

## ORIGINAL ARTICLE

# Patient with *CATSPER3* mutations-related failure of sperm acrosome reaction with successful pregnancy outcome from intracytoplasmic sperm injection (ICSI)

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## Abstract

**Purpose:** This study is intended to investigate the candidate pathogenic gene in a patient with primary infertility but without the defect in routine semen parameters from a consanguineous family and explore the potential impacts of mutations on assisted reproductive technology outcome.

**Methods:** Whole-exome sequencing (WES) was carried out. A variant in his family found by WES was verified by Sanger sequencing. Intracytoplasmic sperm injection (ICSI) was applied to obtain a successful outcome.

**Results:** A Cation Channel of Sperm 3(*CATSPER3*) homozygous variant (NM\_178019.3:exon5:c.707T>A, p.L236\*) was identified for the first time. The anti-CD46 immunofluorescence analysis revealed the failure of sperm acrosome reaction (AR) caused by the mutation. ICSI treatment was successful.

**Conclusion:** This is the first report of a homozygous pathogenic *CATSPER3* mutation. This mutation may cause male infertility with the failure of AR but without the defect in routine semen parameters. ICSI was supposed to be the most appropriate therapy.

## KEYWORDS

acrosome reaction, *CATSPER3*, infertility, intracytoplasmic sperm injection, sperm

Jiaxiang Wang, Hui Tang and Qinyan Zou contributed equally to this work.

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## 1 | INTRODUCTION

Approximately 10%–15% of couples in the world suffer from infertility, 20%–30% of which are due to male factors (Agarwal et al., 2015). Genetic defect is an important factor of male infertility. Infertility caused by genetic anomalies can be divided into two categories: syndromic and non-syndromic; in the latter, gene mutations induce disorders in spermatogenesis without other symptoms (Okutman et al., 2018). The destruction of the Cation Channel of Sperm (CatSper) was reported as a cause of male non-syndromic infertility (Adam et al., 1993; Hildebrand et al., 2010). CatSper is a sperm-specific ion channel involved in sperm function and male fertilization capability indicators, such as sperm motility and egg penetration (Ren et al., 2001). CatSper is composed of four separate pore-forming  $\alpha$  subunits, CatSper1–4. Male infertility cases with defects in *CATSPER1* and 2 have been previously reported (Avenarius et al., 2009; Avidan et al., 2003), but not in *CATSPER3* and 4. However, scarce cases are reported with natural pregnancy and in vitro fertilization (IVF) outcomes in patients having CatSper mutations on acrosome reaction (AR) and sperm motility.

In this study, we described a patient with non-syndromic male infertility from a consanguineous family and revealed a homozygous mutation in human *CATSPER3* by WES. Two intracytoplasmic sperm injection (ICSI) cycles were carried out, and successful pregnancy was finally achieved. Our research findings suggested that *CATSPER3* defects lead to male non-syndromic infertility without routine semen parameter abnormalities and could be rescued by ICSI.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethical approval

This study was approved by the Ethics Committees of the Suzhou Hospital Affiliated to Nanjing Medical University. Signed informed consent was provided by the included patients and the proband's family.

### 2.2 | Participants

The patient, who was 28 years old and his family was recruited from the Suzhou Hospital Affiliated to Nanjing Medical University. The patient had normal external genitalia and bilateral testicular development and hormone levels. No defects were found in the bilateral spermatic veins upon palpation. The results of peripheral blood chromosomes and Y chromosome micro-deletions analysis were normal. We also included a fertile man as healthy control.

### 2.3 | Semen analysis and sperm morphology

Semen evaluation was performed according to the standard methodology proposed by the World Health Organization laboratory manual for the examination and processing of human semen (5th edition). Semen volume, sperm concentration, morphology, and motility were evaluated twice. Sperm morphology was assessed using hematoxylin and eosin (H&E)-stained slides. A total number of 200 spermatozoa in two replicates were examined. Acrosin activity was measured with the commercial human spermatozoa acrosin activity quantitative assay kit (Suxie20182400813, Xindi).

