

Case Report*Open Access, Volume 5***A DHX37 mutation causing azoospermia in a man with sertoli cell-only syndrome***Xian-Ling Wang; Jian-Ming Ba*; Zhao-Hui Lyu; Jing-Tao Dou; Yi-Ming Mu**Department of Endocrinology, The First Medical Center, Chinese PLA General Hospital, Beijing 100853, China.****Corresponding Author: Jian-Ming Ba**

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Abstract

Objective: Azoospermia is a serious form of male infertility and about 10-15% males seeking medical care for infertility suffer from this disorder. We described the clinical characteristic of a Chinese male with Sertoli Cell-Only Syndrome (SCOS) causing by DHX37 gene mutation which was detected with whole-exome sequencing.

Methods: The patient was a 23-year-old male with confirmed azoospermia. A detailed history as well as standardized physical, clinical, and laboratory examinations were carried out. Whole-exome sequencing and data analyses were performed to investigate the cause of azoospermia.

Results: In the patient, the hormonal profile showed slightly low level of serum testosterone and anti-Müllerian hormone. The levels of serum follicle-stimulating hormone elevated, while luteinizing hormone was in normal range. The anatomopathological findings of the testicular puncture was no germ cells present in the seminiferous tubules except for Sertoli cells. A causal mutation (c.2911G>A) was detected in exon 22 of DHX37 gene. This sequence change replaces valine with isoleucine (p. Val971Ile), which is neutral and non-polar. This mutation was predicted deleterious to the protein function.

Conclusion: We firstly described a novel mutation of DHX37 (c.2911G>A, p. Val971Ile) in a Chinese young man with SCOS. It was presumed that this mutation damaged the DHX37 protein structure and reduced enzyme activity, leading to clinically relevant SCOS. Further research is needed to thoroughly understand the mechanism of its impact on this disorder.

Keywords: Azoospermia; Sertoli cell-only syndrome; Male infertility; Spermatogenesis; Gene mutation.

Abbreviations: OA: Obstructive Azoospermia; NOA: Non-Obstructive Azoospermia; SCOS: Sertoli Cell-Only Syndrome; DSD: Differences of Sex Development; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone, Testosterone; AMH: Anti-Müllerian Hormone.

Introduction

Male infertility is a multifactorial, heterogeneous and complex disease of reproductive system. Azoospermia, the complete absence of sperm in the ejaculate, is a more serious form of male infertility and about 10-15% males seeking medical care for infertility suffer from this disorder. This disorder can be divided into Obstructive Azoospermia (OA) subtype and Non-Obstructive Azoospermia (NOA) subtype. NOA is featured with seriously impaired spermatogenesis causing by exogenous or endogenous abnormalities. It can be classified into maturation arrest, hypospermatogenesis, and Sertoli Cell-Only Syndrome (SCOS) according to histological findings of testicular biopsy [1]. The genetic causes of SCOS are various, including chromosomal abnormalities, Y chromosome microdeletions and special mutations/deletions of several Y chromosomal genes. However, the aetiology of SCOS has not been well known. It is supposed to occur before or within the premeiotic proliferation phase of spermatogonia [2]. DHX37 is an ATP-dependent RNA helicase and plays a key role in ribosome biogenesis. It is supposed that mutations in the DHX37 gene may impair ribosome biogenesis and Differences of Sex Development (DSD) associated with defective DHX37 has been confirmed [3]. But, there are no reports about DHX37 mutation in patients with SCOS. Herein we firstly described the clinical characteristics of a Chinese male with SCOS in whom a novel mutation (c.2911G>A; p. Val971Ile) of the DHX37 gene was detected and was presumed to be the cause of azoospermia, to provide new insights for the disease.

Material and methods

Patient: The patient was a 23-year-old male who had sought medical care for smaller testes and semen azoospermia for 2 months. Standardized physical, clinical and laboratory examinations were carried out. All the hormone profiles were investigated, including Follicle-Stimulating Hormone (FSH), Luteinizing Hormone, testosterone (LH) and Anti-Müllerian Hormone (AMH). Chromosome analysis and Y microdeletions examination were performed. Testicular puncture was undergone in the patient. azoospermia was diagnosed when the absence of sperm was observed on two different analyses of centrifuged semen pellets obtained after 5-7 days of sexual abstinence. The exact diagnosis of SCOS was based on diagnostic testicular biopsy and histopathological examination.

