Reciprocal translocation, 4q−; 21p+, giving rise to Down’s syndrome

Summary. A reciprocal translocation is described, t(4;21)(q27;p11), which occurs in a balanced carrier mother and her Down’s syndrome child, 47,XX,t(4q−;21p+)+,+21. A review is presented of Down’s syndrome associated with reciprocal translations involving chromosome No. 21.

The usual translocations involved in Down’s syndrome are Robertsonian translocations between chromosome No. 21 and other acrocentrics. However, a growing number of reciprocal translocations involving chromosome 21 have been discovered in individuals with Down’s syndrome, and the question of the possible role of such rearrangements in causing nondisjunction has arisen.

The purpose of this report is to describe a translocation between the long arm of a No. 4 chromosome and the short arm of chromosome 21, t(4q−;21p+), in a mother and her Down’s syndrome child, and to review the results from other Down’s syndrome kindreds where diverse reciprocal translocations involving G group chromosomes have been described.

Case report

The propositus was born in May 1973, the first child of American Indian parents. Both parents were healthy and the pregnancy and delivery were uneventful. The mother was a 29-year-old primagravida.

Examination at birth revealed epicanthal folds, a simian crease on the right hand, flat nasal bridge, and generalized hypotonia. Motor development was delayed; at 7 months of age the child was unable to sit but could roll over. Physical findings at age 13 months included coarse facies, with protruding tongue, mongoloid slant of the eyes, broad stubby hands, and hypotonia. Her height was 72 cm, weight 9 kg, and head circumference 43 cm (below the third centile). There were no Brushfield spots, no detectable heart abnormality, and the remainder of the examination was unremarkable.

Dermatoglyphic analysis showed a simian crease on the right hand. The palmar triradii were distally located on both hands with adt angles of 79° and 82°. There were interdigital loop IV patterns on both palms and, in addition, a loop III on the right palm. There was a hypothenar loop on the left hand. Both fifth fingers had two creases. There were nine ulnar loops
and one whorl on the digits. The hallucal areas of the soles had a tibial arch (left) and small tibial loop (right).

**Chromosome studies**

Examination of standard orcein-stained preparations from the proband's cultured lymphocytes revealed a missing B-group chromosome and two additional C-group chromosomes. Giemsa banding (Fig. 1) indicated the karyotype to be 47,XX,t(4;21)(q27;p11), +21. Twenty-eight metaphases from two blood samples were analysed; all contained the translocation and the extra G-group chromosome.

The mother was found to be a balanced carrier for the translocation, 46,XX,t(4;21)(q27;p11). Analysis of several other members of the kindred revealed normal karyotypes (Fig. 2). The translocation thus probably arose as a reciprocal event in a germ cell from which the mother was derived.

**Discussion**

Almost 20 families have been described where cases of Down's syndrome are associated with familial reciprocal chromosome 21 translocations (Table). Kontras et al (1966) and Laurent and Robert (1968) proposed that the risk of recurrence of Down's syndrome in families reported by them was as high as 1 in 3 since there may have been only 3 types of viable gametes resulting from centromere segregation from the theoretical trivalent-plus-univalent meiotic figure (these were normal, carrier, and carrier possessing an extra 21 chromosome). Miller et al (1970) pointed out that the actual risk was unknown and might depend on factors unique for each translocation. They concluded that while the risk for Down's syndrome might indeed be increased, its actual magnitude was

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**Fig. 1.** Giemsa-banded karyotype of propositus.

**Fig. 2.** Pedigree.
not possible to determine unless a trivalent-plus-univalent meiotic configuration could be shown in a proportion of meioses or unless the pedigree contained sufficient cases of Down’s syndrome. Some reciprocal translocations involving a G-group chromosome are more likely to yield a trivalent-plus-univalent, e.g., Vogel and Lönö (1973). Others tend towards a quadrivalent, as Chandley et al (1972) concluded after finding 21 chain IV figures and one trivalent-plus-univalent among meioses in a man with a (9;22) reciprocal translocation. Clearly the trend in this particular translocation was strongly towards a quadrivalent at meiosis, implicating discordant orientation of centromeres rather than formation of a trivalent-plus-univalent as the mechanism of production of the observed 3:1 segregation.

Lindenbaum and Bobrow (1975) have recently presented a review of 3:1 disjunction associated with reciprocal translocations in general. Their data indicate an overall empirical risk of recurrence of about 14%. When Down’s syndrome alone is considered in familial reciprocal translocations involving chromosome No. 21, the data can be tabulated as in the Table. In these families there were no reported instances of unbalanced karyotypes due to 2:2 segregation. These data indicate that the risk of recurrence for Down’s syndrome among liveborn children of carriers is around 15% (12/81) which is identical to the overall risk reported by Lindenbaum and Bobrow (1975) for 3:1 disjunction in reciprocal translocations. All the affected offspring listed in the Table who are not probands are children of female carriers except one case in the report of Pfeiffer, Laermann, and Heidtmann (1967).

