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Androgen Receptor Gene Mosaicism in Partial Androgen Insensitivity Syndrome Patient Detected by Whole Exome Sequencing

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Abstract

Androgen insensitivity syndrome is the most frequent etiology of disorders of sex development in 46,XY individuals. It is characterized by evidence of feminization of the external genitalia at birth, abnormal secondary sexual development in puberty, and male infertility. It is an X-linked recessive disease caused by alterations in the androgen receptor (AR) gene, resulting in a spectrum of androgens resistance. The clinical phenotype can be classified into complete, partial, and mild forms. We report a male patient presenting clinical manifestations of partial phenotype: primary infertility, severe oligozoospermia, bilateral gynecomastia, decreased body hair distribution, and hypospadias. Whole exome sequencing (WES) revealed a hemizygous variant in the AR gene with a significantly reduced allele ratio compared with a normal hemizygous allele in male, which is consistent with somatic mosaicism. Mosaic variants in this gene are rare and are associated with incomplete gene dysfunction and subsequently mild or moderate phenotype. AR gene analysis is considered in infertile male patients with genital anomalies and features of under-virilization. Detection of somatic mosaicism is still a major technical challenge. However, WES offers an opportunity to detect lower levels of mosaicism more readily than other traditional methods. Identification of these mutations significantly impacts the diagnosis, management choices and genetic counseling for affected individuals.

Keywords: Androgen insensitivity • Androgen receptor gene • Hypospadias • Male infertility • Mosaicism • WES

Introduction

Disorders of sexual development (DSD) is a group of heterogeneous congenital conditions associated with atypical internal and external genital structure development [1]. Androgen insensitivity syndrome (AIS) is the most common DSD disorder in 46,XY individuals [2]. AIS is an X-linked recessive disease that arises from defects in the AR gene resulting in dysfunction of androgen receptors and thus androgen hormones resistance. According to its clinical heterogeneity, AIS is classified into three broad phenotypes: complete (CAIS), partial (PAIS), and mild (MAIS). CAIS affects 2 to 5 per 100,000 genetically male people, while PAIS and MAIS cases are less common [3].

CAIS individuals have normal female external genitalia with an absence of female internal genitalia and abdominal, inguinal, or labial testes [4]. The PAIS clinical phenotype varies according to the degree of AR residual function, ranging from predominantly female with signs of external genital masculinization to predominantly male with external genital anomalies. MAIS patients usually present with typical male external genitalia, gynecomastia, and infertility in adulthood [4].

AR gene consists of eight exons and encodes for the receptor protein, which is a large polypeptide containing 920 amino acids organized into four functional domains: N-terminal transactivation domain (NTD), DNA-binding domain (DBD), Hinge region (HR), and ligand-binding domain (LBD). AR is a nuclear receptor and functions as a transcriptional regulatory factor [5,6]. It is activated by binding to any of the androgenic hormones (Testosterone and Dihydrotestosterone), forming a complex that migrates inside the nucleus, where it regulates the expression of androgen target genes [7,8]. Androgen-regulated genes are essential for male sex differentiation during embryogenesis (masculinization), development of male secondary sex characteristics after puberty (virilization), and spermatogenesis.

Over 1000 variants in the AR gene have been submitted in the AR database (ARDB) (http://www. mcgill.ca/androgendb, updated in September 2014). Around half of them were identified in AIS patients, and the remaining were associated with other AR-related conditions: Spinal and bulbar muscular atrophy of kennedy, breast cancer, and premature ovarian failure [9]. Several types of genetic defects have been described in AIS individuals: single nucleotide substitution causing missense or non-sens mutations, nucleotide insertions or deletions resulting in frameshift mutations and premature stop codons, complete or partial gene deletions and intronic mutations resulting in abnormal mRMA splicing [9,10].

The introduction of next-generation sequencing (NGS) techniques has advanced our ability to diagnose patients with suspected genetic disorders improving the management and the quality of life for individual patients [11]. WES is still a cost-effective technique compared to whole-genome sequencing (WGS) for studies involving small numbers of patients with rare genetic diseases [12]. This assay can identify various genetic variants, including single nucleotide variants and copy number variants, in disease-causing genes. Molecular diagnostic rates of patients with suspected genetic conditions using WES range from 24% - 68% [13]. Although this technique has demonstrated a significant diagnostic and clinical utility in individuals with genetic conditions, identification of particular genetic variations such as balanced chromosomal rearrangements (inversions, translocations), complex defects, repeat expansions, and mosaic variants is still challenging.

