

## ORIGINAL ARTICLE

**THE INCIDENCE AND TYPE OF CHROMOSOMAL TRANSLOCATIONS FROM PRENATAL DIAGNOSIS OF 3800 PATIENTS IN THE REPUBLIC OF MACEDONIA**Vasilevska M<sup>1,\*</sup>, Ivanovska E<sup>1</sup>, Kubelka Sabit K<sup>1</sup>, Sukarova-Angelovska E<sup>2</sup>, Dimeska G<sup>3</sup>

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**ABSTRACT**

Robertsonian and reciprocal chromosomal translocations are the most frequent type of structural chromosomal aberrations in the human population. We report the frequency and type of detected translocations in 10 years of prenatal diagnosis of 3800 prenatal samples. The materials came from amniocentesis and chorionic villus samples (CVS). We detected seven Robertsonian translocations (0.18%), eight autosomal reciprocal translocations (0.21%) and one sex chromosome translocation (0.03%). The overall frequency of all translocations was 0.42%. Balanced state translocations were 0.29% and the frequency of translocations in an unbalanced state was 0.13%. There was one balanced *de novo* X-autosome translocation [46,X,t(X;10)(p11.23;q22.3)] and one balanced double translocation [46,XX,t(1;21);t(7;16)(1p21;21q11)(7q31;16q23)] inherited from the mother. Most of the detected translocations were the result of unknown familial translocations, but some of them had been previously detected in one of the parents. In order to detect the recurrence risk for future pregnancies, we proposed genetic counseling in each of the cases and we established whether the parents were heterozygous for the same translocation. Histopathological findings

for some unbalanced translocations correlated with phenotypes of detected unbalanced karyotypes.

**Keywords:** Human chromosomal translocations; Karyotype; Prenatal diagnosis.

**INTRODUCTION**

Constitutive chromosome translocations are the most frequent structural chromosomal abnormalities in humans. There are Robertsonian translocations involving acrocentric chromosomes, reciprocal translocations between auto-some chromosomes or sex chromosome translocations. All types of translocations may be presented in balanced and unbalanced states. Mental and physical abnormalities can be expected when the translocation is in an unbalanced state. On the other hand, the phenotype of the balanced translocation carriers is usually normal and the translocation may pass undetected through generations. The birth of a child with an unbalanced form of translocation or infertility in the carriers, usually reveals the existence of a familial chromosomal translocation [1]. Gametogenesis of the carriers is affected by forming trivalents (Robertsonian translocations) or quadrivalents (reciprocal translocations) between translocated and normal chromosomes. The type of gametes produced in meiosis depends on the mode of chromosome segregation. Only alternate segregation can produce normal or gametes with translocations in a balanced state. All other modes can be classified as malsegregation, because of production of unbalanced gametes [2].

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**Table 1.** Referral reasons for 3800 prenatal diagnosis (amniotic fluids and chorionic villus samples).

Referral Reasons	Amniotic Fluid	%	CVS	%
Maternal age	2276	59.89	1130	29.74
Abnormal ultrasound findings	143	3.76	72	1.89
Positive triple test	111	2.92	27	0.71
History of chromosomal abnormalities	26	0.69	15	0.40

Genetic counseling, risk estimation and prenatal cyto-genetic diagnosis are required for the carriers of known balanced chromosomal translocations.

**MATERIALS AND METHODS**

During the period from 2002 to 2012, 3800 prenatal samples [2556 amniotic fluids and 1244 chorionic villus samples (CVS)] were referred to the Department of Diagnostic Laboratories (Cytogenetic Laboratory), Clinical Hospital Acibadem Sistina, Skopje, Republic of Macedonia (ROM). Referral reasons for prenatal diagnosis were advanced maternal age, abnormal ultrasound findings, history of chromosomal abnormalities, positive maternal serum triple test (Table 1).

