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REPRODUCTIVE FAILURES IN A FAMILY WITH INHERITED CHROMOSOMAL TRANSLOCATION t (3; 7) (p21; q34)

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ABSTRACT
An young parent couple, counsulted in the genetic counseling center for reproductive failures is described. From all 4 pregnancies the petients have 1 healthy child, 2 stillborn females with anencephaly and 1 spontaneous abortion in first trimester. No gynecological reasons or data for immunological incompatibility between the patients were established. The cytogenetic analysis performed on prometaphase chromosomes revealed a normal karyotype in the wife and balanced chromosomal translocation, 46, XY, t (3; 7) (p21; q34) in the husband. The same translocation was discovered in husband's father, so the cytogenetic investigation was enlarged and 6 father's sibs and 13 their offsprings were studied. Four new carriers of the translocation were found among the relatives mentioned above. The genealogical study did not reveal other families with reproductive failures, excluding one of the father's sisters who has had 3 children died some months after birth. A combination of polygenic factors and inherited chromosomal translocation is discussed as a cause for the observed reproductive failures. A prenatal diagnosis of neural tube defects and unbalanced karyotype was recommended.

Key words: genetic counseling, chromosomal translocation, reproductive failures, malformative syndromes, partial deletion

INTRODUCTION

Different types of structural chromosome rearrangements raised de novo or inherited are known as a cause of reproductive failures. Various reports from different countries have shown that the frequency of carriers of chromosomal rearrangements in large groups of couples with reproductive problems is between 3, 1% and 5, 3%. The majority, two-third of these chromosomal rearrangements were autosomal balanced translocations (1, 2, 3, and 4). In comparison, approximately one of 500 individuals in the general population is a carrier of balanced reciprocal translocation. Although balanced translocations are usually associated with normal phenotypes, carriers are at an increased risk of reproductive failure and having offspring with unbalanced rearrangements owing to the abnormal segregation of the rearranged chromosomes. Reciprocal translocations produce imbalances by three types of disjunction which are, in decreasing frequency, adjacent 1, 3:1, and adjacent 2. As a result ppartial trisomies, monosomies and duplications are produced.

The chromosome 3 shows relatively frequent breakages, particularly in 3p25 and 3p21 regions (5, 6, and 7) but few patients have been reported with partial deletions (8). In chromosome 7 higher frequency of breakpoints is noted in the long arm, especially in the region 7q32 (9, 10, and 11).

Here we report a large pedigree with an inherited balanced translocation t (3; 7) (p21; q34) and reproductive failures in some of the

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carriers. To our knowledge, this is the first case with such type of translocation.

CASE REPORT

A young couple, the husband 27 and the wife 25 years old, has been referred to the genetic counseling due to neural tube defects (NTD), registered in two of their four pregnancies. From the first one a normal female was born. The second pregnancy terminated in the 8 month with a delivery of female with anencephaly and spina bifida. The next year the wife has had one spontaneous abortion in the first trimester. During the last pregnancy an ultrasound prenatal diagnosis was performed. A female fetus with anencephaly was proved again and the pregnancy was terminated in the 4th month of gestation.

The patients are in good health. No gynecological reasons for the observed reproductive failures were noted.

MATERIALS AND METHODS

Lymphocyte cultures: The blood samples were obtained from the ear vein of one donor. The anticoagulant used was heparin, at a concentration of 30 IU/mL. The blood was transported to the laboratory for cytogenetic analysis immediately after collection and was processed using the micromethod of Hungerford (12). Whole heparinized blood (0.5 mL) was incubated in 7 mL of cell culture medium RPMI 1640 with L glutamine and HEPES buffer, 3 mL thermally inactivated normal calf serum, 0.2 mL resubstituted 2% PHA, 100 IU/mL penicillin, 50 µg/mL gentamicin. Six cultivation flasks were prepared and placed into a thermostat in the absence of light at 37 ^{o}C. On the 70th hour, colchicine at concentration of 0.5 g/mL was added to each flask. The classic lymphocyte culture processing protocol was used. By the end of the 72 nd hour of lymphocyte culture cultivation, chromosome preparations were made for detection of chromosome aberrations. A cytogenetic analysis was performed on lymphocyte prometaphase chromosomes and G-banding (13, 14). The final analysis was conducted based on the International Cytogenetic Nomenclature.

