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RESEARCH ARTICLE

EFFECTS OF CHROMOSOMAL TRANSLOCATIONS ON SPERM COUNT IN AZOOSPERMIC AND OLIGOSPERMIC CASES

Akif Ayaz[1], Sinem Yalcintepe[2], Ozge Ozalp[3], Elif Yilmaz Gulec[4], Alper Gezdirici[5], Ebru Perim Akcay[6], Abdullah Huseyin Koseoglu[6], Yavuz Sahin[7]

[1]Istanbul Medipol University, Genetic Diseases Assessment Center, Istanbul, Turkey
[2]Trakya University, Department of Medical Genetics, Edirne, Turkey
[3]Adana City Training and Research Hospital, Genetic Diseases Assessment Center, Adana, Turkey
[4] Istanbul Medeniyet University, Department of Medical Genetics, Genetic Diseases Assessment Center, Istanbul, Turkey
[5]Basaksehir Cam and Sakura City Hospital, Genetic Diseases Assessment Center, Istanbul, Turkey
[6]Istanbul Medipol University, Genetic Diseases Assessment Center, Istanbul, Turkey
[7] Genoks Genetic Diseases Diagnosis Center, Ankara, Turkey

ORCID: A.A. 0000-0001-6930-7148; S.Y. 0000-0002-8557-8885; O.O. 0000-0002-7343-3064; E.Y.G. 0000-0003-0872-3898; A.G. 0000-0002-2432-9279; E.P.A. 0000-0003-3256-8437; A.H.K. 0000-0003-0240-7691; Y.S. 0000-0002-7831-067X

Corresponding author: Akif Ayaz, **E-mail:** aayaz@medipol.edu.tr

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ABSTRACT

Purpose: A number of mechanisms have been proposed for the effect of chromosomal translocations on spermatogenesis and sperm maturation. However, there are still numerous ambiguous issues regarding these two processes. The aim of this study is to evaluate the effect of chromosome break areas on sperm count in the light of the literature.
Material and Methods: The study was conducted on the data of 16 male patients with reciprocal or Robertsonian translocation among 152 patients who were admitted to Adana Numune Training and Research Hospital and Kanuni Sultan Süleyman Training and Research Hospital Genetic Diagnosis Centers between 2013 and 2016 due to azoospermia and oligospermia.
Results: 11 of these patients had reciprocal and five patients had Robertsonian translocations. All the patients with Robertsonian translocations were detected with azoospermia. Of the patients with reciprocal translocation, five of them were azoospermic and six of them were severe oligospermic.
Conclusion: A total of 21 chromosomal breakpoints were identified in the 11 patients with reciprocal translocations. These chromosomal breakpoints may contribute to the clarification of ambiguous issues related to spermatogenesis and sperm maturation. The results also showed the importance of genetic counselling in patients with translocations.

Keywords: Azospermia, oligospermia, reciprocal, robertsonian

INTRODUCTION

Infertility is an important health problem that is increasingly widespread worldwide as well as treatment options, affecting 10-15% of sexually active couples (1). Many genetic or non-genetic causes, especially chromosomal abnormalities, have been shown to be the primary cause of infertility in 30-50% of couples (2-6). Structural and numerical

chromosomal abnormalities have been reported as the cause of male infertility in 10-23.62% of men with azoospermia and in 1.10-13.33% of men with oligospermia (7-12). Klinefelter syndrome (KS) and deletion of critical AZF regions of the Y chromosome are among the most common genetic abnormalities seen in men with azoospermia and severe oligospermia. On the other hand, rare abnormalities such as reciprocal and Robertsonian translocations have been reported to be 10 times more common in infertile men (13). Reciprocal translocation refers to the reciprocal exchange of genetic material between two different chromosomes, which is called "balanced" if there is no loss or gain of genetic material, and "unbalanced" vice versa. These translocations are usually detected while investigating the causes of recurrent pregnancy losses and multiple congenital anomalies, but it should be known that these balanced chromosomal anomalies will also affect semen quality and result in azoospermia and oligospermia in males. It has also been reported that abnormal chromosomal pairing that occurs during meiosis in balanced translocation carriers may lead to germ cell arrest (14,15).

In this study, we aimed to present two different Genetic Diagnosis Center on reciprocal or Robertsonian translocation detected in 16 male patients with azoospermia and oligospermia chromosome analysis and semen analysis results in Turkey. In addition, we aimed to evaluate the effects of reciprocal and Robertsonian translocations on spermiogram in the light of the literature and to emphasize the importance of genetic counseling given to individuals with these abnormalities.