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Here, we describe the clinical features and the molecular data of an infertile male patient who presented with clinical characteristics of PAIS, WES identified a mosaic mutation in the AR gene.

Materials and Methods

Ethical compliance

This study was approved by the Biomedical Research Ethics Committee of Umm Al-Qura University (Approval Number: HAPO-02-K-012-2022-09-1177). Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Case presentation

A 38-year-old male patient presented with six-year infertility due to severe oligozoospermia. His parents are first-degree cousins, and there was no family history of fertility problems or chronic diseases (Figure 1). He has a history of bilateral mastectomy for bilateral gynecomastia at the age of 25 years and hypospadias repair at the age of 15 years. He stated that he has always had normal puberty development and normal sexual function. He had no history of cryptorchidism, testicular trauma, mumps orchitis, radiation, chemotherapy, drinking, or smoking. Physical examination revealed decreased facial and chest hair, Subcoronal hypospadias, small size of testes (10 cc and 8 cc for right and left testes respectively) and bilateral grade I varicocele. There was normal development of epididymis, prostate, scrotum, and vas deferens. Semen analyses (three times) revealed normal volume but 1-3 motile and immotile sperm cells were seen following centrifugation, indicating cryptozoospermia. Laboratory examination revealed elevated testosterone levels and normal FSH and LH levels (Table 1). Cytogenetics analysis showed male karyotype (46,XY), and no chromosomal abnormalities were detected. Y chromosomal micro-deletions analysis was normal. This patient and his wife were subjected to multiple attempts (ten times) of *in vitro* fertilization (IVF) with intracytoplasmic sperm injection (ICSI) using ejaculated sperms, only one attempt was successful. Whole exome sequencing was performed for the patient using the genomic DNA extracted from peripheral blood lymphocytes.

Whole exome sequencing and variant analysis

WES was performed using the Agilent SureSelect Clinical Research Exome v3 targeted sequence capture method to enrich the exome. Direct sequencing of the amplified captured regions was performed using 2X150bp reads on Illumina NGS systems. Alignment to the human reference genome GRCh Build 37 (hg19) was performed and annotated using the SnpEff software in the targeted region. Variants were called at a minimum coverage of 8 and an alternate allele frequency of 20% or higher. Variant interpretations and classifications were performed using the American College of Medical Genetics (ACMG) standards and guidelines for interpreting sequence variants [14-16]. Variants with allele frequencies higher than 1% in any public databases (gnomAD, dbSNP, EVS) were excluded. Variant allele fraction (VAF) was evaluated as: hemizygous calls were X-linked variants identified in more than 95% of reads in male patients. Homozygous calls applied to autosomal variants in more than 95% of reads. Heterozygous calls were autosomal variants in between 20%-80% of reads. Variants with VAF less than 20% were considered suspicious for mosaicism, and subsequent secondary confirmatory testing by Sanger sequencing was performed.

Results

WES revealed a hemizygous single base pair deletion in exon 1 of the AR gene (NM 000044.6:c.649delG), resulting in a disruption of the reading frame (frameshift) and creation of a stop codon with premature truncation of the protein p.(Ala217Leufs*10). This variant was detected in approximately 31% of the sequencing reads with a depth of 58X at position c.649, indicating a significantly reduced allele fraction compared to normal hemizygous alleles in a male (Figure 2). These results are most likely consistent with mosaicism in this individual. Bioinformatic analysis showed that this variant has not been reported as disease-causing or as a variant in the general population. According to ACMG guidelines, this variant was classified as likely pathogenic.

