

Case Report

Two Novel Familial Balanced Translocations t(8;11)(p23;q21) and t(6;16)(q26;p12) Implicated in Recurrent Spontaneous Abortion

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Abstract

Reciprocal translocations represent one of the most common structural rearrangements observed in humans. Estimates of the population frequency range from 1/673 to 1/1000. We have described two novel balanced translocations in two unrelated families who experienced Recurrent Spontaneous Abortions (RSA) following their separate non-consanguineous marriages. Initial cytogenetic studies were performed on cultured blood cells. High resolution GTG-banding analysis using cytovision software performed on their chromosomes revealed a novel balanced translocation t(8;11)(p23;q21) in a brother (45 years) and his sister (27 years) in one family. The second novel balanced translocation t(6;16)(q26;p12) was observed in a consanguineous couple with 4 RSA. These two families have an increased risk of having children with unbalanced karyotypes or RSA, because of incorrect chromosomal segregation during meiosis.

Keywords: Balanced translocation, karyotyping, t(8;11), t(6;16)

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Introduction

Recombinations in homologous chromosomes normally occur during meiosis, with the exchange of various chromosomal fragments producing different alleles with each normal chromosomal translocation. Reciprocal translocations are frequent structural rearrangements observed in humans where two different chromosomes exchange segments. Studies show that population frequency rates are between 1/673 to 1/1000.^{1,2} Individuals with balanced reciprocal 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.

All 23 sets of homologous chromosomes couple to form 23 paired linear structures or bivalents during normal meiotic prophase. These structures later separate and divide into different daughter cells. Reciprocal translocation results in 21 rather than 23 bivalents in a cell. The reciprocal translocation and their normal homologs form two other derivative chromosomes, a single pairing structure called a quadrivalent. Multiple ways of chromosomal segregation exist within a quadrivalent. Most of the gametes that contain these chromosomal segregations have unbalanced translocations. Theoretically, normal chromosome complements are present in 50% of the resulting gametes and the other 50% are carriers of balanced translocation.

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Alternative segregation patterns for a reciprocal translocation results in unbalanced gametes, producing gametes with partial trisomies and monosomies. Other segregation products may also form, resulting in trisomies and monosomies or tetrasomies and nullisomies. Studies using the sperm obtained from balanced reciprocal translocation carriers have shown that approximately equal numbers of alternate and adjacent segregants are generally formed, and these two groups represent the most common types of segregant. The remaining segregants are infrequent. Corresponding data are not available for female carriers. Unlike studies on spermatocytes, it is difficult to obtain large numbers of oocytes to analyze these translocations. However, female translocation carriers are capable of producing the same types of unbalanced segregants that have been reported in male carriers.^{3,4}

In this report, two novel balanced translocations in two unrelated families were described. A balanced translocation involving chromosomes 8 and 11 occurred in a family with a brother and a sister who experienced recurrent spontaneous abortions (RSA) following their separate non-consanguineous marriages. The distal short arm of chromosome 8 was replaced with the long arm on chromosome 11 (p23;q21). The second novel balanced translocation t(16;6)(q26;p12) was observed in a non-consanguineous couple with four RSA.

Case Report

Two families with different balanced translocations were examined. The first family was a 45-year-old man and his 27-year-old sister who referred to Pardis Clinical and Genetics Laboratory, Mashhad, Iran, during July 2010 with four RSA for the sister and five RSA for the brother's spouse. The phenotypes of both patients were examined. The brother and his wife who were in a non-consanguineous marriage resulted in 8 pregnancies: 2 RSA,

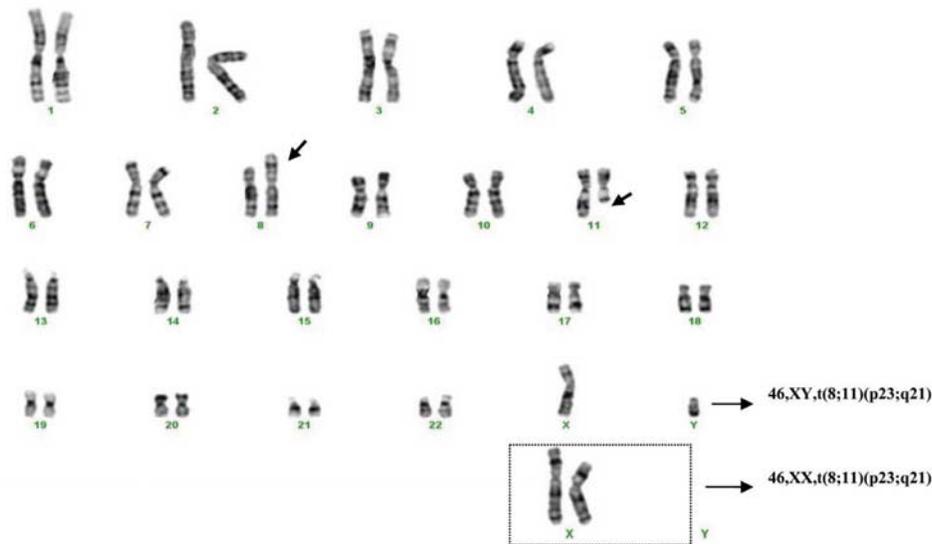


Figure 1. Karotyping of family with balanced translocation 8;11. 46,XY or XX,t(8;11)(p23;q21).

