POLYMORPHISM OF CHROMOSOME 9 AND REPEATED FETAL LOSS

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SUMMARY

Variations in chromosome 9 were observed in 3.99% of 301 couples with history of reproductive loss. This included elongation of heterochromatic region and inversion. In two consanguineously married couples 9qh+ was shared by both the partners. This variation was also associated with Yqh+ or 22ss in two men. Pericentric inversion in chromosome 9 was found to inherited in two instances of four cases examined. Chromosomal analysis of the abortuses of these carrierrs is necessary to draw an inference on their role in the induction of abortions.

INTRODUCTION :

Chromosome 9 is considered to be highly susceptible to structural rearrangements such as inversion and elongation of the heterochromatic region (Hansmann 1976). Increased incidence of these anomalies was reported in couples with history of abortions and those having congenitally abnormal children (Turleau et al. 1979; Tibeletti et al. 1981; Andrews and Roberts 1982; Ford et al. 1982, 1983; Ghosh et al. 1983). Some of polymorphisms have been considered to be normal variations found in general population. (De la Chapelle et al. 1974; Hansmann 1976; Metaxotou et al. 1978).

The incidence of heterochromatic variations of chromosome 9 in 301 couples with history of reproductive loss observed has been presented in this communication.

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MATERIALS AND METHODS :

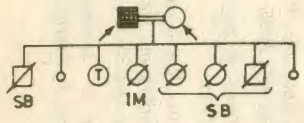
Cytogenetic investigations were carried out in 301 couples with history of fetal loss. Chromosome preparations were obtained from cultural peripheral blood lymphocytes following the method described by Hunderford (1965). G-banded (Seabright 1971) chromosomes were analysed from each individual. In case of variations, their nature and type were confirmed employing C- banded (Summer 1972) and Ag-NOR banded (Howell and Black 1980) preparations.

RESULTS :

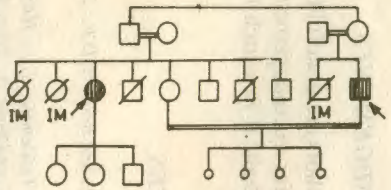
Eight cases of 9qh+ and four cases of inversion in chromosome 9 were observed (Table

Fig. 1

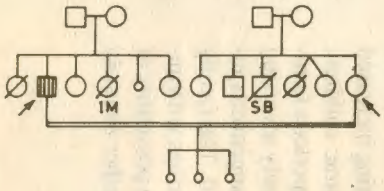
a) Couple no.RA12



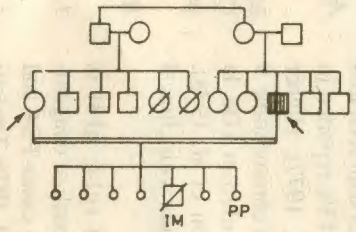
b) Couple no.RA24*



c) Couple no.RA69**



d) Couple no.RA84



46,XY/XX,9qh+

46,XY,9qh+,Yqh-

T 46,XX

SB Still birth IM Infant mortality PP Present pregnancy

* Both partners of couple with 9qh+ variant

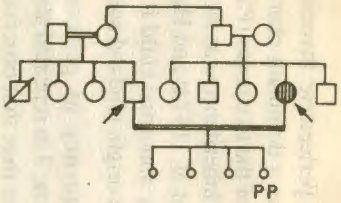
** Familial incidence

Contd...

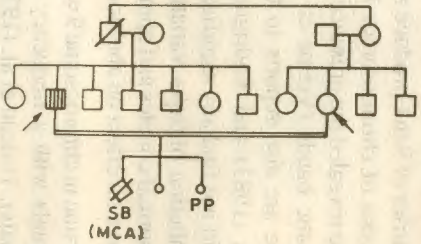
Fig. 1 Contd.

e) Couple no.RA101

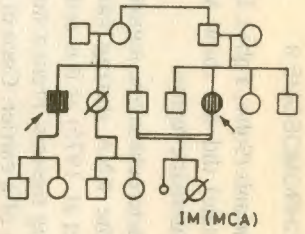
f) Couple no.RA104



g) Couple no.MA30



h) Couple no.MA48*



46,XY/XX,9qh+

SB Still birth IM Infant mortality

MCA Multiple congenital abnormalities PP Present pregnancy

* Both partners of couple with 9qh+ variant

1) among the 301 couples examined. Though other abnormalities were also observed only those instances of polymorphism of chromosome 9 are recorded in this communication ELONGATION OF HERERochromatic REGION (9qh+)

This variation was found in the male partners of 5 aborters (RA12, RA69, RA84, RA101, MA30),in female partner of couple RA104 and in both spouses of two couples (RA24, MA48) (FIG.1) 9qh+ was also associated with Yqh+ variation in the male partner of couple No. RA12 (FIG.3). Elongation of heterochromatic region was, however, not observed in their live female child.

