Familial paracentric inversion of chromosome 15 (q15q24)

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SUMMARY A paracentric inversion of chromosome 15 was observed in the father of two infants who died 29 days and 24 hours, respectively, after birth. The same inversion was found in two sisters of the proband.

An unusual family is described here in which a paracentric inversion of chromosome 15 is probably associated with partial infertility.

Case reports

A clinically healthy, non-consanguineous couple (fig 1, II.2 and II.3) came to our attention following the birth of three children, two of whom (III.1 and III.3) had multiple abnormalities and died in the neonatal period. The clinical and necropsy features are listed in the table.

CYTOGENETICS

Standard techniques were used for lymphocyte cultures. The chromosomes were analysed after GTG and RBA banding. The karyotype of the proband (II.2) was 46,XY,inv(15)(q15q24) (figs 2 and 3). The same inversion was found in his two sisters (fig 1).

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>III.1</th>
<th>III.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of gestation</td>
<td>35 weeks</td>
<td>36 weeks</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2440 g</td>
<td>3230 g</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Skin</td>
<td>Pink, hyperelastic</td>
<td>Widespread cyanosis</td>
</tr>
<tr>
<td>Head circumference</td>
<td>28 cm</td>
<td>32 cm</td>
</tr>
<tr>
<td>Anterior fontanelle</td>
<td>3 x 2 cm</td>
<td>3 x 2 cm</td>
</tr>
<tr>
<td>Nose</td>
<td>Small</td>
<td>Depressed bridge</td>
</tr>
<tr>
<td>Eyes</td>
<td>Skin bridges on median line</td>
<td>Normal</td>
</tr>
<tr>
<td>Ears</td>
<td>Normal</td>
<td>Low set</td>
</tr>
<tr>
<td>Chest</td>
<td>Malformed</td>
<td>Malformed</td>
</tr>
<tr>
<td>Ribs</td>
<td>Normal</td>
<td>Horizontal arrangement</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Voluminous, recti diastasis</td>
<td>Extremely broad</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Hypotonic</td>
</tr>
<tr>
<td>Death</td>
<td>29 days</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

FIG 1 Family pedigree.

FIG 2 Partial karyotype showing inv(15)(q15q24).
Fryns and Van den Berghe\textsuperscript{3, 4} and Jordan \textit{et al}.\textsuperscript{5} tend to exclude any relationship between the various types of inversion and phenotype, with the exception, of course, of abortion. In our opinion, however, and that of others\textsuperscript{6–8} these and other apparently balanced aberrations are often found in cases with complex clinical pictures of uncertain aetiology. The phenotypic variability encountered in these cases may not be the result of a different breakpoint, but it may depend, in our opinion, upon the site of crossover producing various effects at gene level. In fact, a possible double exchange within the meiotic inversion loop would lead to a modification in a particular gene sequence causing a position effect and other mechanisms of action. Moreover, the difficult pairing of the homologues in the inverted segment could give rise to addition or deletion of bases. A gene disorder would thus occur which, depending on the type or quantity of the variable information involved, could be at the origin of the clinical findings and explain why these are not constant and differ from each other. This would also support the principle by which an inversion may suppress exchanges due to difficulty in recombination and is a protection to certain gene sequences.

For example, in the present family, this idea is supported by the clinical pictures in III.1 and III.3 which are reasonably similar, thus suggesting that the segment involved is more or less the same and may be a preferential site for exchange. It is not yet possible to confirm this hypothesis because of incomplete human gene mapping and lack of knowledge regarding gene regulation. Nevertheless, new information may emerge from specific enzymatic tests for the mapped loci. (These tests could not be done in the present study because we did not see the infants.) In our opinion, however, this type of chromosomal modification, even if apparently balanced and showing no effect upon the live offspring generally, may in fact represent a risk factor in reproduction.

It is difficult to evaluate the risk involved on account of the numerous implications, but it may be possible to quantify the risk from published reports and thus throw further light on various aspects of this problem.

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