MATERIAL AND METHODS

The study was conducted on the data of 16 male patients with reciprocal or Robertsonian translocation among 152 patients who were admitted to Adana Numune Training and Research Hospital and Kanuni Sultan Süleyman Training and Research Hospital Genetic Diagnosis Centers between 2013 and 2016 due to azoospermia and oligospermia. Informed consent was obtained from each patient. Approval was obtained from the Istanbul Medipol University Ethics Committee for our study (Date: 07.05.2020; Number: 10840098-604.01.01.-E.14988). In each patient, at least 2 sperm samples were obtained at different times and were evaluated according to World Health Organization (WHO) criteria. Cytogenetic analysis of peripheral blood lymphocytes and GTG-banding were performed by a minimum of two experts by using standard protocols. In only one patient, genomic DNA was extracted from peripheral blood and was analyzed by using a commercially available Human Genome CGH Microarray Kit (Affymetrix Inc., Santa Clara, CA, USA) according to the manufacturers protocols. In each patient, pedigrees were also evaluated in addition to karyotype and spermiogram results for evidence of genetic origin.

RESULTS

Between 2013 and 2016, data of 152 patients who underwent chromosome analysis due to azoospermia and oligospermia in two centers were analyzed and reciprocal and Robertsonian translocations were detected in 16 (%10.5) male patients. Of these, 11 patients had reciprocal and five patients had Robertsonian translocations. All the patients with Robertsonian translocations (P10, P11, P12, P13 and P15) were detected with azoospermia. Of the patients with reciprocal translocation, six of them (P1, P3, P5, P8, and P9) were azoospermic and five of them (P2, P4, P6, and P7) were oligospermic. All the patients were evaluated as infertile, except for one patient with oligospermia (P6) whose wife has a history of recurrent miscarriges. All the mutations identified in the patients were de novo mutations, except two patients with Robertsonian translocations (P10 and P11). Molecular karyotyping was performed in one patient and interpreted as normal. The clinical findings of the patients are in Table 1; partial karyotypes are shown in Figure 1.

DISCUSSION

It has been reported that chromosomal translocations in men may cause adverse effects on spermatogenesis by affecting meiosis (16). Chromosomal abnormalities can trigger checkpoints in meiosis during synapse or recombination, thus causing germ cell disruption or cell cycle arrest. In most men with reciprocal translocation, it has been reported that spermatogenesis is completely blocked at the pachytene stage (17). Ishikawa T et al. (2007) demonstrated that in histopathological examination of an azoospermic patient with 46,Y,t(X;11) (q26;q21), the spermatogenetic process may not work properly at the spermatid level, and although many spermatocytes were detected in the seminiferous

Table 1. Clinical, laboratory and family history findings of the patients.

	Age	Spermiogram	Concentration	Indications	Pedigree	*De novo* /	Karyotype
P1	34	Azoospermia	0 million/mL	Infertility	None	*De novo*	46,XY, t(1;2)(q12;p11.2)
P2	33	Oligospermia	2.1 million/mL	Infertility	None	*De novo*	46,XY, t(2;3)(p15;q27)
P3	30	Azoospermia	0 million/mL	Infertility	None	*De novo*	46, XY, t(2;16)(p25;q23)
P4	28	Oligospermia	1.3 million/mL	Infertility	None	*De novo*	46, XY, t(3;14) (p11.2;q11.2)
P5	37	Azoospermia	0 million/mL	Infertility	None	*De novo*	46, XY, t(4;12)(q21.3;q15)
P6	31	Oligospermia	1,4 million/mL	RPL history in his	RPL history	*De novo*	46,XY, t(4;13)(p11;q22)
P7	26	Oligospermia	1,8 million/mL	Infertility	None	*De novo*	46, XY, t(4;7)(q27;p15)
P8	30	Azoospermia	0 million/mL	Infertility	None	*De novo*	46, XY, t(5;19)(p10;q10)
P9	31	Azoospermia	0 million/mL	Infertility	None	*De novo*	46,XY, t(9;20)(p22;pter)
P10	28	Azoospermia	0 million/mL	Infertility	RPL in his	Familial	45,XY, rob(13;14)(q10;q10)
P11	36	Azoospermia	0 million/mL	Infertility	RPL in his	Familial	45,XY, rob(13;14)(q10;q10)
P12	42	Azoospermia	0 million/mL	Infertility	None	*De novo*	45,XY, rob(13;14)(q10;q10)
P13	28	Azoospermia	0 million/mL	Infertility	None	*De novo*	45,XY, rob(13;14)(q10;q10)
P14	36	Oligospermia	1 million/mL	Infertility	None	*De novo*	46,XY,add(10)(q11.2)
P15	31	Azospermia	0 million/mL	Infertility	Infertility	Familial	45,XY, rob(14;21)(q10;q10)
P16	40	Oligospermia	2,6 million/mL	Infertility	None	De novo	46,XY,(6;12)(p25;p11.2)

