Clinical features of infertile men carrying a chromosome 9 translocation

1 Introduction

Balanced reciprocal translocations are structural chromosomal abnormalities. Male carriers may have high rates of genetically unbalanced spermatozoa and exhibit impaired spermatogenesis, associated with frequent unbalanced embryos, male infertility or increased miscarriages [1-3]. However, clinical cases of normal male fertility with no history of related abortion can also be found for individuals with balanced translocations. Additionally, although in vitro fertilization accompanied by preimplantation genetic diagnosis (PGD) increased the chance of translocation carriers fathering a healthy child [4], some studies suggested that PGD did not make better for live birth rate and repeated miscarriage of couples with balanced translocations [5,6]. Natural conception is still a possible option for these carriers’ couples [7,8]. Hence, genetic counselling remains a challenge for carriers of balanced translocations.

Recently, we reported and reviewed the relationship between translocation breakpoints of chromosomes 2, 3, 5, and 6, and infertility for male carriers [9-13]. Previous studies indicated that chromosome 9 translocations are involved in reduced male fertility and increased chance of miscarriage in the female partner [4,14,15]. The chromosomes and specific breakpoints involved in the translocation are closely related to reproductive abnormalities [16,17]. Chromosomal translocation can increase the frequency of spermatozoa carrying an abnormal chromosome constitution, and some translocation breakpoints can disrupt important genes involved in spermatogenesis [10]. Testis-specific protein kinase I gene (TESKI) is located on chromosome 9p13.3 and is specifically expressed in testicular germ cells [18]. Thioredoxin domain-containing protein 8 gene (TXNDC8), mapped to chromosome 9q31.3, may be associated with late sperm maturation [19]. Additionally, chromosome 9 was the first chromosome found to be frequently associated with infertile patients [20]. Understanding the breakpoints on chromosome 9 with
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respects to providing genetic counselling for male infertility warrants further research.

The aim of this study is to identify potential correlations between clinical characteristics of male infertility and carriers of specific translocation breakpoints in chromosome 9.

2 Methods

Twelve male carriers of chromosome 9 translocations experiencing infertility or receiving counselling were recruited from the outpatient’s department at the Center for Reproductive Medicine, First Hospital of Jilin University, Changchun, China between July 2010 and December 2017. This study included all translocation cases involving chromosome 9, and excluded the patients with varicocele, ejaculatory duct obstruction and the other cause of infertility. Each patient underwent semen and cytogenetic analysis. Abortions due to the female factor were excluded. This study was approved by the Ethics Committee of the First Hospital of Jilin University, and written informed consent was provided by each patient.

For each patient, a semen sample obtained by masturbation after 3-7 days of abstinence was allowed to liquefy at room temperature, and was then analyzed using standard techniques recommended by the World Health Organization guidelines. Patients with oligozoospermia were diagnosed with a sperm count less than 15×10^6/ml in their last three semen samples (taken at intervals of 1–3 weeks). Oligozoospermia and severe oligozoospermia were defined as previously described [2]. Chromosome preparations were obtained from lymphocyte cultures derived from each patient. Karyotype analysis after G-banding of metaphase chromosomes followed our previously reported methods [11].

Male chromosome 9 translocations and specific breakpoints from reported papers were searched using PubMed, Google Scholar and CNKI database. The search keywords were “chromosome/ translocation/spERM” and “chromosome/translocation/ abortion”. This study included male cases of adult fertile-age, and excluded females and newborns carriers, those with complex chromosomal translocations, chimeras or bone marrow detection, and other cases without breakpoints involving chromosome 9 in the reported papers.

