

A Retrospective Study of Balanced Chromosomal Translocations in a Turkish Population

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ABSTRACT The balanced translocations are accepted as chromosomal rearrangements that do not generally reflect any phenotypic evidence. However, phenotypical influences can be seen in children of balanced translocation carriers due to the formation of partial monosomy and partial trisomy of any related chromosome. In this study, 25 cases that detected to have balanced translocation by cytogenetic analyses were evaluated with regard to their phenotypic features. Karyotype analyses of cases were taken out by using conventional peripheral blood culture method. It is estimated that 14 (56%) of these balanced translocation carriers had recurrent miscarriage, 5 (20%) had children with mental retardation, 3 (16%) had infertility, 2 (8%) had amenorrhea and 1 (4%) had mental retardation. When the cases were examined, it is understood that the increase in the frequency of miscarriage is the most frequent phenotypic feature in balanced translocation carriers as a result of the formation of unbalanced gametes.

INTRODUCTION

The chromosomal disorders make a significant contribution to human mortality and morbidity. There are two kinds of chromosomal rearrangements: structural and numerical. Balanced translocations accepted as structural chromosomal abnormalities in humans commonly seen with a frequency of 1/600 (Van Dyke et al. 1983). Balanced translocations have been determined as 0.2% in the neonatal population, 0.6% in infertile couples and 9.2% in cases who have recurrent miscarriages (Stern et al. 1999). Balanced translocations are known as products that erase as a consequence of meiotic recombination event between related chromosomes without loss of any chromosomal material. The phenotype of the balanced translocation carriers is usually normal and may pass through several generations without detection; because of this situation they do not come to medical attention until they experience infertility or the birth of an abnormal child with an unbalanced form of the translocation (Warburton 1991). Carriers of balanced translocations have a high reproduc-

tive risk of conceiving chromosomally abnormal embryos as a result of chromosomal imbalances that take place during meiosis, leading to recurrent miscarriages or to birth of affected offspring. The translocated chromosomes of balanced translocation carriers, pair with their matching homologous at a quadrivalent formation and imbalanced gametes result from the disjunction of these chromosomes for the segregation models at meiosis I (Suguiura-Ogasawara et al. 2004). Offspring of carriers often have 46 chromosomes, including a derivative chromosome, so they are partially trisomic and partially monosomic for the translocated chromosomes. On the other hand, in some balanced translocation carriers, mental retardation and some phenotypic abnormalities can be observed because of disrupted developmental genes that located in the area of breakpoints of translocated chromosomes (Vandeweyer et al. 2009). The risk for phenotypic abnormalities differs between de novo and familial balanced translocations. Warburton et al. (1991) estimated the risk in carriers of de novo reciprocal translocations detected at prenatal diagnosis to be 6.1%, while Madan et al. (1997) revealed that the risk is even higher when the translocation is complex. In familial cases, the increased risk lies mainly in the production of abnormal gametes which leads to multiple miscarriages or to the birth of a child with congenital abnormalities. If the same balanced rearrangement as in the carrier parent is detected at prenatal diagnosis, the risk for

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phenotypic abnormality in the offspring is believed to be very low. However, there are several studies that report patients with abnormal phenotype and the same balanced rearrangement as their phenotypically normal carrier parent (Fryns et al. 1991; Wenger et al. 1995; Ciccone et al. 2005).

The aim of this research was to state the frequency of balanced reciprocal translocations, to identify the chromosomes involved in balanced translocations and to define the phenotypic features of balanced translocation carriers in a Turkish population.

MATERIAL AND METHODS

In this study, undertaken at the Division of Medical Genetics of the Department of Medical Biology of Medicine Faculty of Ondokuz Mayıs University, Samsun, Turkey, the cases, who were balanced translocation carriers, were selected and evaluated. The major reasons of references of these cases to our division were recurrent miscarriage, infertility, mental retardation, amenorrhea (primary or secondary) and mentally retarded offspring. A total of 25 cases selected among 4131 cases that were analyzed cytogenetically at the Division of Medical Genetics.

About 3-5 ml of venous blood was collected from each case with a sterile disposable syringe containing heparin. Chromosomal analyses were performed from peripheral blood samples using conventional GTG-banding techniques at the 550-band level (Verma and Babu 1995). At least 20 metaphases were analyzed microscopi-

cally from each case and visualized by image analyzer (PCI Scientific System) for detection of chromosome constitution. Chromosomal anomalies determined by using the rules of International System for Human Cytogenetic Nomenclature (ISCN) (2009) (Shaffer et al. 2009).