Fetal wastage occurred at a rate of 28.6% (31/112) in pregnancies where either parent was a balanced translocation carrier, compared with 0/36 reported in their chromosomally normal relatives. No chromosome studies were performed on these abortions. Thus, while Down’s syndrome is the only chromosome defect reported in these families, it is probable that other types of chromosome abnormalities occurred but remained undetected.

Since all families reviewed here were discovered because of a proband with a chromosome imbalance the true overall risk to offspring of carriers remains unknown. Though there appears to be a substantial risk in some families, the risk figures given should be regarded as provisional maximums due to the method of ascertainment. It is obvious that prospective studies are the best means of answering many of the questions regarding risks. Such studies, however, are necessarily very difficult because of the low incidence of nondisjunction in reciprocal translocations. Chromosome analysis of cultured amniotic fluid cells is the only means of relieving uncertainty involved with pregnancy in such translocation carriers.

The Table below lists the reciprocal translocations involving G-group chromosomes with the chromosome of the offspring, the number of balanced carriers, the number of unaffected balanced carriers, and the number of affected offspring. The Table also includes a comparison of the overall risk of ascertainment in families with Down’s syndrome due to a reciprocal translocation with the overall risk of Down’s syndrome in general. The data are based on the study of Bobrow and his colleagues (1970; 1975) and the results of other studies reported in the literature.

**Table**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Translocation</th>
<th>Chromosomes in Offspring of Balanced Carriers</th>
<th>Fetal Wastage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>Carrier</td>
</tr>
<tr>
<td>Miller et al (1970)</td>
<td>t(2p–21q+)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Soukup et al (1969; family a)</td>
<td>t(37;Gq+)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Soukup et al (1969; family b)</td>
<td>t(37;Gq+)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Kontras et al (1966)</td>
<td>t(1q–21q+)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Laurent and Robert (1968)</td>
<td>t(2q–21q+)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Giraud et al (1974)</td>
<td>t(7q–21q+)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prieur, Dutrillaux, and Rethoré (1971)</td>
<td>t(18p+21q–)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pfeiffer et al (1967)</td>
<td>t(6q–21q+)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Borgaonkar et al (1973)</td>
<td>t(6p+21q+)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Weiss and Wolf (1968)</td>
<td>t(Cq–21q+)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moric-Petrovic, Zivkovic, and Kal'canin (1969)</td>
<td>t(12p–21q+)</td>
<td>0</td>
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</tr>
<tr>
<td>de a Chapelie, Kolvisto, and Schröder (1973)</td>
<td>t(4q–21q+)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Day and Miles (1965)</td>
<td>t(7+21q–)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vogel and Lönö (1973)</td>
<td>t(19p or q–21q+)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lindenbaum and Bobrow (1975; case 3)</td>
<td>t(7q–21q+)</td>
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<td>0</td>
</tr>
<tr>
<td>Lindenbaum and Bobrow (1975; case 5)</td>
<td>t(2p–21q+)</td>
<td>0</td>
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<tr>
<td>Present case</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (excluding probands)</td>
<td></td>
<td>26</td>
<td>43</td>
</tr>
</tbody>
</table>

* Cases reported as probable Down’s syndrome but not ascertained by chromosome study are indicated by (?).
† Uncorrected total in parentheses.
We thank Dr Arthur Rodriguez and Ms Candace Thompson for their assistance.

M. B. JENKINS and L. BOYD

Human Genetics Unit
Minnesota Department of Health
717 Delaware Street S.E.
Minneapolis, Minnesota 55440
U.S.A.

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Multiple congenital defects associated with trisomy for long arm of No. 4

Summary. The clinical and cytogenetic findings of a male infant with multiple congenital anomalies and trisomy for the distal third of the long arm of No. 4 are described. The abnormal chromosome was inherited from the mother who had a balanced translocation, t(4;9)(q31;q34). Trisomy for the long arm of No. 4 has previously been described in only 3 patients.

Case report

The propositus was born to a 31-year-old woman and her 44-year-old husband after an uneventful pregnancy and a normal delivery. The infant was thought to be 12 days past maturity by dates, though birthweight was only 2722 g. This was the mother’s fourth pregnancy (Fig. 1). The first had resulted in the birth of a ‘deformed’ male who died almost immediately. Necropsy was not performed.

The propositus was noted at birth to have a skin-covered supra-umbilical exomphalos. He had a ‘strange’ face with a suggestion of low set ears. Head circumference was 32 cm. At 1 month infrquent motions led to rectal biopsy and the identification of Hirschsprung’s disease, with aganglionic extending to at least 10 cm up the colon. The mother had a normal delivery. The infant’s neonatal condition was normal, and the postnatal course was uneventful. He was discharged from the hospital on the fourth day of life.

FIG. 1. Pedigree of family showing segregation of translocation, t(4;9)(q31;q34). Year of birth is given.