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ORIGINAL PAPER

Reproductive Risk of the Silent Carrier of Robertsonian Translocation

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Aim: The aim of this study was the evaluation of risk among the couples various types of Robertsonian translocations. **Methods**: Cytogenetic diagnosis has been carried out according to the Moorhead and Seabright method. **Results**: Cytogenetics diagnosis was performed in 17 couples having Robertsonian translocations. Among our examined cases, the most frequent (82.3%) cases were with Robertsonian translocations formed by aberrant fusion between heterologous chromosomes 13q and 14q. Three out of seventeen couples affected with Robertsonian translocation 13q;14q suffered from primary infertility. The total number of pregnancy among the couples with Robertsonian translocation has been 45. Of these 80% of pregnancies resulted in spontaneous miscarriages, while 20% of others have gave birth to alive or dead children. In one couple a Robertsonian translocation was caused as a result of fusion of two homologous chromosomes 15q;15q. A patient with this translocation has had 7 pregnancies and all of them ended with abortions. **Conclusion**: Robertsonian translocation caused the primary infertility in three couples and lowering reproductive abilities in 14 others. Robertsonian translocation between 15q;15q caused intrauterine death and spontaneous failures of all pregnancies of the carrier with this translocation. Key words: reproductive risk, Robertsonian translocation, spontaneous failure.

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1. INTRODUCTION

Chromosomal aberrations are one of the causes of reproductive failure or reduction of reproductive abilities in humans, characterized by infertility, habitual failures, or the birth of children with unbalanced karyotype (1).

The Robertsonian translocations (RT) are created by fusion of two acrocentric chromosomes at or near the centromere. Centromeric fusion can be either between homologous or heterologous acrocentric chromosomes.

Couples experiencing several spontaneous miscarriages can very often be RT silent carriers (2). In the general population RTs represent the largest number of structural chromosomal aberrations account for up to 0.1% of newborns, or in much higher (1.1%) incidence in couples experiencing spontaneous abortions and reaching 2.3% frequency in infertile men (3). The most common RT in humans is the one created between acrocentric chromosomes 13 and 14 (13q;14q) which constitutes 75% of all RTs and has an incidence of 0.97/1000 in newborns (4), reaching up to 9 times higher frequency in infertile males (5).

Silent carriers of these translocations possess varying degrees of risk for spontaneous miscarriages and birth of children with anomalies (6). The risk level depends on which acrocentric chromosomes are involved in RTs carriers and on their sex. Higher risk levels have RTs between homologous acrocentric chromosomes resulting in the formation of only genetically unbalanced gametes (7). Carriers of RT involving homologous chromosomes 13 (13q;13q) or 21 (21q;21q) have chance of giving birth of children with Patau or Down syndrome, any may have habitual failures, but they can not give birth to any normal children (8, 9). RT carriers involving homologous chromosomes 14 (14q;14q) or 15 (15q;15q) are likely to have spontaneous failures only and are unable of giving birth to any children alive due to their unbalanced gametes, which can create only embryos having chromosomal defects incompatible with intrauterine life (10). In these cases, the reproductive risk is high and the same for both sexes.

On the other hand, carriers of RTs between nonhomologous chromosomes have chance of making unbalanced, balanced and normal gametes. Therefore couples possessing this translocation type except having spontaneous miscarriages and births of children with anomalies are also likely to give birth to

normal children (11, 12). In that case, the risk of a child having malformations and recurrent miscarriages is higher if the translocation is carried by the women compared to the man.

Except translocation type 13q;14q, other most common RTs are those between 14q;21q, carriers of which have also risk of having children with Trisomy 21 (Down syndrome with translocation) (13). Patients with Robertsonian translocations 13q;15q and 14q;15q are not very common among humans. However, it has been assumed that of reproductive risk these translocations is roughly similar to those found in 13q;14q translocation carriers.

Genetic counseling and cytogenetics diagnosis of families affected by RTs are important for early prevention of giving birth to a child with an unbalanced karyotype and recurrent abortions subsequently.

