Asian Journal of Andrology (2018) 20, 518–519
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LETTER TO THE EDITOR

Male Health

# Identification of a novel mutation in the *SRD5A2* gene of one patient with 46,XY disorder of sex development

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*Asian Journal of Andrology* (2018) **20**, 518–519; doi: 10.4103/aja.aja_34_18; published online: 25 May 2018

Dear Editor,

46,XY disorder of sex development (DSD) is characterized by a female phenotype in an individual with a normal 46,XY karyotype.[1] The clinical phenotype of 46,XY DSD is characterized by bilateral undescended testes and a normal female appearance, including breasts, female external genitalia, and other secondary sex characteristics, but the absence of a uterus or ovaries.[2] Development of the male external genitalia in the fetal period depends on the biosynthesis of testosterone (T), the conversion of T into dihydrotestosterone (DHT) by steroid 5α-reductase type 2 (SRD5A2), and the response of functionally active androgen receptors in genital tissues.[3] The disruption of any of these stages will block the differentiation of internal and external genitalia and cause 46,XY DSD.

The etiology of 46,XY DSD remains largely unclear. The most common identifiable cause of 46,XY DSD is androgen insensitivity syndrome (AIS). AIS is an X-linked recessive genetic disorder with a normal 46,XY karyotype that is caused by a loss of androgen expression or androgen receptor mutation.[4] The second cause of 46,XY DSD is *SRD5A2* deficiency, which is an autosomal recessive disorder caused by decreased or loss of *SRD5A2* function.[5] The loss of functional *SRD5A2* causes an inability to convert T into DHT, the major hormone responsible for normal male appearance and male sex characteristics.[6] Therefore, mutated *SRD5A2* gene products block the biosynthesis of DHT, resulting in 46,XY DSD. Thus far, more than 60 mutations have been reported in the *SRD5A2* gene.

The primary objective of this study is to identify the etiology of 46,XY DSD. A 2-year-old female was referred to our hospital. A physical examination was performed, including height, weight, and female external genitalia. A color Doppler ultrasonic diagnostic instrument (Voluson E8, GE, Salzburg, Austria) was used to detect male or female internal genital organs, including testis, uterus, and ovaries. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progestin (PROG), T, and prolactin (PRL) for the proband were measured using UniCel Dxl 800 atutomatic immunoassay system (Beckman Coulter, Brea, CA, USA). Chromosome karyotype analysis was used to analyze the proband's karyotype. The genomic DNA was extracted from the peripheral blood samples of the proband and sequencing was performed by the Beijing Genomics Institute (BGI) using the Illumina Genome Analyzer IIx (Illumina Inc., San Diego, CA, USA) for 219 DSD-related genes, including sex chromosomal abnormality, germinal aplasia, and other DSD-related genes. Informed consent was obtained from the child's parents and all experiments were approved by the Medical Ethical Committee of Xingtai People's Hospital Xingtai, China.

The physical examination of the 2-year-old female revealed normal female external genitalia, but a blind-ending vagina. An ultrasound test demonstrated that the proband did not have a uterus or ovaries, but have testis in the left labium majus and right groin. Cytogenetic analysis showed that the patient had a 46,XY karyotype with no apparent anomalies in the chromosome number or chromosomal structure. The hormone test showed that FSH (0.54 mIU ml$^{-1}$), LH (0.12 mIU ml$^{-1}$), and T (<0.1 ng ml$^{-1}$) levels of the proband were lower compared to normal males.

A total of 219 DSD-related genes were sequenced by BGI using the Illumina Genome Analyzer IIx. Sequence analysis showed that the sequences of 17β-hydroxysteroid dehydrogenase type 3 (*17β-HSD3*) and androgen receptor (*AR*) were normal, which synthesize testosterone and respond to DHT, respectively. However, we identified two heterozygous mutations in the *SRD5A2* gene of the proband. The mutation 695A>G changes amino acid 232 from histidine to arginine (p.H232R). This mutation has not been previously reported in the databases of the normal human genome, including the dbSNP, ESP6500, 1000 Genomes, and BGI sequencing databases. The second *SRD5A2* gene mutation was 16C>T, which introduced a stop codon (p.Q6X). This mutation was previously reported and related to the pathogenesis of 46,XY DSD[7] (**Figure 1**).

