A Rare Translocation (47,XY,t(2p-;21q+),21+) Associated with Down's Syndrome

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Chromosomal aberrations are a constant feature of Down's syndrome. The aberrations observed to date have involved a member of the G group, with about 95% of cases possessing trisomy for chromosome 21. Mosaicism and translocation have been observed much less frequently. The most common translocations observed are between the long arms of chromosome 21 and another acrocentric (D or G group). These translocations, in addition to being of interest from the point of view of fundamental cytogenetic knowledge, are of practical clinical importance because they are the potential basis of familial types of Down's syndrome.

In this report we present a case of Down's syndrome associated with familial transmission of a balanced translocation.

Clinical Report

The proband is a male born in 1960 when his mother was 27 years old and his father 35. The mother had six pregnancies and the proband was the product of the fourth. The second pregnancy terminated in a miscarriage at 2 months. The remaining offspring are all healthy normal females. There were no other known cases of Down's syndrome in the pedigree (Fig. 1).

The diagnosis of Down's syndrome was made at birth. In early infancy he had pyloric stenosis which was treated medically. At the chronological age of 4 years 1 month his over-all level of behavioural development appeared to be only 1 year, and he had an assessed IQ of 25. At the age of 5 years he had only a few words, could not walk properly, and was not toilet trained. He could feed himself and co-operate in dressing himself. One of us (J.M.R.) who saw him at this age was impressed by the fact that the child's behaviour was more disturbed than that of the usual mongol and that in fact he was actively unpleasant.

FIG. 1. Pedigree of the proband.

Physically he had many of the characteristic features of Down's syndrome including flat facial features, brachycephaly, general laxity of joints, a moderate number of Brushfield spots, and short stubby fingers with clinodactyly.

Dermatoglyphs. The dermatoglyphic patterns of the fingers, palms, and soles showed some of the features usually observed in Down's syndrome (Miller and Giroux, 1966). On the fingers there were nine ulnar loops and a whorl located in the fourth digit of the right hand. On the palms there was a proximally placed axial triradius bilaterally, but vestigial patterning in the hypothenar area was present. There was a loop distal pattern in the third interdigital area bilaterally. There were no simian creases. On the soles an arch tibial pattern was present in the hallucal area bilaterally.

Chromosomal studies. Chromosomal studies of leucocyte cultures showed the propositus had a chromosome number of 47, but that the karyotype was not typical of trisomy 21 (Fig. 2). There were only 4 G group chromosomes plus a long Y chromosome and 7 D group chromosomes, no one member of which appeared significantly different from the rest. In addition, one of the No. 2 chromosomes had an abnormally short short arm, suggesting that a large portion of the arm had been deleted.

Chromosome studies were carried out on the parents, sibs, and several distant relatives of the propositus (Fig. 1). The father had a normal karyotype with a long Y chromosome. Two of the sibs and two maternal uncles and a maternal great-aunt also had normal karyotypes. The mother had 46 chromosomes but an abnormal karyotype (Fig. 3). All her cells had 3 small and 7 large acrocentric chromosomes with satellites. One member of the No. 2 pair had a short short arm (46,XX,t(2p-;21q+)). The two remaining sibs, the maternal grandmother and a maternal great-aunt, had karyo-

FIG. 2. Karyotype of the propositus.

FIG. 3. Karyotype of mother of propositus.

types similar to that observed in the mother. No other maternal relatives were available for study.

The abnormal karyotypes present in the phenotypically normal individuals are interpreted as a balanced reciprocal translocation between a small portion of the long arm of a G chromosome and a portion of the short arm of a No. 2 chromosome. This gives rise to a chromosome which is morphologically similar to or indistinguishable from those of the D group and one that is similar to but distinguishable from the B group chromosomes. The propositus has an effective trisomy for No. 21 since there are four normal G group chromosomes as well as the portion of No. 21 included in the D-chromosome-like translocation product.

Dermatoglyphic features of the 'carriers'. Penrose and Delhanty (1961) reported microstigmata in the form of abnormal dermatoglyphic features in the 'carrier' relatives of two sibs with translocation t(DqGq) Down's syndrome. These relatives had centrally placed axial triradii similar to those observed in the propositus.

The dermatoglyphic patterns of the carriers in the family in this present report do not show any consistent feature of Down's syndrome. One of the sibs and the grandmother have a distally placed axial triradius bilaterally while the other sib and the mother do not have this feature.

