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Case Report

Next generation sequencing identifies a novel variant in the *NR5A1* gene in a 46,XY female with complete gonadal dysgenesis

Ömer Günbey[1], İhsan Esen[1], Firdevs D. Paksoy[1], Deniz Ökdemir[1]

[1]Division of Endocrinology, Department of Pediatrics, School of Medicine, Fırat University, Elazığ, Türkiye

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ABSTRACT

To report a novel variant in the *NR5A1* gene as a cause of 46,XY complete gonadal dysgenesis (Swyer syndrome). A 12.5-year-old prepubertal girl presented with the complaint of short stature and was evaluated in our clinic after pelvic ultrasonography revealed an absent uterus and ovaries. In pubertal examination, she was at Tanner stage I, had a fully female phenotype, and no clitoromegaly. Gonads were not palpable on examination. Laboratory investigations, including hemogram and biochemical tests, were normal. Celiac antibodies were negative, and thyroid function tests were within normal limits. Patient's serum LH level was 11.7 mIU/mL, FSH 81.3 mIU/mL, estradiol <15 pg/mL, total testosterone <7.0 ng/dL, DHEA-S 64.4 µg/dL, ACTH 18.1 pg/mL, and cortisol 13.4 µg/dL. Magnetic resonance imaging revealed a hypoplastic uterus in a band-like shape, with no visible ovaries. No appearance consistent with testicular tissue was identified. Karyotype analysis revealed a 46,XY pattern. Estrogen therapy was initiated for the patient. No pathogenic variant was detected in the *SRY* gene analysis. As part of the molecular analysis using the next-generation sequencing (NGS) method, a heterozygous p.V15L (c.43G>T) variant was detected in the *NR5A1* gene (NM_004959.5). A total of 26 genes were screened as part of this panel, including *DHX37, SRY, WT1, DHH, ZFPM2, PPP1R12A, NR5A1, GTF2H5, MAP3K1, HSD17B4, SOX9, DMRT3, NR0B1, and GATA4*. In summary, this case report describes a novel heterozygous *NR5A1* variant identified in an adolescent with 46,XY complete gonadal dysgenesis (Swyer syndrome).

Keywords: *NR5A1* gene, 46,XY complete gonadal dysgenesis, Swyer syndrome

INTRODUCTION

First described in 1955, 46,XY complete gonadal dysgenesis (Swyer Syndrome) is a rare disorder of sex development (DSD).[1,2] Its estimated prevalence is approximately 1 in 80,000 live births.[1] The etiology of 46,XY complete gonadal dysgenesis has been associated with variants in several genes, including *DHH, DHX37, DMRT1, LHX9, MAP3K1, NR5A1, SOX8, SOX9, SRY, and ZFPM2*.[3] The *nuclear receptor subfamily 5 group A member 1 (NR5A1)* gene, also known as *steroidogenic factor-1 (SF-1)*, encodes a transcription factor belonging to the nuclear receptor superfamily.[4,5] It is highly expressed in tissues where steroid synthesis occurs, particularly in the gonads and adrenal glands.[5]

During bipotential gonadal development, NR5A1 plays a critical role in promoting regression of Müllerian structures in 46,XY individuals by activating anti-müllerian hormone (AMH) secretion.[5,6] Additionally, it induces testosterone production in Leydig cells, facilitating the virilization of external genitalia and testicular descent.[5,7] Variants in *NR5A1* have been reported in individuals with disorders of sex development (DSD) affecting both 46,XY and 46,XX individuals during the neonatal or pubertal periods.[5] The first *NR5A1* variant was identified in 1999 in a 46,XY individual with adrenal insufficiency and a female phenotype.[8] Subsequent studies have demonstrated that *NR5A1* variants can lead to 46,XY DSD without adrenal insufficiency.[9]

✉ Ömer Günbey ▪ omergunbey50@gmail.com

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Here, we present a previously unreported variant in the *NR5A1* gene in a patient diagnosed with 46,XY complete gonadal dysgenesis without adrenal insufficiency.

CASE REPORT

A 12.5-year-old prepubertal girl presented with the complaint of short stature and was evaluated in our clinic after pelvic ultrasonography revealed an absent uterus and ovaries. Her medical history revealed that she was born at full term via normal spontaneous vaginal delivery with a birth weight of 3300 grams, and her mental and motor development was appropriate for her age. There was a consanguinity between her parents, who are first cousins. She had a healthy younger brother who was three years younger.