2. AIM

The purpose of this study was to determine the frequency of various types of RTs, to assess the reproductive risks in couples carrying various types of RTs, and to clarify the genetic mechanism by which chromosomal changes occur in the carriers of RT offspring.

3. METHODS

Cytogenetic diagnosis has been done in chromosome preparations of lymphocytes cultured from peripheral blood according to Moorhead method (14). For precise identification of chromosomes standard method for G-banding by Seabright was used (15).

4. RESULTS

This study research in 17 couples with RTs has been performed in the Laboratory of cytogenetics at the Obstetrics and gynaecology clinic in Prishtina. Four types of RTs have been identified. The first type between two homologous acrocentric chromosomes 15q;15q, and three others by fusion of unhomologous acrocentric chromosomes: 13q;14q, 13q; 15q and 14q; 15q.

Types of Robertsonian translocations	The number of spouse pairs	%
Robertsonian translocation 13q;14q	14	82.3
Robertsonian translocation 15q;15q	1	5.9
Robertsonian translocation 13q;15q	1	5.9
Robertsonian translocation 14q;15q	1	5.9
Total	17	100,0

Table 1. The frequency of different types of Robertsonian translocations in couples with reduced reproductive ability.

All the RTs subjects studied were phenotypically normal.

Among our examined RTs cases the most frequent (82.3%) have been those with 13q and 14q nonhomologous chromosomes, while three other translocation types were present only in one patient each (Table 1 and 2). RT between 13q;14q was present in 14 patient. Of these 6 males had karyotype 45,XY, der (13;14)(q10;q10) and 8 females had karyotype 45, XX, der (13; 14) (q10; q10) (Figure 1). The data show that this type of translocation was slightly more common in females (57.1%) than in males (42.9%). Three couples affected by translocation type 13q;14q suffered from primary infertility, of which in two of them translocation carriers were males and in one carrier was female.

In couples with RTs total number of pregnancies was 45 (Table 3). Thirty six of them (80%) ended in spontaneous miscarriages. Nine (20%) resulted in giving birth to children, of which five children (11.1%) were born alive, and four others (8.9%) stillbirths. Since the number of spontaneous miscarriages was significantly higher than of children born, couples with RTs clearly have shown reduced reproductive ability.

The genealogical tree data analyses have shown that the highest rate of reproductive risk which have RT couple is formed by fusion of two homologous acrocentric chromosomes 15q;15q, with cytogenetics formula: 45, XX, der (15; 15) (q10; q10) (Figure 2). This female

No.	Identification number	Initials	Chromosome complement		Babies born alive	Babies born dead	Spontaneous miscarriages
			Female partner	Male partner			
1.	179	K.U.	45.XX,der (13;14) (q10;q10)	46,XY			3
2.	781	A.V.	45.XX,der (15;15) (q10;q10)	46,XY			7
3.	840	S.M.	45.XX,der (13;14) (q10;q10)	46,XY	1		1
4.	1184	E.D.	45.XX,der (13;14) (q10;q10)	46,XY		1	3
5.	1777	E.I.	45.XX,der (13;14) (q10;q10)	46,XY			
6.	1872	S.S.	46, XX	45.XX,der (13;14)(q10;q10)			1
7.	2307	B.M.	46, XX	45.XX,der (13;14)(q10;q10)			
8.	2684	M.S.	45.XX,der (13;14) (q10;q10)	46,XY	1		2
9.	2688	S.S.	45.XX,der (13;14) (q10;q10)	46,XY			2
10.	2754	N.G.	45.XX,der (13;14) (q10;q10)	46,XY			3
11.	2838	H.G.	46, XX	45.XX,der (13;14)(q10;q10)		1	1
12.	3019	A.R.	46, XX	45.XX,der (13;14)(q10;q10)			3
13.	3020	G.H.	45.XX,der (13;14) (q10;q10)	46,XY			2
14.	3328	N.Z.	46, XX	45.XX,der (13;14)(q10;q10)	1		4
15.	51/2011	S.I.	46, XX	45.XX,der (13;14)(q10;q10)		2	1
16.	460/2011	S.S.	46, XX	45.XX,der (13;14)(q10;q10)			
17.	862/2012	V.S.	45.XX,der (13;14) (q10;q10)	46,XY	2		3
Total					5	4	36

Table 2. Presentation of the reproductive abilities of couples with Robertsonian translocation.