Problems of counselling. The parents of the propositus decided to limit their family. However, they naturally expressed concern about the potential risk for the offspring of the two daughters who carry the chromosomal aberration. Answers to their questions cannot be sought in statistics derived from analysis of other familial forms of Down's syndrome because, though certain general statements can be made about transmission ratios in such cases, it is clear that because of the complexities of cellular events at the time of meiosis each case must be evaluated individually. That is, the best figure will have to be derived from information provided

by the family itself and a consideration of the unique nature of the chromosomal defect.

Family history. There were no known cases of Down's syndrome, mental retardation, or congenital defect in the pedigree so far as it could be determined (Fig. 1). Of the three married women who possessed the translocation, one (III.5) had one first trimester miscarriage, one (II.1) had four first trimester miscarriages, and one (II.2) had no children. However, the relevance of these observations is of questionable significance in terms of possible abnormal chromosome combinations, because II.1 states that she had signs of threatened abortion in the first trimester of all her pregnancies and was confined to bed for at least one month at these times and II.2 married at the age of 34 years.

Since two translocation carriers occurred in generation II, the aberration must have been present in I.1 or I.2, both of whom are dead. I.1 was the last born of a large sibship (reported to be over 10), only one of whom was alive at the time of our studies. This was a man who was over 80 years and very ill, and his wife was reluctant to have him upset by any questioning. I.2 was also the last born in a sibship of 14, only one of whom was alive at the time of the study. This was a woman living in Eastern Canada, whose son was able to provide extensive pedigree data on his mother's sibs and their offspring. To his knowledge there had been no instances of mental retardation or congenital defect in this family, though there were several instances of infant death of unknown cause.

Discussion

Unlike the more common Robertsonian translocations which have been observed in association with Down's syndrome, the one described here is characterized by the fact that it is a reciprocal translocation in which both products are long stable chromosomes though of unequal size. As outlined in general discussions on the subject (White, 1954; Ford and Clegg, 1969; Hamerton, 1968), the theoretical meiotic segregation products and their fre-

quency differ for Robertsonian and reciprocal translocations.

An outline of the type of gametes and zygotes resulting from the segregation of the metaphase I reciprocal translocation complex of a ring or chain of four chromosomes is presented in the Table. Alternate segregation would produce normal and balanced translocation gametes. Adjacent I and Adjacent II segregation will produce duplication-deficiency gametes which are probably lethal at some stage. None of these segregation events could result in Down's syndrome.

The proband in our pedigree is derived from a fertilized gamete with a chromosome complement of 24 resulting from non-disjunction (or unequal centromere distribution) of a No. 21 chromosome. In view of the occurrence of Down's syndrome in the present case and other carriers of balanced reciprocal translocations involving chromosome 21 (Kontras *et al.*, 1966; Laurent and Robert, 1968; Soukup *et al.*, 1969), the possibility of an increased recurrence risk merits consideration.

As none of the three basic types of reciprocal translocation segregation results in a karyotype compatible with Down's syndrome, exceptional segregation events which would result in a 3:1 distribution of the chromosomes must be considered.

Kontras *et al.* (1966) proposed segregation of a trivalent: univalent meiotic complex to account for Down's syndrome in the offspring of a carrier of a reciprocal translocation involving chromosome 21. This suggestion is attractive because the short length of chromosome 21 increases the probability of lack of formation or precocious terminalization of chiasma. However, contrary to the conclusions of these authors, this does not indicate a 1 in 3 recurrence risk for Down's syndrome among the offspring of balanced carriers of this translocation. In Robertsonian translocations associated with

TABLE
MEIOTIC SEGREGATION, GAMETES, AND PHENOTYPES
RESULTING FROM METAPHASE I TRANSLOCATION COMPLEX

	Types of segregation	Gametes	Phenotypes
Alternate	$\begin{array}{c} \uparrow \qquad \qquad \uparrow \\ 2p- : 2:21q+ : 21 \\ \downarrow \qquad \qquad \downarrow \end{array}$	2,21	Normal
		2p-,21q+	Normal
Adjacent I	$\begin{array}{c} \uparrow \qquad \qquad \uparrow \\ 2p- : 2:21q+ : 21 \\ \downarrow \qquad \qquad \downarrow \end{array}$	2p-,21	Presumably lethal
		2,21q+	Presumably lethal
Adjacent II	$\begin{array}{c} \uparrow \qquad \qquad \uparrow \\ 2p- : 2:21q+ : 21 \\ \downarrow \qquad \qquad \downarrow \end{array}$	21q+,21	Presumably lethal
		2p-,2	Presumably lethal
Proposed segregation producing Down's zygote	$\begin{array}{c} \uparrow \qquad \qquad \uparrow \\ 2p- : 2:21q+ : 21 \\ \downarrow \qquad \qquad \downarrow \end{array}$	2,	Presumably lethal
		2p-,21q+,21	Down's syndrome