The male partners of RA24 and RA69 who were carriers of 9qh+ had low sperm count (30-33.35 millions/ml). A male child was later born to couple RA69. Long period of infertility was reported in RA104 where the female partner was the carrier of this variation.

PERICENTRIC INVERSION IN CHROMOSOME 9

Male partners of two couples (MA68, PS5) and female partners of another two couples (RA49, PS4) exhibited this variation (Fig.2). The

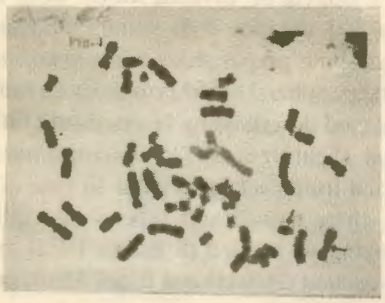


Fig.3 G-banded metaphase showing 9qh+ and Yqh+ variation in the male partner of couple No. RA12

karyotype observed was : 46, XY or 46, XX, inv(9) (pll; q13) (Fig.4).

In each of the couples, PS4 and PS5 (both consanguineous), there was birth of a congenitally abnormal child. Inversion 9 was found to be hereditary. The male partner of PS5 in addition possessed tandem satellites on chromosome 22.

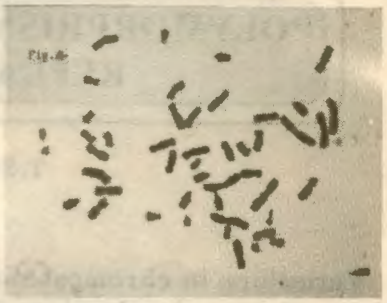


Fig.4 A) Densitometric profile of normal chromosome 9
B) Densitometric profile of inverted chromosome 9

Three (PS4, RA49 and MA68) of these four couples also have normal children.

DISCUSSION:

There are reports suggesting association of variation of chromosome 9 [inv(9) and 9qh+] with reproductive loss (Turleau et al. 1979; Andrews and Roberts 1982; The et al. 1982; Ghosh et al. 1983; Lyberatou-Moraitou et al. 1983). In the present study, 12 of the 301 couples showed these variations (Table 1) exhibiting a frequency of 3.99%.

Sharing of the same variation (9qh+) with their spouses was observed in two consanguinously married couples (RA24 and MA48). Fryns et al. (1984) reports 9qh+ in the aborted fetus of a couple where both parents carried the variants of chromosome 9 [9qh+, inv(9)]. Ford et al. (1983) observed that recurrent aborters carry variants of 9 along with variant combination of other chromosomes. The male partner of couple,

RA12 possessed two variants (9qh+, Yqh+). His only living child (female) did not show any anomaly in the heterochromatic region.

Variation in the heterochromatic region is expected to affect the RNA during early embryogenesis (Stahl et al. 1975) as it is active in RNA synthesis during meiosis. From a study on the unfertilized ova of a carrier, Coco et al. (1986) reported that carrier of 9qh+ produce abnormal gametes. Analysis of chromosomes 1,9 and 16 at prometaphase revealed the presence of eu- and hetero-chromatic bands (Verma et al. 1984). However, there are also reports to the contrary. Maes et al. (1983) and Rodriguez-Gomez et al. (1987) did not find any significant difference in the distribution of 9qh+ variation between aborters and normal couples and opined that this variation to have no effect on abortions.

Pericentric inversion in chromosome 9 was observed in 4 individuals with a frequency of 0.66% (4/602 individuals). Turleau et al. (1979) observed a three-fold increase (3/826 individuals 0.37%) of this anomaly in couples with fetal loss compared to the frequency of 0.13% reported in general population (Lubs et al. 1977). Higher incidence (1%) of inversions in chromosome 9 was reported in general population (De la Chapelle et al. 1974; Metaxotou et al. 1978). These studies include also patients with clinical abnormalities.

Pericentric inversion (9) (p11; q13) is found to be associated with the birth of congenitally abnormal children in two cases PS4 and PS5. There are reports (Boue et al. 1975; Tibiletti et al. 1981; Tho et al. 1982) suggesting increased risk of those couples having trisomic children. Fallstrom and Wahlstrom (1979) reported a family whose members presented not only inversion in 9 but also other structural rearrangements involving the chromosomes 9 and 10. The family had two severely malformed offsprings with unbalanced karyotype, suggesting the possibility of one structural change inducing another anomaly in the karyotype.

