Chromosome 7 translocation breakpoints in male carriers: clinical features and implications for genetic counseling

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ABSTRACT. Balanced reciprocal translocations are associated with reproductive failure. Some reciprocal translocation carriers exhibit azoospermia or oligozoospermia, and an association exists between these chromosomal abnormalities and recurrent abortion. Previous reports have indicated the involvement of chromosome 7 translocations in male infertility and recurrent miscarriage. A translocation breakpoint can occur within an important gene, interrupting its structure and leading to male infertility. However, clinical characteristics resulting from chromosome 7 translocation breakpoints have not been studied. Here, we report such breakpoints and their associated clinical features, to enable informed genetic counseling of carriers. Balanced reciprocal translocations were found in 1.57% of the tested patients. Among these 82 individuals, 14 (17.07%) carried a chromosome 7 translocation, of which, five presented with pregestational infertility and clinical manifestations of oligozoospermia or necrospermia,

while nine presented with gestational infertility (i.e., were able to conceive, but often resulting in miscarriage). Breakpoints at 7q31 and 7q36 were associated with pregestational infertility, whereas those at 7p10, 7q21.2, 7q22, and 7q32 were connected to gestational infertility. However, the breakpoint at 7p15 was associated with both. Chromosome 7 translocation carriers with pregestational or gestational infertility should be counseled on chromosomal breakpoints and the various molecular technologies available for assisted reproduction.

Key words: Male infertility; Chromosome 7; Balanced translocation; Breakpoint; Genetic counseling

INTRODUCTION

Reciprocal translocation is closely related to infertility and recurrent miscarriage. Some reciprocal translocation carriers suffer oligozoospermia or severe oligozoospermia (Zhang et al., 2015c), and couples in which the male partner carries such a chromosomal abnormality are at increased risk of recurrent abortion (Gaboon et al., 2015; Tunç et al., 2016). Reproductive outcome and sperm parameters, including the presence of aneuploidy, in male carriers have received increasing attention over recent years (Li et al., 2015; Pastuszek et al., 2015; Zhang et al., 2015b). These effects are dependent on the specific chromosomes involved in the translocation, the locations of the breaks, and the frequency of chiasmata (Vozdova et al., 2008; Harton and Tempest, 2012; Godo et al., 2013). Previous reports have indicated the involvement of balanced reciprocal translocations of chromosome 7 in male infertility and recurrent miscarriage (Tharapel et al., 1985; Vozdova et al., 2013; Zhang et al., 2015c).

Most balanced chromosomal aberrations are not associated with a clinical phenotype; however, in some male patients, a translocation breakpoint is situated within an important gene, interrupting its structure and leading to infertility (Pernice et al., 2002; Bianco et al., 2011; Harton and Tempest, 2012). The dipeptidyl aminopeptidase-like protein 6 (*DPP6*) and contactin-associated protein-like 2 (*CACNA2D1*) loci, mapped to chromosome 7 and incorporating breakpoints 7q36.2 and 7q21.11, are associated with azoospermia (Li et al., 2014). Ichioka et al. (2005) identified breakpoints at 7q22 and 7q31 from a karyogram of a patient with non-obstructive azoospermia. In addition, most translocation breakpoints on chromosome 7 in men are associated with recurrent miscarriage (Kochhar and Ghosh, 2013; Zhang et al., 2015c; Tunç et al., 2016).

The aim of this study was to determine the correlation between clinical characteristics of male infertility and chromosome 7 translocation breakpoints. Furthermore, the importance of genetic counseling for infertile patients is highlighted.

MATERIAL AND METHODS

Patients

Five thousand two hundred and thirty-five men diagnosed with infertility or receiving counseling for infertility due to genetic causes were recruited from the outpatient clinic of the Centre for Reproductive Medicine at the First Hospital of Jilin University, Changchun,

China, between July 2010 and December 2015. All patients underwent a thorough physical examination and semen analysis, and were required complete a detailed questionnaire pertaining to their smoking habits, marital status, medical history, and working conditions. Azoospermia and oligozoospermia were defined as previously described (Zhang et al., 2015b). The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University, and written informed consent was obtained from all participants.

Cytogenetic analysis

All patients were also subjected to cytogenetic analysis. Peripheral blood (0.5 mL) was collected in sterile tubes containing 30 U/mL heparin. Lymphocytes were cultured in appropriate culture media (Yishengjun; Guangzhou Baidi Biotech, Guangzhou, China) for 72 h, and subsequently treated with 20 mg/mL colcemid for 1 h. G-banding of metaphase chromosomes and karyotype analysis were performed using previously published methods (Zhang et al., 2015a).