Down's syndrome, the anticipated regularity of segregation resulting in a *theoretical* 1 in 3 recurrence risk stems from the fact that an uneven number of centromeres must result in unequal distribution to the gametes. In the balanced reciprocal translocation carrier, an unequal distribution of the centromeres should be increased over the frequency of non-disjunction in normal cells only to the extent that the translocation interferes with or influences meiotic events. The behaviour at meiosis will ultimately depend on the way the chromosomes pair at zygotene, the number of chiasmata formed, and the way the chromosomal configuration is orientated on the spindle (White, 1954). In view of these variables, a 1 in 3 recurrence risk appears to be unjustified unless a trivalent:univalent meiotic configuration could be demonstrated in *all* meiotic figures from a carrier, or the pedigree analysis indicated a 1 in 3 recurrence.

Laurent and Robert (1968), in reporting a family in which there was a translocation apparently identical to the one observed in our pedigree, also favour a segregation giving a theoretical 1 in 3 recurrence risk, though on the basis of the pedigree analysis they conclude the risk is actually in the order of 1 in 5.

Non-random disjunction in translocation heterozygotes has long been recognized in *Drosophila* and maize. This usually results in preferential recovery of orthoploid gametes from alternate segregation (Dobzhansky, 1933; Glass, 1935). There is also accumulating evidence that segregation of balanced Robertsonian translocations in man is non-random, with preferential recovery of balanced heterozygotes over chromosomally normal progeny and a deficiency of unbalanced progeny (Hamerton, 1968). In a recent review of reciprocal translocations in man, Ford and Clegg (1969) consider the accumulated data to be consistent with a 1:1 carrier to normal ratio. Meiotic drive, prezygotic selection, and other mechanisms proposed to explain preferential recovery of expected classes of progeny would not appear to be appropriate for explaining the occurrence of exceptional progeny.

Recent observations on non-random disjunction by Grell (Grell, 1964; Grell and Valencia, 1964) suggest that unequal lengths of the pairing chromosomes may increase the frequency of non-disjunction specifically when no crossing-over occurs. Soukup *et al.* (1969) have drawn attention to Grell's work in a report of an apparently identical balanced translocation observed in two unrelated families both of which were ascertained through a propositus with Down's syndrome. The translocation involved ($3? - ; G?q +$) is very similar to the

one described here. These cases and those of Kontras *et al.* (1966) and Laurent and Robert (1968) conform to the situation described by Grell in that the $21q +$ chromosome is much longer than the normal 21 chromosome, and the small size of the 21 decreases the probability of crossing over.

Though numbers are small it is of interest that in the five kinships mentioned above after correction is made for bias of ascertainment (the families reported by Kontras *et al.* (1966) and Laurent and Robert (1968) were ascertained because of the occurrence of *two* mongols), the ratio of normals to balanced translocation carriers among 41 offspring of carriers is 17:24. These data consider only those instances in which complete karyotype analysis has been done.

Providing counselling advice for the translocation carrier sibs in our pedigree is not an easy matter. As indicated in the Table, there is a risk of zygotes with various duplication-deficiency complexes, most of which would be lethal *in utero*, but the risk of producing a child with Down's syndrome is the same as for any female in their age-group. However, if the meiotic behaviour of the translocation complex is such that non-disjunction is increased, then this risk would be increased by an extent which is unknown.

Summary

The clinical, dermatoglyphic, and cytogenetic features of a boy with Down's syndrome are presented. This patient possesses a rare translocation involving chromosome 21 and part of the short arm of chromosome No. 2 ($47,XY,t(2p - ;21q +),21 +$). Though no other individuals with Down's syndrome were known to have occurred in the pedigree, several carriers for the translocation were observed including the patient's mother and two of his sibs ($46,XX,t(2p - ;21q +)$). In an attempt to determine a risk figure for the offspring of these sibs, segregational events at meiosis are discussed. It is concluded that while the risk figure may be no greater than any female in their age-group, it may be increased by a factor that is impossible to calculate at present.

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