Risk for Short Arm 10 Trisomy

A Segregation Analysis of Eleven Families with Different Translocations

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Summary. A segregation analysis has been carried out for 11 families with trisomy 10p caused by familial translocations involving a segment of the short arm of chromosome 10. The theoretical basis for the analysis is considered in some detail. No differences were found between the segregation pattern in the offspring of carrier mothers and that of carrier fathers. There was a high risk for offspring with trisomy 10p (22%). A phenotypically normal descendant also has a high risk of becoming a balanced translocation carrier (71%). This result does not deviate significantly from the theoretical value of 50%.

Introduction

In the last few years 15 cases of trisomy 10p, derived from familial translocations, have been reported (Insley et al., 1968, confirmed by Hirschhorn et al., 1973; Yanagisawa and Adachi, 1970; Hustinx et al., 1974; Schleiermacher et al., 1974; Cantu et al., 1975; Grosse et al., 1975; Magenis et al., 1975; Nakagome and Kobayashi, 1975; Yunis et al., 1976; Turleau et al., 1976; Morić-Petrović et al., 1976; Stengel-Rutkowski et al., 1977). Because of striking phenotypic similarities among these patients, it has been suggested that a typical dysmorphic syndrome could be delineated for this chromosomal disorder (Schleiermacher et al., 1974; Cantu et al., 1975). Further characterisations of this syndrome have been given by Stengel-Rutkowski et al. (1977). One aim of the present paper is to analyse the segregation pattern of these families.

Previously, segregation analyses of families with reciprocal translocations were made by Ford and Clegg (1969), Hamerton (1971), Lejeune et al. (1970), and Lindenbaum and Bobrow (1975). Although the authors pointed out that all reciprocal translocations are unique and the families should be considered separately, they pooled all families together. Lejeune et al. (1970) further split up kindreds with more than one sibship according to ascertainment of each sibship and pooled all sibships belonging to the same type of ascertainment regardless of

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translocation. From these pooled data the probability of a live-born offspring having an unbalanced chromosome complement was estimated, although it is evident that the probability for such an offspring varies considerably from translocation to translocation. Lejeune et al. (1970) got substantially different estimates from the different ascertainment groups, even though the same translocations were involved.

In the present paper some effort has been made to provide a more satisfactory basis for segregation analysis of reciprocal translocations. This approach is partly based on the model for translocation inheritance developed by Stene (1970c, 1976), in which a separation has been made between probabilities for gametes and zygotes to be formed and probabilities for fetal deaths and live-births. Another part of the new approach is based on statistical methods for segregation analysis of translocation families developed by Stene (1970a, b, c, 1975). These methods do not require splitting up kindreds after type of ascertainment.

Theoretical Basis for the Analysis

Segregation Pattern for One Familial Translocation. A carrier of a reciprocal translocation may form a large number of different types of gametes when cross-over can take place in the interstitial regions, i.e., between the centromere and the break point, and one or more nondisjunctions of the four nontranslocated and translocated chromosomes considered can take place at anaphase II. Ten of these types are formed by 2:2 disjunction (see Ford, 1969; Ford and Clegg, 1969; Hamerton, 1971), 20 by 3:1 disjunction with the possibility of a single nondisjunction at anaphase II (Lindenbaum and Bobrow, 1975). A large number of other types are theoretically possible, by two nondisjunctions at anaphase II after 2:2 disjunction at anaphase I; by one, two, or three nondisjunctions at anaphase II after 3:1 disjunction at anaphase I; and by 4:0 disjunction at anaphase I without or with one, two, three, or four nondisjunctions at anaphase II. Some of these types have been mentioned by Ford (1969). Only a few are likely to be produced.

Of the ten gametes first mentioned, two are formed by alternate segregation, two by adjacent-1 segregation, and the remaining six by adjacent-2 segregation. If cross-over in the interstitial regions occurs, the four gametes produced by alternate and adjacent-1 segregations are morphologically indistinguishable. Two of these gametes are balanced, one carrying two normal chromosomes and the other carrying two translocation chromosomes. The other two of these four gametes are unbalanced. Gametes produced by adjacent-2 segregation, 3:1 and 4:0 disjunctions, and possible nondisjunctions are all heavily unbalanced. See Ford (1969), Ford and Clegg (1969), Hamerton (1971), and Lindenbaum and Bobrow (1975) for details.

Theoretically, the frequencies of gametes carrying normal chromosomes and those carrying balanced translocation chromosomes are equal and depend on the frequencies of alternate and adjacent-1 segregations and the cross-over frequencies in the interstitial regions. The frequencies of these balanced gametes are different from the frequencies of the different types of unbalanced gametes.

Only matings between a translocation carrier and a karyotypically normal individual are considered here. Theoretically, a large number of different zygotes may be produced by such a mating. The different zygotes may have quite different probabilities of developing into a live-born child. Most unbalanced types of zygotes are aborted at an early stage. Usually, at most one such type seems to have a positive probability of surviving the gestation period. The two types with a balanced segmental constitution both have positive probabilities for developing into a live-born infant, and there seems to be no theoretical argument for suspecting these probabilities to be different.

Balanced translocations carriers and karyotypically normal individuals should occur with equal frequencies in the offspring, while offspring with the unbalanced karyotype may occur