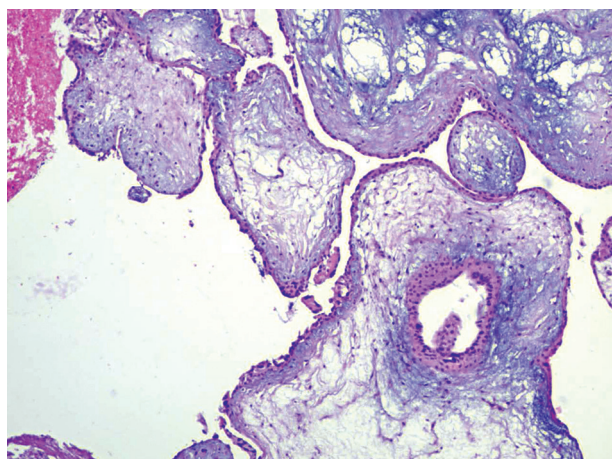
Amniotic fluid samples and CVS were cultivated in Amniogrow complete medium (Cytogen, Sinn, Germany). Peripheral blood samples of the parents (prenatal detection of structural chromosomal abnormality) were cultivated in Lymphogrow medium (Cytogen). At least 15 metaphases were analyzed for each case and 10 metaphases were karyotyped using Bandview software from Applied Spectral Imaging

(Carlsbad, CA, USA). The results were reported according to the recommendations of the International System for Chromosome Nomenclature 2009 [3].

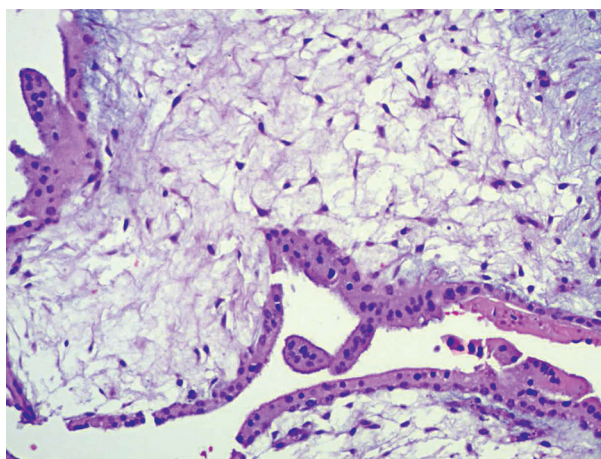
**RESULTS**

During 10 years prenatal diagnosis and 3800 samples provided by amniocentesis and chorion biopsy, we detected seven Robertsonian translocations, eight autosomal reciprocal translocations and one sex chromosome translocation in balanced and unbalanced states (Table 2). Referral reasons for prenatal diagnosis for all cases are represented in Table 1.

An overall frequency of all Robertsonian translocations was 0.18%; all four (13;14) were in balanced state, three of which originated from maternal Robertsonian translocations and only one case of paternal origin. Maternal carriers of this Robertsonian translocation did not have reproductive problems or pregnancies with unbalanced rob(13;14) translocations. The translocation with paternal origin resulted from oligoasthenoteratozoospermia in the paternal carrier of rob(13;14) and conception was achieved after applying techniques of assisted reproduction.



**Figure 1.** The chorionic villi in T14;21 had irregular villus contours (shapes) with mucinous or edematous stroma.



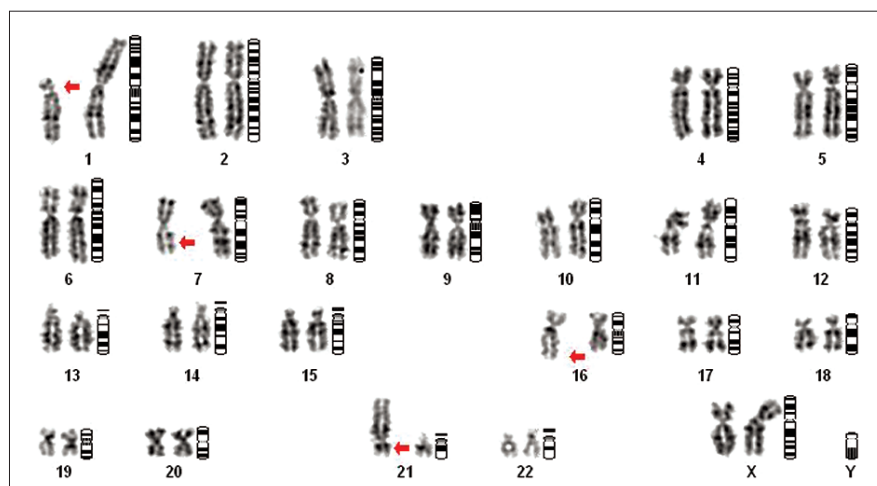
**Figure 2.** The trophoblast on the villus surface showed trophoblastic proliferations in the form of sprouts.