### 2.4 | Acrosome reaction induction and monitoring of acrosome status

As described in a previous study (Frolikova et al., 2016), AR was induced by calcium ionophore (A23187 (Cal), Sigma Aldrich) at a final concentration of 5  $\mu$ M. Then, the sperm samples were incubated at 37°C under 5% CO<sub>2</sub> for 15 min, the sperm was washed three times with PBS, and smeared onto glass slides and air-dried. The sperm slides were next fixed with 4% formaldehyde in PBS at room temperature for 20 min, followed by washing in PBS three times. Slides were then blocked in 5% bovine serum albumin (A8020; Solarbio) and incubated overnight at 4°C with anti-CD46 primary antibody (ab108307, Abcam). Further, incubation was carried out at room temperature for 50 min with the Cy3-conjugated Goat anti-Rabbit IgG (GB21303, Servicebio), followed by threefold washing with PBS. The slides were counterstained with 5 mg/ml of DAPI (G1012, Servicebio) and mounted with mounting media (G1401, Servicebio). Finally, fluorescence images were taken using a confocal microscope (Nikon Eclipse CI, Nikon).

### 2.5 | Scanning and transmission electron microscopy

Fresh sperm specimens were obtained by centrifugation at 400  $g \times 15$  min, twofold washing in PBS, and fixation in 2.5% phosphate-buffered glutaraldehyde. After dehydration and infiltration, the samples for TEM were embedded in Epon 812 (SPI), and ultrathin sections were stained with uranyl acetate and lead citrate. The ultrastructures were next observed and recorded by TEM (TECHAI-10, Philips, Netherlands) with an accelerating voltage of 80 kV. The samples for the SEM examination were sputter-coated by an ionic sprayer meter (ACE200, Leica) and analyzed by SEM (Nova NanoSEM 450, FEI) with an accelerating voltage of 5 kV.

## 2.6 | Whole-exome sequencing and Sanger sequencing validation

Genomic DNA was extracted from the peripheral blood of the patient. Whole-exome sequencing was performed by Shanghai Fulgent Biotech Company using the xGen Exome Research Panel v2.0 (Integrated DNA Technologies) and Illumina HiSeq X10 platform (Illumina). The sequencing raw data were aligned to the hg19 human reference genome using NovoAlign (<http://www.novocraft.com/products/novoalign/>), then variants were called by VarScan2 (<http://dkoboldt.github.io/varscan/>) and annotated using ANNOVAR (<http://annovar.openbioinformatics.org/en/latest/>). The variants were analyzed according to the Standards and Guidelines for the Interpretation of Sequence Variants released by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Kassab, 1973). To confirm the identified variant, exon 5 of *CATSPER3* was amplified by the polymerase chain reaction and then purified and sequenced in both directions using an ABI 3130 Genetic Analyzer (Applied Biosystems). The resulting sequences were compared with the reference sequence of *CATSPER3* (NM\_178019.3) in the NCBI database.

## 2.7 | IVF, rescue ICSI, embryo culture, and embryo transfer

A long protocol for ovulation induction was administrated to the patient's wife. Stimulate follicular development, 250 µg recombinant human chorionic gonadotropin (hCG, OVIDREL, Merck-Serono) injection, and oocyte retrieval were performed as described previously (Yang et al., 2018). The metaphase II oocytes were incubated with the optimized sperm 4–6 h after the retrieval. Due to the failure of IVF, rescue ICSI was carried out on the second day, and the obtained embryos were cryopreserved. The patient's wife underwent two freeze-thaw embryo transfer ICSI cycles.

## 3 | RESULTS

### 3.1 | Patient's infertility was caused by sperm acrosome reaction failure

The patient's sperm parameters and acrosin activities were normal with multiple times of detection (Table 1). Under the light microscope, the morphology of the proband's sperm (Figure 1b) was almost identical to the normal controls (Figure 1a). Similar results were obtained in the SEM observation (Figure 1c,d). Under TEM, similarly to the normal control (Figure 1e,g), the nuclear distribution of the proband's sperm was uniform and dense, the acrosome membrane was intact (Figure 1f), and the flagella were normally assembled