The pericentric inversion is found to be inherited as a dominant character in the family members of the two cases (PS4, PS5) examined. Dominant inheritance was recorded also by De la Chapelle et al. (1974) and Hansmann (1976). In a clinically abnormal child it was reported to be de novo in origin (Judand and Marchese 1987).

Frequency of pericentric inversion in chromosome 9 in repeated aborters was reported to be lower than that observed in the parents of trisomy-21 (Bourrouillou et al. 1985, 1986). In a survey of the literature on couples with history of abortions Campana et al. (1986) reported low incidence of inv(9). Husselein et al. (1982) however, did not consider this variation to be important. The paucity of data precludes an evaluation of the exact role of this anomaly in repeated abortions. Cytogenetic analysis of the abortuses of the couples with polymorphism of chromosome 9 may help in the elucidation of these variations in reproductive performance, if any.

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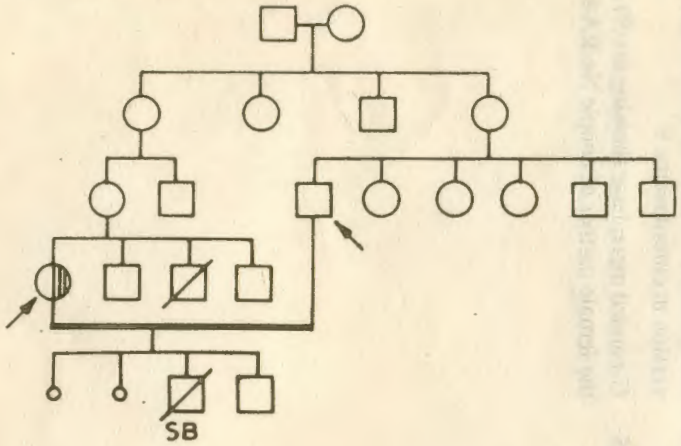
Fig.1 Pedigrees of individuals possesing the 9qh+ variation

Fig.2 Pedigrees of individuals possesing inversion in chromosome 9

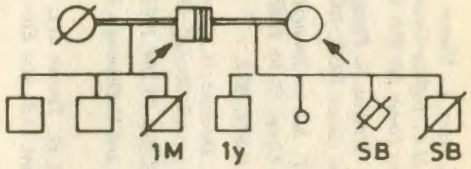
Fig.5 G-banded metaphase showing inv(9) in the female partner of couple No.RA49

Fig. 2

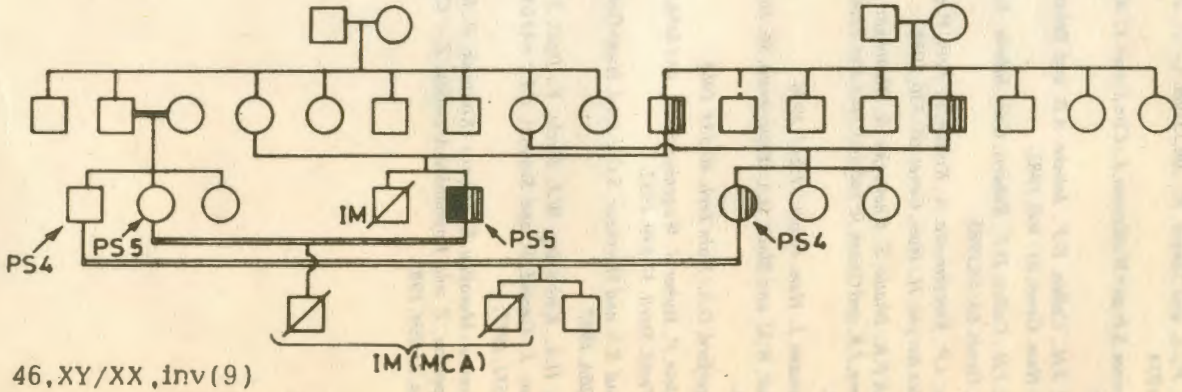
a) Couple no.RA49



b) Couple no.MA68



c) Couple no.PS4 and Couple no.PS5



46,XY/XX,inv(9) (Plate-10a)

46,XY,inv(9),22ss (Plate-10b)

SB Still birth IM Infant mortality MCA Multiple congenital abnormalities (Spleen belly syndrome)