CYTOGENETIC AND GENEALOGICAL STUDIES

A cytogenetic analysis was carried out on lymphocyte GTG-banded prometaphase chromosomes according to standard procedures. All husband's cells showed a balanced reciprocal translocation 46, XY, t (3; 7) (p21; q34) **(fig. 1 and fig. 2)**. The wife and daughter have had normal karyotypes.

Fig. 1. Proband's total karyotype

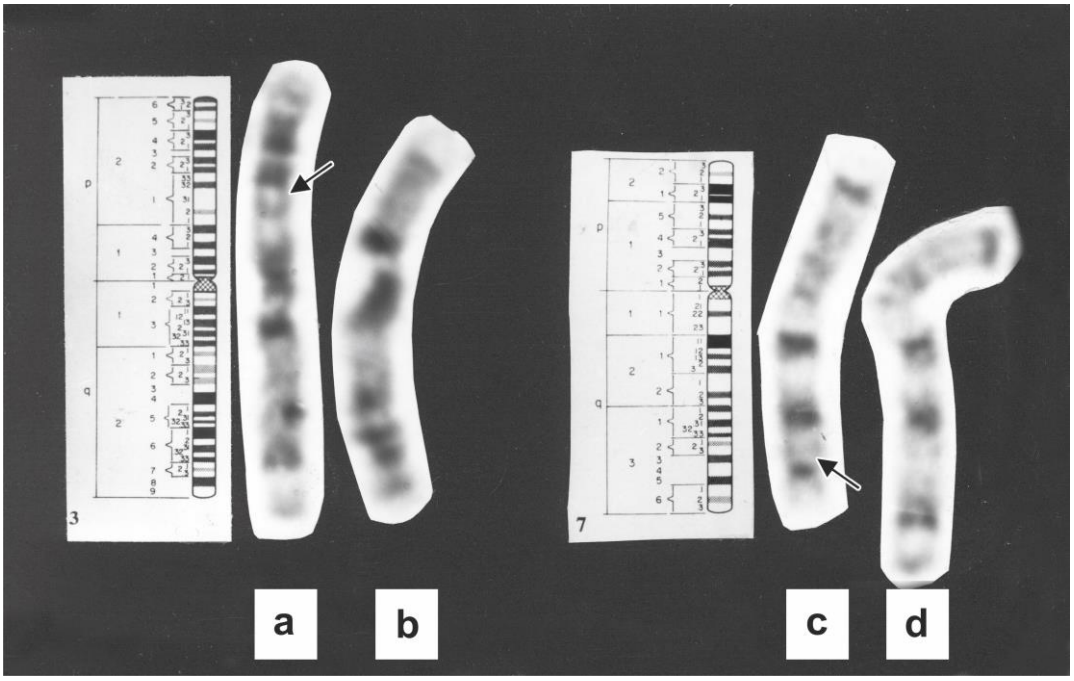

Fig. 2. Proband's partial karyotype with suddested break points:
a. normal chromosome 3; b. derivate chromosome 3;
c. normal chromosome 7; d. derivate chromosome 7.

The same translocation was established in the husband's father (II.5), and the cytogenetic study was enlarged and performed in 25 relatives. Five of them, proband's brother (III.6), father's sibs (II.6 and II.10) and two of their children (III.11 and III.18) have been proved to be carriers of the translocation **(fig.3).**