TABLE 1 Sperm parameters of the proband determined by several semen analyses

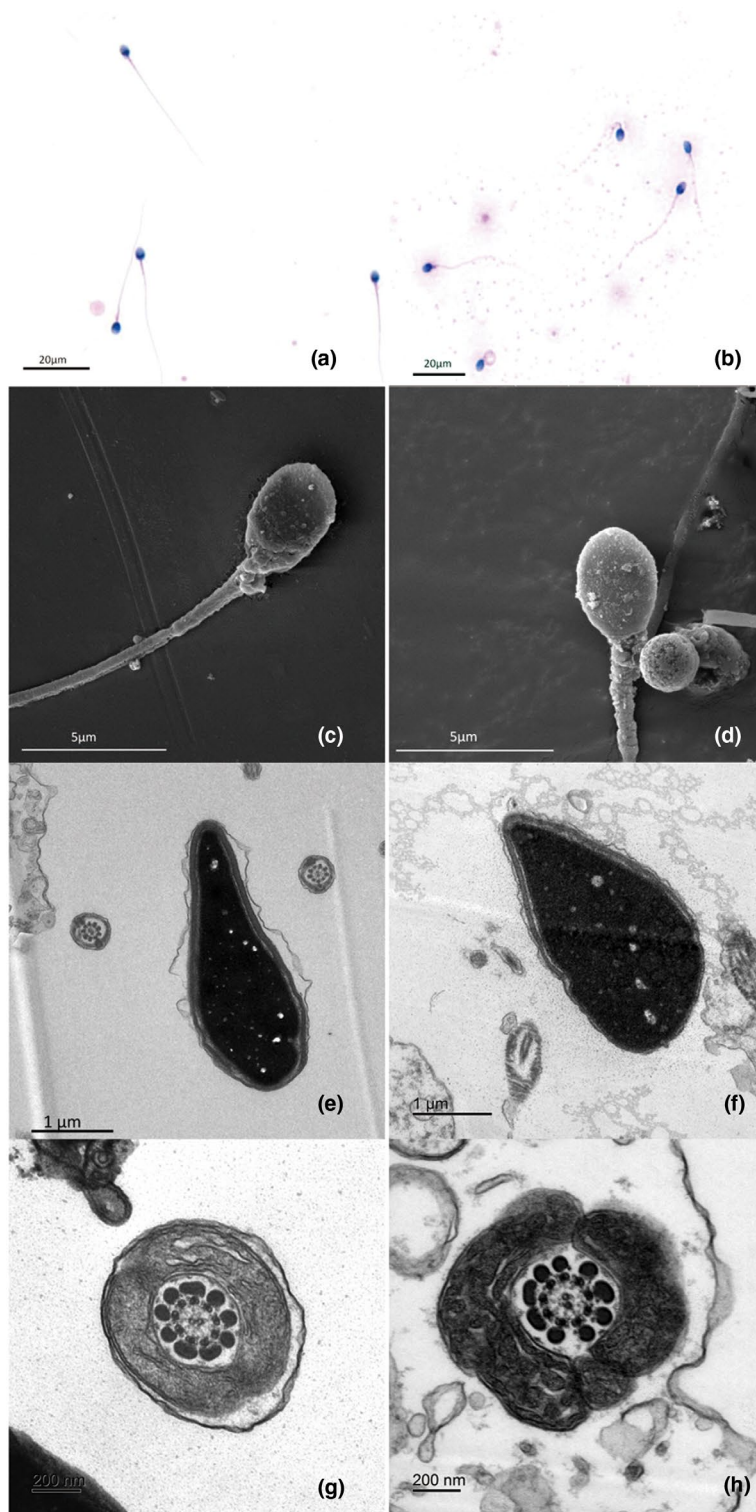
Indicators	1	2	3	4
Semen volume (ml)	4.2	4.5	4.6	4.8
Concentration (10 <sup>6</sup> /ml)	17.1	15.7	15.8	15.5
Total motility (%)	54.6	40.2	57.3	57.4
Progressive motility (%)	48.8	32.7	49.0	50.2
Normal sperm morphology (%)	5.0	ND	4.5	ND
Acrosin activity (IU/10 <sup>6</sup> spermatozoa)	41.4	ND	54.6	ND

Note: ND indicates that the project was not determined at that time.

(Figure 1h). Although the proband's sperm appeared normal, the invisible fluorescence of CD46 revealed the failure of the acrosome reaction (Figure 2).

