MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 4162-4168
DOI: 10.12659/MSM.911170

Received: 2018.05.06
Accepted: 2018.06.06
Published: 2018.06.18

Clinical Features of Chromosome 6 Translocation in Male Carriers: A Report of 10 Cases and Review of the Literature

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Source of support: This work was supported by the Science and Technology Funds of the Education Department of Jilin Province, P.R. China (JJKH20170846KJ)

Background: The literature indicates that chromosome 6 is involved in balanced translocation and is involved in reproductive failure. This aim of this study was to explore the clinical features of chromosome 6 translocation in male carriers.

Material/Methods: We identified 10 patients who were carriers of chromosome 6 translocations and excluded the patients with varicocele, ejaculatory duct obstruction, and the other cause of infertility. The karyotype was analyzed using G-banding. A search for translocations on chromosome 6 involved in male infertility was performed using PubMed. We included cases of balanced chromosome 6 translocations involving adult men of fertile age and excluded those cases of live-born children, or those without breakpoints involving chromosome 6, or those with complex chromosomal translocations or chimeras.

Results: All 10 patients underwent genetic counseling for infertility. Semen analysis showed that 1 case had azoospermia, while 9 cases exhibited normal semen criteria. The respective partners of the 9 cases with normal semen parameters had a tendency to miscarry: 3 experienced spontaneous and induced abortion because of abnormal embryos; 3 experienced 3 incidents of spontaneous abortion, 2 experienced double spontaneous abortion, and 1 experienced biochemical pregnancy on 3 occasions. Most of the chromosome 6 breakpoints in translocation carriers obtained by the PubMed search were associated with spontaneous abortion.

Conclusions: Chromosome translocations involving chromosome 6 influence fertility status and lead to increased risk of miscarriage. Cytogenetic screening before opting for assisted reproductive technology and the breakpoints of chromosome 6 translocation should be considered for infertile male carriers.

MeSH Keywords: Chromosome Breakpoints • Cytogenetics • Infertility, Male

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/911170

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Background

Male-factor infertility is implicated in half of infertile couples [1]. Chromosomal aberrations are one of the most common causes of male infertility [2] and chromosomal disorders in non-obstructive azoospermia affect spermatogenesis [3]. The literature has demonstrated that structural chromosomal abnormalities in males can lead to abnormal sperm concentrations, influence fertility status, and lead to an increased risk of miscarriage [4–6]. Reduced fertility or a spouse experiencing recurrent miscarriage is the most common feature for the carriers of balanced translocations [7].

The specific chromosomes and breakpoints involved in translocations play an important role [7,8]. In some carriers, the location of a translocation breakpoint is closely related to an important gene, thus leading to spermatogenesis failure [9,10]. Previous studies indicate that chromosome 6 is involved in balanced translocation and is associated with reproductive failure [11–13]. There are important genes located on chromosome 6 that are associated with the complex and vital process of spermatogenesis. For example, the activator of cAMP-responsive element modulator in testis (*ACT*) gene was mapped to chromosome 6q16.1–16.3 and may be associated with the differentiation of spermatids into mature spermatozoa [14]. Furthermore, the sperm acrosomal membrane-associated protein 32 gene (*SAMP32*) located on chromosome 6q15–16.2 encodes a testis-specific protein that is involved in binding of sperm to the oocyte complex [15]. Genetic variants located within the human leukocyte antigen, Class II, DR alpha *(HLA-DRA)* region at 6p21.32 have been identified as risk factors for non-obstructive azoospermia [16].

Several previous publications by our group described the clinical features and genetic counseling of male patients with translocation breakpoints in chromosome 3, 4, and 5 [17–19]. This aim of this study was to explore the clinical features of chromosome 6 translocation in male carriers and genetic counseling for infertile carriers for these genetic anomalies.