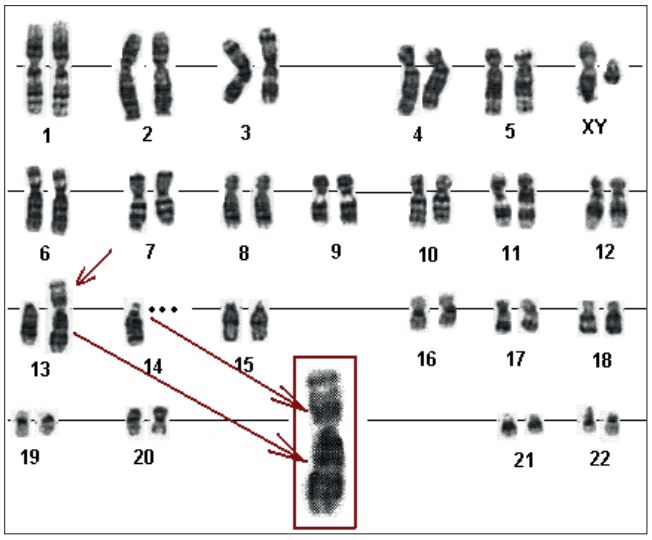

Figure.1. Karyotype of silent carrier with Robertsonian translocation: 45, XX, der (13; 14) (q10; q10).

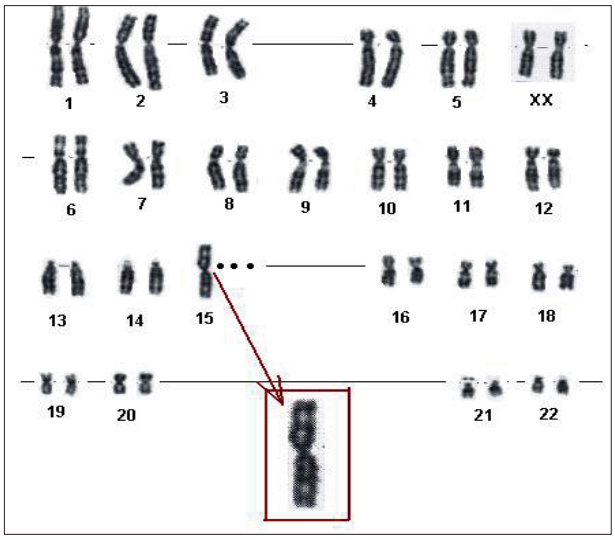

Figure 2. Karyotype of silent carrier with Robertsonian translocation: 45, XX, der (15; 15) (q10; q10).

partner had 7 pregnancies all ended in spontaneous abortions (Figure 3).

In one of the families studied, there were 2 different types of RTs present. The mother had RT 45,XX, der(14;15) (q10;q10), whereas her child had a new type of RT 46,XY,+21, der (21;21) (q10;q10) characteristic for Down syndrome. Both types of RTs occurred de novo. In the human population, two different types of Robertsonian translocations within a family rarely occur.

5. DISCUSSION

Reproductive status of the cases presented in this paper have shown all harmful actions of RTs in reproductive abilities of carriers and in this line our results are consistent with the results presented by other authors (8, 9, 10, 11, 12, 13).

