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Case Report

A case of 46,XY complete gonadal dysgenesis with a novel missense variant in *SRY*

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Highlights

- A novel missense variant c. 271A>T, p.Ser91Cys in *SRY* was detected.
- Genetic analysis should be considered to aid in the diagnosis of DSD.

Abstract. Disorders of sex development (DSD) with mild external genital abnormalities may be diagnosed after puberty. Here, we report a case of 46,XY complete gonadal dysgenesis with a novel missense variant in sex-determining region Y (*SRY*), diagnosed after primary amenorrhea. A 15-yr-old patient presented to our gynecology department with a chief complaint of amenorrhea. The patient was diagnosed with a 46,XY karyotype, and SRY gene positivity. Gonadotropin levels were high, whereas testosterone levels were low. A pelvic magnetic resonance imaging (MRI) revealed a hypoplastic uterus; however, no gonads could be identified. Laparoscopy revealed bilateral streak gonads, fallopian tube-like structures, and the uterus. The gonads were removed based on the risk of gonadal malignancy. Comprehensive genetic analysis of DSD revealed a previously unreported *SRY* variant, c.271A>T, p.Ser91Cys, and *in silico* analysis predicted the variant to be pathogenic. The patient was diagnosed with 46,XY complete gonadal dysgenesis with a novel missense variant in *SRY*. The patient continued female hormone replacement therapy and experienced breast enlargement and cyclic menstruation. Determining the etiology of DSD can be difficult, causing anxiety in patients and their families. In addition to surgical scrutiny, genetic analysis is important to aid in diagnosis and reassure patients and their families.

Key words: complete gonadal dysgenesis, Swyer syndrome, *SRY*

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Introduction

46,XY complete gonadal dysgenesis, also known as Swyer syndrome, is a disorders of sex development (DSD) where the external and internal genitalia are female-like despite a 46,XY karyotype. It was first described by Swyer in 1955 (1). Its estimated incidence is one in 80,000 (2). It is believed to be caused by a defect in the differentiation process from undifferentiated gonads to fetal testes. The main axis of differentiation of the testicular pathway is sex-determining region Y (*SRY*), and 10–20% of patients have a deletion or variant in the gene (2, 3). In these cases, the SRY protein does not function normally, resulting in the absence of anti-Müllerian hormone secretion. The uterus, fallopian tubes, and upper vagina derived from the Müllerian ducts remain. The external genitalia are entirely female, and the patients present with delayed puberty (2–5). The gonads are streak-like and have a 15–35% chance of developing gonadoblastoma or dysgerminoma (6). Therefore, bilateral gonadectomy is recommended once a diagnosis is made (7).

Androgen insensitivity syndrome is common in 46,XY females, and the low testosterone levels observed in our patient was atypical. In such cases, morphological evaluation via laparoscopy and genetic analysis are essential. Herein, we report a case of 46,XY complete gonadal dysgenesis with a novel missense variant in *SRY*.

Case Report

A 15-yr-old girl presented to our gynecology department with a chief complaint of amenorrhea. She had no significant medical or family history of DSD. Her height was 156.8 cm (50–75th percentile), and her weight was 51.0 kg (25–50th percentile). The breasts and pubic hair were both at the developmental stage of Tanner Stage 1, and the external genitalia was female with mild clitoromegaly as Prader Stage 1 (8). The patient was referred to us with a 46,XY karyotype and SRY gene positivity by fluorescence in situ hybridization. Endocrinological examination revealed hypergonadotropinemia with LH 39.8 mIU/mL and FSH 92.0 mIU/mL. Serum levels of testosterone, estradiol, and anti- Müllerian hormone were 0.16 ng/mL, ≤ 5 pg/mL, and 0.01 ng/mL, respectively. Gonadotropin showed a hyper-response to the luteinizing hormone-releasing hormone loading test (**Table 1a**). The testosterone levels did not respond to the human chorionic gonadotropin loading test (**Table 1b**). Pelvic magnetic resonance imaging (MRI) revealed a hypoplastic uterus, and no gonads could be identified (**Fig. 1a**).

