Novel balanced chromosomal translocations in females with recurrent spontaneous abortions: Two case studies

ABSTRACT

Two couples with a history of recurrent pregnancy losses were referred to the Institute of Genetic Medicine and Genomic Science for cytogenetic evaluation. Chromosomal analysis of the phenotypically normal couples was done to investigate whether there are any new chromosomal abnormalities present in either of the couples caused recurrent pregnancy losses. Clinical and hormonal profile of the couples revealed normal parameters. The ultrasound scan of the females showed normal uterine and ovarian structures. Chromosomal analysis of the couples revealed normal 46, XY karyotypes in both the male partners, and novel balanced reciprocal translocations 46, XX, t (5;8) (q35.3;q24.23) and 46, XX, t (4;13) (q12;q14) chromosomal constitutions in the female partners. Further, corroboration of the chromosome abnormalities was carried out by high resolution banding analysis. Unique and novel balanced reciprocal translocations were reported as an original investigation in two female partners from two different unrelated families both with the history of recurrent pregnancy losses.

KEY WORDS: Balanced translocation, high-resolution banding analysis, recurrent pregnancy loss, t (5;8) (q35.3;q24.23), t (4;13) (q12;q14)

INTRODUCTION

Recurrent spontaneous abortion (RSA) is one of the most common complications of pregnancy, responsible for significant emotional distress to the couple desiring children. The cause being multifactorial is mostly associated with the advanced maternal and paternal age, endocrine dysfunction, autoimmunity, infectious diseases, environmental toxins, congenital and structural uterine anomalies and genetic abnormalities, etc.\[^1\]

Balanced translocations are frequent structural chromosomal rearrangements observed in humans where two different chromosomes exchange their segments. Studies show that population frequency rates are between 1/673 and 1/1000.\[^4\]\ Here both the individuals, which are females, with balanced translocations are clinically normal; however, they have an increased risk of having progeny with unbalanced karyotypes with interference in the meiotic segregation of their abnormal chromosomes.

Case Report

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Fetal aneuploidy is the reason for the majority of miscarriages before the 10th week of gestation. Most human aneuploidies have their roots in errors during the first meiotic division of the oocyte, which is initiated before the time of birth and is incomplete until ovulation.\[^3\]

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MATERIALS AND METHODS

Cytogenetic analysis was carried out based on phytohemagglutinin -stimulated peripheral blood lymphocyte cultures, of the couples—both the male and the female partner. Lymphocyte culturing and GTG-banding were performed following standard protocols as described by the AGT cytogenetics laboratory manual.\[^5\]\ Karyotypes were described according to the International System for Cytogenetic
CASE REPORT

In both the RSA cases, there was no known exposure to recognized teratogens. They were healthy and phenotypically normal. The present study was approved by the Institutional Ethical Committee. Informed consents were obtained from the couples before investigation. They were initially referred to the infertility center for investigation. Hormonal and anatomical factors of the uterus and ovaries were normal, and the mother had no underlying disease related to such abortions. Therefore, they were referred to our cytogenetic laboratory for chromosomal analysis. Chromosomal studies were performed on the basis of G-banding technique at high resolution.

In the first case, we are reporting the history of RSAs in a couple with an unknown cause in a 34-year-old man and a 37-year-old woman. Reproductive history of the female revealed six intra-uterine fetal deaths (IUFD) before the 16th week of pregnancy. The cause and genetic status of the miscarriages were not known. The results showed balanced chromosomal translocations between the long arm of chromosome 5 and the long arm of chromosome 8 only for the female partner (46, XX, t[5;8] [q35.3; q24.23]) [Figure 1] with clinically normal phenotype, but normal genotype [46, XY] in the male partner.

In the second case, the couples have experienced four IUFD before the 16th week of pregnancy. The results showed balanced chromosomal translocation between the long arm of chromosome 4 and the long arm of chromosome 13 only for the female partner (46, XX, t[4:13] [q12; q14]) [Figure 2] with clinically normal phenotype, here also the male partner is of normal genotype [46, XY].

High Resolution banding analysis (done by Cyto-vision software) revealed “Gain of material in chromosome 5 at q35.3” and “Loss of material on chromosome 8 at q24.23” in comparison with their normal ones in the first case [Figure 3.1a-d], and “Loss of material on chromosome 4 at q12” and “Gain of material in chromosome 13 at q14” in comparison to their normal ones in the second case [Figure 3.2a-d].

To the best of our knowledge translocation at these particular point are the unique and novel familial transmission of balanced reciprocal translocations in females with recurrent pregnancy losses.