Material and Methods

Subjects

Between July 2010 and December 2015, we recruited 5235 males experiencing infertility or receiving counseling from the Outpatient Department at the Center for Reproductive Medicine, First Hospital of Jilin University, Changchun, China. This study included all translocation cases involving chromosome 6 and excluded patients with varicocele, ejaculatory duct obstruction, and the other cause of infertility. For all patients, a clinical questionnaire, physical examination, and semen analysis were used according to previously described methods [20]. Their spouses had normal hormone levels. Chlamydia, Mycoplasma, and Ureaplasma detection was negative for these infertile couples. Abortions due to the female factor were excluded. The study was approved by the Ethics Committee of the First Hospital of Jilin University. Written informed consent was obtained from all study participants.

Cytogenetic analysis

Cytogenetic analysis was carried out for all patients. The protocol of blood sample collection, lymphocyte culture, chromosome preparation, and karyotype analysis were performed using previously described methods [20].

Analysis of identified balanced reciprocal translocations breakpoints

Balanced reciprocal translocations identified in chromosome 6 from infertile males were searched using PubMed on December 8, 2016. The keywords for PubMed searches were “chromosome/translocation/sperm” and “chromosome/translocation/abortion”. We included cases of balanced chromosome 6 translocations involving adult fertile-age men, and excluded those cases of live born children, or those without breakpoints involving chromosome 6, or those with complex chromosomal translocations, and chimeras. The relationships of translocation breakpoints with male infertility and recurrent pregnancy loss were analyzed.

Results

A total of 82 balanced reciprocal translocations carriers were detected among the 5235 male patients recruited for this study. Of these 82 translocation carriers, 10 patients (10/82; 12.2%) were carriers of a chromosome 6 translocation. The karyotypes obtained from these 10 cases are shown in Figure 1. All 10 patients underwent genetic counseling for infertility (mean age=32.8±4.9 years, normal phenotype). Testicular size was normal on physical examination. Semen analysis showed that 1 patient had azoospermia while 9 showed normal semen criteria. Of the 9 with normal semen parameters, their partners were able to conceive but experienced abortion: 3 partners experienced spontaneous and induced abortion because of abnormal embryos; 3 experienced 3 incidents of spontaneous abortion, 2 experienced double spontaneous abortion, and 1 experienced biochemical pregnancy on 3 occasions. The breakpoint at 6q15 was associated with pre-gestational infertility, while other breakpoints were related to gestational cases. Karyotype results from the 10 patients expressing chromosome 6 translocations are summarized in Table 1.