To promote breast development and bone mineral density, female hormone replacement therapy was initiated at 15 yr and 2 mo of age. By the age of 15 yr and 9 mo, breast and pubic hair development were both at Tanner stage 2, and menstruation started. Pelvic MRI revealed an enlarged uterus, and a tissue with a gonad-like structure on the right side was identified (**Fig. 1b**). At the age of 16 yr and 3 mo, laparoscopy with gonadectomy was performed to avoid the risk of malignant transformation. Laparoscopy revealed a uterus in the midline of the pelvis with the fallopian tubes extending from the uterus. The bilateral gonads were streak-like and significantly smaller than those of the normal ovaries; they were attached to the fallopian mesentery (**Fig. 2**). Both the gonads and fallopian tubes were surgically removed. No histological abnormalities were observed in the fallopian tubes. Both gonads were atrophic; however, storiform ovarian stroma was observed (data not shown). No neoplastic lesions, such as gonadoblastoma or dysgerminoma and testicular differentiation, were observed on hematoxylin and eosin staining. The patient and her parents agreed to a comprehensive genetic analysis for DSD. A novel missense variant, c.271A>T, p.Ser91Cys was detected in *SRY* in this case. A missense variant of the same amino acid residue replaced with a different amino acid, p.Ser91Gly, was previously reported in 46,XY females (9). Based on *in silico* analyses, the variant was suspected to be pathogenic. Variant mutational analysis using PolyPhen-2 revealed that the missense variant was probably damaging. SIFT analysis revealed that this missense variant was damaging. The father's *SRY* was normal. Based on the clinical characteristics, we considered the variant to be pathogenic. Based on these results, a 46,XY complete gonadal dysgenesis diagnosis with a novel missense variant in *SRY* was made.

Written informed consent was obtained from the guardian for genetic testing and publication of this case report.

Table 1. Results of the loading test

a) LH-RH loading test (100 μg)

	LH (mIU/mL)	FSH (mIU/mL)
Pre-load	8.5	40.1
30 min	90.6	67.7
60 min	99.3	79.7
90 min	82.5	76.5
120 min	70.0	74.0

LH-RH, luteinizing hormone-releasing hormone.

b) hCG loading test (3000 IU × 3 consecutive days)

	Testosterone (ng/mL)
Pre-load	0.16
Post-load*	0.22

hCG, human chorionic gonadotropin. * 72 h after the first hCG administration.

Discussion

SRY is responsible for 10–20% of the genetic variants found in complete gonadal dysgenesis (2, 3). Other causative genes include *NR5A1*, *SOX9*, *DHH*,

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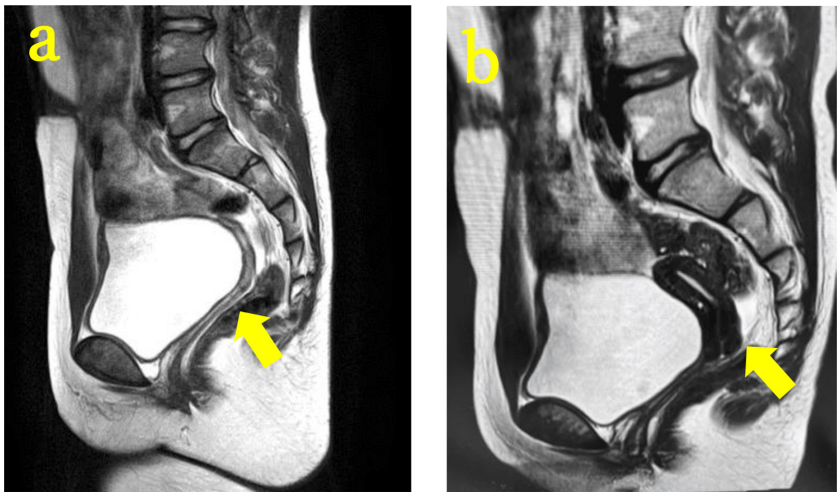

Fig. 1. Pelvic magnetic resonance imaging examination (T2-weighed image). (a) The figure shows a hypoplastic uterus (yellow arrow) before hormone replacement therapy, and the gonads cannot be identified. (b) The figure shows an enlarged uterus (yellow arrow) after hormone replacement therapy.

