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Case Report

NR5A1 Pathogenic Variant Identified in Non-Syndromic 46, XY Ovotesticular Disorder of Sexual Development

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Abstract

Ovotesticular Disorders of Sexual Development (DSD), formerly known as true hermaphroditism, is defined by the histologic presence of testicular and ovarian tissue in the same individual. Ovotesticular DSD is rare, particularly in the 46, XY karyotype. The nuclear receptor 5A1 (NR5A1) gene has been found in recent years to contribute to a wide variety of DSD phenotypes, notably the p.(Arg92Trp) heterozygous mutation in 46, XX ovotesticular DSD. However, NR5A1 pathogenic variants have not been previously implicated in 46, XY ovotesticular DSD. We report the case of a 9-year-old phenotypic male who initially presented for evaluation of short stature and was subsequently found to harbor a likely pathogenic variant in NR5A1 gene. He was born with a pseudovagina, ovary, fallopian tube, testes, and club feet for which he had already undergone surgical repair. The child's family history is significant for a father with unrepaired hypospadias and a maternal half-brother with genitourinary issues. All known females in the family are phenotypically normal. Karyotype and chromosomal microarray were both normal, 46, XY. An Invitae DSD panel returned a likely pathogenic variant in NR5A1 c.1227C>G (p.Tyr409*). This is the first case of non-syndromic 46, XY ovotesticular DSD to be associated with a pathogenic variant in NR5A1.

Keywords: NR5A1; Ovotesticular Disorders of Sexual Development; True Hermaphroditism

Introduction

Disorders of Sex Development (DSD) are common, affecting approximately 1 in 4500-5500 live births [1]. These children require a multidisciplinary evaluation, which typically includes endocrinology and genetics. DSD are classified into three major categories: sex chromosome DSD, 46, XY DSD, and 46, XX DSD. Ovotesticular DSD (OTDSD), formerly known as true hermaphroditism, is a subset of 46, XY and 46, XX DSD defined by the histological presence of both testicular and ovarian tissue in the same individual. OTDSD is rare and is most often associated with a 46, XX karyotype (60%), while 33% have some form of sex chromosome mosaicism. Only approximately 7% of OTDSD are 46, XY karyotype [2].

Here we report a child with 46, XY OTDSD who was determined to have a heterozygous likely pathogenic variant in NR5A1 c.1227C>G (p.Tyr409[*]). Known heterozygous variants of NR5A1, c.274C>T p.(Arg92Trp) and c.275G>A p.(Arg92Gln), have been implicated in 46, XX OTDSD [3-5]. However, NR5A1 variants have not been associated with 46, XY OTDSD but only partial or complete gonadal dysgenesis in 46, XY patients [1]. Thus, this report presents both a novel pathologic variant of NR5A1 as well as the first known NR5A1 variant associated with 46, XY OTDSD.

Case Report

A 9-year-old phenotypic male presented to Children's of Alabama Genetics Clinic accompanied by his step-mother. His primary reason for presentation was to be evaluated for short stature.

The child was born to a 19-year-old G2P1001 Caucasian female, and the step-mother noted possible prenatal drug exposure during the pregnancy. The child was born with hypospadias, a pseudovagina, one ovary, one fallopian tube, and bilateral testes. At 12 months of age he underwent a salpingo-oophorectomy, hypospadias repair, and reconstruction of the urethra. He also

had clubbed feet at birth which required bracing. His step-mother reported that genetic testing was done to determine whether the child was "Male or Female", but records of the results were not available. Family history is significant for a 28-year-old biological father with unrepaired hypospadias who required "Braces" for his feet. A paternal half-sister who is 2 years of age was diagnosed with osteopenia but had a normal array CGH and no known genital abnormalities. Little is known about the biological mother and biological mother's family, but the step-mother reported that a maternal half-brother also has "genitourinary problems."

On physical examination, the right testis was not palpable. The left testis was appropriate in size for the patient's age. Examination of the phallus showed an outpouching on the ventral side of the urethra consistent with previous hypospadias repair. The penis appeared small, but the scrotum was well-developed. The remainder of the physical exam was within normal limits. Growth parameters are reported below.

Height: 125.00 cm (4th percentile

Weight: 33.40 kg (72nd percentile)

Head Circumference: 52cm (19th percentile)

The child is also followed by urology for urinary incontinence. Renal ultrasound showed bilateral kidneys with normal shape, size, position, and echogenicity. The urinary bladder was grossly normal. Abdominal x-ray was also performed due to coinciding encopresis which showed sclerosis of the left capital femoral epiphysis concerning for a history of avascular necrosis but was otherwise normal.

Results

Cytogenetic testing was performed by UAB Cytogenetics. Chromosomal analysis, FISH for X and Y chromosomes, and reflex array CGH were completed. An additional DSD panel was sent to Invitae for analysis. FISH returned a normal complement with karyotype 46, XY. Results from the array CGH were normal. However, the Invitae DSD panel returned with a heterozygous likely pathogenic variant in NR5A1 c.1227C>G (p.Tyr409*).