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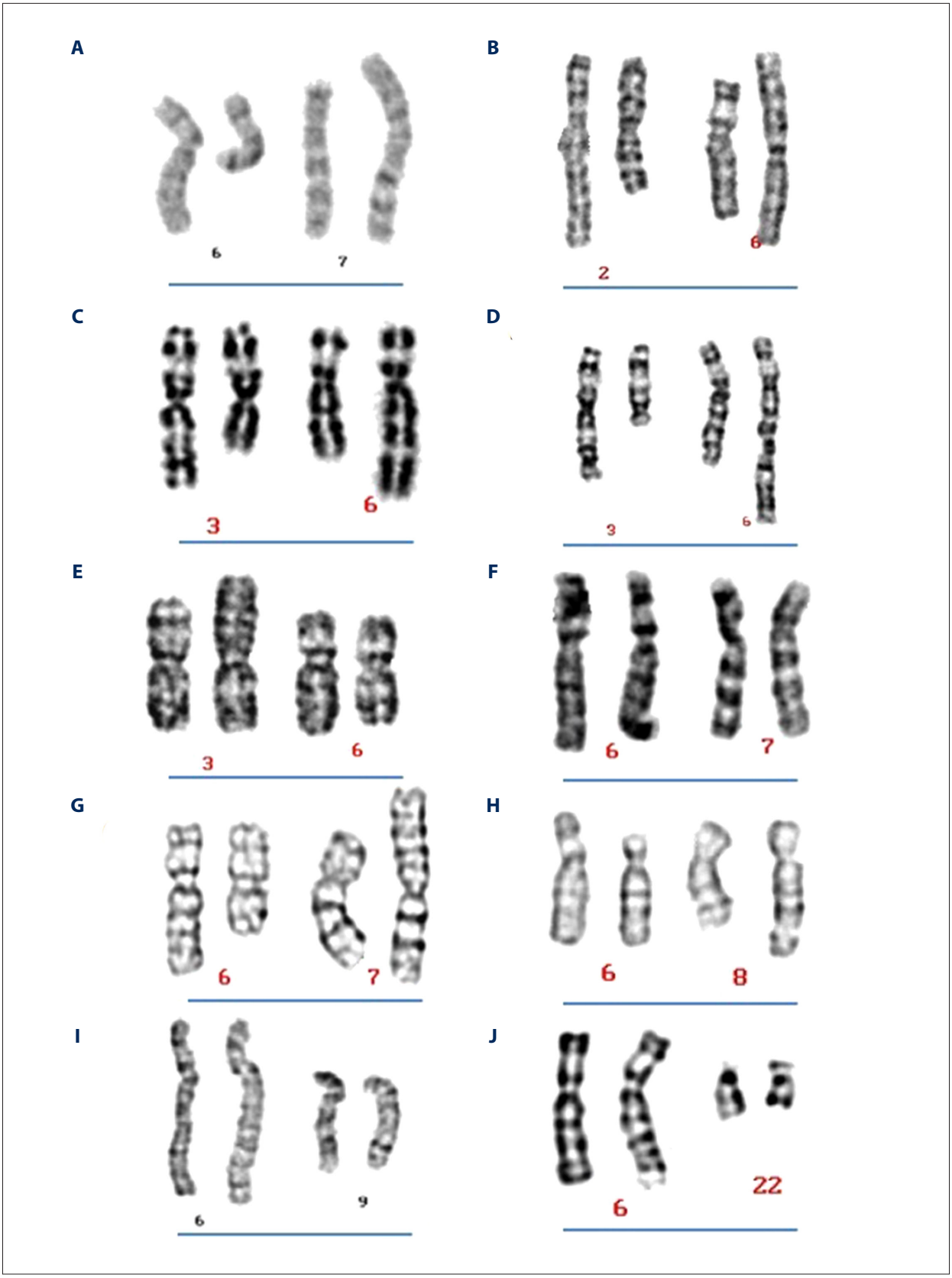

Figure 1. Partial karyotypes of the 10 cases possessing chromosome 6 translocations.

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Table 1. Clinical and cytogenetic features of chromosome 6 translocation carriers.

Infertility type	Sperm concentration ($\times 10^6$/ml)	Karyotype	Karyotype of spouse	Frequency of abortion	Figure No.
Pregestational	0	46,XY,t(6;7)(q15;p15)	46,XX	Nil	1A
Gestational	27	46,XY,t(2;6)(q21;p21)	46,XX	3 biochemical pregnancies	1B
	44	46,XY,t(3;6)(q21;q25)	46,XX	2 spontaneous and 2 induced abortion of abnormal embryos	1C
	49	46,XY,t(3;6)(q12;q27)	46,XX	2 spontaneous abortions	1D
	61	46,XY,t(3;6)(q10;q10)	46,XX	2 spontaneous abortions	1E
	42	46,XY,t(6;7)(q25;p15)	46,XX	3 spontaneous abortions	1F
	99	46,XY,t(6;7)(q13;p15)	46,XX	3 spontaneous abortions	1G
	36	46,XY,t(6;8)(p21;q24)	46,XX	2 spontaneous and 1 induced abortion of abnormal embryos	1H
	46	46,XY,t(6;9)(q26;p13)	46,XX	3 spontaneous abortions	1I
	32	46,XY,t(6;22)(q27;q13)	46,XX	1 spontaneous and 1 induced abortion of abnormal embryos	1J

Table 1 also shows that breakpoints at locations 6p21, 6q25, and 6q27 were observed more than once. The breakpoints at 6p21, 6q10, 6q13, 6q25, 6q26, and 6q27 were associated with gestational infertility. Most of the chromosome 6 breakpoints in translocation carriers obtained in the PubMed search were associated with spontaneous abortion (Table 2). Analysis of previous reports showed that carriers of chromosome 6q15 exhibited pre-gestational infertility, while the carriers of the other breakpoints exhibited gestational infertility.