Whole-exome sequencing and data analyses: DNA extraction from the patient's peripheral blood was undertaken using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Whole exome library was acquired using the xGen Exome Research Panel (Integrated DNA Technologies, Skokie, USA) and high-throughput sequencing was performed on Illumina NovaSeq 6000 sequencing platform. Filtered clean reads were compared with the human reference genome (GRCh37, hg19) by BWA-MEM. GATK Best Practices were applied to guide the variant calling. This study protocol was approved by the Ethics Committee of the First Medical Center of Chinese PLA General Hospital and performed in accordance with the approved guidelines. The patient had signed a written informed consent prior to participation.

Results

Clinical findings: The patient was born with normal body size

and male external genital manifestations. His pubertal development was similar with normal peers during adolescence. His height was 163 cm and weight was 60 kg. He presented with normal intellectual function, facial appearance and no signs of femininity. Pubic hair was at IV Tanner stage and penile stretch length was 8 cm. Each testicle volume was about 3 ml. The hormonal profile revealed slightly low level of serum testosterone (5.06 ng/mL, 4.27-28.24 ng/ml) and AMH (0.42 ng/ml, 0.96-13.34 ng/mL). The level of serum FSH elevated (20.63 U/L, 1.4-18.1 U/L) while LH was in normal range (8.31 U/L, 1.5-9.3 U/L). Chromosome karyotype was 46, XY and no Y chromosome microdeletion was revealed. Multiple tests of semen showed that the number of sperm were 0. The anatomopathological findings of the testicular puncture was no germ cells were observed in the seminiferous tubules except for Sertoli cells; however, the tubular architecture was not damaged by fibrosis.

Identification of the mutation: A causal mutation (c.2911G>A) was detected in exon 22 of DHX37 gene, p. Val971Ile. This sequence change replaces valine with isoleucine (p. Val971Ile), which is neutral and non-polar. This variant is present in dbSNP database (rs151265243). To our knowledge, this mutation was predicted deleterious to the protein function.

Discussion

In this report, we identified a novel mutation in DHX37 which might further expand the spectrum of mutations in azoospermic patients and supported the possible role of DHX37 in male fertility. Genetic disorders related with male infertility include chromosomal abnormality, Y chromosome microdeletions, gene polymorphisms, gene mutations, and epigenetic disorders. Chromosomal abnormality is the common genetic cause. Klinefelter syndrome was most frequently present in the majority of patients, followed by Yq11 (AZFa sub-region) microdeletions. Except for genetic disorders, a lot of genetic modifications associated with SCOS have also been detected [4]. Spermatogenesis is a very complex process, including various genes which have a ubiquitous expression pattern or a special function in spermatogenesis or reproductive tissues. SCOS featured with the complete absence of germ cells, only Sertoli cells in seminiferous tubules, lack of histological degeneration in the testes, meanwhile smaller testicular with normal secondary gender characteristics. It is one of the most serious forms of NOA, usually with a poor reproductive prognosis [5]. It has been described that in patients with SCOS, basal serum FSH level is higher, but basal serum LH level was similar to that of normal adult man. Elevated serum FSH level suggests Sertoli dysfunction or inhibin B production reduced because of absence of germ cells. Such endocrinological disorder has clearly been observed in this patient [6]. The clinical characteristics of SCOS are extremely different. The majority of patients with SCOS have a normal karyotype, smaller testes and higher levels of serum FSH. So sometimes it is difficult to confirm the diagnosis of SCOS only based on clinical characteristics [7]. As a result, genetic investigation is essential for its diagnostic value, clinical decision making, and genetic counselling, as described in the patient [8]. Till now, some etiologies of SCOS have been reported. However, the exact causes of this disorder have not been well known. DHX37 is an autosomal gene located at chromosomal region 12q24.31 and includes 27 exons, which can encode a putative RNA helicase of 1157 amino acids in the DEXD/H-box helicases family [9]. The gene has ever