### 3.2 | Biallelic mutations in *CATSPER3*

DNA from the patient was subjected to whole-exome sequencing. Approximately 94.82% of the targeted bases were sufficiently covered, and the average sequencing depth was 116.59×. After filtering variants, variants through databases, including 1000 Genomes Project database (<http://www.1000genomes.org/>) and Exome Aggregation Consortium (ExAC) (<http://exac.broadinstitute.org/>), we identified a homozygous nonsense variant (c.707T>A, p.L236\*) in the exon 5 of *CATSPER3* gene. Sanger sequencing validated the homozygous variant in the patient and revealed that the patient's parents were heterozygous for the c.707T>A variant (Figure 3b). A pedigree of the family is displayed in Figure 3a. The c.707T>A variant was recorded in the dbSNP ([rs755190371](http://www.ncbi.nlm.nih.gov/SNP/), <http://www.ncbi.nlm.nih.gov/SNP/>) that had very low allele frequencies in the ExAC (A = 0.000008245, 1/121292) and gnomAD (A = 0.00000397845, 1/251354) databases, which was only detected heterozygous in the East Asian population. The c.707T>A variant was not recorded in the 1000 Genomes Project database or the database of Chinese genomes in diseaseDX (<http://diseasedx.virgilbio.com/>). The c.707T>A variant creates a premature stop codon (p.L236\*), which is predicted to be disease-causing by Mutation Taster with a probability value of 0.99999999 (<http://www.mutationtaster.org/>) and damaging by CADD with a Phred-scaled CADD score of 39 (<https://cadd.gs.washington.edu/snv>). As can be seen in Figure 3c,d, the c.707T>A variant produced a premature stop codon and a truncated protein (p.L236\*), which was predicted to be deleterious. The truncated protein lost C-terminal 162 amino-acid residues of *CATSPER3*, including the sixth transmembrane region and a coiled-coil protein-protein interaction region (Lobley et al., 2003).

