Chromosome 1q21 translocation and spermatogenesis failure
Two case reports and review of the literature

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Abstract
Rationale: For the carriers of chromosome reciprocal translocation, the reason why some are fertile and others are infertile remains unclear. Here, we describe 2 patients who are carriers of chromosome 1q21 translocation with azoospermia.

Patient concerns: A 29-year-old male and a 33-year-old male presented at the clinic with a diagnosis of infertility.

Diagnosis: Both patients with azoospermia were diagnosed with Routine semen analysis, cytogenetic diagnosis and detection of serum reproductive hormones. The karyotype results of 2 patients were 46,XY,t(1;17)(q21;q23) and 46,XY,t(1;10)(q21;p12), respectively.

Interventions: After genetic counseling and informed consent, 1 patient (Case 2) chose microscopic testicular sperm extraction (micro-TESE).

Outcomes: After micro-TESE, no sperm was found for the patient. Finally, both patients chose clinical treatment through artificial insemination with donor sperm.

Lessons: These outcomes suggest that breakpoint at 1q21 should be paid attention by physician in genetic counseling, may harbor some genes associated with spermatogenesis, and deserves further be studied on the function of related genes.

Abbreviations: FSH = follicle stimulating hormone, HORMAD1 = horma domain-containing 1, LH = luteinizing hormone, OAZ3 = ornithine decarboxylase antizyme 3, T = testosterone.

Keywords: azoospermia, breakpoint, chromosome 1, genetic counseling

1. Introduction
Infertility affects approximately 22% of couples in reproductive age,[1] and about 50 million couples worldwide.[2] Male infertility constitutes 50% of these couples,[3] affects approximately 4% of all men worldwide.[4] Several studies have shown that male infertility is attributed to multiple causes, mainly due to a failure in spermatogenesis.[5] The spermatogenic failure directly results in azoospermia or severe oligozoospermia.[6] Although the cause of the severe cases often remains unknown, genetic factors can lead to spermatogenic impairment. Chromosomal abnormalities or microdeletions of the AZF region on Y chromosome can disrupt spermatogenesis.[6]

Reciprocal chromosome translocations are one of the main genetic factors for the male carriers with reproductive failures. The certain translocations or chromosomal breakpoints directly disrupt spermatogenesis, and result in abnormal sperm concentration.[7] Chromosome breakpoints involved in translocations has been paid attention to in recent years.[8–10] Paoloni-Giacobino et al[11] reported a familial t(6;21)(p21.1;p13) translocation is associated with male-only sterility, and male carrier showed abnormal spermatoocyte meiosis. Ananthapur et al[1] reported a male carrier with de novo chromosomal translocation t(2;11)(p14;q21), and the translocation may result in the disruption of genes responsible for spermatogenesis. If translocation breakpoints interrupt a vital gene structures, the carrier likely suffer spermatogenic failure.

Previous studies have shown that chromosome 1 could harbor an important domain whose integrity is very important for spermatogenesis, and that chromosome 1q21 is the largest number of breakpoints.[12] This study was established to identify 2 male cases of chromosome 1q21 translocation. Combining published cases, this paper also discuss the association between this breakpoint and spermatogenesis.

2. Case reports
This study included 2 male carriers with chromosome 1q21 translocation, which showed azoospermia. Approval of this study was obtained from the Ethics Committee of the Second
Hospital, Jilin University (No. 2019-032). Patients have provided informed consent for publication of 2 cases.

2.1. Case 1

A 29-year-old man presented at the clinic with a diagnosis of infertility. The patient had normal appearance and intelligence, and went to the andrology outpatient department because of being childless after 5 years of marriage. He was subjected to 2 routine semen analyses, which were 2 weeks interval. No sperm was found twice. Then the patient underwent serum reproductive hormone and cytogenetic detection. The results of reproductive hormones were as follows: FSH: 25.8U/L, LH: 8.6 U/L, T: 18.6 nmol/L (Normal reference value of serum reproductive hormones: FSH: 1.5–12.4 U/L; LH: 1.7–8.6 U/L; T: 9.9–27.8 nmol/L). G band karyotype analysis was 46,XY,t(1;17)(q21;q23) (Fig. 1A).

2.2. Case 2

A 33-year-old man presented at the clinic with a diagnosis of infertility. The patient had normal appearance and intelligence, and went to the andrology outpatient department experiencing infertility after 10 years of marriage. No sperm was found to undergo 2 semen analyses at intervals of 2 weeks. The detection of reproductive hormone indicated that E2 and T were both lower than normal reference value (FSH: 10.6 U/L, LH: 7.5 U/L, T: 1.63 nmol/L). The results of cytogenetic was 46,XY,t(1;10)(q21;p12) (Fig. 1B). After genetic counseling and informed consent, the patient chose microscopic testicular sperm extraction. Unfortunately, no sperm was found.