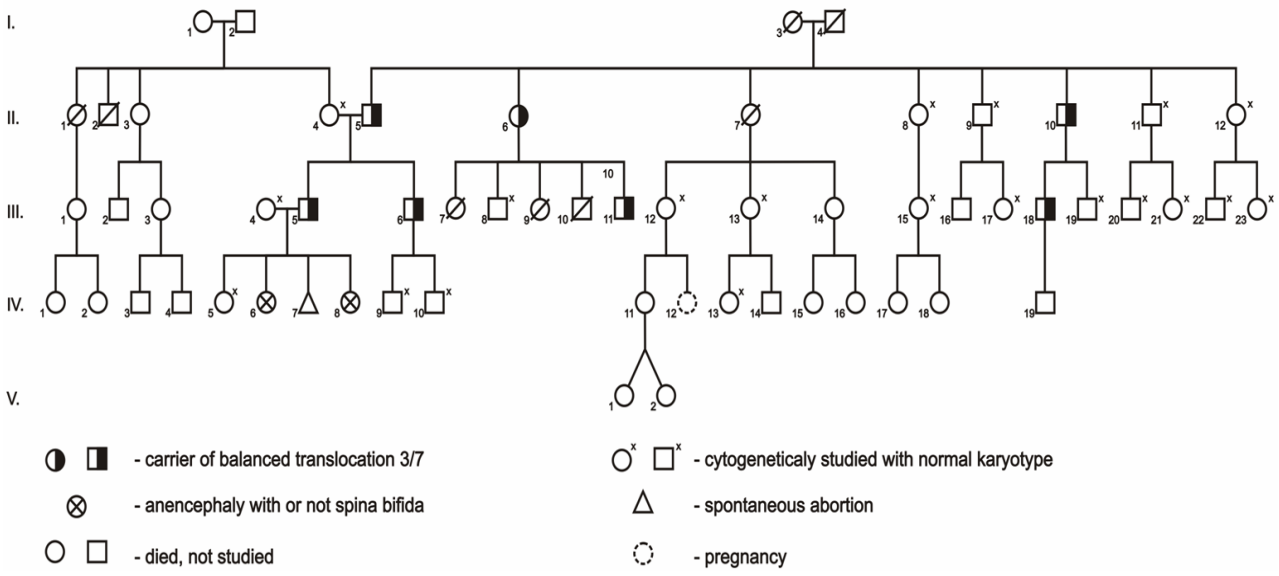

Fig. 3. Proband's pedigree with inherited chromosomal translocation 3/7.

The pedigree analysis, including 49 relatives in 5 generations, did not reveal another cases with neural tube defects or inborn malformations. Only the father's sister (II.6), carrier of the translocation, has had three children died some month after the birth, but without available information for malformations.

DISCUSSION

Usually the neural tube defects, anencephaly alone or in combination with spina bifida is considered as polygenic, multifactorial diseases. On the other side the inherited or de novo arisen reciprocal translocations are well known as a frequent cause for pregnancy

losses and malformations (1, 3). In our case one of the parents is a carrier of inherited balanced translocation between the short arm of chromosome 3 and the distal part of the chromosome 7 long arm. Two possible explanations of observed NTD in the family may be taken in consideration. The first one is that the neural tube defects in the family have a polygenic determination and the chromosome translocation is inherited separately and is a cause for the spontaneous abortion in third pregnancy. The other one is that some genes located in the breakpoints are involved the pathogenesis of NTD formation. Recently it has been suggested that several structural chromosomal abnormalities may be associated with NTD. Deletions and duplications of 3p, 3q an7q regions (7, 15, 16, 17, 18). Perinatal identification of NTDs should alert one to the possibility of chromosomal abnormalities and prompt a thorough cytogenetic investigation and genetic counseling. On the other hand future investigation in large families with structural chromosomal abnormalities by new methods as array CGH and linkage analysis may be useful for positional cloning of genes involved in the pathogenesis of NTD (19, 20).

Nevertheless that the reasons for the observed reproductive failures in our family are not clear, an ultrasound and cytogenetic diagnosis was recommended in future pregnancies. Genetic counseling was carried out with proband's relatives, carriers of the translocation and prenatal diagnosis in future pregnancies was also proposed to the brother and cousins.

In conclusion the chromosomal analysis is an important and necessary part of the etiological investigation in couples with reproductive failures.

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