46,Xinv(Yp+q-) in Four Generations of an Indian Family

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Pericentric inversion of the human Y chromosome has been reported infrequently but it is known to be an inherited anomaly. Several individuals with such an inversion had concomitant karyotypic irregularities, amongst which trisomy 21, gonosome mosaicism, and the 47,XXY karyotype were common (Sparkes, Muller, and Veomett, 1970). This led to speculation that inversion of the Y chromosome signalled an increased tendency for non-disjunction to occur in the progeny of 46,Xinv(Yp+q-) carriers. The discovery by Walzer, Breau, and Gerald (1969) of an inverted Y in 2 of 1332 phenotypically normal newborn males suggested that the inversion might be relatively common.

The family reported here is descended from an immigrant pair who arrived in Durban during the 1880s from the Kathor province of India. The family was first identified when 3 of 4 sibs with congenital disorders were brought for investigation. It was found (Grace and Harris, 1970) that both sexes were affected; the parents were first cousins, and the affected boys and their normal father had a pericentric inversion of the Y chromosome. The present study was done in an attempt to find the origin of the unusual Y chromosome.

Family Study

The family, whose pedigree is shown in Fig. 1, consisted of 74 living males and 39 living females. Of the males, only one (III.7) refused to cooperate and 15 were not available for examination. Peripheral blood and buccal mucosal scrapes were taken from 58 males. Metaphase karyotypes were prepared from cultured lymphocytes: in every instance the karyotype was 46,Xinv(Yp+q-). Representative partial karyotypes are shown in Fig. 2. Preparations of buccal mucosa, buffy coat, and metaphase chromosomes were stained with 0.25% quinacrine dihydrochloride (Sigma) for 20 minutes.

The preparations were rinsed in tap water and mounted in buffer. Examination was done using a Zeiss microscope with ultraviolet illumination in conjunction with exciter filter BG 12 and barrier filters 53/44.

When first examined, typically fluorescent Y-spots were seen in only 6% of the interphase nuclei (Fig. 3) and a fluorescent Y chromosome was found in only 8 metaphase spreads. However, repeat examination of fresh slides after slight modification of the method (the concentration of the stain was increased to 0.5% and staining was done at 37° C) revealed that in almost every metaphase spread the Y chromosome was fluorescent (Fig. 4). There was little difference in the number of interphase nuclei showing a Y-spot; the highest score was 22% positive and the mean score of all buccal and lymphocyte preparations was 7%.

Consanguineous matings were recorded between the following pairs: III.5 and IV.3; III.4 and III.2; IV.1 and III.9; IV.17 and IV.28; V.3 and IV.29; and V.5 and IV.30. Very few of the children born to these pairs were abnormal: VI.1, VI.6, VI.7, and VI.8 showed only choreic ataxia and macular degeneration with gross lateral nystagmus. Few individuals had died prematurely: it was reported that IV.27 died aged 18 from a 'heart attack'; the sibs IV.7 and IV.8 died in infancy, as did V.1, from unknown causes; VI.26 was killed in an accident. A single female (IV.24) with Down's syndrome was reported: she was born of a 40-year-old mother and although the family denied access to her, it is reasonable to assume that she had age-dependent trisomy-21.

Discussion

Absence of fluorescence in interphase and metaphase preparations was reported in an infertile patient with an inverted Y chromosome (Retief and van Niekerk, 1971). It would seem that the cause of infertility was oligospermia: there is evidence that the fluorescent segment of the Y is not essential

FIG. 1. Family pedigree.

for normal male development (George and Polani, 1970; Borgaonkar and Hollander, 1971), probably because the male determinants are on the short arms (Jacobs and Ross, 1966). It has also been reported that short and dicentric Y chromosomes did not fluoresce (Borgaonkar and Hollander, 1971) whilst an exceptionally long Y was shown to have duplicated fluorescent segments (Bühler *et al*, 1971). There is no obvious reason why an inverted Y

chromosome should not fluoresce since there should be no significant loss of material from the long arms. In the subjects of this study the inversion involved only the portion of the long arms distal to the fluorescent segment.

It is difficult to explain the rarity of a Y-spot in the interphase nuclei of our subjects. Technical phenomena and observer error cannot be excluded but are unlikely because control slides from normal

FIG. 2. Partial karyotypes of 3 males showing D, E, F, and G groups and the inverted Y chromosome.

males were adequately stained and were correctly identified. Interpretation may vary: for instance, Lewin and Conen (1971) noted small but distinct Y-spots in the interphase nuclei of 3 individuals with a small Y, but Borgaonkar and Hollander (1971) reported similar individuals to be negative. Inter-individual variation has been reported (Van

der Hagen and Berg, 1970) and just as normal females may show a low percentage of cells with what appears to be a Y-spot (Conen, Lewin, and Vakil, 1971; Polani and Mutton, 1971), so some males might not show it. However, there is no explanation for this unexpected observation and further studies will have to be made.

FIG. 3. Y-spot in buccal epithelial nucleus.

The remarkable difference between the 1st and 2nd preparations of metaphase chromosomes made during this investigation serve as further indication for caution in interpreting the results of fluorescent stains.

As Sparkes *et al* (1970) recounted, several authors have suggested a possible relationship between the presence of the inverted Y and subsequent non-disjunction in the offspring. That only a single person, a female, in the large family reported here had what was almost certainly age-dependent trisomy-21 suggests that there is no correlation between inversion of the Y chromosome and the dynamics of either the autosomes or X or Y. It is interesting to note that fertility and viability were not impaired and no fetal wastage was recorded. No subject complained of contrasexual features and the carriers of the abnormal chromosome showed no phenotypic irregularities. These observations confirm those of Walzer *et al* (1969) that inversion of the Y chromosome may be a common variant in phenotypically normal males.

In this family it seems probable that each of the 2nd generation males inherited an inverted Y chromosome, it being very improbable that the inversion arose spontaneously in each of the 4 sibs. Therefore, the unusual chromosome must have been donated by I.1, but beyond this ancestor the family history is remote and further deductions concerning the origin of the benign structural rearrangement of the Y chromosome cannot be made.

Summary

In 58 males from 4 generations of an Indian family in Durban, the Y chromosome showed peric-

FIG. 4. Dark field photomicrograph showing the fluorescent inverted Y chromosome in a representative metaphase spread. A non-fluorescent photomicrograph of the same metaphase is also illustrated.

centric inversion. The marker chromosome was fluorescent in the metaphase state but rarely in the interphase nucleus. Implications of this observation are discussed. The rearrangement of the Y chromosome is not pathogenic; it does not impede the production of viable, fertile sperm and it does not predispose to non-disjunction of autosomes or gonosomes in the progeny. It is suggested that the inversion has been in the family for more than 6 generations.

We wish to thank the family for their cooperation, and Dr B. G. Grobbelaar, Director of the Natal Institute of Immunology, for permission to publish this report.

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