3 Results

This study clinically examined a total of 12 men with chromosome 9 translocations. Karyotype results and G-banding karyotypes from these 12 patients are shown in Table 1 and Figure 1, respectively. Three cases had oligozoospermia or severe oligozoospermia (pregestational infertility), while nine cases had normal semen. Of the former three cases, the carrier with t(1; 9) (p32; p24) showed oligozoospermia, and the other two carriers manifested severe oligozoospermia. After genetic counselling and informed consent, the use of intracytoplasmic sperm injection combined with PGD should be carefully considered for these patients. Of the latter nine cases, it was evident that the carriers’ wife had a tendency to miscarry (gestational infertility); two cases with t(3;9)(q21;q22) and t(8;9)(q24;q32) produced a phenotypically normal child as confirmed by amniocentesis, respectively, and the other seven cases had experienced recurrent miscarriage. For these patients, PGD or prenatal diagnosis should be considered to improve pregnancy rates and reduce abortion rates.

From a review of the literature, clinical feature, karyotype, and specific breakpoints on chromosome 9 were collected and are summarized in Table 2. The reported paper included 76 carriers of chromosome 9 translocations. Combined with the 12 cases reported in this study, chromosome 1 (11 cases) is the most frequently involved with chromosome 9 translocation. In cases of male infertility, the distribution of other chromosomes involved in the translocation with chromosome 9 is shown in Figure 2. The distribution suggests that balanced translocation is

![Figure 1: G-banding karyotypes of the 12 cases identified as possessing chromosome 9 translocations. a: t(1;9) (p22;p24); b: t(1;9) (p32;p24); c: t(9;15) (p13;q11); d: t(1;9); e: t(3;9); f: t(4;9); g: t(6;9); h: t(8;9); i: t(5;9); j: t(7;9); k: t(9;15) (p24;q22); l: t(9;10).]
closely related to male fertility, and multiple breakpoints on chromosome 1 are involved in these translocations. However, chromosome 11 was not found to be involved in translocation with chromosome 9.

The breakpoints at 9q32, 9p24 and 9p13 were observed in 12 cases (13.6%), 10 cases (11.4%) and 9 cases (10.2%) respectively. The breakpoints at 9p12, 9p11, 9p10 and 9q34.1 were related to pregestational infertility, while breakpoints at 9p21, 9q10, 9q11, 9q13, 9q21.1, 9q22, 9q22.2, 9q22.3, 9q34, 9q34.2 and 9q34.3 exhibited gestational infertility. Other breakpoints were found with cases of either pregestational or gestational infertility (Table 3).

### 4 Discussion

This study reports the karyotype and clinical manifestations of 12 cases with chromosome 9 translocations. Three cases had oligozoospermia or severe oligozoospermia, seven cases were associated with recurrent spontaneous abortions, and two cases each produced a phenotypically normal child (confirmed by amniocentesis). Pregestational and gestational infertility are the most typical two types for infertile male [21]. This study included three cases that exhibited pregestational infertility, and seven cases that exhibited gestational infertility. These patients may consider intracytoplasmic sperm injection or PGD combined within vitro fertilization to reduce subsequent miscarriage rate. The two cases that produced a phenotypically normal child indicated that carriers have a chance of natural conception. The live birth rate in patients with chromosomal translocations choosing to conceive naturally was reported to be 37–63% for the first pregnancy, and then a cumulative rate of 65–83% [22].

| Infertility type | Clinical findings                          | Karyotype                                           | Figure No. |
|------------------|-------------------------------------------|-----------------------------------------------------|------------|
| Pregestational   | Oligozoospermia or severe oligozoospermia | 46,XY,t(1;9)(p22;p24)                                | Figure 1a  |
|                  |                                           | 46,XY,t(1;9)(p32;p24)                                | Figure 1b  |
|                  |                                           | 46,XY,t(9;15)(p13;q11)                               | Figure 1c  |
| Gestational      | Normal sperm density; a history of miscarriage or Natural pregnancy | 46,XY,t(1;9)(p36;q32)                                | Figure 1d  |
|                  |                                           | 46,XY,t(3;9)(q21;q22)                                | Figure 1e  |
|                  |                                           | 46,XY,t(4;9)(q35;p13)                                | Figure 1f  |
|                  |                                           | 46,XY,t(6;9)(q26;p13)                                | Figure 1g  |
|                  |                                           | 46,XY,t(8;9)(q24;q32)                                | Figure 1h  |
|                  |                                           | 46,XY,t(5;9)(p13;q22)                                | Figure 1i  |
|                  |                                           | 46,XY,t(7;9)(p10;q10)                                | Figure 1j  |
|                  |                                           | 46,XY,t(9;15)(p24;q22)                               | Figure 1k  |
|                  |                                           | 46,XY,t(9;10)(q21;q22)                               | Figure 1l  |
Table 2: Breakpoints in chromosome 9 translocation carriers and clinical features reported in previous literature

