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 Clinical features of III.1 and III.3.

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

FIG 1 Family pedigree.

FIG 2 Partial karyotype showing inv(15)(q15q24).

FIG 3 Breakpoints and sequence of paracentric inversion: $inv(15)(pter \rightarrow q15::q24 \rightarrow q15::q24 \rightarrow qter)$.

Subjects III.1 and III.3 were not brought to our attention and therefore we were unable to carry out cytogenetic studies on them.

Discussion

Paracentric inversion of chromosome 15, observed in several members of the present family, appears to have been transmitted by I.1 and to be the cause of reduced fertility with spontaneous abortion in generations II and III, neonatal death (III.1 and III.3), and infant death (II.1 at 11 months and II.4 at 2 months).

Are these events correlated with the chromosomal rearrangement or are they quite independent? It is worth reporting cases of inversion, particularly those of a paracentric nature, because of their implication in genetic counselling. While the inversion itself has no phenotypic effect, it constitutes, theoretically, a risk to heterozygote carriers of producing unbalanced offspring.

If a single crossover occurs in the inverted segment of a paracentric inversion this may lead to the production of acentric and dicentric chromosomes and to reduced fertility.

As might be expected, this type of rearrangement is only rarely described in cases of reduced fertility,^{1,2} whereas numerous reports include inversion in various pathological conditions, which, however, fail to offer an explanation for the cause.

Fryns and Van den Berghe^{3,4} and Jordan *et al*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 others⁶⁻⁸ 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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