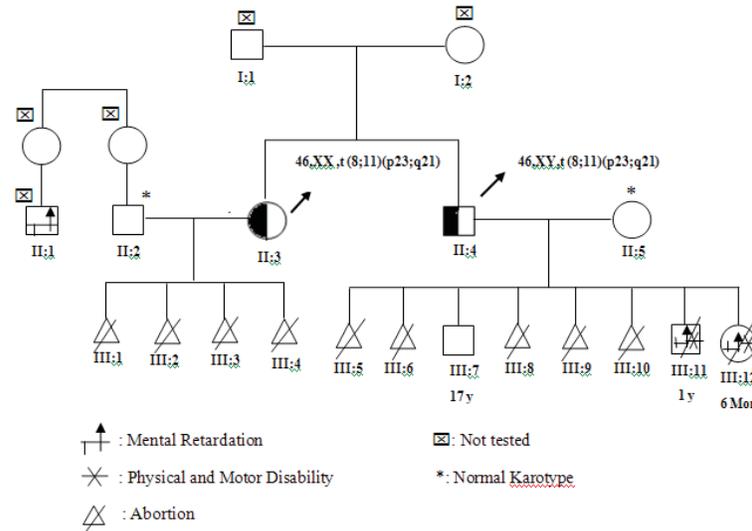


Figure 2. Family pedigree with balanced translocation 8;11 (p23;q21).

1 normal 17-year-old boy, 3 RSA, and 2 deceased children (one boy and one girl who died before the age of one). The normal boy inherited a normal chromosome 8 and 11 from his mother and balanced translocation 8 and 11 from his father. Therefore, his karyotype is similar to his father. The deceased children had developmental delays and hypotonia. There was no clear diagnosis for the deceased children. Both parents had normal phenotypes and hormonal tests. Other non-genetic reasons for RSA were ruled out. Karyotyping was performed using cultured blood cells and high resolution banding followed by Cytovision software analysis on the chromosomes. The karyotyping result for his wife was normal, however, the brother had a balance translocation between chromosomes 8;11 [46,XY,t(8;11)(p23;q21)]. In this family, the 27-year-old sister had four RSA. Her karyotype analysis showed the same balance translocation between chromo-

somes 8;11[46,XX,t(8;11)(p23;q21)] as her brother (Figure 1). Other laboratory findings such as complete blood count (CBC), TORCH, and hormones were normal. This family's pedigree with balanced translocation is shown in Figure 2.

The second family consisted of a 34-year-old man and his wife, aged 26 years. This couple whose marriage was consanguineous had four abortions, however, the phenotype of the man and his wife were normal. Karyotype analysis was performed for both. Metaphase spreads were studied on the basis of GTG technique at high resolution banding, which revealed 46 chromosomes. However, both had a balance translocation between the long arm of chromosome 6 and short arm of chromosome 16 as follows: [46,XY or XX,t(6;16)(q26;p12)] (Figure 3). The pedigree of this family is shown in Figure 4.

All four individuals from both pedigrees that carry the bal-

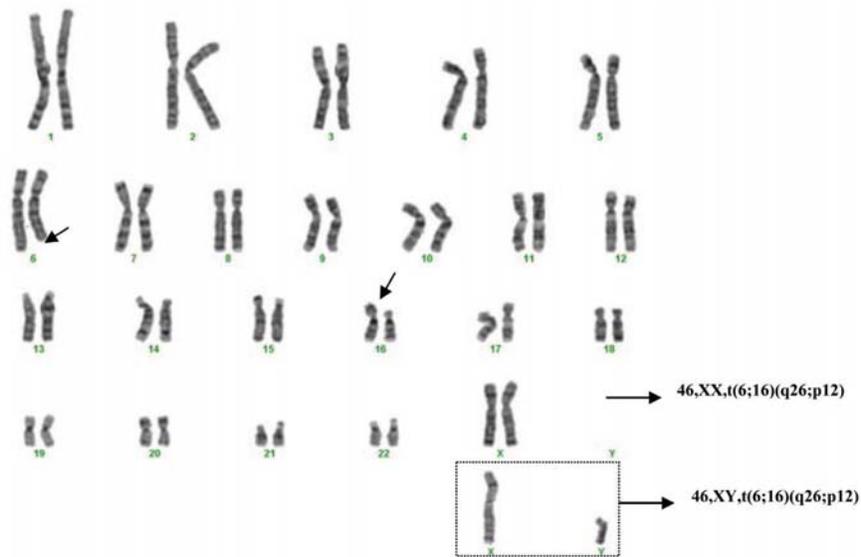


Figure 3. Karotyping of family with balanced translocation 6;16. 46,XX or XY,t(6;16)(q26;p12).