| Cases | Karyotype | Breakpoints | Clinical findings | Reference |
|-------|-----------|-------------|------------------|-----------|
| 1     | t(1;9)    | 1q11;9p24  | Severe oligozoospermia | Yoshida et al., 1997 [75] |
| 2     | t(1;9)    | 1q43;9p23  | Oligoasthenozoospermia | Perrin et al., 2013 [45] |
| 3     | t(1;9)    | 1q11;9p13  | Azoospermia or severe oligozoospermia | Mierla et al., 2014 [14] |
| 4     | t(1;9)    | 1q12;9q13  | PGD               | Zhang et al., 2014 [81] |
| 5     | t(1;9)    | 1q23;9q22.3| Recurrent miscarriage | Dutta et al., 2011 [38] |
| 6     | t(1;9)    | 1q42.3;9q22.3| Recurrent miscarriage | Sugiura-Ogasawara., 2008 [56] |
| 7     | t(1;9)    | 1q22;9q31  | Infertility       | Martin, 1992 [61] |
| 8     | t(1;9)    | 1p32.1;9q34.3| Normal sperm count | Matsuda et al., 1992 [36] |
| 9     | t(2;9)    | 2q21;9p22  | Infertility       | Martin et al., 1990 [60] |
| 10    | t(2;9)    | 2q32;9q31  | ICSI              | Gekas et al., 2001 [52] |
| 11    | t(2;9)    | 2q33;9q34  | PGD               | Findikli et al., 2003 [51] |
| 12    | t(2;9)    | 2q37;9q22  | 2 fetal losses    | Adamoli et al., 1986 [42] |
| 13    | t(2;9)    | 2q37.3;9q12| Normal semen      | Dul et al., 2012 [54] |
| 14    | t(3;9)    | 3p25;9q32  | Infertility       | Honda et al., 1999 [64] |
| 15    | t(3;9)    | 3q21;9q34  | Infertility       | Honda et al., 1999 [64] |
| 16    | t(3;9)    | 3q28;9q32  | Azoospermia or severe oligozoospermia | Mierla et al., 2014 [14] |
| 17    | t(4;9)    | 4p15.2;9p13| Recurrent spontaneous abortions | Celep et al., 2006 [78] |
| 18    | t(4;9)    | 4q23.2;9q22.3| Recurrent pregnancy loss | Kochhar et al., 2013 [15] |
| 19    | t(4;9)    | 4q25;9p22  | Infertility       | Moretti et al., 2009 [73] |
| 20    | t(4;9)    | 4q31.1;9p24| Recurrent spontaneous abortions | Celep et al., 2006 [78] |
| 21    | t(5;9)    | 5p15.1;9q22.1| Primary infertility | Vozdova et al., 2013 [4] |
| 22    | t(5;9)    | 5p13;9q22  | PGD               | Zhang et al., 2014 [81] |
| 23    | t(5;9)    | 5p12;9p11  | Infertility       | Pellestor et al., 2001 [66] |
| 24    | t(5;9)    | 5q10;9q10  | Infertility       | Rouen et al., 2017 [35] |
| 25    | t(5;9)    | 5q23.2;9q22.3| Spontaneous abortion | Stephenson et al., 2006 [48] |
| 26    | t(5;9)    | 5q23.3;9p24| Repeated miscarriages | Iyer et al., 2007 [55] |
| 27    | t(6;9)    | 6p12;9q13  | PGD, No pregnancy | Escudero et al., 2003 [76] |
| 28    | t(7;9)    | 7p15.2;9q34.1| Primary infertility | Vozdova et al., 2013 [4] |
| 29    | t(7;9)    | 7p14.2;9q32| Recurrent miscarriage | Pundir et al., 2016 [57] |
| 30    | t(7;9)    | 7p13;9p23  | ICSI              | Gekas et al., 2001 [52] |
| 31    | t(7;9)    | 7p13;9q21  | Teratozoospermia  | Rouen et al., 2013 [39] |
| 32    | t(7;9)    | 7q31;9q34  | Early miscarriage | Olszewska et al., 2017 [43] |
| 33    | t(7;9)    | 7q33;9p21  | Infertility       | Pellestor et al., 1997 [63] |
| 34    | t(7;9)    | 7q36.2;9p21.2| Normal semen      | Wiland et al., 2008 [74] |
| 35    | t(8;9)    | 8p21;9p24  | Spontaneous abortions | Bourrouillou et al., 1986 [47] |
| 36    | t(8;9)    | 8p21;9q34  | Early miscarriage | Olszewska et al., 2017 [43] |
| 37    | t(8;9)    | 8q24.2;9q32| Infertility       | Estop et al., 1998 [68] |
| 38    | t(8;9)    | 8q24.3;9p21.2| Severe oligozoospermia; | Olszewska et al., 2017 [43] |
| 39    | t(8;9)    | 8q24.2;9q32| Infertility       | Estop et al., 2000 [65] |
| 40    | t(8;9)    | 8q24.3;9p24| Infertility       | Ferfouri et al., 2013 [71] |
To study the role of breakpoints on chromosome 9 in male infertility, the previously published literatures were reviewed. The clinical findings and karyotype regarding chromosome 9 are shown in Table 2. For all carriers from our study and reported literature, the most common chromosome and breakpoint involved chromosome 9 translocation were t(1;9) (12.5%) and 9q32 (13.6%) respectively. Chromosome 1 was most involved with chromosome 9 translocation in this study. For translocation carriers involved in chromosome 1, the clinical phenotype is more likely to be related to chromosome 1. Previous literatures have reported that there are more genes related to spermatogenesis on chromosome 1 [23,26]. The breakpoints on chromosome 1 could interfere with spermatogenesis,
Clinical features of infertile men carrying a chromosome 9 translocation leading to azoospermia. In genetic counselling, the breakpoints on chromosome 1 should be considered for the translocation carriers involved in t (1; 9).