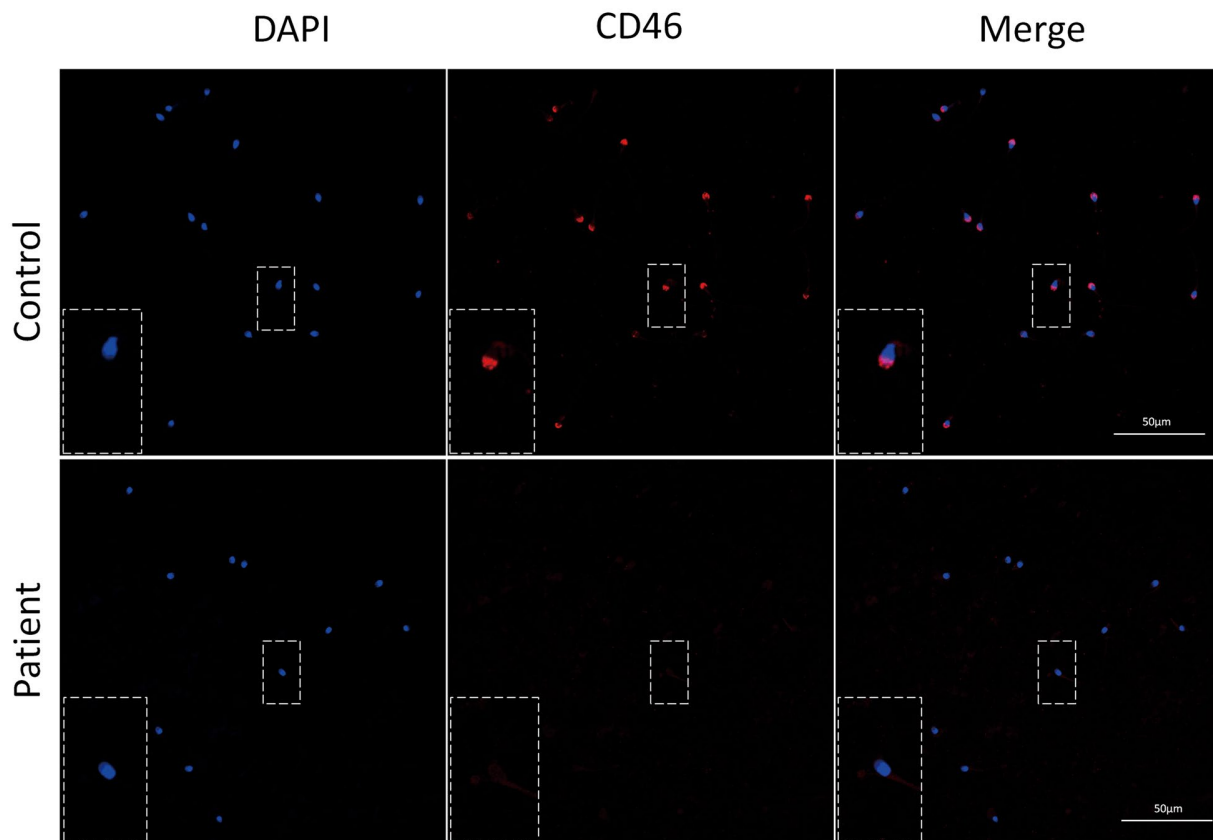


**FIGURE 1** Light, scanning, and transmission microscopy images of *CATSPER3*-deficient patient's sperms (b, d, f, and h) and normal ones (a, c, e, and g)

### 3.3 | Reproductive history of the *CATSPER3*-deficient patient

The patient had had three marriages and unsuccessful natural pregnancy for a decade with his first wife. Later, he and his

second wife tried IUI twice, with viable sperm parameters (Table 2) that qualified after the semen optimization treatment, but no pregnancy was achieved again. Afterward, he and his third wife received IUI treatment three times, which optimized his semen quality (Table 2), but the following



**FIGURE 2** Immunofluorescence of CD46 displays  $\text{Ca}^{2+}$ -induced AR in the normal (line 1) and *CATSPER3*-deficient patient (line 2)