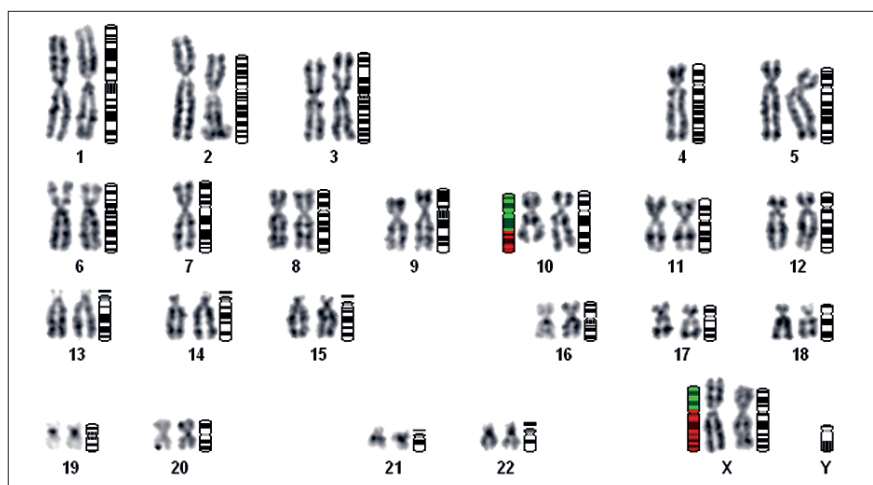
**Table 2.** Detected translocations from prenatal diagnosis of 3800 cases.

	Chromosomal Translocation	Breakpoints	Familial/ <i>De Novo</i>	Balanced/ Unbalanced	Referral Reason
1	45,XY,rob(13;14)	(q10;q10)	paternal	balanced	intracytoplasmic sperm injection; oligoasthenozoospermia
2	45,XY,rob(13;14)	(q10;q10)	maternal	balanced	maternal age
3	45,XX,rob(13;14)	(q10;q10)	maternal	balanced	positive maternal triple test
4	45,XX,rob(13;14)	(q10;q10)	maternal	balanced	known translocation
5	46,XY,rob(14;21)+21	(q10;q10)	maternal	unbalanced	child with Down's syndrome
6	46,XY,rob(14;21)+21	(q10;q10)	maternal	unbalanced	ultrasound abnormalities
7	46,XY,+13,der(13;13)	(q10;q10)	<i>de novo</i>	unbalanced	ultrasound abnormalities
8	46,XY,t(6;10)	(p21;q26)	paternal	balanced	two previous miscarriages
9	46,XY,t(9;16)	(q12;q11)	paternal	balanced	ultrasound detected choroid plexus cysts
10	46,XX,t(2;17)	(q14.3;q23)	paternal	balanced	maternal age
11	46,XY,t(7;12)	(q32;q24.1)	paternal	balanced	previous child with multiple malformations
12	46,XY,t(12;19)	(12qter::19q13→19qter)	paternal	balanced	maternal age
13	46,XX,t(1;21)t(7;16)	(1p21;21q11)(7q31;16q23)	maternal	balanced	one previous miscarriage; infertility
14	45,X,t(2;21)	(p10;p10)	?	Turner syndrome	ultrasound hydrops fetalis
15	45,XY,t(18;21)	(p11;q11),18p-	<i>de novo</i>	18p-	IVF ultrasound abnormalities
16	46,XX,t(X;10)	(p11.23;q22.3)	<i>de novo</i>	balanced	IVS thawed embryo, maternal age