Breakpoints at 9p12, 9p11, 9p10 and 9q34.1 were found with pregestational infertility, while breakpoints at 9p21, 9q10, 9q11, 9q13, 9q21.1, 9q22, 9q22.2, 9q22.3, 9q34, 9q34.2 and 9q34.3 exhibited gestational infertility. Therefore, more chromosome 9 breakpoints exhibited gestational (compared with pregestational) infertility, in which the carriers’ wife had a tendency to miscarry. Other breakpoints were found with cases of pregestational or gestational infertility. Previous studies have shown that certain genes on chromosome 9 are involved in spermatogenesis. For example, the aquaporin 7 gene (AQP7), located on chromosome 9p13.3, is expressed during the late stages of spermatogenesis [25]. Spermatogenic failure 8 gene (SPGF8), mapped to chromosome 9q33.3, is associated with severe spermatogenic failure [26]. The outer dense fiber of sperm tails 2 gene (ODF2), mapped to chromosome 9q34.11, has a key role in the formation of sperm flagella [27]. Doublesex-and mab3-related transcription factor 1 (DMRT1) and DMRT3, mapped to chromosome 9p24.3, are expressed in germ cell and Sertoli cells [28]. Relaxin 1 (RLN1) and RLN2, mapped to chromosome 9p24.1, are highly expressed in the prostate and testis [29]. Lysine-specific demethylase 4c (KDM4C) located on chromosome 9p24.1 regulates histone modifications and androgen receptor function [30]. Testis expressed 48 (TEX 48) and TEX53, mapped to chromosome 9q32, are testis-specific genes [31]. The specific function of these genes needs further investigation. Kim et al [32] reported that breakpoints at 9p22; 9p11.2, 9q21.2 and 9q22 were found with cases of impaired spermatogenesis, and breakpoints at 9p23.24, 9p23, 9p12 and 9q22 were associated with recurrent abortion. The key difference between the above paper and our current study is that their subjects had complex chromosomal rearrangements. The carrier is more likely to have normal sperm in semen when they involve balanced translocation of two chromosomes. For the carriers of complex chromosomal rearrangements, the probability of abnormal spermatogenesis increase greatly.