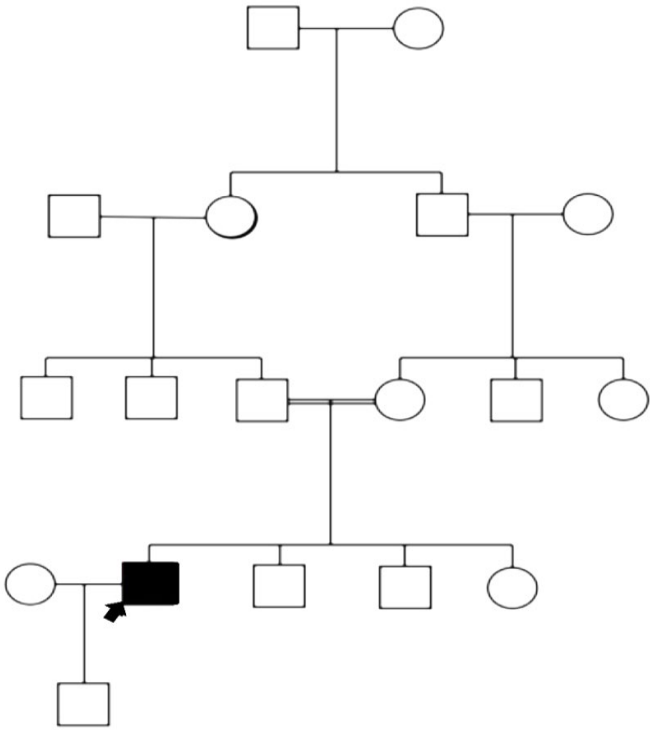

Figure 1. Family pedigree, the proband is indicated by a small arrow.

Table 1. Laboratory hormone values for the proband.

Hormonal Profile	Result	Normal values
Estradiol (pg/ml)	24	11-44
LH (mlU/ml)	5.92	1.7-8.6
FSH (mlU/ml)	5.08	1.5-12.4
Testosterone (ng/ml)	10.24	2.49-8.36
Prolactin (ng/ml)	16.67	4.04-15.2

Note: FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, E2: Estradiol, TT: Total Testosterone, PRL: Prolactin.

Discussion

PAIS is the incomplete form of androgen resistance and represents 10% of individuals with this disorder, which results from partial inability of body cells to respond to androgens. At birth, the typical phenotype in PAIS is a fully developed male reproductive system but is associated with hypospadias, micropenis, and bifid scrotum with descended or undescended testes [17]. The more serious condition is caused by a severe degree of under-masculinization of external sexual organs, and affected individuals display female external genitalia with an enlarged clitoris, posterior labial fusion, or even ambiguous genitalia. At puberty and adult age, PAIS patients present features of under-virilization, characterized by gynecomastia, decreased secondary hair, and infertility [18]. In the current patient, Subcoronal hypospadias, bilateral gynecomastia, reduced body hair, and primary infertility with cryptozoospermia were considered the clinical findings of PAIS.

The reproductive hormone profile in CAIS and PAIS patients is similar [19,20]. It is characterized by elevated or normal serum testosterone levels associated with normal or high serum LH levels consistent with androgen resistance [21]. In AIS patients, FSH and estradiol levels tend to be normal or slightly elevated for males [2]. Our patient has normal gonadotropins and high serum testosterone levels, which suggest the diagnosis of androgen insensitivity and exclude some other conditions associated with incomplete virilization of external genitalia. Androgen biosynthesis defects and 46, XY