RESULTS

Conventional cytogenetic analysis identified a reciprocal translocation in 82 (1.57%) participants, of which, 14 (17.07%) carried a chromosome 7 translocation. Of these, five (5/14) exhibited pregestational infertility (with clinical manifestations of oligozoospermia, severe oligozoospermia, or necrospermia), and the remaining nine (9/14) suffered gestational infertility (the patients' partners were able to conceive, but tended to miscarry). Karyotyping of the 14 patients carrying chromosome 7 translocations is summarized in Table 1.

Table 1. Karyotypes of chromosome 7 translocation carriers and their clinical features.

Infertility type	Clinical findings	Karyotype
Pregestational	Oligozoospermia, severe oligozoospermia or necrospermia	46,XY,t(6;7)(q15;p15) 46,XY,t(7;15)(p15;q15) 46,XY,t(1;7)(p34;q36) 46,XY,t(7;14)(q31;p12) 46,XY,t(7;15)(q31;q22)
Gestational	Normal sperm density; history of miscarriage	46,XY,t(6;7)(q13;p15) 46,XY,t(6;7)(q25;p15) 46,XY,t(7;9)(p10;q10) 46,XY,t(7;10)(q22;p13) 46,XY,t(3;7)(p23;q21.2) 46,XY,t(7;8)(q32;p23) 46,XY,t(7;10)(q32;q22) 46,XY,t(7;10)(q32;q21) 46,XY,t(7;8)(q32;q22)

The most common breakpoints were at 7p15 and 7q32, being observed in four patients each. Those at 7q31 and 7q36 were associated with pregestational infertility, and those at 7p10, 7q21.2, 7q22, and 7q32 with gestational infertility. One breakpoint, 7p15, was connected to both infertility types (Table 2).

Table 2. Incidence of breakpoints on chromosome 7.

Breakpoint	Number of patients with pregestational infertility	Number of patients with gestational infertility	Total (%)
p15	2	2	4 (28.57)
p10		1	1 (7.14)
q21.2		1	1 (7.14)
q22		1	1 (7.14)
q31	2		2 (14.29)
q32		4	4 (28.57)
q36	1		1 (7.14)

DISCUSSION

Karyotype analysis remains the most powerful and affordable of all molecular diagnostic techniques; therefore, this method continues to be widely applied in this field (Pasquier et al., 2016). Carriers of reciprocal translocations, while phenotypically normal, may experience reduced fertility and spontaneous abortions (Harton and Tempest, 2012). Previous studies have reported the involvement of balanced reciprocal translocations on chromosome 7 in male infertility and recurrent miscarriage (Tharapel et al., 1985; Vozdova et al., 2013; Zhang et al., 2015c). In the current investigation, reciprocal translocation was identified in 82 (1.57%) infertile men, 14 of whom (17.07%) carried chromosome 7 translocations. The major limitation of this study was the small number of such carriers; moreover, the molecular effect of these translocations was not investigated here, necessitating further research.

Balanced chromosomal translocations are associated with increased risk of pregnancy loss, fetal death, and male infertility (Godo et al., 2013). The latter is divided into two types of reproductive failure: pregestational and gestational infertility, both of which were found to be associated with chromosome 7 breakpoints in this study. Breakpoints at 7q31 and 7q36 were found in patients with pregestational infertility, whereas those at 7p10, 7q21.2, 7q22, and 7q32 were identified in men suffering gestational infertility. However, a breakpoint at 7p15 was associated with both infertility types. A breakpoint at 7q31 was identified in two pregestational infertility patients. The sperm adhesion molecule 1 (*SPAM1*) gene maps to the long arm of chromosome 7, at this same position (Jones et al., 1995), and epididymal SPAM1 is a marker of sperm maturation (Martin-DeLeon, 2006). In addition, *RNF32*, located on chromosome 7q36, is expressed during spermatogenesis, suggesting a possible role in sperm formation (van Baren et al., 2002). These observations indicate that breakpoints at 7q31 and 7q36 may affect spermatogenesis by altering the functionality of these genes. The breakpoint at 7q15 was identified in two pregestational and two gestational infertility patients. In the former, breakpoints at 6q15 and 15q15 were also noted. *SAMP32*, encoding a testis-specific, isoantigenic sperm acrosomal membrane-associated protein, maps to chromosome 6q15 (Hao et al., 2002), and *CATSPER2*, a gene associated with nonsyndromic male infertility, is located on 15q15 (Avidan et al., 2003). This suggests that the breakpoint at 7p15 may not in fact affect spermatogenesis. Consistent with our findings, Vozdova et al. (2013) reported a correlation between a 7q36 breakpoint and impaired spermatogenesis. And the associations between those at 7q21.2, 7q22, and 7q32 and recurrent abortion are also reported (Niroumanesh et al., 2011; Kochhar and Ghosh, 2013, Zhang et al., 2015c). A survey of related, recently published articles revealed a close link between chromosome 7 translocation breakpoint carriers and male infertility and reproductive failure. Chromosome 7 karyotypes and breakpoints and their related clinical effects are summarized in Table 3. In general, breakpoints at 7q31 and 7q36

tend to be associated with pregestational infertility, while those at 7q21.2, 7q22, and 7q32 demonstrate a relationship with gestational infertility.