2.3. Literature review

A search for reports on chromosome 1q21 translocations from infertile men was performed using PubMed. The keywords were “chromosome 1/ translocation / infertility / male” for the search. The cases of chromosomal 1 translocations were collected and classified. We included cases of chromosome 1q21 translocation for adult fertile-age men, and excluded 2 cases without clinical manifestation. A total of 19 carriers involving chromosomal 1q21 translocation were found. Karyotype and clinical findings involved chromosome 1q21 breakpoints from literature analysis are shown in Table 1. The results showed that 94.7% (18/19) of the cases presented with spermatogenesis disorder.

3. Discussion

In this study, we report 2 cases of chromosome 1q21 translocation in infertile men who are azoospermic patients. One case presented with an increased level of FSH, and the other case was a decrease in serum testosterone level. Previous studies have confirmed that FSH is essential for the regulation of spermatogenesis, and also T plays an important role.[19] Dong et al.[14] once reported that chromosomal translocations may cause reductions in testosterone level. Similarly, Uccellatore et al.[15] speculated that some translocation may be accompanied by reproductive hormone disorders. But, the exact relationship between chromosome translocation and reproductive hormone disorders is not clear. The special mechanism deserves further study.

For the carriers of chromosome reciprocal translocation, the reason why some are fertile and others are infertile remains unclear. It might be speculated that the specific chromosomes and interaction of genetic factors are responsible for these differences.

Table 1

Chromosome 1q21 breakpoints in translocation carriers reported in previous literature.

| Case | Karyotype | Clinical findings | References |
|------|-----------|------------------|-----------|
| 1    | 46,XY,t(1;2)(q21;p23) | Azoospermia | Wang et al.[19] |
| 2    | 46,XY,t(1;2)(q21;q37) | Azoospermia | Wang et al.[19] |
| 3    | 46,XY,t(1;3)(q21;q23) | Azoospermia | Goddijn et al.[21] |
| 4    | 46,XY,t(1;4)(q21;q33) | Azoospermia | Bache et al.[12] |
| 5    | 46,XY,t(1;4)(q21;q33) | Oligoasthenozoospermic | Bache et al.[12] |
| 6    | 46,XY,t(1;5)(q21;1q31.2) | Oligoasthenozoospermic | Bache et al.[12] |
| 7    | 46,XY,t(1;6)(q21.2;q31.2) | Oligoasthenozoospermic | Bache et al.[12] |
| 8    | 46,XY,t(1;6)(q22;q32) | Oligoasthenozoospermic | Bache et al.[12] |
| 9    | 46,XY,t(1;6)(q21.3;p13) | Oligoasthenozoospermic | Bache et al.[12] |
| 10   | 46,XY,t(1;9)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 11   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 12   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 13   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 14   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 15   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 16   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 17   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 18   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
| 19   | 46,XY,t(1;10)(q21;p11) | Oligoasthenozoospermic | Gekas et al.[20] |
breakpoints are involved in the translocation, and some breakpoints can disrupt the structure of an important gene, leading to spermatogenic disorders. Some studies have suggested that chromosome 1 may harbor a critical domain, which are essential for male fertility. Bache et al. reported that breakpoint at 1q21 is the largest number reported in male infertility patients. Wang et al. reported that the breakpoint at 1q21 were associated with pre-gestational infertility, which characterized by failure to fertilize eggs. Chromosome 1q21 translocation was involved in our 2 cases. The breakpoint at 1q21 involving translocation was searched and analyzed by PubMed. Of the 19 carriers, 94.7% had spermatogenesis disorder. This suggests that specific chromosome breakpoint should be paid attention by physician in genetic counseling.

By OMIM search, we found 17 genes expressed in testis, located the breakpoint on chromosome 1q21. List of genes located on chromosome 1q21 were collected and summarized in a supplementary file (Table S1, http://links.lww.com/MD/D551). The function of these genes in testis is not clear. Of the 17 genes, hroma domain-containing 1 (HORMAD1) gene is located on chromosome 1q21.3, and its expression in testis coincided with the onset of meiosis I. Ornithine decarboxylase antizyme 3 (OAZ3) gene, mapped on chromosome 1 at 1q21.3, began to express in the early stage of spermatogenesis and ended in the late spermatid phase. The relationship between these genes and azoospermia needs further study.

A limitation of this study is the lack of the research on the function of the genes involving breakpoint. Therefore, we are unable to confirm whether the genetic structure associated with spermatogenesis has changed. The suggested detection of gene function needs to be validated in more cases.