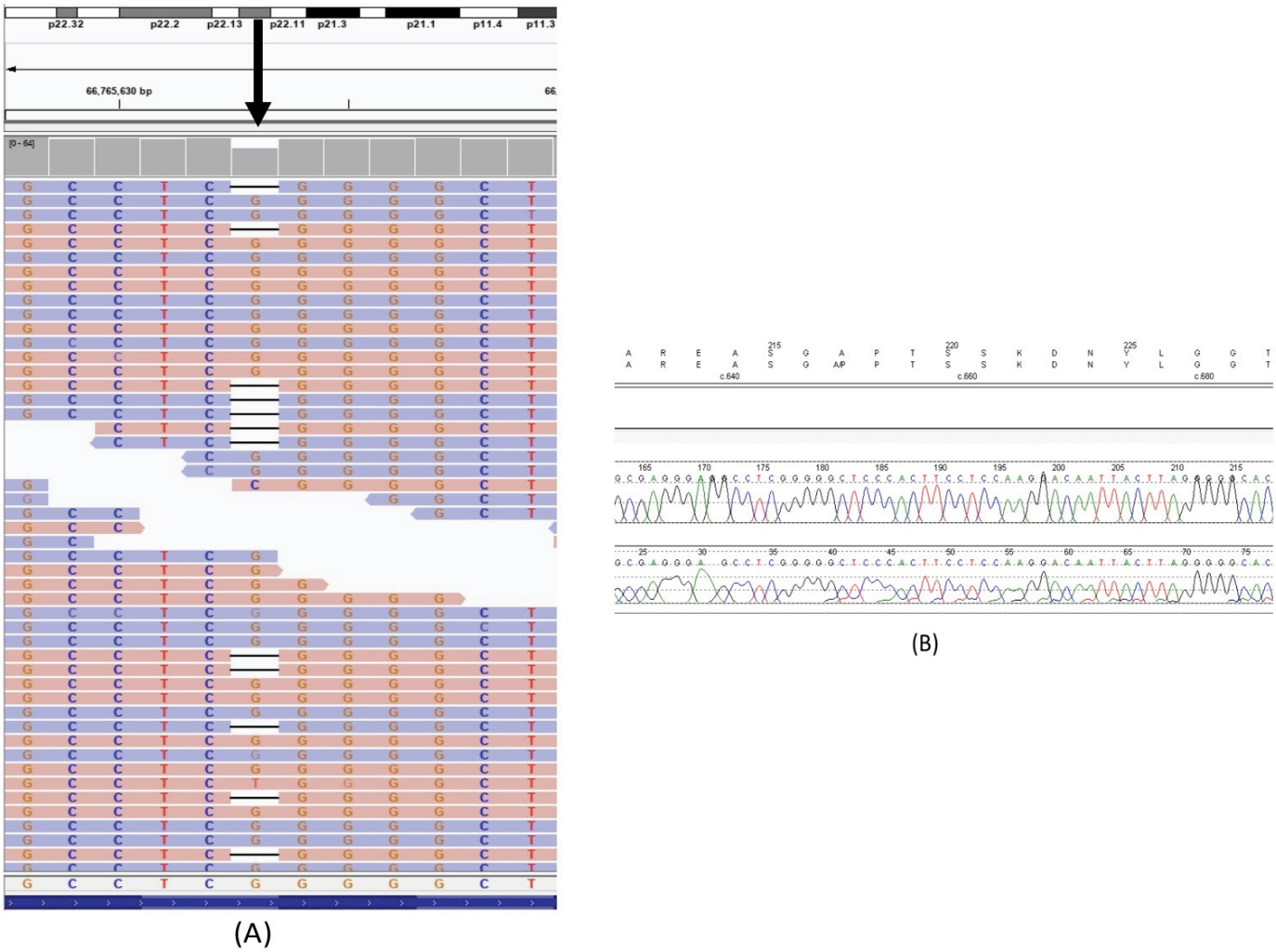

Figure 2. (A). WES reads showing a single nucleotide (G) deletion at position (chrX:66765633) in AR gene with alternate allele percentage (31%) suggesting mosaicism and (B). Sanger sequencing confirming the identification of c.649delG variant.

partial gonadal dysgenesis manifest as PAIS-like phenotype and high serum gonadotropins, but serum testosterone levels are often decreased [22,23].

Normal male reproduction depends on an intact AR because testosterone and FSH are essential endocrine factors for the initiation and maintenance of spermatogenesis in males. Therefore, infertility is nearly a constant consequence in men with AIS. In a few cases with mild AIS phenotype, infertility is the only clinical manifestation of AR dysfunction [4]. The severity of spermatogenic failure in cases with PAIS or MAIS phenotypes is variable. Affected individuals can present azoospermia (no sperms), oligozoospermia (sperm counts between 5 and 15 million sperm/mL), or severe oligozoospermia (sperm counts between 0 and 5 million sperm/mL) [16]. Preserved fertility has been described in isolated cases with mild androgen insensitivity [24,25]. Histological examination of the testes in patients with complete AR resistance revealed incomplete or absent spermatogenesis and normal or hyperplastic Leydig cells [17]. The clinical diversity can be attributed to three hypotheses: 1. Some mutations cause incomplete AR dysfunction, which can be overcomed by the action of coregulatory factors involved in spermatogenesis [26]. 2. The variable expression of cofactors may play a role in determining the overall clinical outcome, including infertility [27]. 3. Somatic mosaicism can contribute to partial AR dysfunction in some cases. Although a mosaic variant is found in our case, he is suffering from a very severe form of spermatogenic impairment, making the chance of spontaneous conception very low. This severity may be explained by the presence of a high level of AR mutation in germ cells compared with other AR-sensitive tissues.