On physical examination, vital signs were normal. Her height was 143.7 cm (-1.80 SDS), weight 33.8 kg (-1.88 SDS), and body mass index (BMI) 16.4 kg/m² (-1.29 SDS). Systemic examination findings were normal. On pubertal examination, Tanner stage was I, and the patient's External Masculinization Score (EMS) was 0; the external genitalia had a completely female appearance. Gonads could not be palpated on examination.

Laboratory investigations, including hemogram and biochemical tests, were normal. Celiac antibodies were negative, and thyroid function tests were within normal limits. Patient's serum LH level was 11.7 mIU/mL, FSH 81.3 mIU/mL, estradiol <15 pg/mL, total testosterone <7.0 ng/dL, DHEA-S 64.4 µg/dL, ACTH 18.1 pg/mL, and cortisol 13.4 µg/dL (Table 1). Because the patient's basal cortisol level was above 10 µg/dL, we did not perform an ACTH stimulation test.

Bone age was 10.5 years using the Greulich-Pyle method on hand and wrist X-rays. Magnetic resonance imaging revealed a hypoplastic uterus in a band-like shape, with no visible ovaries. No appearance consistent with testicular tissue was identified. Karyotype analysis revealed a 46,XY pattern. Estrogen therapy was initiated for the patient. No pathogenic variant was detected in the *SRY* gene analysis. As part of the molecular analysis using the next-generation sequencing (NGS) method, a heterozygous p.V15L (c.43G>T) variant was detected in the *NR5A1* gene (NM_004959.5) (Figure 1). A total of 26 genes were screened as part of this panel, including *DHX37, SRY, WT1, DHH, ZFPM2, PPP1R12A, NR5A1, GTF2H5, MAP3K1, HSD17B4, SOX9, DMRT3, NR0B1, and GATA4*. Segregation analysis revealed no detectable variant in the other family members, including the mother, father, and sibling. The variant identified in our patient was considered to be de novo. Due to the risk of a gonadal tumor, gonadectomy was initially planned. However, the procedure could not be performed because informed consent for gonadectomy was not obtained from the patient and their family. The family is advised to have gonadectomy at each follow-up appointment. If consent is obtained during follow-up, gonadectomy will be reconsidered.

Table 1. Laboratory data of the case

Test	Result	Reference range
Alpha-fetoprotein (AFP) (ng/mL)	< 0.1	0-8.2
Beta Human Chorionic Gonadotropin (ß-hCG) (mIU/mL)	< 0.1	0-4
Dihydrotestosterone (DHT) (µg/L)	0.19	0.016 - 0.07
Free Testosterone (ng/L)	0.78	<8.4
1,4 Delta Androstenedione (µg/L)	< 0.30	0.77-2.25
17-Hydroxyprogesterone (17OHP) (µg/L)	0.53	0.18-2.3
Follicle Stimulating Hormone (FSH) (IU/L)	81.3	0.6-4.1
Luteinizing Hormone (LH) (IU/L)	11.7	<0.02-0.3
Estradiol (pg/mL)	<15	<20
Testosterone (ng/dL)	<7	<20
Anti-mullerian Hormone (AMH) (ng/mL)	0.01	<8.6
Adrenocorticotropic Hormone (ACTH) (pg/mL)	18.1	0-46
Cortisol (µg/dL)	13.4	3-21
Fasting Blood Sugar (mg/dL)	84	70-100
Sodium (Na) (mmol/L)	140	135-145
Potassium (K) (mEq/L)	4.6	3.5-5.1

DISCUSSION

Heterozygous *NR5A1* variants are known causes of gonadal dysgenesis.[3] To date, more than 180 different mutations in the *NR5A1* gene have been identified.[4] The loss of function of the *NR5A1* gene can cause complete or partial gonadal dysgenesis in 46,XY individuals. Different clinical phenotypes may occur in patients carrying the same variant.[5] The frequency of *NR5A1* variants in cases of complete gonadal dysgenesis is reported to be 4-10%.[4,10] *NR5A1* variants are commonly encountered in cases of 46,XY Disorders of Sex Development (DSD).[5] In this case report, we present a novel variant in the *NR5A1* gene as the cause of 46,XY complete gonadal dysgenesis (Swyer syndrome).