In conclusion, this study reported 2 carriers of chromosome 1q21 translocation with azoospermia. The breakpoint should be paid attention by physician in genetic counseling. Breakpoint at 1q21 may harbor some genes associated with spermatogenesis, deserves further be studied on the function of related genes.

**Author contributions**

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**References**

[1] Ananthapur V, Avvari S, Veena K, et al. Non-Robertsonian translocation t(2;11) is associated with infertility in an oligospermic man. Andrologia 2014;46:453–5.

[2] Ray PF, Touré A, Metzler-Guillermine C, et al. Genetic abnormalities leading to qualitative defects of sperm morphology or function. Clin Genet 2017;91:217–32.

[3] Ilacqua A, Izzo G, Emerenziani GP, et al. Genetic abnormalities affecting sperm concentration and motility in young men: a review. Hum Reprod 2018;33:1087–98.

[4] Barcelo M, Mata A, Bassas L, et al. Exosomal microRNAs in seminal plasma are markers of the origin of azoospermia and can predict the presence of sperm in testicular tissue. Hum Reprod 2018;33:1087–98.

[5] Song SH, Chua K, Ramasamy R, et al. Recent advances in the genetics of testicular failure. Asia J Androl 2016;18:330–5.

[6] Donker RB, Vloeberghs V, Groen H, et al. Chromosomal abnormalities in 1663 infertile men with azoospermia: the clinical consequences. Hum Reprod 2017;32:2574–80.

[7] Mayeur A, Ahdad N, Hesters L, et al. Chromosomal translocations and semen quality: a study on 144 male translocation carriers. Reprod Biomed Online 2019;38:46–55.

[8] Zhang H, Wang R, Li L, et al. Clinical feature of infertile men carrying balanced translocations involving chromosome 10: Case series and a review of the literature. Medicine (Baltimore) 2018;97:e0452.

[9] Li G, Ishib F, Wang L, et al. Meiotic defects and decreased expression of genes located around the chromosomal breakpoint in the testis of a patient with a novel 46,Xi(1)(p11.3)xp31) translocation. Int J Mol Med 2017;40:367–77.

[10] Zhang H, Wang R, Yu Y, et al. Non-Robertsonian translocations involving chromosomes 13, 14, or 15 in male infertility: 28 cases and a review of the literature. Medicine (Baltimore) 2019;98:e14730.

[11] Paoloni-Giacobino A, Kern I, Rumpler Y, et al. Familial t(6;21)(p21.1; p13) translocation associated with male-only sterility. Clin Genet 2000;58:324–8.

[12] Bache I, Assche EV, Cingoz S, et al. An excess of chromosome 1 breakpoints in male infertility. Eur J Hum Genet 2004;12:993–1000.

[13] Ruwanpura SM, Mclachlan RL, Meachem SJ. Hormonal regulation of male germ cell development. J Endocrinol 2010;205:117–31.

[14] Dong Y, Du RC, Jiang YI, et al. Impact of chromosomal translocations on male infertility, semen quality, testicular volume and reproductive hormone levels. J Int Med Res 2012;40:2274–83.

[15] Uccellatore F, Padova G, Squatrito S. Reproductive hormone studies in three subjects with a Robertsonian translocation. J Endocrinol Invest 1983;6:479–84.

[16] Zhang HG, Wang RX, Pan Y, et al. A report of nine cases and review of the literature of infertile men carrying balanced translocations involving chromosome 5. Mol Biomed Online 2019;11:10.

[17] Paliwal P, Sharma A, Sahoo J, et al. An unusual association of hypospadias with partial deletion of chromosome 1q. Fertil Steril 2010;93: 2413, e11–13.

[18] Wang RX, Zhang HG, Pan Y, et al. Translocation breakpoints of chromosome 1 in male carriers: clinical features and implications for genetic counseling. Genet Mol Res 2016;15:doi: 10.4238/gmr.15048707.

[19] Pargas SA, Yan W, Matzuk MM, et al. Restricted germ cell expression of a gene encoding a novel mammalian HORMA domain-containing protein. Gene Expr Patterns 2004;4:5257–63.

[20] Ivanov IP, Rohrwasser A, Terreros DA, et al. Discovery of a spermatogenesis stage-specific ornithine decarboxylase antizyme: antizyme 3. Proc Natl Acad Sci USA 2000;97:4808–13.

[21] Goddijn M, Joosten JH, Knoet AC, et al. Clinical relevance of diagnosing structural chromosome abnormalities in couples with repeated miscarriage. Hum Reprod 2004;19:1013–7.

[22] Gekas J, Thepot F, Turleau C, et al. Chromosomal factors of infertility in candidate couples for IVF: an equal risk of constitutional aberrations in women and men. Hum Reprod 2001;16:82–90.