

# Maternal inheritance of a 10/15 translocation in a female with a history of obstetric problems

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## ABSTRACT

The karyotype 46,XX, -10, -15, t(10;15) (p15;q22) was observed in a lymphocyte culture of an Indian female with multiple abortions. Similar chromosome abnormalities were present in her mother, one brother, and three of her sisters. The presence of ascitis, cyanosis, and hepatic renal problems in her three daughters indicated possible effects of such chromosomal rearrangements.

## INTRODUCTION

Chromosomal abnormalities have long been suspected to be responsible for birth defects and in many cases for cancer predisposition (Pathak, 1983 and 1992; Pathak *et al.*, 1989). Of these, balanced translocations are the most frequent causes of miscarriages, malformed infants, and sterility in carriers (Giovanni *et al.*, 1983; Therman, 1985). In a survey of 25,217 newborn infants, the incidence of such chromosomal abnormalities was estimated to be between one and two per 1,000 liveborn children (Nielsen and Sillesen, 1975; Hamerton *et al.*, 1975). Furthermore, the risk of miscarriages and of births of malformed and/or mentally retarded children depends on the types of inherent translocations (Aurias *et al.*, 1978). Translocations involving human chromosomes 10 and 15 have been previously reported in family

members experiencing recurrent abortions (Bourrouillou *et al.*, 1986). In most of these studies, the breakpoints in chromosomes 10 and 15 appear to be different.

## CASE REPORT

A 26-year old phenotypically normal Indian female was referred for cytogenetic investigation because of repeated spontaneous abortions. She was married at the age of 21 years and there was no consanguinity involved. On clinical investigation, she had a height of 146 cm, and a weight of 41 kg. Her husband was found to have a normal chromosome pattern, 46,XY, with optimal sperm counts. All other living family members were phenotypically normal, in good physical health, and did not have a history of miscarriages, especially her mother. The proband had eight pregnancies (Figure 1). In four pregnancies the fetal growths were unsuccessful and miscarriages occurred during the first trimester. The remaining three pregnancies all resulted in births of females with various birth defects and they died at very early ages. Of these, the first child developed cyanosis and died three days after birth. The second baby developed

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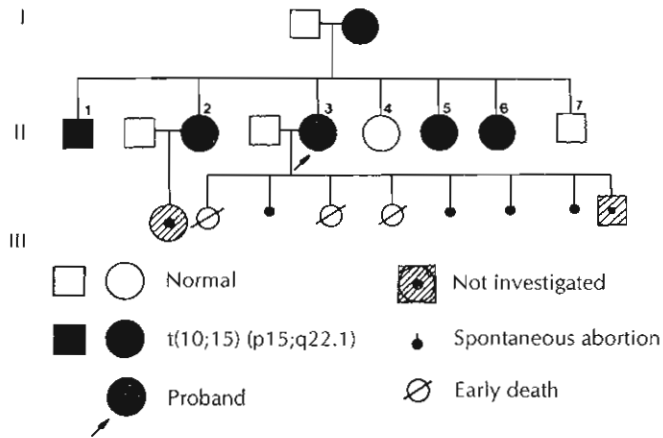


Figure 1 - A pedigree showing the carriers of  $t(10;15)$  and the incidence of spontaneous abortion and early infant death.

hepatomegaly and expired at the age of three months. The third girl developed hepatic and renal problems. Ultrasonographic findings showed free ascitis around the liver and spleen and her bowels showed dilation. X-ray and ultrasonographic findings were both suggestive of bilateral cardiac/renal disease, and she died at the age of four months.

The couple was counselled and followed up thereafter and a subsequent pregnancy resulted in the birth of a phenotypically normal son.

## CYTOGENETIC ANALYSIS

Chromosome analyses of the proband and her live family members were performed on standard phytohemagglutinin (PHA)-stimulated lymphocyte cultures grown at  $37^{\circ}\text{C}$  for 72 h. Optimally-aged slides were Giemsa-banded following routine laboratory techniques (Pathak, 1976).

Examination of 300 banded metaphases from the proband revealed that she had a  $46,XX, -10, -15, t(10;15) (p15;q22)$  chromosome constitution in all her cells (Figure 2A). Her mother also showed a similar chromosome constitution with a  $t(10;15)$ , as shown in Figure 2B. Three of her sisters and one brother also showed identical translocations involving chromosomes 10 and 15 (karyotypes not shown). Her father, one brother, and one sister had normal  $46,XX$  or  $46,XY$  chromosome constitutions, depending on their genders. There was no evidence of chromosomal mosaicisms in these samples.

A diagrammatic sketch shows breakpoints in chromosomes 10 and 15, and their subsequent translocation products (Figure 3). Very rarely a cell or

