Translocation and Trisomic Down's Syndrome in a Family with a Familial D/G Translocation

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Received August 30, 1968

The reports on familial Down's syndrome (mongolism) date in the medical literature from the 20th years of this century. Familial Down's syndrome is now well-described event but relatively rare. Penrose states that pairs of affected sibs appear about once for every 100 single cases of mongolism collected at random (quoted by Soltan et al. 1964). About two-thirds of the mongoloids are close relations and one third of the cases is of more distant relationship. Owing to the high incidence of Down’s syndrome in the general population, it is possible to speak about random coincidence in some cases in the latter group (Zellweger 1964). For a short time the prevailing opinion was that translocation Down’s syndrome is the most common cause of familial

Fig. 1. Pedigree of kindred with familial Down's syndrome.
Down's syndrome. The recent investigations have brought evidence that translocation Down's syndrome may explain only a part of the familial cases (about one quarter). In most cases of the familial Down's syndrome the regular trisomy 21 was found. In this report we present a family with familial D/G translocation and with cases of translocation and trisomic Down's syndrome.

Patients and findings

The genealogical and cytogenetical information showing the position of affected relatives in pedigree is illustrated in Fig. 1. The individuals in the generation I and II died before the begin of the investigation. We determined the karyotypes of all living members of the IIIrd generation and we found four carriers of D/G translocation. In the generations IV and V we examined all offsprings of translocation carriers and then mainly the individuals with clinical features of Down's syndrome and individuals with physical diagnostic features of neuropsychomotoric retardation. On the whole we studied 39 individuals by chromosomal analysis from all 69 living members of 3 generations. Of these 39, 11 were D/G translocation carriers, two cases translocation Down's syndrome and two cases Down's syndrome with regular trisomy 21. There is no in-

Fig. 2. A metaphase cell and karyotype of the proband/V-14/, a D/G translocation Down's syndrome.
formation concerning possible mongoloid or other pathological stigmata in the group of 30 individuals, who were not studied. The proband was a 6 days old newborn (V-14) and the mother was 23 years old at his birth. He revealed a typical picture of Down's syndrome. Chromosome analysis showed D/G translocation (Fig. 2). His mother (IV-27), her two brothers (IV-28, -29) and their father (III-18) were carriers of D/G translocation. From three father's cousins (translocation carriers, III-2, -3, -19), one was single (III-3), the second (III-19) had 3 living children and all were translocation carriers. The third (female carrier of D/G translocation, III-2) had three children and one spontaneous abortion. Her first child was a case of Down's syndrome with D/G translocation (IV-2). The mother was 20 years old at the time of the girl's birth. The second child (IV-3) did not inherit a translocation chromosome, the third was a translocation carrier (IV-4). The maternal and paternal ages at the times of birth of the children with trisomy 21, were 45 and 47 years for III-4, -5, and 24 and 24 years for IV-11, -10. The parents' karyotypes of both children with trisomy 21 were normal. The grandfather (III-6) of one child with trisomia 21 died at the age of 54 years of chronic leukaemia and his cousin (III-8) of cancer. Two children (V-4, -9) showed serious features of neuropsychomotoric retardation. Theirs karyotypes were normal. Psycho-
logical evaluation of one translocation carrier (IV-34) showed a subnormal intelligence and an impulsive behavior. All the other translocation carriers had no sign of mental or physical abnormalities. We have found three spontaneous abortions and two stillbirths in the whole family. Consanguinity was not found.

All the chromosome analyses were carried out on cultured leukocytes from peripheral blood according to micro-method (Macek 1965). In most individuals 30 to 50 cells were examined and 3 to 10 karyotypes were made.

Discussion

The balanced G chromosome translocation in one parent gives a satisfactory explanation for the occurrence of the translocation Down's syndrome in some of the offspring. However, the majority of cases of the familial Down's syndrome does not come from the translocation but have their origin in regular trisomy 21. The explanation and eugenic advice in the latter cases is more difficult. The occurrence of translocation and trisomic mongols in one family is not rare. There was found often that if the translocation patients had mongoloid relatives, these relatives proved to be regular trisomic mongols. In most investigated cases the translocation have arisen de novo (Barnicot et al. 1963, Priest et al. 1963, Sergovich et al. 1964, Soltan et al. 1964, Ingalls and Henry 1968
A familial D/G translocation and cases of translocation Down’s syndrome with trisomic mongol in the distant relatives described Hustinx (1966), a familial D/G translocation and one mongoloid child with trisomy 21 described Moorhead et al. (1961).

In our family the translocation was traced through three generations and there is evident that the translocation existed in the generations preceding the three which were studied. Carrier mothers in this kindred have produced two translocation mongols, one normal child and one carrier while examined carrier fathers have produced only carrier offspring. These findings agree with the practical experience that the risk of having progeny with Down’s syndrome appears to be greater for female than for male translocation carriers. It is also interesting to note that we have found two cases with various degree of neuropsychomotoric retardation and one case of chronic leukaemia in this kindred. We should like to draw attention to long Y chromosome that we have found in some individuals (III-16, -18, IV-3, -25, -26, -28, -29). It seems to be proved that variants of the normal chromosome picture, especially of the length of the Y chromosome occur more often in parents of the patients with Down’s syndrome than in the normal population (Mikkelsen 1967). We considered this chromosome as long when it was at least of the same size as the chromosome of the 17-18 group. We measured the length of the Y chromosome in 3 to 10 well spread metaphase cells from each case and we recorded only those cases when we found the long Y chromosome evidently in most of the cells. The poorly defined centromere, the unseparated chromatids of the long arm, the absence of satellite on the short arm served us in most cases as criteria for the identification of the Y chromosome. Figures 3 and 4 are representative metaphase figures and karyotypes of the individuals with abnormally long Y chromosome. A relationship between the length of aberrant Y chromosome and Down’s syndrome is not established with certainty. It seems possible that minor chromosomal variations in ancestors increases the risk of major chromosomal abnormalities in an offspring.

Summary

39 individuals in three generations of large kindred were studied by chromosomal analysis of cultured leukocytes. Of these 39, 11 are carriers of D/G translocation, two D/G translocation mongols and two mongols of the regular trisomic type. The translocation was carried through three generations which were studied. By some men an abnormally long Y chromosome was observed. The simultaneous occurrence of these chromosomal changes in one kindred is briefly discussed.

Acknowledgements

I am grateful for technical assistance to Mrs. H. Matoušková and Mrs. T. Svitáková.
References