RPL: Recurrent Pregnancy Loss

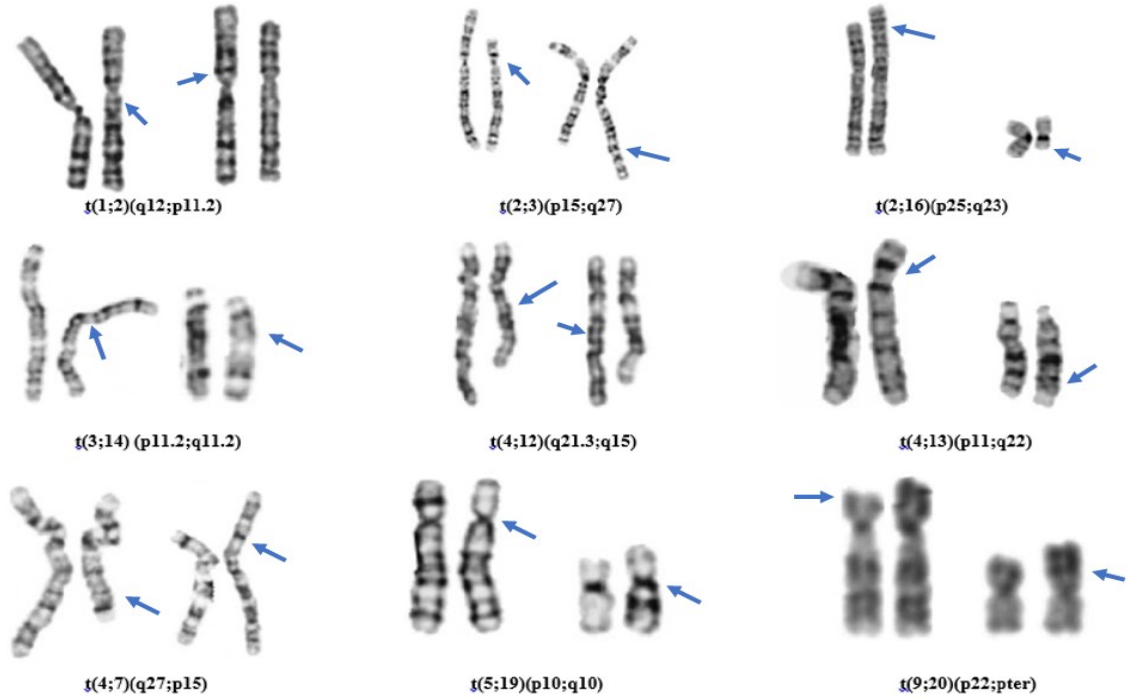

Figure 1. Partial karyotypes of patients P1, P2, P3, P4, P5, P6, P7, P8 and P9 are shown sequentially with fracture regions.

tubules, only a few germ cells were present at the spermatid level (18).

Azoospermic individuals with Robertsonian and reciprocal translocations have been extensively reported in the literature (13). We detected reciprocal and Robertsonian translocations in 16 (%10.5) of our 152 patients with azoospermia and oligospermia, in accordance with the literature (7-12). Balanced translocation carriers are typically known to have a high risk (19-80%) of sperm cells with an unbalanced chromosomal structure as a result of abnormal spermatogenesis (19). In another study, it was revealed that this ratio was between 19-77% and chromosomes not included in translocations also cause aneuploid sperm production due to abnormal segregation and interchromosomal effects (20,21). As a result of human sperm chromosomal abnormalities, the probability of not only infertility but also spontaneous/missed abortion or multiple congenital anomalies increases significantly. As shown in the table 1, there was a history of infertility and recurrent pregnancy loss in the families of 4 (P6, P10, P11, P15) of the cases included in this article. It was observed that the translocations detected in three (P10, P11, P15) of these cases were de novo. Based on these findings, we believe that these couples should recieve genetic counseling to avoid having a child with multiple congenital anomalies or miscarriage. With this counseling, couples should be informed about other clinical practices such as prenatal diagnosis and preimplantation genetic diagnosis (PGD).