Discussion

Whole-exome sequencing and array-comparative genome hybridization analyses have been increasingly applied in many medical fields in recent years, but these technologies fail to detect balanced reciprocal translocations or inversions, which sometimes have very detrimental effects on gene structure and function [21]. In contrast, karyotype analysis easily detects balanced reciprocal translocations and remains a powerful and cheap technological method [21]. This technology thus represents a powerful diagnostic tool and provides valuable information for genetic counseling of infertile males [22]. Balanced reciprocal translocation is one of the major chromosomal abnormalities in male infertility [6]. The incidence of balanced reciprocal translocation was reported to be approximately 1 in 625 (0.16%) in the general population [23]. In the present study, the frequency of balanced reciprocal translocations in infertile males was 1.57% (82/5235). Therefore, the incidence of balanced translocations was about 10 times higher in infertile men than in the general population.

In clinical practice, pre-gestational and gestational infertility are distinguished in infertile male patients [24]. Pre-gestational infertility patients exhibit abnormal semen parameters and their partners are not able to conceive. Gestational cases have partners who are able to conceive but have miscarriages. In particular, chromosome 6 translocation has often been associated with male infertility and recurrent pregnancy loss [12,25,26]. In the present study, 10 of our cases were identified as carriers of chromosome 6 translocations. Our findings showed the carriers of chromosome 6q15 exhibited pre-gestational infertility, while the carriers of the other breakpoints exhibited gestational infertility. Ni et al. [27] reported that low-frequency germline variants across locations 6p21.33 to 6p22.2 were associated with non-obstructive azoospermia in Han Chinese men, and disrupted the process of spermatogenesis. This finding is supported by the fact that the zinc finger gene *ZNF165,* which is mapped to 6p21, and the *SAMP32* gene, mapped to 6q15–16.2, are both specifically expressed in the testes [15,28]. The carriers of the breakpoints at 6q13, 6q25, 6q26, and 6q27 had partners who had recurrent pregnancy loss. These results are consistent with previous reports [8,11,13,26,29]. In the literature, the breakpoints at 6p24, 6p23, 6p22, 6p21, 6p12.1, 6p11, 6q11.2, 6q13, 6q21.3, 6q21 6q25, 6q26, and 6q27 were associated with fetal abortion [11,26,29–35], and the breakpoints at

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Table 2. Clinical features and chromosome 6 breakpoints in translocation carriers reported in previous literature*.

