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Case Report

Familial reciprocal translocation t(8;17)(p23;q21) in a woman with recurrent spontaneous abortion

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ABSTRACT

This work presents the results of cytogenetic analysis of a couple referred to our genetics laboratory with ten first trimester abortions and one IVF failure. The male showed a normal (46, XY) karyotype whereas the female was found to carry an apparently balanced reciprocal translocation [46, XX, t(8;17)(p23;q21)]. Two sisters and two brothers of the eight siblings of the female proved to have the same translocation. Although the female's father is deceased and his sample was not available for investigation. The origin of this translocation must be paternal since the female's mother harbored a normal karyotype. It is concluded that the history of recurrent pregnancy losses in the couple is due to the production of unbalanced gametes in the female as a result of the reciprocal translocation she has and the couple was advised to undergo a PGD for embryo selection prior to their future IVF trials. The authors also recommend that all RSA couples with normal routine work-up results should be offered chromosomal analysis without delay.

Keywords: Reciprocal translocation, t(8;17)(p23;q21), Recurrent spontaneous abortion, Karyotype

INTRODUCTION

Studies on pregnancy disorders indicate that spontaneous abortion is the most common complication amounting 15-20% of all clinically recognized pregnancies.[1] Recurrent spontaneous abortion (RSA) is currently defined as the occurrence of ≥2 consecutive pregnancy losses before 20th week of gestation and it has been shown that about 2% of women suffer from RSA.[2] RSA can be due to one of several causes, including: genetic and endocrine abnormalities, immune dysfunction, anatomic uterine defects, infection and chromosomal disorders.[3,4]

Results from numerous studies in different countries have shown that in about 2-8% of couples with RSA, at least one of the partners has a chromosomal abnormality.[5-9] The chromosomal abnormality, when present, is usually of structural nature. The most common of these abnormalities are balanced translocations, reciprocal and robertsonian.[10]

Although the carrier of a balanced translocation is usually phenotypically normal, this structural abnormality may cause pregnancy loss because unusual segregation of misaligned chromosomes during meiosis results in unbalanced gametes with consequent fetal loss. The risk of miscarriage in couples with reciprocal translocations is approximately 25 to 70%.[11]

In this report a couple with a history of 10 recurrent spontaneous abortions and one IVF failure was evaluated for their chromosomal make-up to search for chromosomal abnormalities.

CASE REPORT

A 34 years old woman and her family-unrelated 39 years old husband presented to the Genetics lab at the Islamic University of Gaza for chromosomal study. The couple had a history of 10 first trimester abortions and one unsuccessful IVF trial. According to their physician and the laboratory investigation reports they had no

underlying cause related to their abortions and therefore they were subjected to chromosomal analysis using routine GTG-banding. The results revealed that husband has a normal (46, XY) karyotype whereas the female has a balanced chromosomal translocation between the short arm of chromosome 8 and the long arm of chromosome 17 [46, XX, t (8;17)(p23;q21) as illustrated in Figure 1. In order to verify whether this translocation is *de novo* (sporadic) or familial (inherited) the female's family was investigated for presence of this chromosomal abnormality. The pedigree relevant to this work is presented in Figure 2. The proband's mother proved to have a normal chromosomal constitution. Four of the proband's siblings (two un-married brothers and two married sisters) however, harbored this translocation. Moreover, the proband's mother had experienced two spontaneous abortions, her 33 years old sister translocation-carrier suffers from infertility and her 38 years translocation-carrier had experienced one spontaneous abortion and one IVF failure. It was concluded that this translocation is familial and must have been inherited from the proband's father. The father, however, is dead and therefore we could not test his sample. The case couple and her translocation-carrying sisters were advised to consult an advanced IVF center in order to undergo PGD for this translocation. Moreover, genetic consultation was recommended for all the carriers of the translocation.