Robertsonian translocations were detected in five patients (P10, P11, P12, P13 and P15). It has been reported that a trivalent structure is observed between normal and translocated chromosomes during meiosis in patients with Robertsonian translocations (22). In this study, azoospermic was observed in a total of 5 patients, four patients with rob (13; 14) (q10; q10) and one patient with a karyotype rob (14; 21), in accordance with the literature.

While it is widely known that a sex vesicle containing the X and Y chromosomes is formed during the pachythenic stage in men, this sex vesicle does not form during meiosis in women (23). In patients with Robertsonian translocations, a trivalent structure is formed between normal and translocated chromosomes during meiosis, and this situation significantly increases the possibility of aneuploidy (22). In addition, during spermatogenesis an transient inactivation occurs both in X and Y chromosomes by means of epigenetic mechanisms such as histone modifications (24,25). With the interaction of a translocated chromosome and the X chromosome in

the sex vesicle, the inactivation of the X chromosome is inhibited and a gametogenesis can occur, resulting in azoospermia or oligospermia (26). During meiosis, homologous chromosomes form a synapse through a protein-RNA complex called the synaptonemal complex for the interchange of genetic material between them. It is known that errors in this process can also cause meiosis to stop and may be among the causes of infertility (27). Studies in the germ cells of rats have shown that meiotic inactivation is not only limited to sex chromosomes but also occurs in autosomal chromosomes (28,29). In this study, all translocations detected in our patients were between autosomal chromosomes.

Apart from some known genetic and non-genetic factors, we think that sperm parameters may vary greatly among translocation carriers, from azoospermia to oligospermia, depending on the chromosome involved in the translocation, as well as whether it is balanced or unbalanced, the chromosome breakpoint and position effect. In our study, all patients with Robertsonian translocation had azoospermia, while five of the patients with reciprocal translocation had azoospermia and six had oligospermia. Some specific genes including zinc finger protein 76 (6p21.3-p21.2), 165 (6p22.1), glutathione peroxidase 5 (6p21.32), and casein kinase 2 beta (6p21.33), which have a role in spermatogenesis and sperm maturation, have been shown to exist at the chromosomal breakpoints in patients with balanced translocations (30). In current study, no translocation involving chromosome 6 was detected in any patient.

Another theory proposed to explain the relationship between chromosomal translocations and infertility is the position effect that affects the activation status of genes at the breakpoints. In our study where we defined 21 different breakpoints, each of the chromosome breakpoints of 11 patients with reciprocal translocation were different from each other. However, we detected a reciprocal translocation between 10th chromosome and another autosomal chromosome that we have not yet detected in oligospermic patient numbered P14. The 1q12 breakpoint detected in P1 was the same as one of the five different breakpoints localized in chromosome 1, which were identified in a cohort study on infertile men conducted by Bache I et al. (31). In addition, a case with non-obstructive azoospermia with (Y;1)(q12;q21) karyotype has also been reported in the literature (32). Interestingly, the 13q22 breakpoint detected in P6 and the 9p22 breakpoint detected in P9 were reported by Lee IW et al. as constitutional complex chromosomal rearrangements in an azoospermic man (33). In addition, the 12q15 breakpoint detected in one of our azoospermic patients (P5) was also reported in the karyotype of an azoospermic man (X;12)(p22;q15) by Quack B. et al. (34). We consider that the chromosomal breakpoints that have been identified in our study for the first time in the literature may involve critically important genes that may contribute to the clarification of ambiguous issues related to spermatogenetic process and sperm maturation.

CONCLUSION

In conclusion, there are various theories proposing that both reciprocal and Robertsonian translocations have an effect on the number of sperms in semen. The chromosomal breakpoints identified in this study may contribute to the clarification of ambiguous issues related to spermatogenesis and sperm maturation. Moreover, our results also showed the importance of chromosome analysis in the etiology of azoospermia and oligospermia and the importance of genetic counselling in patients with translocations.

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