been confirmed to associated with gonadal development and some kinds of DHX37 gene mutation have been described in the development of DSD [10]. DHX37 expression is highly enhanced in male gonads than female ovaries, indicating its key role in regulating the development of male gonads. So the mutant DHX37 is responsible for the disorder of testis development [11]. We further analyzed how the p. Val971Ile mutation, occurring at the exon-intron boundaries, affected the DHX37 protein structure and reduced enzyme activity in this patient. This mutation has not been reported in large-scale population frequency database literature [12]. Combined with the clinical manifestations exhibited in the patients, we inferred that the novel mutation might lead to clinically relevant DHX37 dysfunction. After confirmation of azoospermia in patients seeking medical care for infertility, clinically distinguishing NOA from OA should be performed through the analysis of diagnostic information, including history, physical examination, and hormonal profile analysis. The most valuable diagnostic test for distinguishing among NOA subtypes is a testicular biopsy and histopathologic examination, such as the findings of testicular histopathology described in this patient. The reproductive prognosis of affected patients is quite poor, as sperm could only be found in the seminiferous tubules in 20% male with SCOS azoospermic with testicular sperm extraction procedure. There have been few ways to cure the disorder and help patients to breed a biological child. In most cases, donor's semen is used when the couple are interested in pregnancy. In summary, we firstly identified a novel mutant of DHX37 (c.2911G>A, p. Val971Ile) in a Chinese young man affected with SCOS. Further investigation is necessary to completely understand the mechanism of its impact on this disorder.

Declarations

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Conflict of interest: The authors declare that they have no conflict of interest.

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References

1. Stouffs K, Gheldof A, Tournaye H, et al. Sertoli Cell-Only Syndrome: Behind the Genetic Scenes. *Biomed Res Int.* 2016; 6191307.
2. Wdowiak A, Bień A, Iwanowicz-Palus G, et al. Impact of emotional disorders on semen quality in men treated for infertility. *Neuro Endocrinol Lett.* 2017; 38(1): 50-58.
3. Ra AG, Evans PJ, Awasthi A, Srinivas-Shankar U. Pituitary hyperplasia with Sertoli cell-only and 47, XYY syndromes: An uncommon triad. *BMJ Case Rep.* 2020; 13(5): 233100.
4. Ghanami Gashti N, Sadighi Gilani MA, et al. Sertoli cell-only syndrome: etiology and clinical management. *J Assist Reprod Genet.* 2021; 38(3): 559-572.
5. Bartmann A. Sertoli Cells Only Syndrome. *JBRA Assist Reprod.* 2021; 25(2): 331-323.
6. Yang Q, Huang YP, Wang HX, et al. Follicle-stimulating hormone as a predictor for sperm retrieval rate in patients with nonobstructive azoospermia: A systematic review and meta-analysis. *Asian J Androl.* 2015; 17(2): 281-4.
7. Cioppi F, Rosta V, Krausz C. Genetics of Azoospermia. *Int J Mol Sci.* 2021; 22(6): 3264.
8. Da Silva TE, Gomes NL, Lerário AM, et al. Genetic Evidence of the Association of DEAH-Box Helicase 37 Defects With 46, XY Gonadal Dysgenesis Spectrum. *J Clin Endocrinol Metab.* 2019; 104(12): 5923-5934.
9. McElreavey K, Jorgensen A, Eozenou C, et al. Pathogenic variants in the DEAH-box RNA helicase DHX37 are a frequent cause of 46, XY gonadal dysgenesis and 46, XY testicular regression syndrome. *Genet Med.* 2020; 22(1): 150-159.
10. Buonocore F, Clifford-Mobley O, King TFJ, et al. Next-Generation Sequencing Reveals Novel Genetic Variants (SRY, DMRT1, NR5A1, DHH, DHX37) in Adults With 46, XY DSD. *J Endocr Soc.* 2019; 3(12): 2341-2360.
11. Globa E, Zelinska N, Shcherbak Y, et al. Disorders of Sex Development in a Large Ukrainian Cohort: Clinical Diversity and Genetic Findings. *Front Endocrinol (Lausanne).* 2022; 13: 810782.
12. Wan Y, Yu R, Luo J, et al. A novel DEAH-box helicase 37 mutation associated with differences of sex development. *Front Endocrinol (Lausanne).* 2023; 14: 1059159.