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De novo translocation heterozygote with three reciprocal translocations

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SUMMARY An extremely rare case of a child with three balanced reciprocal translocations involving six different autosomes is described. These abnormalities have apparently arisen de novo and seem to have only relatively minor phenotypic effects. The meiotic possibilities are discussed and cytogenetic markers suggest that the damage may have occurred in a paternal gamete.

It is rare to find more than a single translocation in a person¹ and extremely rare to find more than two.² Complex chromosome rearrangements involving exchanges between three or more chromosomes in a circular fashion show certain similarities to the present case, in that as many as four or five derived chromosomes can be seen in the karyotype of the carrier.³⁻⁴ The observation of six de novo abnormal chromosomes in a live-born child is unrecorded to the best of our knowledge.

Case report

This boy presented at the age of 9 years because of maternal anxiety about his short stature. It was reported that he had always been short and had been overtaken by his sister who is 2 years younger at the age of 5 years. At the age of 10 years his height was 4 cm below the 3rd centile, and his height velocity over the previous year had been just below the 10th centile. Radiology at this time showed his bone age to be about 2 years delayed.

Despite this problem he was found to be a healthy, well proportioned boy whose performance at school

was average. He showed no indications of malabsorption. Both his parents and his two sisters were of average height and no one else in the family was reported to have short stature. There was no evidence of consanguinity.

The mother appeared to have had a normal uneventful pregnancy and an induced birth at 38 weeks' with normal delivery. At birth the child was found, at 2497 g, to be 100 g below the 10th centile. The neonatal period was normal and developmental progress was satisfactory, if a little slow. His intelligence remained normal but his speech was rather slow and he had been given speech therapy at 4 years of age.

Materials and methods

Chromosome preparations were made from conventional phytohaemagglutinin stimulated cultures of whole blood. The metaphases were G banded⁵ and sequentially C banded.⁶

Results

One hundred cells were examined revealing a grossly abnormal karyotype: 46,XY,t(1;7)(q42;q22), t(5;9)(q31;q32),t(13;16)(q21;q22) (figs 1 and 2). The three translocations appeared to be reciprocal and balanced. Parental karyotypes were normal.

Comparison of C band polymorphisms showed that the derived chromosomes der (1), der (9), and der (16) were of paternal origin while the normal homologues were from the mother (fig 2). In addition, the mother had a marker chromosome 13ps+ which was unaltered in the child, while the father had a marker chromosome 5ph+ which could be identified as the derived chromosome 5 in the child

FIG 1 Karyotype of proband: 46,XY,t(1;7),t(5;9),t(13;16) (G banding).

FIG 2 Diagram illustrating the breakpoints involved in the three reciprocal translocations.

(fig 3). This indicates that at least five of the six chromosomes participating in the translocations originated from the father. The sixth chromosome (No 7) had no distinguishing features to enable its origin to be determined.

Discussion

Although it is theoretically possible that the three separate reciprocal translocations occurred at different times, it is more plausible to consider them to be the result of a single event, arising either in the zygote or in a parental gamete. While some authors have considered the former possibility to be more likely,³ the weight of evidence in the present case suggests the latter. It is fortunate that five of the six derived chromosomes have outstanding cytogenetic markers allowing unambiguous parental identification. The odds against finding five chromosomes

FIG 3 Partial karyotypes (C banding) showing the probable paternal origin of the derived chromosomes 1, 9, 5, 13, and 16.

FIG 4 Diagram illustrating the meiotic segregation possibilities in the triple translocation heterozygote.

from the same parent participating in three translocations if the event(s) occurred post-fertilisation is ($\frac{1}{8}$)⁴, so that fertilisation by a damaged sperm becomes the most likely explanation. It is interesting that the only cytogenetic markers in the case of Fitzgerald *et al*³ were also paternal in origin and the father was noted to have had a bacterial rash at the approximate time of conception.

There was no evidence of imbalance in any of the three translocations to account for the mild phenotypic effects in the child, so that the short stature may be unrelated to the chromosome damage or may be the result of sub-microscopic addition or deletion.⁴ Pre- and immediately post-conception history gives no indication of any specific aetiology, although something has caused what may be described as a 'mutation shower'.

Meiosis is likely to be complicated and error-prone since one can predict three pachytene crosses as the most likely meiotic configurations. However, viable gametes have been formed in cases where three chromosomes are involved in a single translocation⁷⁻¹² and in double reciprocal translocation carriers.¹ This, however, is most likely to be a very biased sample as the majority of such cases are detected via abnormal unbalanced offspring.

There is no theoretical expectation for the segregation ratios of human reciprocal translocations since the relative frequencies for the orientation of a specific ring or chain are unknown.¹³ In plants and insects, orientation is affected by the relative length of the chromosomes and translocated segments, centromere distance from breakpoints, and chiasmata frequency and position.¹⁴ However, no observations have been made of the orientation of translocation configurations in humans, so that the basis for predicting how a specific translocation will segregate can merely be guessed at. If we make the somewhat unrealistic assumption that four terminal chiasmata form per pachytene cross configuration and further suppose that each of the three configurations adhere to the simplest of segregation rules (that is, alternate, adjacent 1, adjacent 2 disjunctions occurring with equal frequency), we can predict a minimum of six possible gamete types from each, making 216 (6³) types of gametes in total (fig 4). Crossing over and 3 : 1 disjunction will undoubtedly further compound the complexity of this situation (see fig 4), although no adequate basis for the latter event can be given.¹⁵

Therefore, one balanced or normal sperm to every 27 unbalanced or inviable sperm is certainly an overestimate. It is therefore highly likely that this boy will be infertile. In the event of partial fertility, antenatal diagnosis would be essential.

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