Some authors indicate that RTs involving homologous chromosomes 15q;15q possess a 100% risk for spontaneous miscarriages and inability of carrying pregnancies through to a live birth (10). This type of translocations has rare incidence in the general population. Similarly to other authors, in our study the high level of reproductive risk has couple with RT t(15q;15q) in the mother: cytogenetic formula 45,XX,der(15;15)(q10;q10) (Figure 2). Because of a meiotic mis-segregation (nondisjunction) of translocated chromosomes 15 (during gametogenesis) it leads to the patient only unbalanced gamete (nullisomic and disomic) production. By joining these gametes with

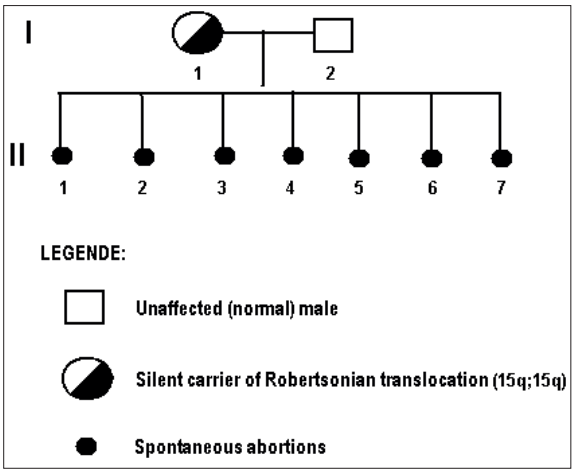

Figure 3. Family pedigree affected by Robertsonian translocation 15q ;15q.

normal gametes of partner, there can be created either monosomic or trisomic zygotes for translocated chromosomes 15q;15q (Figure 4). Since monosomy or trisomy of the chromosome 15 is incompatible with intrauterine life, all of the carrier pregnancies end in spontaneous abortion. Therefore the patient has 100% risk for spontaneous miscarriages and no chance of having any children born alive either normal or with anomalies. This also confirms the real reproductive condition of the female patient studied who have had 7 pregnancies, all resulted in spontaneous miscarriages (Figure 3).

Other authors reports that carriers of RTs 13q;14q have reduced reproductive abilities reflected in various ways like primary infertility, habitual failures and the birth of children with malformations (11, 12). In our study the data collected from the cases affected by RT 13q;14q have shown reduced reproductive ability. Three couples had primary infertility.

As presented in our paper, the genetic mechanism of offspring formation with trisomy involving translocated chromosome 13, of silent carrier offspring with RT 13q;14q and of normal offspring can

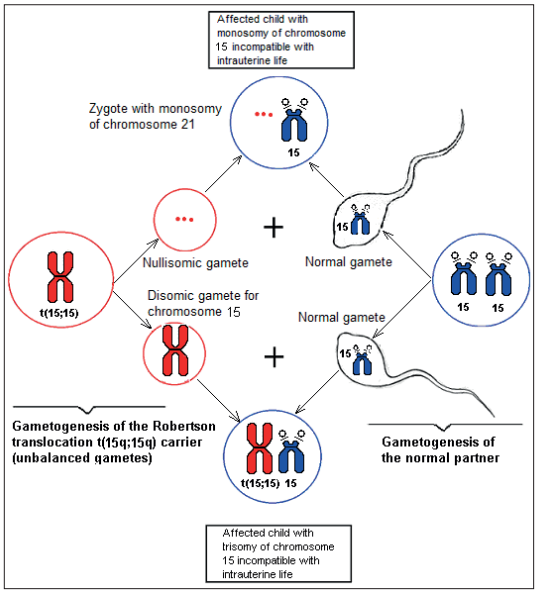

Figure 4. Schematic representation of the offspring creation with unbalanced karyotype to the Robertsonian translocation 15q;15q silent carrier.

be clarified through meiotic disjunction of chromosomes during gametogenesis of the RT 13q;14q silent carrier. During gametogenesis of the RTs carrier, zigonem of prophase I of meiosis results in a trivalent form (called pachytene diagram) due to the rearrangement of the two homologous normal chromosomes with translocated chromosome (Figure 5).