Table 3. Chromosome 7 translocation breakpoints and associated clinical features reported in previous publications.

Karyotype	Breakpoints	Clinical findings	Reference
t(1;7)	1p32;7q22	Oligoasthenospermia	Vozdova et al., 2013
t(2;7)	2p23;7p22	Recurrent fetal wastage	Fryns and Van Buggenhout, 1998
t(2;7)	2p13;7q34	Normospermia	Vozdova et al., 2013
t(2;7)	2p13;7q32	Oligoasthenospermia	Vozdova et al., 2013
t(2;7)	2q31;7q34	Asthenospermia	Vozdova et al., 2013
t(3;7)	3p23;7q21.2	Recurrent spontaneous abortion	Zhang et al., 2015c
t(4;7)	4q31;7p22	Recurrent pregnancy loss	Kochhar and Ghosh, 2013
t(4;7)	4q2.7;7p14	Normospermia	Vozdova et al., 2013
t(4;7)	4q2.7;7p14	Normospermia	Vozdova et al., 2013
t(5;7)	5p13;7p15	Recurrent pregnancy loss	Kochhar and Ghosh, 2013
t(5;7)	5p15;7p14	Recurrent spontaneous pregnancy loss	Gada Saxena et al., 2012
t(6;7)	6p22;7q34	Recurrent fetal wastage	Fryns and Van Buggenhout, 1998
t(6;7)	6q15;7p15	Recurrent spontaneous abortion	Zhang et al., 2015c
t(6;7)	6q25;7q34	Normospermia	Vozdova et al., 2013
t(7;8)	7q32;8q22	Recurrent spontaneous abortion	Zhang et al., 2015c
t(7;9)	7p15.2;9q34.1	Normospermia	Vozdova et al., 2013
t(7;10)	7p15.1;10q23.2	Normospermia	Vozdova et al., 2013
t(7;10)	7q34;10q24	Normospermia	Vozdova et al., 2013
t(7;10)	7q36;10q24.3	Teratospermia	Vozdova et al., 2013
t(7;10)	7q32;10q21	Recurrent spontaneous abortion	Zhang et al., 2015c
t(7;12)	7p13;12q15	Normospermia	Vozdova et al., 2013
t(7;13)	7q11.22;13q21.3	Teratospermia	Vozdova et al., 2013
t(7;13)	7q22;13q24	Abortions	Niroumanesh et al., 2011
t(7;13)	7p15;13q33	Recurrent fetal wastage	Fryns and Van Buggenhout, 1998
t(7;13)	7q31;13q31	Recurrent fetal wastage	Fryns and Van Buggenhout, 1998
t(7;13)	7q35;13q13	Infertility	Gada Saxena et al., 2012
t(7;13)	7p13;13q21.2	Recurrent pregnancy loss	Kochhar and Ghosh, 2013
t(7;14)	7pter;14q22	Recurrent spontaneous abortion	Tunç et al., 2016
t(7;14)	7q36;14q11	Recurrent spontaneous abortion	Tunç et al., 2016
t(7;14)	7q33;14q32.3	Recurrent miscarriage	Dutta et al., 2011
t(7;15)	7p15;15q15	Oligozoospermia	Zhang et al., 2015c
t(7;16)	7q32;16q24	Recurrent pregnancy loss	Kochhar and Ghosh, 2013
t(7;17)	7q32;17q21.2	Infertility	Gada Saxena et al.,2012
t(7;18)	7p21.3;18q12.2	Repeated spontaneous abortion	Ghazaey et al., 2015

Carriers of balanced translocations must receive appropriate counseling to inform them of suitable fertility treatment options (Zhang et al., 2015b). Patients with pregestational infertility related to oligozoospermia must be counseled regarding chromosomal breakpoints and *in vitro* fertilization/intracytoplasmic sperm injection. Likewise, those with gestational infertility should be given guidance concerning prenatal testing or preimplantation genetic diagnosis, as these patients are at increased risk of implantation failure and miscarriage (Vozdova et al., 2013).

In conclusion, balanced reciprocal translocations were observed in 1.57% of the infertile male patients tested. Of these, 14 (17.07%) carried chromosome 7 translocations, five presenting with pregestational and nine with gestational infertility. Breakpoints at 7q31 and 7q36 were associated with pregestational infertility, while those at 7q21.2, 7q22, and 7q32 correlated with gestational infertility. Carriers of chromosome 7 translocations suffering infertility of either type should be counseled on chromosomal breakpoints and the various molecular technologies available to assist reproduction.

Conflicts of interest

The authors declare no conflict of interest.

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