High resolution of a small pericentric inversion of chromosome 11

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SUMMARY A pericentric inversion 11 (p11q13.3) segregating in two generations is described. A high degree of resolution of the inversion was achieved by using prophase and prometaphase chromosomes from methotrexate-synchronised cells. The inversion occurred in a mother and three of her ten children. It had no detectable clinical consequences.

With better methods of chromosomal banding, increasing numbers of pericentric inversions are being detected. Some inversions do not appear to carry any appreciably increased risk of unbalanced offspring¹ and may even be referred to as harmless variants (for example, the common inversion in chromosome 9). Heterozygotes for other inversions have produced unbalanced offspring.² It has been proposed that 'large' inversions are more likely than 'small' ones to produce unbalanced offspring,³ but exceptions to this rule do occur. Careful reporting of adequately studied cases can help shed light on this problem.

We report here a previously unrecorded inversion of chromosome 11 which could be accurately characterised by the use of prophase and prometaphase mitoses.⁴ The inversion is compared to three previously reported pericentric inversions of chromosome 11.^{5,6}

Methods

Lymphocytes were cultured and harvested by standard methods. To one portion of each sample, methotrexate (Lederle) was added at a concentration of 10^{-7} M after 72 hours' incubation at 37°C. The methotrexate block was released 17 hours later by the addition of thymidine at a concentration of 10^{-5} M. The cells were then allowed to grow at 37°C for 5 to 5½ hours and treated with colcemid during the final 15 minutes. This was a modification of the methods described by Yunis⁴ and Yunis *et al.*⁷ Slide preparations were made and air-dried for 24 hours. G-banding,⁸ C-banding,⁹ and R-banding¹⁰ were used.

Received for publication 28 March 1979

Results

The proband was a 24-year-old woman married for 5 years to a healthy man. She was referred for chromosome analysis as a routine part of a thorough clinical investigation for primary sterility. There had been no miscarriages. She was markedly obese and was repeatedly found to have a high level of plasma testosterone. The hormonal imbalance was thought to be the most probable cause of her sterility.

The proband had inherited the inverted chromosome from her mother (fig 1) who had had 10 children, all healthy, and no miscarriages. Two of the proband's brothers had died in accidents. The remaining 7 sibs were karyotyped; two of these were inversion heterozygotes and five were not. The wives of the two brothers with the inversion had not had any miscarriages. The proband and her twin sister were dizygotic; they resembled each other very little. The proband's husband was cytogenetically normal.

FIG 1 Pedigree of family.

FIG 2 Karyotype of proband. Note metacentric appearance of inverted chromosome 11 (right)

The abnormality in one of the chromosomes 11 was first recognised in ordinary mid-metaphase mitoses by its almost metacentric appearance (fig 2). The breakpoints were difficult to determine from such cells, but prophase and prometaphase chromosomes were very useful (fig 3). The lightly staining band referred to as q13 in the Paris nomenclature had at least two fine dark bands detectable by high resolution techniques (fig 4A),⁴ while no such 'new' dark band was seen in the light band on the short arm side of the centromere p11. In favourable cells it could be clearly seen that the more proximal of the faint dark bands in q13 (q13.2) was displaced to the short arm, while the more distal one (q13.4) remained in the long arm. The inversion could thus be written $\text{inv}(11)(\text{p11q13.3})$ as illustrated in the diagram (fig 4B). Thus, even though this was a small pericentric inversion involving 15% of the chromosome or less, its effect on the position of the centromere (more

FIG 3 Prometaphase chromosomes 11 from two cells of proband. Inverted chromosome is to the right.

metacentric) was so definite that it was detectable at mid-metaphase. R-banding corroborated the above interpretation. In the right-hand (inverted)

FIG 4 (A) Diagram of prometaphase bands in normal chromosome 11. Designation of bands immediately adjacent to centromere conforms with the Paris nomenclature, although the bands observed would suggest a different designation. Arrows indicate break-points. (B) Diagram of bands in inverted chromosome 11.

FIG 5 (a) Chromosomes 11 from a G-banded and an R-banded cell from a member of the present family. *Inv(11)(p11q13.3)* chromosome to the right. (b) Chromosomes 11 from a G-banded and an R-banded cell from the proband described by Simola *et al.*⁵ *Inv(11)(p15q23)* chromosome to the right.

chromosome in fig 5a the major feature is as expected: the dark band q13 is smaller and the dark band p11 correspondingly larger in the inverted chromosome.

C-banding showed no abnormality. The inverted

chromosome could be identified even without sequential banding by its metacentric appearance. Its C band was located in the middle of the centromere as expected.

Discussion

We are aware of three other pericentric inversions of chromosome 11, namely an *inv(11)(p11q11)* detectable by C-banding only,⁵ an *inv(11)(p15q14)* described by Boué and Boué,⁶ and an *inv(11)(p15q23)* described in this laboratory.⁵ The first two are quite different and can hardly be confused with the present one. However, the third greatly resembles the present one in appearance, since both lead to a nearly metacentric chromosome 11 whose major bands appear undisturbed. In spite of the apparent similarities, the breakpoints have been interpreted considerably differently. According to Simola *et al.*⁵ their inversion comprised most of the chromosome (p15q23), while the present one is small (p11q13). Since it is of considerable interest to establish the extent of the inverted segment in each reported case we re-examined the chromosomes of the proband described by Simola *et al.*⁵ The present

findings (fig 5b) support the earlier interpretation. Note, for instance, the R-banded chromosomes at the extreme right in each line. In the lower line (the patient of Simola *et al*) the dark bands in the end regions (p15 and q23) are affected but the pericentromeric bands are unaffected, while in the upper line (present proband) the pericentric dark bands are of altered appearance with respect to the normal homologue. We conclude that in the present family a very small, and in the family described by Simola *et al*,⁵ a very large pericentric inversion is segregating.

From the pedigree it can be deduced that the present inversion carries little risk for unbalanced offspring or even miscarriages. This knowledge may possibly be used in the clinical handling and counselling of this family. However, even though 'large' inversions tend to carry a higher risk for unbalanced offspring than 'small' ones,³ we confirm here the presence of a large inv(11) in a previously described family with no malformed children.⁵ Conversely, 'small' inversions have occasionally produced unbalanced offspring. While this is biologically quite understandable, it implies that all newly detected pericentric inversions must be regarded as potentially harmful. Only careful family studies in each case can give a clue to the likely outcome of meiosis and gametogenesis in the individual carrier.

This work was supported by grants from the Sigrid Jusélius Foundation and the Nordisk Insulinfond.

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