Discussion

Disorders of Sexual Development (DSD) result from abnormal phenotypic differentiation of the internal ducts and external genitalia due to improper gene dosage or expression levels of genes. The approach to patients with suspected DSD begins with karyotyping. A history and physical exam to look for syndromic features and palpate for the presence of gonads should follow [6]. If karyotyping reveals 45, XO or 47, XXY, a sex chromosome and syndromic cause of DSD is confirmed, suggesting either Turner or Klinefelter syndrome respectively. Syndromic causes of 46, XY or 46, XX karyotype DSD include Smith-Lemil-Opitz (SLO), Denys-Drash, WAGR, and Genitopatellar syndrome. SLO syndrome is caused by a defect in 7-dehydrocholesterol-Δ^7-reductase which results in decreased plasma and tissue cholesterol and elevated toxic metabolites of cholesterol synthesis. This metabolic defect manifests clinically as hypotonia and cognitive impairment from defective myelination as well as poor growth, microcephaly, anteverted nares, broad alveolar ridges, and syndactyly of the 2nd-3rd toes [6]. Denys-Drash syndrome is caused by a mutation in the Wilms' tumor 1 (WT1) gene, resulting in gonadal dysgenesis, diffuse mesangial sclerosis leading to renal failure within the first year of life, and an increased risk for developing Wilms tumor [7]. WAGR syndrome is caused by an 11p13 deletion that includes PAX6 and WT1 genes resulting in an increased risk for Wilms' tumor, aniridia, genital abnormalities, and mental retardation [8]. Genitopatellar syndrome (GPS) is characterized by genital and renal anomalies, absent or displaced and undeveloped patellae, skeletal anomalies, and cognitive impairment. Though it's exact etiology is largely unknown, Schlaubitz et al. (2007) found a 3.07 Mb deletion including the NR5A1, NR6A1, PBX3, LMXB1, ANGPTL2, and GARNL3 genes in a 12-year-old phenotypic female with the clinical findings of Genitopatellar syndrome.

In the absence of sex chromosome DSD or overt syndromic cause of DSD remaining workup aims to rule out non-syndromic causes of DSD. Foremost, Congenital Adrenal Hyperplasia (CAH) should be ruled out in 46, XX patients by hormonal investigation, as CAH is the most common cause of 46, XX DSD and can be life threatening. Additional testing for androgen and anti-Müllerian hormone levels should be performed for karyotype 46, XY DSD [6]. However, hormonal investigation alone often yields ambiguous results due to overlap between DSD variants. Such ambiguity necessitates the need for DSD gene panels that can provide clarity for patients and their families.

The nuclear receptor 5A1 (NR5A1) gene is typically included in DSD panels, as GPS is the only syndromic association with NR5A1 to date. NR5A1 is located on chromosome 9q33.3 and codes for steroidogenic factor 1 (SF1). SF1 plays a crucial role in the biosynthesis of adrenal and gonadal steroids as well as the development of the ventral nucleus of the hypothalamus. Expression of SF1 in conjunction with Wilms tumor gene (WT1) is also necessary for proper activation of the SRY gene and the production of Anti-MüLlerian Hormone (AMH) [9]. NR5A1 null mice have been shown to lack adrenal glands and gonads, and male NR5A1 null mice specifically have been shown to possess female internal genitalia due to loss of AMH [10].

Homozygous NR5A1 variants were initially characterized in phenotypic females with gonadal dysgenesis, karyotype 46, XY and adrenal failure [11]. However, the phenotype associated with NR5A1 continues to expand. It is now thought that 10-15% of non-syndromic 46, XY DSD can be explained by NR5A1 gene

variants. Phenotypic findings range from normal female external genitalia to hypospadias and a micropenis [12]. Most recently, the heterozygous NR5A1 variant p.Arg92Trp has been implicated in both 46, XX and 46, XY DSD. The p.Arg92Trp variant was also identified in 46, XX OTDSD, making this the first NR5A1 variant associated with OTDSD [3,4]. However, insertion of this variant into mice models shows variable penetrance, with several 46,XX female carriers of the p.Arg92Trp variant being unaffected [13]. A missense variant in NR5A1 p.Arg92Gln was subsequently discovered in a 46, XX patient with bilateral ovotestes [5]. Codon 92 is a critical amino acid in the "A-box" DNA binding region of NR5A1, thus alteration of this codon is thought to be responsible for the above phenotype [14]. To our knowledge, ours is the first case of 46, XY OTDSD to be associated with an NR5A1 variant. The clinical phenotype of our patient with a heterozygous NR5A1 p.Tyr409 variant is comparable to others with heterozygous variants in NR5A1, which suggests the equal importance of codon 409 in proper expression or function of SF-1. Additionally, only the males in our patient's family were noted to have gonadal dysgenesis. The presence of unaffected females within the family may support the finding of variable penetrance in 46, XX carriers of this novel NR5A1 variant p.Tyr409 though further investigation is necessary.

Conflict of Interest: We have no conflicts of interest to disclose.

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