DISCUSSION

In general, the couples planning their first pregnancy remains unaware of any reproductive problems. It is estimated that approximately one in six couples experiences difficulties in the reproductive outcome[6]. According to studies the frequency of chromosomal aberrations, is approximately 8% of cases suffering reproductive failure such as infertility and pregnancy losses[7]. Around 15–20% of all pregnancies in humans end in spontaneous abortions. RSA is historically defined as three or more consecutive pregnancy losses before 20–22 weeks of gestation[8]. However, some investigators feel that even two spontaneous losses constitute recurrent miscarriage and deserve evaluations. In a patient with a history of two miscarriages, the subsequent risk of pregnancy loss rises to about 25%, whereas three abortions raise the risk of a fourth miscarriage to 33%. The prevalence of chromosomal abnormalities in those abortions is as high
as 50%. Although the cause is unknown in many instances, the parental chromosomal abnormality is one of the possible causes for recurrence of miscarriages within the first 3 months of pregnancy.\[9\]

The evaluation of patients with a history of repeated spontaneous abortions requires careful consideration of potential genetic, anatomic, endocrine, infectious, and immunologic factors. Assigning proper etiological role to each of these contributing factors is often unclear, however the specific information about the cytogenetic makeup of the couples and if possible of the abortus, remains a primary focus during evaluation of such cases.

It has been reported that, the most common cause of spontaneous abortion in the first trimester (approximately 50%) is chromosomal abnormalities. The majority of chromosomal anomalies (95%) are numerical, about 60% are trisomy’s, 20% are X monosomy and the remainder are (15%) polyploidy especially triploidy.\[9,8\] On the other hand, half of the structural abnormalities may be inherited from a parent who is carrying a balanced chromosomal translocation that is at a higher risk of having children with chromosomal abnormalities.\[10\] It has been reported in some related articles that, the risk of RSA is increased in couples where one of them has such balanced rearrangement of the normally fertilized embryo 20% were abnormal segregation of the translocation. This is considerably higher than the theoretical risks at prenatal diagnosis, probably because in vivo most abnormal embryos would fail to establish a pregnancy. Screening out of the embryos with an unbalanced product of the robertsonian translocation prior to birth would be expected to increase the chance of a successful pregnancy.

Reciprocal (nonRobertsonian) translocations are one of the most frequently occurring human chromosomal aberrations, occur in about 1 in 600 persons in the general population, whereas they have a frequency of about 7% in couples with recurrent miscarriages.\[11\] These rearrangements are twice more common in females than males. In most cases, carriers of balanced reciprocal translocations have a normal phenotype but may experience reproductive issues such as infertility or multiple miscarriages. Nearly, 6% of apparently balanced de novo translocations are associated with clinical abnormalities.\[12\] In our study, the female partners had no endocrinological and uterine abnormalities.

Recently, it has been shown by molecular analyses (e.g., array comparative genomic hybridization) that up to 40% of the apparently balanced reciprocal chromosome translocations in patients with an abnormal phenotype are accompanied by a chromosome imbalance.\[13\] The present study revealed two unique balanced translocations in females with reproductive failure.

Most of the chromosomal abnormalities can be readily diagnosed by standard cytogenetic analysis. However, further refinements like subtle chromosome rearrangements and intrachromosome exchanges can be identified by advanced molecular cytogentic techniques such as high-resolution banding analysis or chromosome profiling.

Couples with balanced reciprocal translocation have a 50% chance of having RSAs and a 20% risk of having

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Figure 3.1: (a) Normal chromosome 5. (b) Gain of material in chromosome 5 at q35.3. (c) Normal chromosome 8. (d) Loss of material in chromosome 8 at q24.23

Figure 3.2: (a) Normal chromosome 4. (b) Loss of material in chromosome 4 at q12. (c) Normal chromosome 13. (d) Gain of material in chromosome 13 at q14
children with abnormal genetic makeup. The formation of balanced, unbalanced and normal gametes is dependent on the basis of the breakpoints and also on the chromosomes involved. Balanced chromosomal translocations may also lead to sequence rearrangements of the functional genes that may result in the reproductive errors accompanied by repeated abortions. Further break point analysis and molecular characterization involved here might enlighten to understand the basis of recurrent abortions.

The present study thus reported novel balanced reciprocal translocations that could result in generation of unbalanced gametes due to meiotic errors associated with first trimester recurrent pregnancy losses. Cytogenetic analysis, therefore, should be mandatory for all the couples with reproductive failures. Thus, the carriers of such abnormalities should be informed about the risk of the birth defects in their offspring due to de novo submicroscopic rearrangements. Adequate genetic counseling strategies should also be offered which could allow the parents/couples to make an informed reproductive decision regarding subsequent pregnancies.

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