To date, over 60 mutations in the *SRD5A2* gene have been reported in patients with 46,XY DSD.[8] In this case report, we identified the compound heterozygous mutation (p.H232R/p.Q6X) in a Chinese patient with 46,XY DSD. The compound heterozygosity has two

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Received: 13 October 2017; Accepted: 07 April 2018

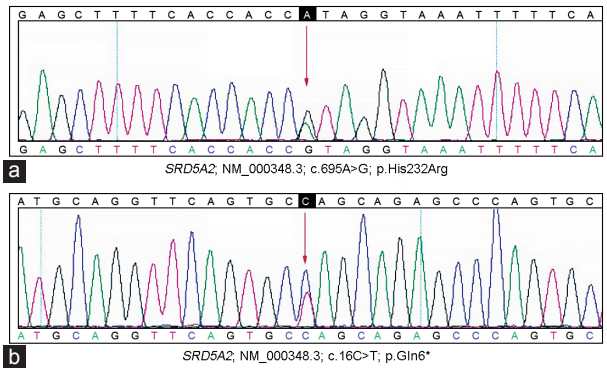


**Figure 1:** Sequencing analysis of the *SRD5A2* mutation of the proband. (**a**) The 695A>G mutation changes amino acid 232 from histidine to arginine (p.H232R). (**b**) The 16C>T mutation found in the *SRD5A2* gene introduced a stop codon. *SRD5A2*: steroid 5α-reductase type 2.

different recessive alleles at a particular locus that can cause genetic disease in a heterozygous state. This paper is the first report to identify the p.H232R mutation in a subject with 46,XY DSD. In a previous report, p.H230P and p.H231R mutations in exon 4 of the *SRD5A2* gene were found to cause 46,XY DSD. Histidine 232 of SRD5A2 is located in a stretch of three histidines (residues 230–232). Mutations in two of these histidines (residues 230 and 231) inactivate or impair SRD5A2 function.[9] Therefore, we speculate that the p.H232R mutation in SRD5A2, like the mutations at amino acids 230 and 231, affects the domain function and thus inactivates SRD5A2 enzyme activity. The second *SRD5A2* gene mutation (p.Q6X) results in a stop codon. The mutation produces a truncated protein, which has lost its ability to bind the testosterone receptor. The compound heterozygous p.G203S/p.Q6X mutations were identified in patients with hypospadias and 46,XY DSD.[7] In most cases of *SRD5A2* mutation, the testes located in the inguinal region that implied DHT may play a critical role in testis descent.[1] We also found that the patients with the compound heterozygous mutation p.H232R/p.Q6X is related to the abnormality of testis descent. Based on our results, the compound heterozygous mutation p.H232R/p.Q6X in SRD5A2 should be regarded as a causative mutation of 46,XY DSD.

In conclusion, our molecular diagnosis of a patient with 46,XY DSD identified a previously unknown mutation (p.H232R) and the previously reported mutation (p.Q6X) in the *SRD5A2* gene. To our knowledge, this is the first report that a patient with *SRD5A2* deficiency carries the p.H232R *SRD5A2* mutant. Our findings expand the mutation spectrum associated with the 46,XY DSD and may contribute to the elucidation of the molecular mechanisms of the H232R mutant in SRD5A2 functional defects.

## AUTHOR CONTRIBUTIONS

SPL, LWL, XXC, XFW, ZKL, SYZ, DCZ, and SXG carried out the molecular genetic studies. SPL, LWL, and MXS carried out the immunoassays. XWD participated in the sequence alignment. SPL, LWL, SJL, and XWD participated in the design of the study and drafted the manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declared no competing interests.

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