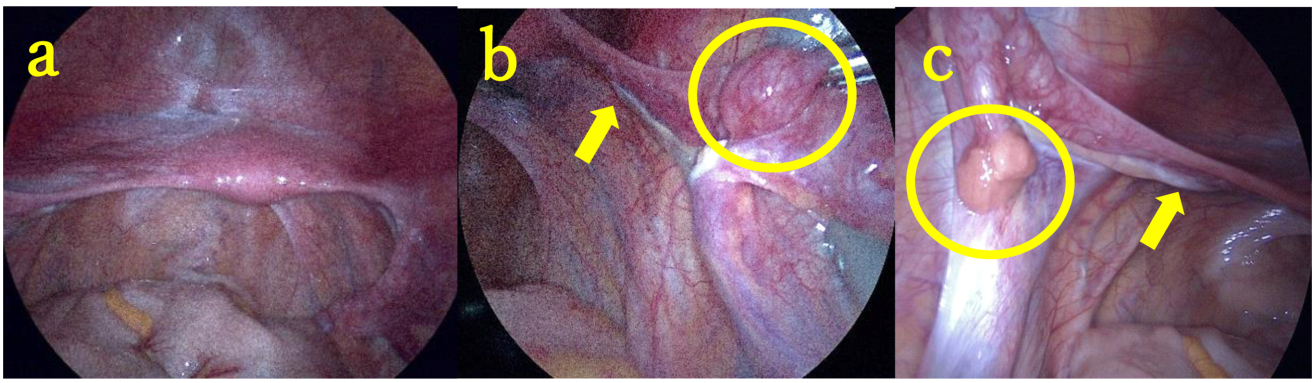

Fig. 2. Operative findings. (a) Uterus. (b) Right gonad (yellow circle), right fallopian tube (yellow arrow). (c) Left gonad (yellow circle), left fallopian tube (yellow arrow). The bilateral gonads were cordate and significantly smaller than the normal ovaries but were still attached to the fallopian mesentery.

GATA4, *WT1*, *DMRT1*, *NR0B1*, *WNT4*, and *MAP3K1* (10–12). *SRY* promotes testicular differentiation and is important for male sex determination. It is located on the short arm of the Y chromosome and encodes 204 amino acids. *SRY* has a homeodomain called the high-mobility group (HMG). Numerous variants are thought to occur in HMG, thereby altering DNA binding and preventing the nuclear transport of the SRY protein (4, 13, 14). Dysfunction of the variant of *SRY* results in the failure of testicular differentiation and secretion of anti-Müllerian hormones, leading to female-like external and internal genitalia. In this case, the c.271A>T, p.Ser91Cys variant of the *SRY* was a novel variant. However, a pathogenic variant with a different amino acid (p.Ser91Gly) was previously reported in a 46,XY female patient. The Ser-to-Gly variant is believed to occur in helix II of HMG, which changes the polarity of the protein and, thus, its binding strength to DNA (13). Our experience has expanded the variant spectrum of *SRY*. However, one limitation is that we did not perform a functional analysis of the novel SRY variant in our case.

The patient and her parents were relieved when a genetic cause was identified. Most *SRY* variants associated with 46,XY complete gonadal dysgenesis occur *de novo*. However, in some cases, the *SRY* variant is inherited from the father (15, 16). The family sought to understand whether the *SRY* was inherited as it may have an influence on her siblings. The finding in this case that the SRY variant was de novo indicated that the disease was not hereditary and that further examination of other relatives was unnecessary. In addition, understanding the mechanism of genital abnormalities and symptoms caused by the *SRY* variant will facilitate the diagnosis of the disease.

Although it may be difficult to perform functional analysis of genes in all cases, we believe that genetic analysis not only benefits the diagnostic process but also helps reassure the family.

Conclusions

Herein, we report a case of complete gonadal

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dysgenesis associated with a novel missense variant in *SRY*. Identifying the pathophysiology of DSD can be challenging because of its rarity and the wide variety of differential diagnoses. Physical examination and imaging studies are important; however, genetic analysis should also be considered to aid in the diagnosis and for the family.

Conflicts of interests: The authors declare no conflicts of interest.

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