)	47, XX, t(1p-; 17q+), +G	De La Chapelle <i>et al.</i> (1975)
t(Ap-; Eq+)	47, XY, t(3p-; 17q+) pat, +G	Šubrt and Prchlíková (1969)
t(Bp+; Cq-)	47, XX, t(Bp+; Cq-) mat, +G	Kahn and Abe (1969)
t(Bq-; Cp+)	47, XX, t(5q-; 7p+) mat, +21	Yanagisawa (1972)
t(Bp+; Eq-)	47, XY, t(4p+; 17q-) mat, +21	Present case
t(Cq-; Dq+)	47, XX, t(6q-; 18q+) mat, +21	Tenconi <i>et al.</i> (1974)

occur before first meiotic division. The first, called 'exchange pairing', requires chromosome homology. It is followed by 'distributive pairing' during which chromosomes that did not participate in the exchange of genetic material have a second chance of pairing and segregating. They form part of the 'distributive pool'. According to Grell (1971) a heterozygous chromosome rearrangement is a condition that favours nonexchange. This situation contributes to the distributive pool and increases the chance of heterologous interaction. A distributive pool with structurally rearranged chromosomes and normal nonexchange chromosomes may lead to the formation of nondisjunctional gametes when segregation occurs ('distributive nondisjunction'). Findings in maize suggest a similar occurrence (Bianchi *et al.*, 1961).

Because chromosomes of pair 21 have a low exchange frequency, Grell (1971) hypothesizes that the presence of homologous 21s together with structurally altered chromosomes in the distributive pool duplicates the circumstances that produce aneuploidy in *Drosophila*. Such a suggestion may apply to our case and to similar examples. We suggest (Fig. 2) that the small translocated chromosome 17q- in our case could influence chromosome 21 and vice versa, and we postulate a 'dual attraction' between one 21, its homologue, and the 17q-, all of similar size. Grell's hypothesis would predict distributive segregation of chromosome 4 and 4p+

and 17 and 17q-. However because the 17q- influences the two 21 autosomes, they would not segregate regularly but would undergo distributive nondisjunction. This would result in the production of a gamete with the two chromosomes involved in the reciprocal translocation but containing also the two number 21s.

Chromosomes other than number 21 may be involved. Chrysostomidou *et al.* (1971) reported a primary trisomy-18 with a paternally inherited D/G balanced centric fusion. De la Chapelle and Schröder (1973) identified a familial translocation between autosomes 4 and 11 and aneuploidy involving the X chromosomes. A case of Klinefelter's syndrome and a simultaneous familial D/D centric fusion (Sparagana and Smith, 1975) has also been described. One of us (Aya *et al.*, 1967) has studied a family with a B/C reciprocal translocation, and a high number of spontaneous abortions which may be due to non-viable zygotes produced by distributive nondisjunction.

In conclusion, the implications of this study are twofold. First, further data are necessary to determine both the reality and the numerical incidence of primary trisomy secondary to an 'unrelated' balanced translocation. For this, families segregating for balanced translocations, not ascertained through a primary trisomic child, are essential. Second, translocation carriers should be informed of the potential risk of producing an 'unrelated' primary

Fig. 2 Possible pathway of acquisition of genome.

trisomic child. Additional evidence is needed to provide the necessary information for proper counselling.

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