Male carriers of chromosome translocations are phenotypically normal, but may produce genetically unbalanced spermatozoa, leading to unbalanced embryos and miscarriage. Translocations may alter the process of spermatogenesis, resulting in azoospermia or oligospermia [33]. To explain the associated clinical pregestational or gestational infertility, three hypotheses have been proposed, including a break within a gene, a positional effect, and cryptic deletion or duplication [34]. During genetic counselling, physicians should consider the breakpoints involved in the translocation. When receiving genetic counselling, the carriers of chromosome 9 translocations should consider suitable reproductive options, including continued attempts at natural conception or in vitro fertilization accompanied by PGD.

Limitations of this study include the small number of carriers of chromosome 9 translocations, and the lack of detailed research regarding the specific molecular effects of each translocation by molecular-cytogenetic methods.

### Table 3: Incidence of breakpoints on chromosome 9

| Breakpoints | Number of patients with pre-gestational infertility | Number of patients with gestational infertility | Total (%) |
|-------------|-----------------------------------------------------|-----------------------------------------------|-----------|
| p24         | 5                                                   | 5                                             | 10(11.4%) |
| p23         | 2                                                   | 1                                             | 3(3.4%)   |
| p22         | 2                                                   | 1                                             | 3(3.4%)   |
| p21.2       | 1                                                   | 1                                             | 2(2.3%)   |
| p21         | 2                                                   |                                               | 2(2.3%)   |
| p13         | 2                                                   | 7                                             | 9(10.2%)  |
| p12         | 2                                                   |                                               | 2(2.3%)   |
| p11         | 1                                                   |                                               | 1(1.1%)   |
| p10         | 1                                                   |                                               | 1(1.1%)   |
| q10         | 3                                                   |                                               | 3(3.4%)   |
| q11         | 2                                                   |                                               | 2(2.3%)   |
| q12         | 1                                                   | 2                                             | 3(3.4%)   |
| q13         | 2                                                   |                                               | 2(2.3%)   |
| q13.4       | 1                                                   |                                               | 1(1.1%)   |
| q21         | 4                                                   | 2                                             | 6(6.8%)   |
| q21.1       | 1                                                   |                                               | 1(1.1%)   |
| q22         | 5                                                   |                                               | 5(5.7%)   |
| q22.1       | 1                                                   | 2                                             | 3(3.4%)   |
| q22.2       | 1                                                   |                                               | 1(1.1%)   |
| q22.3       | 4                                                   |                                               | 4(4.5%)   |
| q31         | 2                                                   | 1                                             | 3(3.4%)   |
| q32         | 3                                                   | 9                                             | 12(13.6%) |
| q34         | 5                                                   |                                               | 5(5.7%)   |
| q34.1       | 1                                                   |                                               | 1(1.1%)   |
| q34.2       | 1                                                   |                                               | 1(1.1%)   |
| q34.3       | 2                                                   |                                               | 2(2.3%)   |
According to our knowledge, this study is the first review of male carriers involved in chromosome 9 translocation published in previous literature, which will provide reference for clinical genetic counselling.

5 Conclusion

In the present study, the most common breakpoints involving chromosome 9 translocation were t(1;9) and 9q32 respectively. Most breakpoints at chromosome 9 exhibited gestational infertility. Carriers of chromosome 9 translocations should be counselled to consider in vitro fertilization accompanied by PGD.

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