Male Infertility

Case study of a patient with cryptozoospermia associated with a recessive TEX15 nonsense mutation

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Dear Editor,

Male infertility, which affects approximately 20 million people worldwide, is commonly caused by spermatogenic dysfunctions, including severe oligozoospermia, cryptozoospermia, and nonobstructive azoospermia, which are largely genetic in origin.1–3

Here, we report a case of cryptozoospermia in a 33-year-old patient, who sought treatment for primary sterility that had been ongoing for 5 years. The patient had intercourse with his spouse without contraception two to three times per week, but they had not achieved pregnancy. The patient was born of consanguineous parents who were maternal cousins (Figure 1). He had no history of adverse sexual contact or inappropriate hobbies. He was 161 cm tall and weighed 80 kg, and his external genital organs were normally developed, with both testes around 6 ml in size, and no palpable abnormality in his bilateral spermatic veins.

The patient underwent three semen examinations in our hospital and other institutions. In our hospital, the semen analysis was carried out according to the guidelines in the WHO Laboratory Manual for the Examination and Processing of Human Semen.4 The patient’s semen volume was 3.0–3.5 ml, pH 7.2–7.5, and spermatozoa were absent from his semen smear. Semen centrifugal sediment smear showed a sperm count of 0–2 cells per high-power field (HPF), and very few active spermatozoa were observed. Staining with Diff-Quik indicated normal morphology in 2.5%–4.0% of spermatozoa. Sex-hormone levels were measured (Table 1).

Because the patient’s parents were consanguineous, bioinformatics analysis was performed to identify inheritance of recessive characteristics. All the homozygous mutations were screened to identify potentially pathogenic gene alterations related to spermatogenesis, through phenotype and genotype correlation analysis. A novel nonsense mutation was identified at exon 1:c.6934G>A (p.R2312X) of the testis-expressed 15 (TEX15) gene, which resulted in a truncated TEX15 protein. This mutation was confirmed by Sanger sequencing. Both parents of the proband were carriers of this mutation (Figure 2). We speculated that this mutation was at least in part the cause of the spermatogenic dysfunction. Because of the extremely limited availability of the patient’s spermatozoa, detection of TEX15 mRNA or TEX15 protein in spermatozoa was not possible.

Spermatogenesis is a highly complex process of cell differentiation, which is necessary for the formation of haploid spermatoza. The core of this process is meiosis in spermatocytes, during which synopsis and recombination of homologous chromosomes occur. TEX15 was first identified as a protein that is required for chromosomal synopsis and meiotic recombination in 2008.5 In TEX15-deficient male mice, DNA double-strand breaks (DSBs) are formed and not repaired, suggesting that TEX15 functions in the repair of DSBs via regulation of the loading of DNA repair proteins (RAD51 and DMC1) onto sites of DSBs. Homozygous deletion of TEX15 in mice also leads to significantly reduced tests volume.6 In an analysis of single-nucleotide polymorphisms (SNPs) in TEX15, rs323346 and rs323347 were identified as genetic risk factors for spermatogenic failure in the Chinese Han population.6 In 2015, Okutman and colleagues reported that a nonsense mutation (c.2130T>G, p.Y710X) screening was carried out according to the European Academy of Andrology (EAA) guidelines by real-time fluorescent PCR using the Y Chromosomal Microdeletion Test Kit (Shanghái Telligen Corporation, Shanghái, China), which detected the sY84 and sY86 sequence-tagged sites (STSs) of azoospermia factor a (AZFa), the sY127 and sY134 STSs of AZFb, and the sY254 and sY255 STSs of AZFc. All six STSs were present, indicating that the patient did not have a Y-chromosome microdeletion. The initial clinical diagnosis was primary infertility with cryptozoospermia, bilateral testicular dysplasia, and high-gonadotropin gonadal-function decline. With the approval of the Ethics Committee of Yantai Yuhuangding Hospital and with the patient’s informed consent, peripheral blood was extracted for exome sequencing.

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in TEX15 caused infertility in three of seven brothers in a Turkish family with consanguineous parents.\textsuperscript{7} The sperm concentrations of patients with TEX15 mutations declined over time, and early-stage sperm cryopreservation was recommended.\textsuperscript{7}

In summary, our study identified a novel homozygous nonsense mutation in TEX15 in a patient with cryptozoospermia. This mutation could be the cause of cryptozoospermia, with TEX15 deficiency resulting in the failure of spermatogenesis. The mutation was inherited from the patient’s parents, who were both heterozygous carriers, indicating a recessive pattern of inheritance. With the development of precision medicine, TEX15 could become a clinical marker for detection of nonobstructive azoospermia or cryptozoospermia.

**AUTHOR CONTRIBUTIONS**

YWS and ZLG designed the study; XW analyzed data and wrote the manuscript; HRJ analyzed high-throughput sequencing data and screened for candidate genes; YQC extracted DNA and performed Sanger sequencing; and JC collect clinical data. All authors read and approved the final manuscript.

**COMPETING INTERESTS**

All authors declared no competing interests.

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**REFERENCES**

1. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod* 2007; 22: 1506–12.
2. Poongothai J, Gopenath TS, Manonayaki S. Genetics of human male infertility. *Singapore Med J* 2009; 50: 336–47.
3. Krausz CG, Carrell DT. Advances in understanding the genetics underlying male infertility and evolving diagnostic and treatment options. *Andrology* 2014; 2: 302–3.
4. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. 5th ed. Geneva: WHO Press; 2010.
5. Yang F, Eckardt S, Leu NA, McLaughlin KJ, Wang PJ. Mouse TEX15 is essential for DNA double-strand break repair and chromosomal synapsis during male meiosis. *J Cell Biol* 2008; 180: 673–9.
6. Ruan J, He XJ, Du WD, Chen G, Zhou Y, et al. Genetic variants in TEX15 gene conferred susceptibility to spermatogenic failure in the Chinese Han population. *Reprod Sci* 2012; 19: 1190–6.
7. Okutman O, Muller J, Baert Y, Serdarogullari M, Gultomruk M, et al. Exome sequencing reveals a nonsense mutation in TEX15 causing spermatogenic failure in a Turkish family. *Hum Mol Genet* 2015; 24: 5581–8.

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