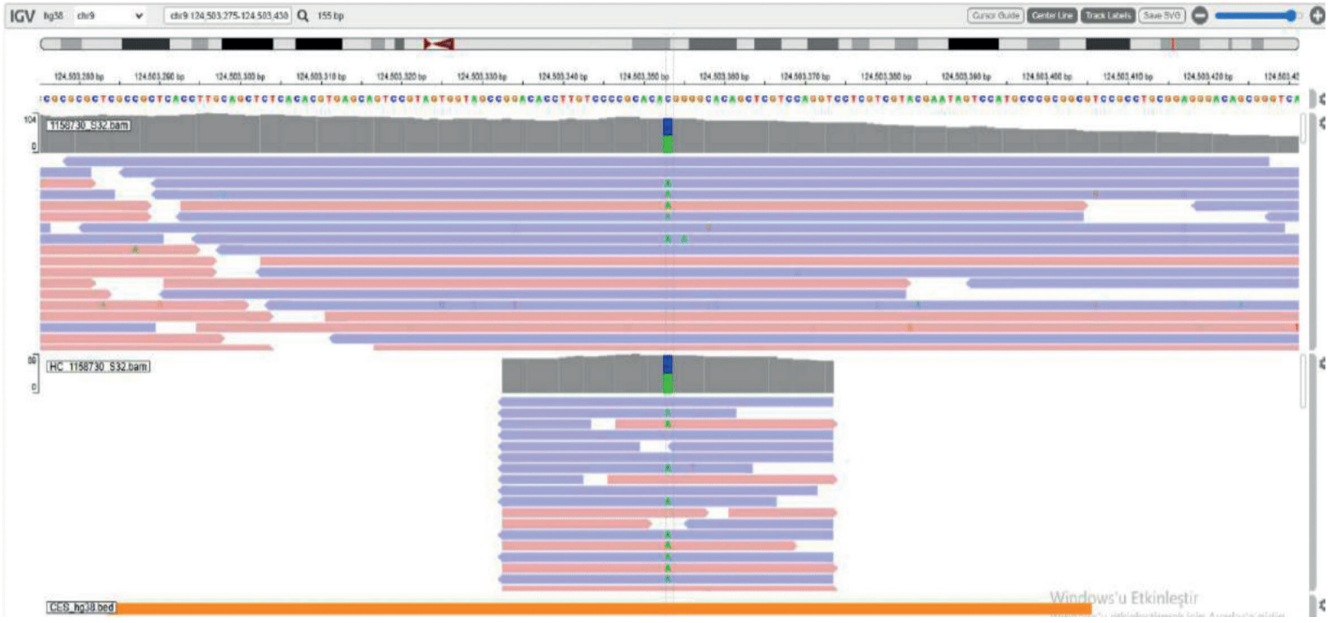

Figure 1. Heterozygous p.V15L (c.43G>T) variant detected in exon 9 (NM_004959.5) in the *NR5A1* gene

In a cohort of 289 patients with 46,XY DSD, 143 patients (49.5%) were diagnosed with 46,XY DSD. Among the 45 patients with a genetic etiology identified for 46,XY DSD, a variant of the *NR5A1* gene, p.Tyr138Ter (c.414C>G/wt), was found in one patient (2.2%).[11] In another cohort of 400 individuals with sex development disorders, the frequency of *NR5A1* mutations was 4% in patients with complete gonadal dysgenesis, while it was 20% in those with partial gonadal dysgenesis and partial androgen insensitivity syndrome.[10] Complete androgen insensitivity syndrome should be considered in the differential diagnosis of karyotype 46,XY, phenotype female cases. Complete androgen insensitivity syndrome was excluded in this case because she was 12 years old, had no pubertal findings, and had no findings in favor of testicular tissue in laboratory and imaging tests. The majority of *NR5A1* variants affect DNA binding activity, and phenotypic differences can be observed depending on the characteristics of the encoded protein.[9] A study reviewed 81 cases of 46,XY CGB with *NR5A1* gene variants published until 2014.[9] In that study, the appearance of external genitalia varied, with ambiguous genitalia in 31%, clitoromegaly in females in 25%, complete female phenotype in 16%, complete male phenotype in 17%, and hypospadias in males in 11%.[9] The clinical spectrum is variable, with 46,XY individuals displaying a female phenotype or ambiguous genitalia, while milder cases may result in infertility.[5] Our adolescent case, who was born with a female phenotype and raised as a girl, exhibited a completely female phenotype, despite having a 46,XY karyotype.