According to ARDB, most CAIS patients harbor a genetic defect in AR. However, around forty percent of individuals with a classical phenotype of PAIS have AR mutations [9]. Described AR variants are distributed along all exonic regions and thus all protein domains. Most genetic defects are located in the NTD domain (encoded by exon 1) and LBD domain (encoded by exons 4-8). NTD domain represents half of the receptor, and its role is to regulate the transcription of androgen-target genes. Therefore, functional or structural alterations in the NTD domain result in significant disruption in the androgen signaling pathway and severe AR dysfunction. Although most mutations located within the first exon are associated with the CAIS phenotype, different variants in the same coding region have been described in individuals with partial and mild forms of AIS, depending on the severity of AR dysfunction [9,28]. Frameshift and nonsense mutations in NTD cause the formation of a premature stop codon and the production of truncated protein. These mutations generate a complete loss of receptor function and the development of the CAIS phenotype [29-31]. Missense mutations in NTD produce complete and incomplete insensitivity toward androgen hormones resulting in CAIS and PAIS phenotypes, respectively [28,32,33]. The previously unreported frameshift mutation (Ala217Leufs*10) identified in our patient lies in the NTD domain of AR. His clinical presentation differed from previously reported CAIS cases with frameshift variants in the same domain [15,16,34]. The partial virilization phenotype in our patient might be explained by the substantial residual function of the androgen receptor due to mosaicism.

Mosaicism is characterized by the presence of a genetic variation in only a subset of cells that are derived from the same zygote. This defect is acquired during mitosis at any stage after fertilization resulting in the development of two or more genetically distinct cell populations in the same individual. Mosaicism can be confined to the germline cells (gonadal mosaicism), non-germline tissue (somatic mosaicism), or both (gonosomal mosaicism). Mosaic variants in the

AR gene have been described in a small number of AIS cases [19,35-37]. It is understood that mosaic variants cause mild or moderate AR dysfunction due to the expression of the residual wild-type AR gene. However, it is reported that individuals with features of complete AR resistance carry mosaic variants [37]. The phenotypic spectrum of AR mosaic variants can vary even with the same mutation and is dependent on the timing of the genetic error during embryogenesis, variant distribution across tissue types, and the proportion of cells harboring this variant [28,38].

Molecular identification of mosaicism can be difficult because the somatic alteration might be present only in a small number of cells. Traditionally, detecting somatic variants requires excellent sequencing techniques with repeated PCR amplification using different primers. Furthermore, a second blood sample may be necessary for definitive confirmation [35]. Recent advances in NGS methodologies and bioinformatics processing have allowed the identification of disease-associated variants at low variant allele fraction (VAF; the proportion of reads with the variant allele compared with wild-type allele reads), indicating somatic mosaicism. Few cohort studies have performed diagnostic WES to detect somatic mosaicism. Among these studies, disease-causing mosaic variants were noted in 1%-4% of individuals with diverse genetic conditions in both pediatric and adult populations [36,37]. Although the detection rates of somatic variants were low compared with constitutional variants, these results have expanded our understanding of the attribution of somatic mosaicism in the development and the prognosis of genetic diseases. To date, AR somatic variants in AIS cases were detected through complete gene sequencing utilizing the traditional method (Sanger sequencing) [35,38-41]. To our knowledge, the present report is the first case study to detect somatic variants in AR using NGS technology such as WES.

Conclusion

We report the first PAIS case with a mosaic variant in the AR gene diagnosed using whole exome sequencing. It is noted that Mosaic variants in the AR gene have a wide phenotypic spectrum ranging from complete to mild androgen insensitivity. We recommend utilizing NGS techniques for male infertility with or without genital anomalies. Nowadays, NGS techniques have the opportunity to replace traditional methods for mutation detection particularly somatic variants.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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