Familial pericentric inversion 19

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SUMMARY Several members in two families were found to have a pericentric inversion of chromosome 19. A review of four previous cases, together with those reported here, suggests that inversion of chromosome 19 is not related to the phenotypic features of the probands. Furthermore, there has been no report of an affected subject resulting from a duplication deficiency product of inverted chromosome 19 among the offspring of inversion heterozygotes. The suggested association of aneuploidy in the inversion carriers is also discussed.

Pericentric inversion of chromosome 19 has been described in only four cases.¹⁻⁴ This paper reports two additional families with inversion 19 carriers, all of whom are phenotypically normal.

Case reports

In family 1, the proband (fig 1, II.2), a healthy 25-year-old female, was referred for cytogenetic study because of the early death of her newborn infant. The infant girl was born at term, weighing 3.5 kg, to the proband, who was gravida 1, para 0, aborta 0. The pregnancy and delivery were uncomplicated. Physical examination at birth in an outside hospital revealed a normal infant without any congenital malformations. At the age of 4 days the infant developed jaundice, lethargy, and acidosis. A diagnosis of 'Reye's syndrome' was proposed and

the infant died at 13 days of age. The necropsy examination revealed acute liver necrosis. Chromosome study was not performed on the infant. The family history was negative for birth defects, mental retardation, and miscarriages. There was no consanguinity.

The proband of family 2 (fig 2) presented with bilateral congenital cataracts of unknown aetiology. There were no other congenital malformations and intellect was within normal limits. All other family members were clinically normal.

CHROMOSOME STUDIES

In family 1, G banded, C banded, and unbanded chromosome preparations obtained from peripheral lymphocyte cultures revealed pericentric inversion 19 in all cells of the proband. The normal 19 had a centromeric dark band located mainly on the short arm. In the abnormal chromosome 19, this single centromeric dark band appeared to have been split

FIG 1 Pedigree of family 1.

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FIG 2 Pedigree of family 2.

FIG 3 *G banded karyotype of proband of family 1: 46,XX,inv(19)(p11q13)mat.*

FIG 4 *G banded (A), unbanded (B), and C banded (C) F and G group chromosomes of the proband of family 1.*

FIG 5 *G banded F and G group chromosomes from two different cells of the proband of family 2.*

into two small bands, one located at the centromere and the other one half way down the long arm. If we assume that the inverted chromosome arose from a normal 19 of the same morphology as its homologue, then one break would have to have been in p11 in order to split the dark band, and the other break would then be distally placed in the q arm (q13). Therefore, the proband's karyotype could be formulated as: 46,XX,inv(19)(p11q13)mat (fig 3, 4). However, it may not be safe to assume that both homologous chromosomes had the same morphology.⁵ If the chromosome 19 that gave rise to the inversion had the dark centromeric band extending to both arms, it would be difficult to distinguish between the above breakpoints and breaks at p13 and q11. The mother of the proband, a phenotypically normal 54-year-old female (fig 1, I.2), had the identical inversion 19. Both the husband and the father of the proband (fig 1, II.1 and I.1, respectively) had normal karyotypes.

The abnormal 19 in family 2 had the same appearance as that in family 1. As described above, it could be interpreted as either 46,XX,inv(19)(p11q13) mat, or as inv(19)(p13q11)mat (fig 5).

Discussion

The cytogenetic findings and method of ascertainment of the previously reported cases of inversion 19, along with the cases presented here, are summarised in the table. In all four previous cases the chromosome inversion appears to be unrelated to the clinical problems of the proband. In the first family presented here, the proband is phenotypically normal. In the second family the proband has cataracts only, which appear to be unrelated to his

TABLE Cytogenetic data on pericentric inversion 19 carriers and method of ascertainment

Karyotype	Method of ascertainment	Parental karyotype		Affected sibs or offspring
		Father	Mother	
46,XY,inv(19)(p13q12 or 13) ¹	Delayed puberty	inv(19)	—	—
47,XY,inv(19)(p13q13)+21 ²	Down's syndrome	—	inv(19)	—
46,XY,inv(19)(p13q13) ³	Survey of mentally retarded patients	—	inv(19)	—
47,XY,+i(17p),inv(19)(p13q13) ⁴	Psychomotor retardation	inv(19)	—	—
46,XX,inv(19)(p11q13)*	Had an infant who died in newborn period	—	inv(19)	—
46,XY,inv(19)(p11q13)†	Bilateral cataracts	—	inv(19)	—

*Proband in family 1

†Proband in family 2

chromosomal abnormality. Therefore, we may conclude that inversion 19 carriers are either phenotypically normal, or that their clinical features are unrelated to the chromosome inversion. This is expected since there is no obvious deletion or addition of the chromosome 19 material.