Based on characteristics observed in *NR5A1* knockout mice, initial human studies focused on 46,XY individuals with primary adrenal insufficiency, complete gonadal dysgenesis, and Müllerian structures.[4] Subsequent studies have identified individuals with *NR5A1* variants who have normal adrenal function.[9] In studies, adrenal insufficiency was seen more frequently in homozygous variations in the *NR5A1* gene.[4,9] The variant in our case is heterozygous, and adrenal insufficiency was not detected. The most important laboratory finding in cases of complete gonadal dysgenesis, as observed in our case, is elevated FSH and LH levels, indicating hypergonadotropic hypogonadism, along with low estradiol levels.[2]

In a case of a 46,XY individual with complete gonadal dysgenesis associated with an *NR5A1* variant, the mother, who also carried the same variant, was diagnosed with 46,XX primary ovarian insufficiency.[7] This suggests that the same variant can cause complete gonadal dysgenesis in 46,XY individuals and ovarian insufficiency in 46,XX individuals. The heterozygous variant detected in our case is consistent with dominant inheritance or a de novo mutation. Genetic analysis of the *NR5A1* gene performed on our patient's mother, father, and sibling revealed NO variant. The variant detected in our patient is thought to be de novo.

Molecular analysis of the DNA sample obtained from our patient using next-generation sequencing revealed a change in the first zinc finger of the *NR5A1* gene's DNA-binding domain, where valine was replaced by leucine (V15L heterozygous). To the best of our knowledge, this variant has not yet been associated with any clinical condition and is reported to be extremely rare in population databases.[12] In silico analyses suggest that the variant may be deleterious.[12] Previously, the V15M heterozygous variant at the same position in the *NR5A1* gene has been associated with gonadal dysgenesis and ovarian insufficiency.[13-15] Three cases involving this variant have been reported: the first being a 4-month-old infant with 46,XY karyotype (*SRY* positive) and partial gonadal dysgenesis; the second being a 28-year-old female with 46,XX karyotype and premature ovarian insufficiency; and the third being a case of primary ovarian insufficiency in a study that evaluated 269 patients for 18 genes.[13-15] A comparison of these cases with ours is provided in Table 2.

In Swyer syndrome, estrogen replacement therapy is required to develop secondary sexual characteristics.[1] This is typically followed by cyclical estrogen and progesterone replacement therapy until around the age of 50.[1] Early initiation of estrogen therapy is crucial to ensure adequate bone mineral density during adolescence.[16] Delayed treatment can lead to a decrease in bone mineral density.[16] Estrogen therapy was initiated at the time of diagnosis in our case.

In Swyer syndrome, early diagnosis is important due to the risk of gonadal malignancy.[16] The risk of gonadoblastoma and dysgerminoma is estimated to be between 15-35%.[16] Bilateral gonadectomy is recommended as soon as the diagnosis is made, as there is no role for gonadal biopsy.[17] In our case, laparoscopy with gonadectomy was recommended to the family, but they declined. The patient will be followed up with imaging and laboratory tests for the potential development of gonadal tumors.

This case report describes a novel heterozygous p.V15L (c.43G>T) variant in the *NR5A1* gene identified in a 12.5-year-old girl diagnosed with Swyer syndrome, characterized by short stature and delayed puberty. It adds to the growing body of literature on the genetic basis of Swyer syndrome. The management of 46,XY complete gonadal dysgenesis requires a multidisciplinary approach, emphasizing the importance of early identification for effective counseling. This includes guidance on hormone replacement therapy, bone health, sexual function, fertility options, and the potential risk of gonadal malignancy. The heterozygous p.V15L variant in the *NR5A1* gene should be investigated as a cause of Swyer syndrome in girls with 46,XY karyotype and no adrenal insufficiency who present with short stature and delayed puberty. A novel *NR5A1* variant associated with complete gonadal dysgenesis may not only aid clinicians in interpreting genetic screening results but also inform the development of future therapeutic approaches. More studies are needed to elucidate the phenotype-genotype relationship of the *NR5A1* gene.

Table 2. Comparison of *NR5A1* gene V15M variant cases with our case.

Case	V15M [13]	V15M [14]	V15M [15]	V15L*
Age	4 months	28 years		12.5 years
Clinical	Partial gonadal dysgenesis	Secondary amenorrhea	Primary ovarian insufficiency	Complete gonadal dysgenesis
Phenotype	Female	Female	Female	Female
FSH (IU/L)	9.5	29		81.3
LH (IU/L)	2.3	10.7		11.7
Estradiol (pg/mL)	-	26		<15
Testosterone (ng/dL)	<3	-		<7
AMH (ng/mL)	7.3	0.4		0.01 (2.6–80)
ACTH (pg/mL)	19	-		18.1
Cortisol (µg/dL)	12	-		13.4
Karyotype	46,XY	46,XX		46,XY
Laparoscopy	Bilateral labial testes, epididymis, and vas deferens, no Müllerian structures	-		-

* The case reported in this article

Ethical approval

Informed consent was obtained for the case report.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: ÖG, İE, DÖ; data collection: FDP, ÖG; analysis and interpretation of results: ÖG, İE; draft manus preparation: ÖG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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