Globozoospermic infertility associated with balanced DPY19L2 translocation/gene deletion at the chromosomal breakpoint

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Dear Editor,

We report here a rare case of DPY19L2 gene deletion at chromosome 12 breakpoints caused by a 46, XY, t (4; 12); (q27; q15) balanced translocation. The patient eventually developed globozoospermia. A 32-year-old male had experienced infertility issues for 4 years. The patient exhibited normal appearance, intelligence, and body type, with a height of 175 cm and a weight of 75 kg. He was a college-educated office worker with no history of contact with environmental hazards. The patient's secondary sexual characteristics were normal, the external genital organs were well developed, and sex life after marriage was normal. The patient had a sister who had given birth twice and had a normal phenotype. The patient's parents were healthy and nonconsanguineous. While his mother was pregnant with him, the father had been working as a welder for 2 years, and the mother did not work. The chromosomes of the parents and sister were normal. Repeated semen analyses revealed that the average sperm concentration was $1.03 \times 10^6 \text{ ml}^{-1}$; 39% of the sperm were forward-moving, and 100% of the sperm were roundheaded (Figure 1a). No Y chromosome microdeletion was observed, and all hormonal indicators were in the normal range. The abnormal karyotype was found to be 46, XY, t (4; 12), (q27; q15) (Figure 1b). CNVseq detected a missing fragment of about 200 kb in the 12q14.2 (63920001–64120000 bp) segment; the DPY19L2 gene (chr12: 63950693–64064354 bp) was deleted from this segment (Figure 1c). The patient had not received any assisted reproductive technology treatment.

Globozoospermia is a rare and severe disorder demonstrating abnormal sperm morphology. In patients with globozoospermia, sperm are roundheaded and completely lack acrosomes. Several cases of partial globozoospermia in which a proportion of sperm (20.0%–90.0%) have acrosomes have been reported in families with two or more brothers, indicating that globozoospermia is a hereditary disease.¹,² Currently, three genes, SPATA16, PICK1, and DPY19L2, are known to be associated with globozoospermia in humans. Among these, mutations in the DPY19L2 gene are common whereas mutations in SPATA16 and PICK1 are relatively rare.³ A study on 18 individual cases found that 11 patients (61.1%) had a homozygous deletion of a 200-kb fragment of the DPY19L2 gene, two (11.1%) had a homozygous nonsynonymous mutation in exon 8 (p.R298C), one (5.6%) had a homozygous new splice site mutation at the junction of exon–intron 16 (c.1579_1580 + 4delAGGTAAinsTCAT), and four (22.2%) had no mutations in DPY19L2, SPATA16, or PICK1. In humans, the DPY19L2 gene is located on chromosome 12, and the full-length gene is 109.66 kb. DPY19L2 is an essential gene responsible for sperm head elongation and acrosome formation.

Here, we report a case of 46, XY, t (4; 12) (q27; q15) balanced translocation. CNVseq found a homologous deletion of a 200-bp

Figure 1: (a) Morphology of the patient's sperm. (b) Peripheral blood karyotype of the patient. (c) CNV test results. CNV: copy number variation.
A fragment on chromosome 12, and this fragment contains only the \textit{DPY19L2} gene; loss of which will eventually lead to globozoospermia. Studies have indicated that the product of the \textit{DPY19L2} gene stabilizes acrosomes, allows the anchoring of the acroplaxome to the nuclear membrane, and mediates the formation of normal sperm morphology, eventually promoting sperm head elongation and acrosome formation.\textsuperscript{5,6}

Knudsen \textit{et al.}\textsuperscript{7} have confirmed the genotoxicity of stainless steel welding. They found a higher frequency of chromosomal aberrations, such as translocations, double minutes, exchanges, and rings, in stainless steel welders than in nonwelders. Chromosome breakage is associated with more than 1 year of exposure to welding fumes without the use of a mask. After 4 months of exposure, the chromosomal breakage rate increases significantly. In our study, the patient’s father worked as a welder when he was young. Chromosome aberrations may have occurred owing to the lack of protective measures for welders in the 1950s.

In patients with globozoospermia, the lack of sperm acrosomes causes failure of natural egg fertilization, leading to infertility. Although intracytoplasmic sperm injection plus preimplantation genetic diagnosis (PGD)-assisted reproduction may help overcome the patient’s infertility problems, the success rate of this therapy is low.

\textbf{AUTHOR CONTRIBUTIONS}

LKZ, ZYJ, and RHT collected and provided all the clinic information; YWS wrote the manuscript; LBM, QZ, and LD carried out all the related examinations; PL designed the study, supervised the data collection and examinations, and reviewed the paper.

\textbf{COMPETING INTERESTS}

All authors declared no competing interests.

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