Structural rearrangements in the parents of children with primary trisomy 21

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SUMMARY A retrospective cytogenetic study was carried out on the parents of children with regular trisomy 21 Down's syndrome. In a total of 128 parents referred routinely to our laboratory after the birth of their affected child, three structural abnormalities, a reciprocal translocation and two pericentric inversions not involving chromosome 21, were detected. This is about 10 times the frequency expected based on current figures from consecutive newborn studies. In addition, the brother of one of nine older people with trisomy 21 referred for cytogenetic analysis for the first time was found to have a reciprocal translocation.

This supports the contention made by others that an interchromosomal effect does exist in man. It is suggested that centres who routinely analyse the parents of trisomy 21 referrals in an unbiased fashion should review their records. They will almost certainly contain useful information regarding the possible existence of this phenomenon and may even contain clues as to its nature. In addition to its undoubted scientific value, such data should prove useful in the genetic counselling of carriers of structural rearrangements.

Structural aberrations involving chromosomes other than 21 have occasionally been observed in families ascertained through the birth of a child with Down's syndrome. These usually involve apparently balanced familial reciprocal translocations. Those finding such associations may be of the opinion that there could be some mechanistic connection. The term 'interchromosomal effect' has been coined to refer to such a hypothetical interaction. These associations, however, remain rare and, apart from the recent large study of Lindenbaum et al., reports mainly describe a few isolated cases where the possibility of a fortuitous coincidence cannot be excluded. On the other hand, it seems reasonable to suggest that the records of most clinical cytogenetics laboratories may contain potentially useful information if it has been their policy over the years to perform non-selective banded analyses of the parents of Down's syndrome referrals.

This laboratory, which serves a population of ½ million, has maintained such a policy since 1973. During this period, 87 newborn referrals were found to have primary trisomy 21 Down's syndrome of whom three had parents with a structural abnormality, while others had parents exhibiting structural or numerical mosaicism. It is suggested that other, mostly larger, laboratories may search their records for such information. An accumulation of such results should be of extreme importance in determining the existence of an interchromosomal effect in man.

Materials and methods

The period of this study was from October 1973 to July 1985. During this time, 87 paediatric referrals up to three years of age were found to have primary trisomy 21 (group I). Also included in this study is a second group (group II) of nine older trisomy 21 subjects ranging in age from 10 to 54 years, who were born and clinically diagnosed as having Down's syndrome before chromosome analysis was available. Translocation and mosaic Down's syndrome subjects are not included.

In 60 of the group I referrals we obtained blood samples from both parents, in seven referrals samples from the mother only were analysed, and in one referral only the father's sample was received. Consequently we have cytogenetic records of 61 mothers and 61 fathers giving a total of 128 parents. No samples from parents from the group II referrals were received. It is important to emphasise that...
our standard policy to request samples from parents of group I referrals and over recent years these have been sent without the need for a special request.

Results

Of the 87 group I referrals, three were found to have a parent with a structural rearrangement not involving chromosome 21. There were two inversions, one carried by the mother which was not found in the proband (inv(4)(p14q23)), and one by the father which had been transmitted to the proband (inv(X)(p22q11)). About half the cells of this child also contained a very small unidentified supernumerary chromosome. In addition, there was an apparently balanced reciprocal translocation carried by a mother which had been transmitted in the balanced form to the proband (t(1;13)(q23;q22)). Thus, of the 128 parents examined on a non-selective basis other than by the livebirth of a child with Down’s syndrome, we have a frequency of 2/128 (1-56%) for pericentric inversions and 1/128 (0-78%) for reciprocal translocations or 3/128 (2-3%) structural abnormalities.

In addition to these cases, the brother of one of the nine group II referrals was found to have a reciprocal translocation between chromosomes 7 and 13 (t(7;13)(p15q32)) which was not found in the proband. Their sister was found to have a normal mitotic karyotype as was the daughter of the translocation carrier. A later pregnancy of the carrier’s wife terminated as an intrauterine death with an unbalanced karyotype (46.XX,der(13),t(7;13)(p15q32))pat. The parents of these brothers could not be examined, but conceivably one could also have been a translocation carrier.

During the period of this study, a parent of each of three further group I referrals were found to exhibit mosaicism: (1) 46,XX/47,XXX (77-3 or 4%); (2) 46,XY/46,XY,t(7;14)(q32;q11) (23-2 or 8%); and (3) 46,XX with 40% of cells with non-specific damage including gaps, breaks, and supernumerary chromosomes.

Discussion

The first suggestion that interchromosomal effects may be present in man was made by Lejeune.3 From a study of published reports, Mikkelsen4 estimated that women carrying Robertsonian translocations between D group chromosomes had a significantly higher risk (of about 2%) of having a child with Down’s syndrome. Aurias et al5 reported three reciprocal translocations and two pericentric inversions (excluding the polymorphic inversion of 9qh) not involving chromosome 21 among 762 children with trisomy 21 and their parents. These are in excess of what might be expected and the authors suggested that the meiotic segregation of chromosomes such as 21 may be influenced by balanced structural rearrangements following the hypothesis of Lejeune.3 Stoll et al6 have also suggested the existence of an interchromosomal effect between non-disjunction and balanced translocations.

Most of the data on which those analyses were based were from a few or even single cases with the attendant hazard of biased reporting. Jacobs7 has pointed out the dangers of putting too much weight on analyses based on anecdotal evidence and biased data. In fact, she claims that critical analysis does not support the proposition of an interchromosomal effect in man. It must also be remembered that the balanced structural rearrangements were found in the parents of trisomic subjects. The hypothesis of Lejeune,8 on the other hand, suggests a mechanistic connection the other way round with the structural rearrangement causing the trisomy. The real requirement is to determine the probability of a structural rearrangement resulting in a trisomy.

Only very recently9 has an effort been made to obtain unbiased data from a large series. As in our much smaller study, these data were obtained retrospectively with a consequent reduction in bias. However, they restricted their study to translocations and disregarded inversions and other structural rearrangements. They concluded that there was a considerable rise in the frequency of reciprocal translocations in the parents of children with regular trisomy 21 Down’s syndrome over the newborn population reported by van Dyke et al6 and that this may reflect a real interchromosomal effect in man.

The 95% confidence interval for reciprocal translocations in the newborn reported by van Dyke et al6 is 0-01 to 0-19% (mean 0-10%) and in our study is 0-1 to 4-4% (mean 0-78%), while for pericentric inversions the newborn interval is 0-00 to 0-13% (mean 0-06%) and in our study is 0-4 to 5-6% (mean 1-56%). In both cases there is a marked rise over the newborn population. In this study, the mean overall frequency of structural rearrangements is 2-34%, 10 times that of the newborn frequency reported by van Dyke et al6 of 0-23%. Tentatively, we suggest that our figures also support the contention of an interchromosomal effect.

In addition to the need for further evidence of this phenomenon, several questions remain to be answered. It is of importance, for example, to try to determine if the carrier parent is the source of the non-disjunction. The maternal age effect associated with Down’s syndrome may differ in translocation carriers. The sex of the translocation carriers may
affect the probability of non-disjunction. The nature of the structural rearrangement may also affect the chances of having a Down’s syndrome child. The answers to such questions may suggest the nature and mechanism of the interchromosomal effect and more directly allow for better genetic counselling of carriers. Consequently, we consider it important that as many diagnostic cytogenetic laboratories as possible review their records of the parents of primary trisomy 21 Down’s syndrome children. If they have been obtained in a regular unbiased fashion the results, especially if pooled with those of other centres, may shed some light on the questions posed above.

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References


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