RESULTS

In this study, the frequency of the balanced translocations determined, was 0.6%. So, 25 cases were found as carriers of balanced chromosomal translocation (12 males and 13 females) among 4131 cases who were cytogenetically analyzed. The most commonly involved chromosomes that participate to form balanced configurations were chromosomes 7 and 9 (6 times), 1 (5 times), 4, 13 and 17 (4 times), 2 and 3 (3 times). The maximum number of balanced translocations was among the autosomes (24 cases); remaining 1 case was of X – autosomal translocation. The ages of cases were between 14-43 years. It was estimated that among 25 cases, 14 cases (56%) had history of recurrent miscarriage, 5 cases (20%) had mentally retarded offspring history, 3 cases (16%) had infertility, 2 cases (8%) had amenorrhea and 1 case (4%) had mental retardation (Table 1). G banding partial karyotype and schematic drawing of balanced translocations were shown in Figure 1.

DISCUSSION

Balanced chromosomal translocations are usually harmless rearrangements in carriers.

Table 1: The distribution of gender, indications and karyotypes of cases with balanced translocation

| Indication | Karyotype | |
|-------------------------------------|----------------------------|-----------------------------|
| | Female | Male |
| History of recurrent miscarriage | 46,XX,t(12;17)(p13.31;q24) | 46,XY,t(4;9)(q21;q13) |
| | 46,XX,t(7;13)(q33;q33) | 46,XY,t(2;7)(q33;p22) |
| | 45,XX,t(13q;14q) | 46,XY,t(5;9)(q34;q31) |
| | 46,XX,t(1;3)(p26.4;p21) | 46,XY,t(4;7)(q34;q33) |
| | 46,XX,t(3;7)(p21;q36) | 46,XY,t(3;6)(p22;q22) |
| | 46,XX,t(4;7) | 46,XY,t(9;11)(p12;p11.2) |
| | 46,XX,t(8;13)(p12;q14) | 46,XY,t(16;17)(p13.3;q11.2) |
| Mentally retarded offspring history | 46,XX,t(7;10)(q36;q11) | 45,XY,t(14;21)(14q;21q) |
| | 46,XX,t(4;9) | 46,XY,t(5;10)(p15.3;q24.3) |
| | 46,XX,t(1;17) | |
| Amenorrhea | 46,XX,t(X;6)(q25;q16) | |
| | 46,XX,t(9;20)(q13;q11.2) | |
| Infertility | 46,XX,t(1;2) | 46,XY,t(1;2) |
| | | 46,XY,t(9;13) |
| Mental retardation | | 46,XY,t(1;17)(p34;q25) |