There were two rob(14;21) translocations detected in an unbalanced state, both of them of maternal origin. In one of the patients with familial rob(14;21) the microscopic analysis of the curetted placental tissue showed abnormalities that suggested chromosomal abnormalities consistent with trisomy. The chorionic villi had irregular villus contours (shapes)

with mucinous or edematous stroma (Figure 1). The villous blood vessels were diminished and nucleated erythrocytes were absent. The trophoblast on the villous surface showed trophoblastic proliferations in the form of sprouts (Figure 2). There is one case with *de novo* 46,XY, +13,der(13;13) with detected ultrasound abnormalities. The autopsy of the fetus showed

**Figure 3.** 46,XX t(1;21)(1p21;21q11);t(7;16)(7q31;16q23)mat.



**Figure 4.** *De novo* balanced translocation 46,X,t(X;10)(p11.23;q22.3?) in a thawed IVF embryo.

multiple anomalies. The fetus had cheilognathopalatoschisis, hexadactyly on both toes. The visceral organs did not show any abnormalities. These findings were consistent with a Patau's syndrome phenotype.

The frequency of autosomal reciprocal translocations was 0.21% (eight cases). Five conceptions with reciprocal translocations of autosome chromosomes in a balanced state (paternal origin) were achieved normally. There was one double translocation 46,XX t(1;21)t(7;16) with normal ultrasound parameters from maternal origin, mother was the *de novo* carrier for both translocations, without phenotypic abnormalities (Figure 3). There was only one *de novo* 45,XY,t(18;21)(p11;q11),18p- case associated with ultrasound abnormalities detected after a pregnancy was achieved with the assistance of IVF. One case, 45,X, t(2;21)(p10;p10) of unknown origin, was represented with ultrasound hydrops fetalis that was associated with Turner Syndrome phenotype.

There was one *de novo* case of apparently balanced sex chromosome translocation [46,X,t(X;10)(p11.23; q22.3)] in a single pregnancy achieved after transfer of three thawed embryos (Figure 4). The karyotypes of the parents were normal.

## DISCUSSION

Chromosomal translocations are represented in our study with an overall frequency of 0.42%. The frequency of translocations in a balanced state were 0.29% and of translocations in an unbalanced state was 0.13%.

There were seven Robertsonian translocations detected in our study, six of them being inherited

from a parent who was a carrier of a Robertsonian translocation. All four detected rob(13;14) were in a balanced state. Three of them were of maternal origin, and in all cases there was no evidence of reproductive problems. One case of rob(13;14) was of paternal origin, and the analyzed pregnancy was achieved by assisted reproduction because of the father's severe oligoasthenozoospermia. The two cases of rob(14;21) detected in our study were in an unbalanced state and of maternal origin.

Our results correlate with the European collaborative study [4], where all karyotypes of 280 prenatal samples [parent rob(13;14) carrier] were in a balanced state. It was noted by several investigators that meiotic segregation products in male carriers of all Robertsonian translocations result mostly from alternate segregation mode (>75.0%) [5-7]. Analysis of meiotic prophase cells in heterozygous carriers of different Robertsonian translocations showed that the predominance of a preferential *cis*-configuration of the meiotic trivalent structure could promote alternate segregation [8,9].

The risk for translocation trisomy 21 (Down's syndrome) at amniocentesis in female heterozygote was estimated to be about 15.0% [4,10]. The risk of having a live-born child with translocation trisomy 21 was around 10.0%. There was an about 1.0% risk for paternal transmission of translocation trisomy 21 [2].

In our study, there was one case of *de novo* unbalanced homologous translocation with karyotype 46,XY, rob(13;13)(q10;q10)+13. The histopathological findings of this terminated pregnancy confirmed a Patau's syndrome phenotype. According to the con-

sulted references, 90.0% of cases with t(13;13) are *de novo* and estimated mutation rate for *de novo* t(13;13) is 0.5% per  $10^5$  gametes at conception [11]. Bugge *et al.* [12] used 20 polymerase chain reaction (PCR)-based DNA polymorphisms to determine whether trisomy 13 due to *de novo* t(13q;13q) in six cases is caused by translocation (13q;13q) or isochromosome (13q;13q), and to determine the parental origin of the rearrangements and the mechanisms of formation. In five cases, isochromosomes with two identical q arms were revealed, one of maternal origin and four of paternal origin. Only one case had a Robertsonian translocation of maternal origin [12].