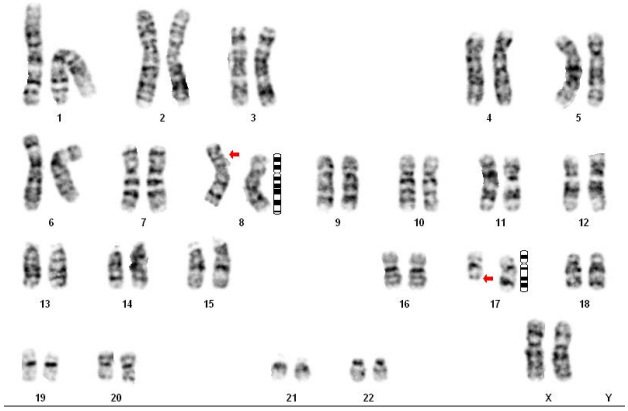

Figure 1: Karyotype of the case female. Chromosomes involved in the reciprocal translocation are indicated by arrows.

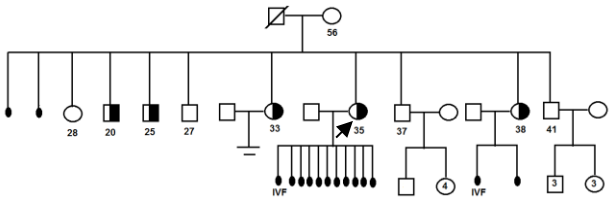

Figure 2: Pedigree of the translocation carrying female proband. Half-filled symbols indicate carriers of the translocation. The proband is indicated by arrow.

DISCUSSION

Naturally, pregnancy is a complicated process that ends up with an abortion in about 15 to 20% of married couples, and 1-2% of couples experience RSA. Structural chromosome abnormality, usually observed in one partner, constitute a significant fraction of known causes of RSA, approaching 10%.[9,12] On the other hand, in 3 to 5% of RSA couples one partner has a reciprocal translocation.[13]

Reciprocal translocations, like the one presented here, are usually observed in otherwise phenotypically normal individuals. This indicates that such abnormalities, termed as balanced, have no apparent effect on the phenotype of the carrier individual and the major concern is on his/her reproductive ability in terms of production of unbalanced gametes that may lead to infertility, abortion, or the production of a malformed offspring. Unbalanced gametes are produced by those individuals because of the abnormal alignment and consecutive abnormal segregation of their chromosomes during meiotic division in the gametogenesis process. This explains the infertility and the frequent miscarriages observed in the study family.

The risk for a pregnancy to end up with a miscarriage varies with the type of the structural abnormality and whether it is carried by the male or the female partner. For example, 50 to 70% of the gametes of reciprocal translocation carriers are unbalanced.[14] Most carriers of structural chromosome abnormalities, however, have a chance of producing also a phenotypically normal offspring, though we did not observe that in our case couple.

Reciprocal translocations may be either inherited (familial) or sporadic (*de novo*) where in the latter one neither parent has the rearrangement. In our case the translocation is of the former type as it was documented in 5 (including the proband) of the 9 siblings. The translocation must have been inherited from the deceased father and due to the hereditary transmission of this chromosomal abnormality genetic consultation was recommended for the unmarried carriers of the translocation.

The reciprocal translocation presented here has not been reported before and therefore it can be considered of the "non-recurrent" type. So far, four "recurrent" reciprocal translocations appeared in the literature namely; t(11;22)(q23;q11), t(8;22)(q24.13;q11.21), t(4;8)(p16;p23) and t(4;11)(p16.2;p15.4). "Recurrent" reciprocal translocation has been shown to arise by non-allelic homologous recombination (NAHR) mechanism, facilitated by inter-chromosomal paralogous low copy number repeats (LCRs).[15] In the matter of fact, we searched for sequence homology between 8p23 and known LCRs in 17q21[16] but no sequences of significant homology were encountered. This may indicate that the translocation reported here is

not mediated by NAHR and that the underlying mechanism may be non-homologous end joining (NHEJ). This further explains the "non-recurrent" nature of this translocation.

Finally, the importance of detecting chromosomal abnormality lies in providing the necessary information for genetic counseling, risk for having a consequent abortion, and discussion of the various reproductive options that are available to couples with RSA problem. Preimplantation genetic diagnosis (PGD) using versatile molecular techniques (FISH, array-CGH and PCR-based STRs) is becoming a routine procedure[17] and a feasible option for couples with chromosomal abnormalities to have a healthy offspring.

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