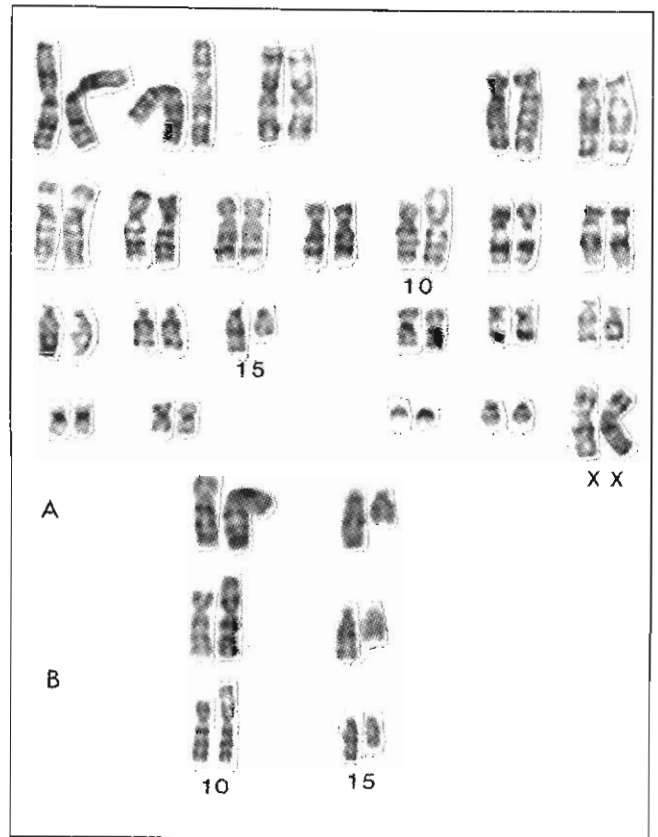


Figure 2 - A G-banded karyotype from the lymphocytic metaphase spread of the proband showing a  $t(10;15)$ . All other chromosomes appear normal. The rearranged and normal homologs from another cell of the proband are arranged on the bottom row of the karyotype (A). Partial karyotypes showing similar translocations from two metaphase spreads of the mother are shown in the two bottom rows (B).

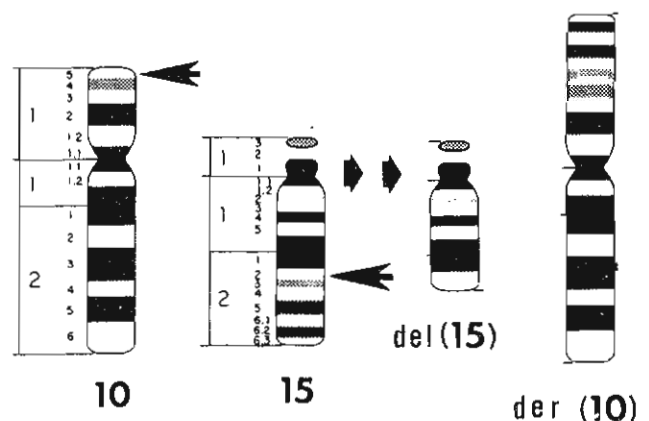


Figure 3 - A diagrammatic sketch showing the breakpoints (large arrows) in chromosomes 10 and 15 and the formation of altered chromosomes.

two showed chromatid breaks in the mother's and proband's metaphases. C-banding and Ag-NOR analyses did not reveal any unusual patterns in these samples.

## DISCUSSION

High incidence of spontaneous abortions and miscarriages is more frequently noticed in patients who have autosomal translocations, when compared to sex chromosomal abnormalities, since the latter often lead to gonadal dysfunctions (Diedrich *et al.*, 1983). The translocation identified in the lymphocyte cultures of our proband and some of her family members is interesting because of the different breakpoints involving t(10;15) (p15;q22), as compared to cases reported earlier (Aurias *et al.*, 1978). We have not observed any other gross clonal chromosome abnormalities in the PHA-stimulated lymphocyte cultures of this family. Bourrouillou and associates (1986) reported repeated spontaneous abortions in a carrier of t(10;15) (p15;q22) involving the same break-points as in our proband. A patient with reproductive risk was found to have a translocation involving chromosomes 10 and 15 (Giovanni *et al.*, 1983). Francke (1972) reported an unusual translocation involving chromosomes 10 and 15:46,XX,t(10q;15pt). Hirschhorn *et al.* (1973) reported transmission of a 46,XX,t(10;15) (q11;q24) karyotype from a mother to the daughter.

Yunis and Sanchez (1974) reported multiple congenital anomalies and renal complications in a baby with t(10;15) (q24;q26). Tsenghi and associates (1981) reported a t(10;15) (p11;p11) of maternal origin in a boy. This couple had a history of spontaneous abortions, stillbirths, and children born with congenital malformations. These earlier reports and the present observations indicate that the occurrence of balanced translocations is higher among couples who, in addition to experiencing consecutive abortions, also have children with multiple birth defects.

The obvious question to ask in the present pedigree is why the mother with the t(10;15) did not experience fetal wastage or abortion but the proband had experienced such problems? The break points involved at various sites in chromosomes 10 and 15 in patients with bad obstetric history may suggest that these chromosomes have inherent genetic instability in different regions. Fetal wastage and neonatal death in the proband and their absence in her mother could be due to the rearranged chromosomes 10 and 15 were not transmitted from the mother to the daughter. What was transmitted from one generation to the next was the inherent instability in these two chromosomes (Pathak *et al.*, 1989; Pathak, 1992; Pathak, S. and Hopwood, V.L., unpublished data on two large families). Examination of chromosomes from other tissues, i.e., skin or other repeat blood samples, might show mosaicism in such cases.

The development of hepatic and renal disorders in two sibs of the proband in the present family is noteworthy. It could be due to hepatic lipase deficiency, the gene for which is located in the 15q21 → 15q23 region (Sparkes *et al.*, 1987; Datta *et al.*, 1988; Ameis *et al.*, 1990).

In conclusion, timely cytogenetic investigation and prenatal diagnosis followed by accurate identification of breakpoints involved in the rearrangements can lead to more definitive genetic counselling and may prevent the birth of such malformed babies and hence decrease the risk of spontaneous fetal wastage. More such families should be investigated in order to establish a possible "syndrome" involving translocations between chromosomes 10 and 15. Such research is going on in one of our laboratories.

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## RESUMO

O cariótipo 46,XX, -10, -15, t(10;15) (p15;q22) foi observado em uma cultura de linfócitos de uma mulher indiana com múltiplos abortos. Anormalidades cromossômicas similares estavam presentes em sua mãe, um irmão e três irmãs. Ascite, cianose e problemas hepato-renais presentes nas três filhas talvez sejam decorrentes de tais rearranjos cromossômicos.

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