Reciprocal translocations of different autosome chromosomes were presented in our study with six cases in a balanced state, five of them of paternal origin and one double translocation inherited from the mother. Only the cases of 46,XY,t(6;10)(p21;q26) pat. and double translocation 46,XX,t(1;21)t(7;16) mat. were associated with reproductive problems. All other cases were of paternal origin and did not report reproductive abnormalities; they have other children with normal phenotypes.

It was noted that if the same (balanced) karyotype found in the carrier parent was detected at prenatal diagnosis, there was no increased risk of phenotypic abnormality in the child [2]. However, there are mechanisms where apparently balanced translocation may have phenotypic consequences in the progeny of translocation carriers. These are: cryptic unbalanced defect [13], post zygotic loss of a derivative chromosome in one cell line [14], position effect [15], and uniparental disomy. Gametogenesis of reciprocal translocation carriers is affected by different segregation modes at meiosis and unbalanced gametes lead to infertility, recurrent miscarriages and fetal multiple malformations. Genetic counselling for prenatal cytogenetic diagnosis in all future pregnancies of a parent heterozygous for reciprocal translocation is required. Genetic counselling for a double translocation is the same as for a single translocation, although the risk for future pregnancies is increased [16].

We found two unbalanced karyotypes with reciprocal translocations. One unbalanced state was the result of monosomy X (Turner syndrome) associated with translocation (2;21) of unknown origin. If there is a parent carrier of the same translocation, this karyotype may be the result of ICE (interchromosomal effect) [17].

The other one is a *de novo* 45,XY,t(18;21)(p11;p11) 18p- (IVF pregnancy) in parents with normal karyotypes. Random error in parental gametogenesis seems to be the reason for this translocation and the recurrence risk is low.

Regarding the normal phenotype of the girl with the *de novo* apparently balanced sex chromosome translocation 46,X,t(X;10)(p11.23;q22.3), we can assume that there was early replication of the translocated X chromosome in all cells. However, reproductive failure and recurrent miscarriages can be expected later in life and genetic counselling as well as prenatal diagnosis is required.

Sex chromosome translocations (X-autosome) are distinct from autosome translocations because of transcriptional silencing of an extra X chromosome in the female [18]. Inactivation pattern is crucial for phenotypes of affected female carriers. Silencing of a normal X chromosome is required for a normal phenotype. Even so, there is a risk of gene disruption or position effect in X-autosome female carriers. In the review of 122 cases of balanced X-autosome translocations in females [19], with respect to the X inactivation pattern, the position of the X breakpoint and the resulting phenotype, there were 77.0% of the patients where translocated X chromosome was replicated early in all cells analyzed. The breakpoints in these cases were distributed all along the X chromosome. Most of these patients were either phenotypically normal or had gonadal dysgenesis, some had single gene disorders, and less than 9.0% had multiple congenital anomalies and/or mental retardation. In the remaining 23.0% of the cases, the translocated X chromosome was late replicating in a proportion of the cells. In these cells, only one of the translocation products was reported to replicate late, while the remaining portion of the X chromosome showed the same replication pattern as the homologous part of the active, structurally normal X chromosome. The analysis of DNA methylation in one of these cases confirmed non inactivation of the translocated segment. Consequently, these cells were functionally disomic for a part of the X chromosome.

## CONCLUSIONS

Most of the prenatal chromosomal translocations were the result of familial translocations. We detected three *de novo* translocations, one balanced X-autosome translocation, one unbalanced t(18;21)(p11;q11), 18p- and one unbalanced der(13;13). The frequency of all

translocations was 0.42%. In each case, genetic counseling was required to establish whether the parents were heterozygous for the same translocation and to establish the recurrence risk for future pregnancies.

**Declaration of Interest.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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