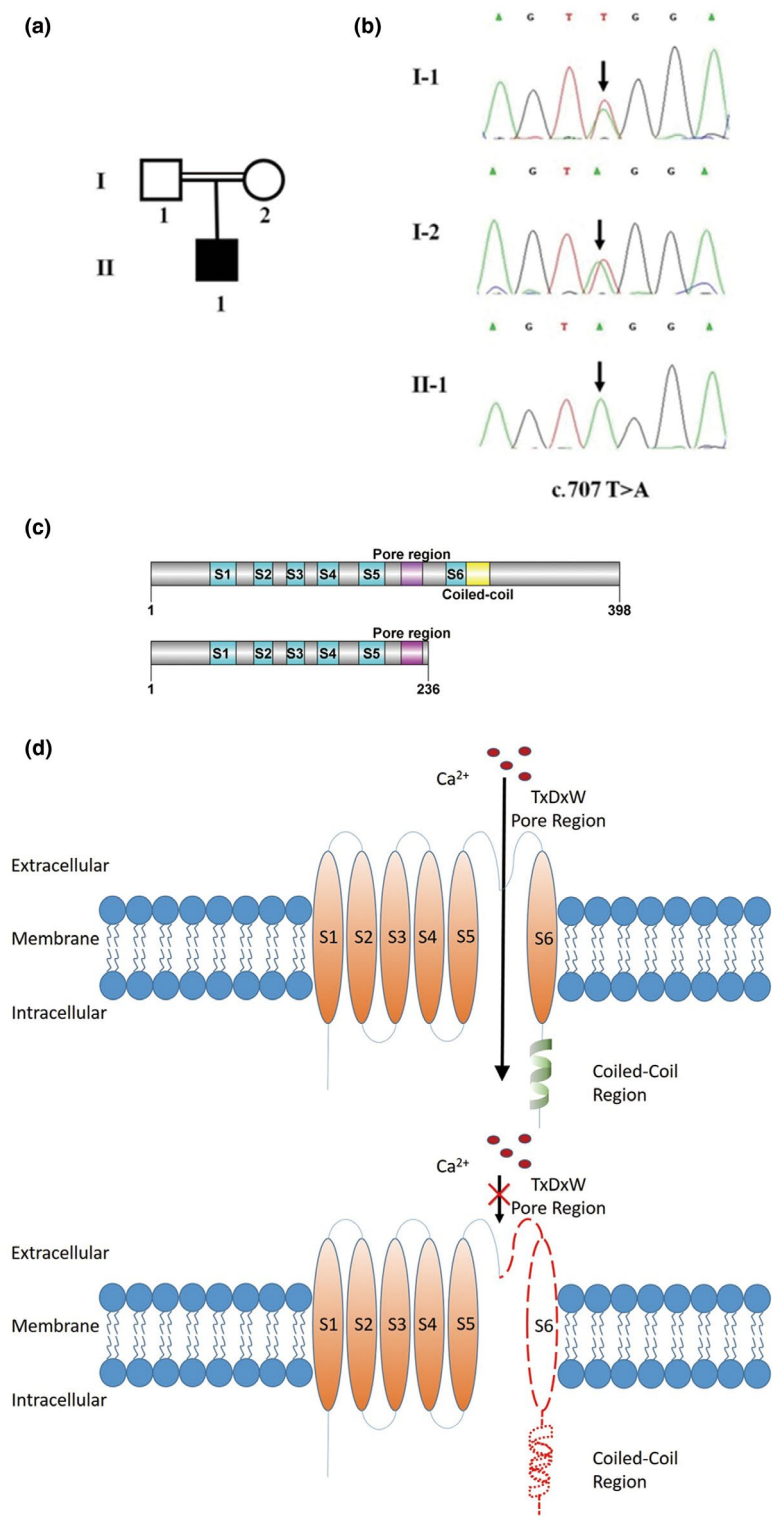
treatments also failed. Then, he was subjected to IVF treatment. Seven oocytes were retrieved and incubated with the optimized sperms, but no sperm penetration occurred and no second polar body was detected after the observation of the early polar body. Thus, early rescue ICSI was carried out. A total number of six eggs were rescued, five of which were successfully fertilized. Four fifth-day high-quality blastocysts (4AA, 4AB, 4BB, and 3BB) were obtained and underwent whole embryo freezing. The patient's wife underwent two cycles of frozen-thawed embryo transfer, and a 4AA embryo was transferred for the first time, but no pregnancy was achieved. We attributed this failure to the inflammation in the pelvic cavity of the patient's wife at the treatment time. After she recovered from the inflammation, a 4AB embryo was transferred in the second cycle that was successfully implanted. The images of the embryos of the IVF and rescue ICSI cycles are presented in Figure 4. The successful pregnancy was confirmed by the HCG test and ultrasound 12 days after the transplantation.

## 4 | DISCUSSION

*CATSPER 3* is a component of the Cation Channel Sperma subunit which is specifically expressed in human testis. *CatSper 1* and *2* were originally identified in mouse and

human sperm in previous research on  $\text{Ca}^{2+}$  channels (Quill et al., 2001; Ren et al., 2001). Furthermore, *CATSPER3* was also detected in mouse and human spermatozoa by in silico gene identification and prediction techniques (Lobley et al., 2003). *CATSPER3* (MIM\* 609120) is located on chromosome 5q31.1, consists of eight exons and seven introns, and encodes a 398-amino-acid protein (Arias et al., 2003). Similar to *CatSper1* and *CatSper2*, *CatSper3* contains a single six-transmembrane repeat domain, in which the fourth transmembrane region resembles a voltage sensor and a pore region containing the consensus sequence T × D × W (Jin et al., 2005). The sequences of *CATSPER3* have been established to be highly conserved in several mammalian species during evolution, ranging from 61.1% (mouse vs. rat) to 99.2% (chimpanzee vs. human) (Jin et al., 2005). In our study, a novel homozygous c.707T>A variant was identified in the *CATSPER3* gene of the patient, which was inherited from his parents. A truncated protein was produced in the experimental the variant, which had a loss of its sixth transmembrane region and a coiled-coil protein-protein interaction region. These defects might have affected cation transportation in sperm and could have been the main cause of this patient's phenotype.