During the anaphase, chromosomes that have formed the pachyten diagram got separated and they move forwards the opposite poles of a cell. In the RT 13q;14q carrier, there are three possibilities of disjunction and movement of chromosome during gametes formation process:

- Disjunction 2:1, adjacent segregation type -1;
- Disjunction 2:1, adjacent segregation type -2;
- Disjunction 2:1, alternate segregation.

As a result of these disjunctions, the silent female carrier of 13q;14q RT may produce six types of gametes (Figure 5). After fertilization of these gametes by normal partner gametes, 6 types of embryos with different chromosomal constitution can be produced. Two of these six types of embryos can continue embryo developing, born and live, whereas four other embryos types are incompatible with intrauterine life or experience early death after birth.

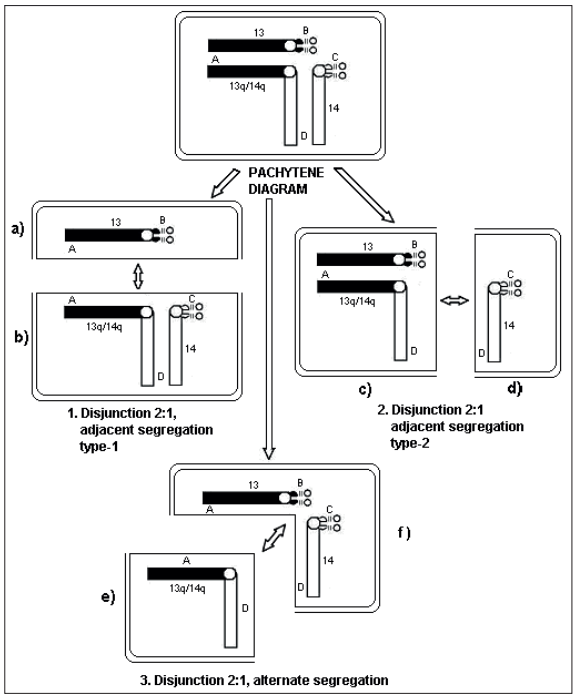

Figure 5. Chromosomal disjunction and segregation during meiosis in gametogenesis of the Robertsonian translocation 13q ;14q silent carrier (a) Nullisomic gamete of chromosome 14; b) Disomic gamete of chromosome 14; c) Disomic gamete of chromosome 13; d) Nullisomic gamete of chromosome 13; e) Unbalanced gamete with Robertsonian translocation 13q;14q; e) Normal gamete with a normal chromosome 13 and 14).

Offsprings	No	%
Spontaneous miscarriages	36	80,0
Children born alive	5	11.1
Children born dead	4	8.9
The total number of pregnancies	45	100,0

Table 3. The offspring's of couples with Robertsonian translocation

By joining of gamete with disomy in chromosome 13 (Figure 5c) with normal gamete by normal partner results a baby with Patau's syndrome who experiences early death after birth. The joining of balanced gamete 13q;14q (Figure 5e) with normal gamete by normal partner results in having silent carrier offspring with RT 13q;14q, like one of the child's parents is.

Finally, joining of normal gametes (Figure 5f) with normal gametes by normal partner genetically and phenotypically normal offsprings are produced.

Most of embryos have incompatible chromosomal constitution with intrauterine life, and such embryos are lost through spontaneous miscarriages. This also confirms the real reproductive conditions of 14 couples in our study, with 13q;14q RT who generally have had 31 pregnancies. Of these 25 pregnancies (80.6%) resulted in spontaneous miscarriages, while only 6 other pregnancies (19.4%) have had children, either born alive or dead.

6. CONCLUSION

Based on cytogenetics and pedigree analyses of carriers of RTs the conclusions are as follows:

The highest frequency RTs was that between 13q;14q which is found in 82.3% of our investigated cases.

Couple affected by RTs 15q;15q resulted in 100% risk for spontaneous miscarriages.

In couples with RTs 80% of their pregnancies resulted in spontaneous failures, while other 20% in children birth alive or dead.

In three couples the RT 13q;14q resulted to be their primary infertility cause in two males and in a female studied.

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