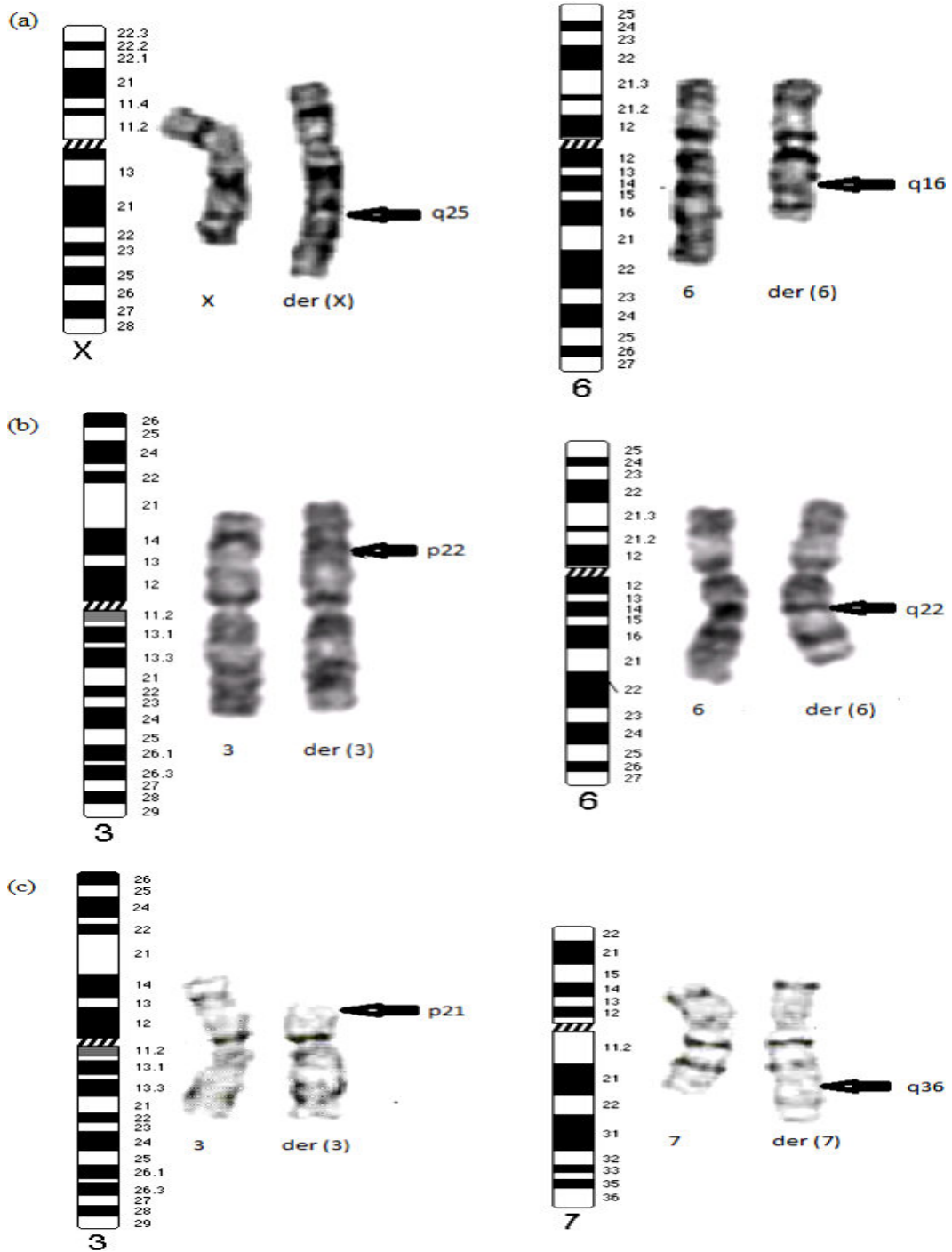


Fig. 1. G banding partial karyotype and schematic drawing of balanced translocations. (a) chromosomes X and 6 balanced rearrangement, (b) chromosomes 3 and 6 balanced rearrangement, (c) chromosomes 3 and 7 balanced rearrangement.

However there are some cases of carriers with mental retardation or phenotypic other abnormalities. It was estimated that 30–50% of the de novo balanced translocations with abnormal phenotype were associated with causative cryptic imbalances (Gribble et al. 2005; De Gregori et al. 2007; Sismani et al. 2008). In the remaining 50–70% of the patients, the phenotype might be caused by other mechanisms such as inter-uption of a dosage sensitive gene, or by uniparental disomy or by unmasking of a recessive mutated gene on the homolog chromosome or finally by position effect with variable expression of a gene(s) near the translocation breakpoint. However a disruption of a recessive gene might occur at the breakpoints of the translocation without a phenotypic effect (Baptista et al. 2008). On the other hand, balanced translocation carriers have the risk of producing unbalanced gametes because of the formation of derivative chromosomes during the matching of homolog chromosomes as a quadrivalent figure at meiosis I (Tsui et al. 1996; Shaffer et al. 1996; Nazarabadi et al. 2005). Unbalanced gametes may cause miscarriage and also birth of mentally retarded offspring (Suguiura-Ogasawara et al. 2004). So, an important accordance has been observed between the results of literature and the results of this study. Especially high prevalence of recurrent miscarriage and mentally retarded offspring (76%) also show the same accordance with literature (Nazarabadi et al. 2005). Also a suitable concordance was found between the results of reported cases with mental retardation and phenotypic other abnormalities and the results of 6 cases with infertility, amenorrhea and mental retardation that evaluated in this study (Vandeweyer et al. 2009). In literature, the preferentially involved chromosomes in infertility and in giving rise to karyotypically abnormal live births with mental retardation and multiple congenital abnormalities were: 4,7,9,11,18,21,22 (de Braekeleer and Dao 1990) which was also concordance with our results Genetic variants at 1p13.3, 1p36.32 and 12p12.1 were also implicated in the etiology of non-obstructive azoospermia (NOA) (Hu et al. 2011). There are several cases of balanced autosomal translocations in primary amenorrhea and premature ovarian failures have been reported (Kopakka et al. 2012). The results of cases with balanced translocation showed that carrying balanced translocation cause recurrent miscarriage with a high frequency, because of cre-

ating unbalanced gametes. Observing infertility, amenorrhea and mental retardation in some cases was thought that these phenotypic features becoming as a result of changing in genes located at the breakpoint area balanced translocations remain a challenge for geneticists especially when they are detected prenatally.

CONCLUSION

When the cases were examined, it is understood that the increase in the frequency of miscarriage is the most frequent phenotypic feature in balanced translocation carriers as a result of the formation of unbalanced gametes. On the other hand, we convinced that balanced translocations may cause infertility, amenorrhea and mental retardation in some cases due to the changing of the genes at the area of the breakpoints. Consequences getting from this study showed that balanced translocation carriers must be followed for life, given genetic consultation and directed to preimplantation genetic centers for having healthy generations.

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