In a mouse model, similar to the negative effects of the defects of *Catsper1*, *2*, *Catsper3* and *Catsper4* defects caused complete infertility due to a loss of motility and failure of



**FIGURE 3** Genetic analysis of the patient's family. (a) The pedigree of the family showing the father (I-1) and mother (I-2) with their offspring numbered II-1; (b) Sanger sequencing chromatographs of the *CATSPER3* gene in available family members revealed a mutation in the proband and their parents. Mutations are indicated by black arrows. The color version of this figure is available at: <http://imr.sagepub.com>; (c) Schematic diagram of *CATSPER3* protein domain structures of the patient (line 2) and normal population (line 1) showed the mutation caused the truncation of the *CATSPER3* protein with a loss of S6 domain and a coiled-coil protein-protein interaction region; (d) The variant caused a loss of the S6 domain and a coiled-coil protein-protein interaction region, which affected the trans-membrane transportation of the  $Ca^{2+}$

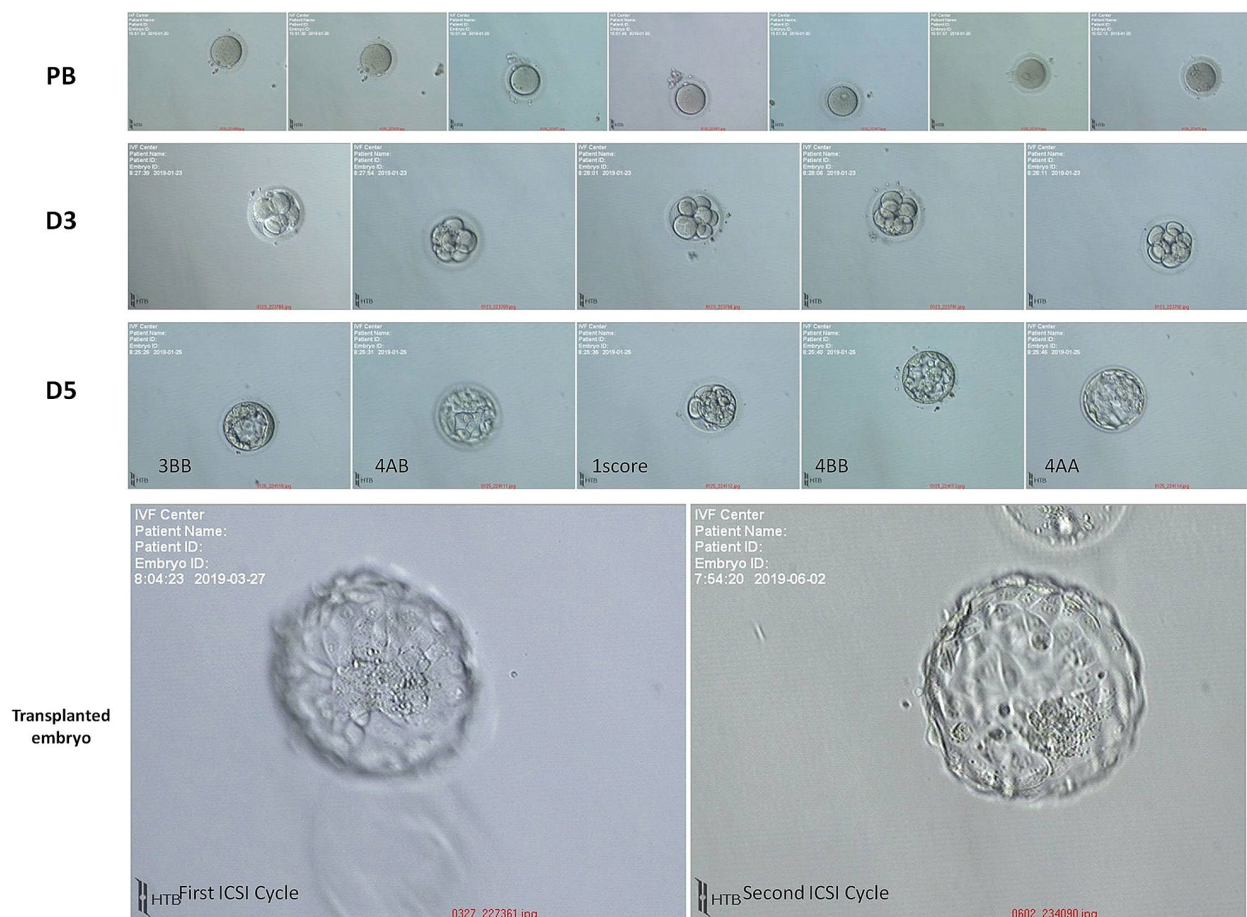
penetration cumulus cells and zona pellucida (Jin et al., 2007). In contrast to the results obtained in the mouse model, the patient's sperm motility observed in our study was normal. Previous reports interpreted that *CATSPER*-deficient (not including *CATSPER3*) cases failed to fertilize at IVF but had normal motility and concentration (Williams et al., 2015), which was similar to our results but in contrast to those of earlier reports (Alasmari et al., 2013; Tamburrino