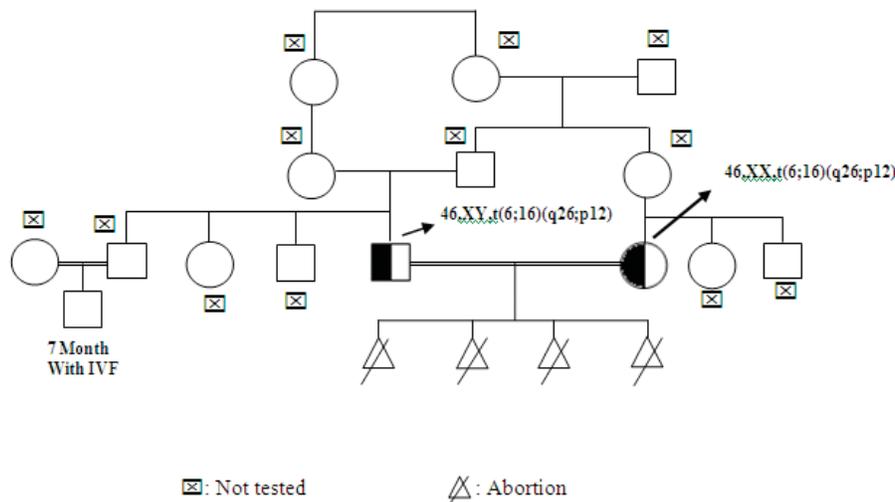


Figure 4. Family pedigree with balanced translocation 6;16 (q26;p12).

anced reciprocal translocations are themselves clinically normal. The gametes obtained from their parents do not have any duplicated or deleted fragments in chromosomes 8 and 11, or 6 and 16. Therefore, they are balanced translocation carriers, similar to their fathers or mothers. Additionally, both families went through extensive genetic counseling and prenatal diagnosis (PND) was strongly recommended. There is a 50% chance of an unbalanced translocation being inherited in each future generation of these families. An increased risk of having children with unbalanced karyotypes secondary to meiotic malsegregation of their translocation also exists in future generations.

Discussion

The family members who carry these novel balanced translocations

and have normal phenotypes can transfer unbalanced translocations to their fetuses, causing either RSAs or other congenital abnormalities such as developmental delays and/or hypotonia. Different studies have shown that the risk of having a live born child with an unbalanced karyotype is 2%–10%, however, most are aborted.^{3,4} Reciprocal translocations can be inherited or occur as new or *de novo* mutations. The risk for having *de novo* balanced translocations is greater than rearrangements inherited from a normal parent and has been reported to be approximately 6%–9%.² In this family, only 50% of the resulting gametes would carry a normal chromosome complement or would be balanced translocation carriers similar to the father or mother. The other 50% of the resulting gametes are including two variations. One of the variants has been ascertained to the birth of a clinically abnormal fetus with the derivative chromosome 8, but not the com-

plementary abnormal chromosome 11. These variations include an abnormal fetus with monosomic chromosome 11 long arm material and trisomic chromosome 8 short arm materials. Other variants have an abnormal fetus that has the derivative chromosome 11, but not complementary abnormal chromosome 8. These fetuses are monosomic for the short arm of chromosome 8 and trisomic for the long arm of chromosome 11. In both cases, the fetus is aborted.

Therefore, for individuals with balanced translocation, PND is recommended. Fluorescent *in situ hybridization* (FISH) may be used to detect chromosomal abnormalities in preimplantation genetic diagnosis (PGD) or PND.⁵

The primary aim of PGD is to reduce recurrent spontaneous abortions and to increase the pregnancy success rate in infertile couples. Therefore, PGD has been offered to carriers of translocations for PND and pregnancy termination of abnormal fetuses.⁶

These two novel translocations are the first report for these breakpoint rearrangements between chromosome 8;11 and 6;16. Although in 2000, Fert-Ferrer et al. have described unbalanced translocation t(8;11), however, the breakpoints are different. The new translocation is t(8;11)(p23.2;p15.5). These researchers have analyzed two fetuses and shown that they carried the same unbalanced translocation with monosomy for chromosome 8 and trisomy for chromosome 11. The phenotypes of the fetuses were similar to Beckwith-Wiedemann syndrome (BWS).⁷

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