The question arises whether this particular inversion would give rise to genetically unbalanced gametes through crossing over within the inverted segment. If crossover occurs within the inversion loop, unbalanced gametes with duplication deficiency of chromosome 19 would be produced. Liveborn infants with congenital anomalies resulting from unbalanced products of inversion involving different chromosomes other than 19 have been reported, and they are reviewed by Trunca and Opitz.⁶ No such cases, however, have been found in the sibs or offspring of inversion 19 carriers in the previous reports (table). Although no cytogenetic study was performed on the infant of the proband in the first family reported here, she had no congenital anomalies or prenatal growth retardation to suggest a chromosomal abnormality.

The risk of an inversion carrier having a child with congenital anomalies as a result of unbalanced gametes depends on the probability of meiotic crossover occurring within the inversion loop and on the probability that a child with an unbalanced recombinant chromosome will be born alive.⁶ If the inversion is small, the probability of a crossover occurring within the inverted segment is small since the number of crossovers appears to be proportional to chromosome length. However, the inverted segment in the families presented here comprises approximately half of the 19, so the probability of crossovers within this inversion loop resulting in abnormal recombinant chromosomes is comparatively high when the overall size of the chromosome is considered. If a recombinant chromosome were produced as a result of a crossover within the inversion loop, this chromosome would have a long duplicated or deficient segment relative to its overall

size since the duplication deficiency involves the chromosomal segment outside the inversion loop. In the present cases, the segments outside the inversion loop comprise approximately one half the total length of the chromosome. Therefore, most of the embryos or zygotes carrying such a large duplication deficiency chromosome might be lost through failure of implantation or early spontaneous abortion.

Whether this type of inversion is associated with a higher risk of non-disjunction resulting in an aneuploid condition in the inversion carriers is a question that has been raised.⁷ In two of the five cases with inversion 19 there was associated aneuploidy (table). Two cases of Turner's syndrome associated with pericentric inversion of chromosome 2 have been reported.^{8,9} Léonard *et al*⁷ have reported a case of Turner's syndrome and five cases of autosomal trisomy associated with pericentric inversion of various chromosomes. In reviewing our file, accumulated since 1973, we found 13 cases with inversion 9, one case with inversion 3, one case with inversion 5, and one case with inversion 10 in approximately 260 abnormal karyotypes. In these 16 inversions, three inversion 9 cases had associated aneuploidy.

One should be cautious in interpreting such data to mean that inversions interfere with meiotic disjunction resulting in an aneuploidy in the inversion carriers. These are heavily biased figures obtained from a few selected subjects that were referred for cytogenetic studies because of the suspected chromosomal abnormalities. As such, these are instances of inversions detected in patients with chromosomal aneuploidy, not instances of aneuploidy found in patients ascertained as inversion carriers. Therefore, the associated aneuploidy in inversion carriers may be a coincidental finding and its frequency in this group the result of ascertainment bias.

Given the uncertainty of the significance of this cytogenetic finding, how should one counsel a carrier of a pericentric inversion? Sutherland *et al*⁸

proposed separate consideration of families in which there has been a patient with a recombinant chromosome. The risk of recurrence in such families was estimated to be 5 to 10%, depending on the sex of the carrier. In the absence of an affected subject with a recombinant chromosome in the family, they estimated the risk to be about 1%. We feel, however, that prenatal cytogenetic diagnosis should be offered to all inversion carriers except for those carrying pericentric inversion of chromosome 9, since apparently no unbalanced offspring have resulted from this frequent condition.⁶ Although our report suggests that pericentric inversion of 19 is also not associated with affected unbalanced live-born infants, future studies are needed to determine whether or not prenatal diagnosis will be necessary for these carriers.

Finally, it is noteworthy that the dark narrow band halfway down the long arm of the inverted 19 chromosome of the proband in family 1 was C and G band positive (fig 4). This provides evidence that a C and G positive band was split by a break, which is thought to be a very rare event.

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