et al., 2014). Furthermore, previous studies also showed that the lack of *Catsper3* or *Catsper4* did not influence spermatogenesis or the initial motility of mice sperm (Qi et al., 2007). It is noteworthy that in a mouse model, the cellular location of *CatSper3* (mainly in the sperm acrosome) was different from those of the *CatSper1* and *2* (the sperm principle piece and flagella) (Jin et al., 2005). We thus supposed it was a potential explanation for the differences in the impacts between *CATSPER3* and other *CATSPERs* on the sperm parameters.

Fertilization failure is a common natural cause for unsuccessful assisted reproduction. One of the reasons for fertilization failure is the unsuccessful zona pellucida binding and egg penetration of sperm, whereas a successful occurrence of sperm AR is an important prerequisite for the successful outcome of these key steps. Various ionic channels were established to be involved in AR, one of which is  $Ca^{2+}$  channels (Beltrán et al., 2016). Our CD46 fluorescence analysis showed the mutation of *CATSPER3* in our study resulting in the failure of the AR. The ART outcome reports of various *CATSPER* gene-deficient patients are rare. Caused by hyperactivation and AR abnormalities, the dysfunction or low level of

**TABLE 2** Sperm parameters after the semen optimization treatment in IUI

Indicator	1	2	3	4	5
Semen volume (ml)	0.5	0.5	0.5	0.5	0.5
Concentration ( $10^6/ml$ )	25	46	68	42	27
Total motility (%)	92	91.3	94.1	95.2	88.9
Progressive motility (%)	88	91.3	94.1	95.2	88.9



**FIGURE 4** Images of the embryos of the IVF and rescue ICSI cycles. Line1: After the IVF treatment, no second polar body was found in all seven oocytes. Lines 2 and 3: Day3 and Day5 embryos. The embryo scores are displayed in the images. Line4: Two transferred embryos. Four AA for the first cycle and four AB for the second

CATSPERs obviously caused IVF failure (Bhilawadikar et al., 2013; Williams et al., 2015). Therefore, ICSI is an approach recommended to help such patients (Adam et al., 1993; Smith et al., 2013); this approach was successfully used in males with *CATSPER2* deficiency (Zhang et al., 2009). Our study is the first report of a successful ICSI outcome in a *CATSPER3*-deficient patient. This patient's sperm DNA fragment index was 13.69 (<15 considered normal); the nuclear electron density determined by TEM was normal as that of a fertile man. Hence, embryos of high quality were obtained after the ICSI procedure. Therefore, we supposed that *CATSPER3* mutations might not affect the outcome of ICSI due to the maturity and integrity of the *CATSPER3*-deficient sperm nucleus, which is critical to human embryonic development.

In conclusion, we present the first case report of a man with a homozygous mutation *CATSPER3* which caused AR failure and primary male infertility. Nevertheless, we established an insignificant adverse effect of that mutation on sperm motility and morphology. Good prognosis of the ICSI treatment of such patients is expected, which provides novel insights and a recommendation for its application in the clinical therapy of *CATSPER3*-deficient patients.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

## AUTHORS' CONTRIBUTIONS

Hui Tang and Jingjing Xiang analyzed and interpreted the patient WES data. Jiaxiong Wang performed the morphological and histological examination of the sperm and testis, and was a major contributor in writing the manuscript. Aiyan Zheng, Qinyan Zou, Hong Li, and Shenmin Yang collected and organized patient clinical data. All authors read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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