Karyotype	Breakpoints	Clinical findings	Reference
t(1;6)	1q44; 6p11	Abortion	Vozdova et al., 2013 [11]
t(1;6)	1q25; 6q16	Infertility	GadaSaxena et al., 2012 [29]
t(2;6)	2q34; 6p24	Recurrent spontaneous pregnancy loss	GadaSaxena et al., 2012 [29]
t(3;6)	3q25.3; 6q11.2	Recurrent fetal wastage	Fryns et al, 1998 [30]
t(3;6)	3q28; 6q13	Infertility	Mierla et al., 2015 [31]
t(3; 6)	3q29; 6q21	Recurrent pregnancy loss	Kochhar et al, 2013 [32]
t(4;6)	4q31.3; 6q21	Recurrent spontaneous pregnancy loss	GadaSaxena et al., 2012 [29]
t(4;6)	4q33; 6q27	Asthenospermia, abortion	Vozdova et al., 2013 [11]
t(4;6)	4q31.3; 6q21	Recurrent spontaneous pregnancy loss	GadaSaxena et al., 2012 [29]
t(4;6)	4q23; 6q21	Repeated spontaneous abortion	Ghazaey et al., 2015 [26]
t(5;6)	5p13.3; 6q27	Recurrent spontaneous pregnancy loss	GadaSaxena et al., 2012 [29]
t(6;7)	6p22;7q22	Four spontaneous abortions	Resim et al., 2013 [33]
t(6;7)	6p22; 7q34	Recurrent fetal wastage	Fryns et al, 1998 [30]
t(6;7)	6q25; 7q34	Abortion	Vozdova et al., 2013 [11]
t(6;7)	6q15; 7p15	Recurrent spontaneous abortion	Zhang et al., 2015 [13]
t(6;8)	6p21; 8q24	Recurrent spontaneous abortion	Zhang et al., 2015 [13]
t(6;8)	6q21.3; 8q23.2	Recurrent fetal wastage	Fryns et al, 1998 [30]
t(6;8)	6q26; 8p12	Normozoospermia	Godo et al., 2013 [8]
t(6;8)	6q13; 8p12	Recurrent spontaneous pregnancy loss	GadaSaxena et al., 2012 [29]
t(6;8)	6p23; 8q12.2	Repeated spontaneous abortion	Ghazaey et al., 2015 [26]
t(6;9)	6q26; 9p13	Recurrent spontaneous abortion	Zhang et al., 2015 [13]
t(6;10)	6p21;10q26	Two previous miscarriages	Vasilevska et al,. 2013 [34]
t(6;10)	6p25; 10p11.2	Repeated spontaneous abortion	Ghazaey et al., 2015 [26]
t(6;10)	6q23; 10p13	Early pregnancy loss	Li et al., 2012 [24]
t(6;11)	6q15; 11p15	Oligoazoospermia	Pernice et al., 2002 [9]
t(6;11)	6p12.1; 11q25	Recurrent spontaneous abortion	Celep et al., 2006 [35]
t(6;14)	6q13; 14p10	Oligoazoospermia	Li et al., 2012 [24]
t(6;14)	6q24.2; 14q24.2	Abortion	Vozdova et al., 2013 [11]
t(6;15)	6p21; 15q26.1	Recurrent fetal wastage	Fryns et al, 1998 [30]
t(6;15)	6q25; 15q14	Recurrent spontaneous pregnancy loss	GadaSaxena et al., 2012 [29]
t(6;16)	6q26; 16p12	Repeated spontaneous abortion	Ghazaey et al., 2015 [26]
t(6;21)	6p21.1;21p13	Azoospermia	Paoloni-Giacobino et al., 2000 [25]

* All breakpoints were listed from 6pter to 6qter to facilitate easy search of the publication.

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6q13, 6q15, and 6q21.1 were associated with oligoazoospermia or azoospermia [9,24,25]. Hence, it is noteworthy that another breakpoint involving balanced translocation should be considered in these pre-gestational individuals.

In genetic counseling, physicians should consider different breakpoints and different reproductive treatment options for the carriers of chromosome 6 translocations. Studies have shown that key genes associated with spermatogenesis are predominantly located on 6p21–22 and 6q15–16 [15,27,28]. Male patients with chromosome 6 breakpoints and pre-gestational infertility should be counseled regarding the potential application of intracytoplasmic sperm injection (ICSI). However, males with gestational infertility and their partners at risk of recurrent pregnancy loss should be counseled regarding the potential use of preimplantation genetic diagnosis (PGD) or prenatal diagnosis [11].

The limitations of this study included the small number of carriers of chromosome 6 translocations and the fact that we did not assess the specific molecular effects of the translocations we identified. However, this study is clinically useful because it provides additional information for male carriers of chromosome 6 translocation when seeking reproductive therapy.

Conclusions

We identified 10 patients who were carriers of chromosome 6 translocations. Combined with previous reports, the analysis of our new cases indicated that the breakpoints identified at location 6q15 exhibited pre-gestational infertility, while the other breakpoints exhibited gestational infertility. Chromosome translocations involving chromosome 6 influence fertility status and lead to an increased risk of miscarriage. Cytogenetic screening before opting for assisted reproductive technology and the breakpoints of chromosome 6 translocation should be considered for infertile male carriers.

Conflict of interest

None.

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