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A DHX37 Mutation Causing Azoospermia in a Man with Sertoli Cell-Only Syndrome

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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; AMH: Anti-Müllerian Hormone

1. Abstract

1.1. Objective: Azoospermia is a serious form of male infertility, affecting 10-15% of men seeking medical care. This study describes the clinical characteristics of a Chinese male with Sertoli Cell-Only Syndrome (SCOS) caused by a DHX37 gene mutation, detected via whole-exome sequencing.

1.2. Methods: A 23-year-old male with confirmed azoospermia underwent comprehensive medical examinations. Whole-exome sequencing and data analyses were performed to investigate the genetic cause of azoospermia.

1.3. Results: The patient's hormonal profile showed slightly low serum testosterone and anti-Müllerian hormone. Follicle-stimulating hormone (FSH) levels were elevated, while luteinizing hormone (LH) was normal. Testicular puncture findings revealed the absence of germ cells in seminiferous tubules except for Sertoli cells. A mutation (c.2911G>A) in exon 22 of the DHX37 gene was identified, which replaces valine with isoleucine (p.Val971Ile) and is predicted to be deleterious.

1.4. Conclusion: This is the first description of a DHX37 mutation (c.2911G>A, p.Val971Ile) in a young Chinese man with SCOS. The mutation likely disrupts DHX37 protein structure and enzyme activity, contributing to SCOS. Further research is essential to understand its mechanism in this disorder.

2. Introduction

Male infertility is a multifactorial, heterogeneous and com- plex disease of reproductive system. Azoospermia, the com- plete 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 bedevided 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 maturationarrest, 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 mu- tations/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 ofspermatogonia [2]. DHX37 is an ATP-dependent RNA helicase and plays a key role in ribosome biogenesis. It is supposed thatmutations in the DHX37 gene may impair ribosome biogene- sis and Differences of Sex Development (DSD) associated with defective DHX37 has been confirmed [3]. But, there are no re- ports 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 provid new insights for the disease.

3. Material and Methods

3.1 Patient: The patient was a 23-year-old male who had seeked 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 investi- gated, including Follicle-Stimulating Hormone (FSH), Luteiniz- ing Hormone, testosterone (LH) and Anti-Müllerian Hormone (AMH). Chromosome analysis and Y microdelitions examination were performed. Testicular puncture was undergone in the pa- tient. 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 andhistopathological examination.

3.2 Whole-exome sequencing and data analyses: DNA extraction from the patient's peripheral blood was underwent using the QIAamp DNA Blood Mini Kit (Qiagen, Hidden, 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 No- vaseq 6000 sequencing platform. Filtered clean reads werecompared 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 Eth- ics Committee of the First Medical Center of Chinese PLA Gen- eral Hospital and performed in accordance with the approved guidelines. The patient had signed a written informed consent prior to participation.

4. Results

4.1 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 hor- monal 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 mi- crodeletion was revealed. Multiple tests of semen showed thatthe number of sperm were 0. The anatomopathological findingsof 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.

4.2 Mutation Identification

A causal mutation(c.2911G>A) was detected in exon 22 of DHX37 gene, p. Val- 971Ile. This sequence change replaces valine with isoleucine (p.Val971Ile), which is neutral and non-polar. This variant is pres- ent in dbSNP database (rs151265243). To our knowledge, this mutation was predicted deleterious to the protein function.

5. Discussion

In this report, we identified a novel mutation in DHX37 whichmight further expand the spectrum of mutations in azoosper- mic patients and supported the possible role of DHX37 in malefertility. Genetic disorders related with male infertility include chromosomal abnormality, Y chromosome microdeletions, gene polymorphisms, gene mutations, and epigenetic disor- ders. Chromosomal abnormality is the common genetic cause. Klinefelter syndrome was most frequntly present in the majority of patients, followed by Yq11 (AZFa sub-region) microdeletions.Except for genetic disorders, a lot of genetic modifications asso-ciated 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 spermato- genesis or reproductive tissues. SCOS feathered with the com- plete absence of germ cells, only Sertoli cells in seminiferous tubules, lack of histological degeneration in the testes, mean- while smaller testicular with normal secondary gender char- acteristics. 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 en-docrinological disorder has clearly been observed in this patient [6]. The clinical characteristics of SCOS are extremely diffrent. The majority ofpatients with SCOS have a normal karyotype, smaller testes and higher levels of serum FSH. So sometimes it is difficult to confirm the dignosis of SCOS only based on clinical characteristics [7]. As a result, genetic investigation is essencial for its diagnostic value, clinical decision making, and genetic counselling, as described in the patient [8]. Till now, some etiol-ogies of SCOS have been reported. However, the exact causes ofthis disorder have not been well known. DHX37 is an autosomalgene located at chromosomal region 12q24.31 and includes 27exons, which can encod a putative RNA helicase of 1157 aminoacids 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 thedevelopment of DSD [10]. DHX37 expression is highly enhancedin 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, occur-ring at the exon-intron boundaries, affected the DHX37

proteinstructure and reduced enzyme activity in this patient. This mu-tation has not been reported in large-scale population frequency database literature [12]. Combined with the clinical mani- festations 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 shouldbe 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 histopathologicexamination, such as the findings of testicular histopathology described in this patient. The reproductive prognosis of affectedpatients is quitely 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 biologi- cal child. In most cases, donor's semen is used when the coupleare interested in pregnancy. In summary, we fistly identified a novel mutant of DHX37 (c.2911G>A, p. Val971Ile) in a Chinese young man affected with SCOS. Further investigation is neces- sary to completely understand the mechanism of its impact onthis disorder.

6. Declarations

6.1. Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors.

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

6.3. Acknowledgment: The manuscript is an original work. We thank all patients for agreeing to participate in this study. We are grateful to the research team from the endocrinology de- partment in First Medical Center of Chinese PLA General Hospital for its contribution to research design and article modification.

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