

Primary amenorrhea in a 46,XY adolescent girl with partial gonadal dysgenesis: identification of a new *SRY* gene mutation

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Objective: To determine the genetic cause of primary amenorrhea in a 46,XY adolescent girl.

Design: Case report.

Setting: Pediatric endocrinology and gynecologic unit of an academic hospital.

Patient(s): A 16-year-old adolescent referred for primary amenorrhea.

Intervention(s): Endocrine and surgical investigation, *SRY* mutational analysis.

Main Outcome Measure(s): Plasma gonadotropin levels, estradiol and testosterone levels, and pathologic findings.

Result(s): We report a new mutation of the *SRY* gene in a 46,XY sex-reversed patient. We observed two unusual features. First, partial pubertal development has rarely been described in association with *SRY* gene mutation. Second, the location of the mutation was in the HMG box region of the *SRY* gene, in contrast to the other partial cases of 46,XY gonadal dysgenesis. In addition, the presence of a gonadoblastoma underlines the necessity of removing the gonads quickly in 46,XY sex-reversal cases, and raises several questions about the role of the *SRY* gene in the development of such tumors.

Conclusion(s): Partial pubertal development in a 46,XY sex-reversed patient does not exclude *SRY* gene mutation. (Fertil Steril® 2007;88:1437.e21–5. ©2007 by American Society for Reproductive Medicine.)

Key Words: *SRY* gene, primary amenorrhea, 46,XY sex-reversal

Adolescent amenorrhea is a frequent reason for consultation in pediatric endocrinology and gynecology. Primary amenorrhea may result from congenital abnormalities in the development of the gonads, genital tract, or external genitalia or from a disturbance within the hypothalamic-pituitary-ovarian axis. The failure to menstruate by the age of 15 years requires investigation; we recently demonstrated that the mean age at menarche is 12.6 years, with the 97th percentile at 14.6 years (1). After the physical examination, endocrine assessment, pelvic imaging, and karyotyping should be systematically performed: chromosomal abnormalities (X0 or XY) may be associated with primary amenorrhea with hypergonadotropism.

There may be several causes of 46,XY complete sex reversal, including a genetic defect in fetal testis determination, failure of the fetal testis to produce testosterone, or complete

insensitivity to androgens. When plasma testosterone is low, an abnormality in the genes involved in fetal testis determination, such as *SRY*, *SFI*, *SOX9*, *WT1*, and *DMRT1*, should be considered.

The key factor for male sex determination is *SRY*, which is located in the distal region of the Y chromosome. The *SRY* gene encodes a protein containing a DNA-binding motif known as the highly conserved HMG box (high mobility group). Most patients with 46,XY sex reversal associated with a *SRY* gene mutation also usually present with a complete form of gonadal dysgenesis, with bilateral streak gonads and no pubertal development (2). We report here an unusual case of partial gonadal dysgenesis related to a new *SRY* gene mutation in a 46,XY adolescent girl referred for primary amenorrhea and incomplete pubertal development.

This was a collaborative study of a patient sent to our clinic by Charvet (Service de Pédiatrie, Hôpital de Hyeres, France). The patient was managed in our pediatric endocrinology clinic by Paris and Sultan (Unité d'Endocrinologie et de Gynécologie Pédiatrique, Service d'Hormonologie, CHU de Montpellier, France). Genetic analysis was performed

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by Philibert and Lumbroso (Service d'Hormonologie, CHU de Montpellier, France), the surgery by Galifer (Service de Chirurgie Viscérale Pédiatrique, CHU de Montpellier, France), and the pathologic analysis by Baldet (Service d'Anatomie et Cytologie Pathologiques, CHU de Montpellier, France).

MATERIALS AND METHODS

Patient

The patient was referred to our pediatric endocrinology unit at the age of 16 years for primary amenorrhea. This adolescent was obese, weighing 79 kg for a height of 162 cm (body mass index 30 kg/m²). Her pubertal status, based on the Tanner III scale, was B3, P3, A1. The laboratory data suggested gonadal dysgenesis with high follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels of 74 U/L (normal range: 3–8 U/L) and 20 U/L (normal range: 1.5–6.0 U/L), respectively. Plasma sex steroid hormones were within the normal range for a peripubertal girl: estradiol, 30 pg/mL (normal range: 25–100 pg/mL); testosterone, 0.3 ng/mL (normal <0.6 ng/mL); and dehydroepiandrosterone sulfate (DHEAS), 1.4 µg/mL (normal range: 0.5–2 µg/mL). Plasma prolactin levels were normal at 6.6 ng/mL (normal range: 3–20 ng/mL). Pelvic ultrasonography revealed neither gonads nor uterus. The karyotype was 46,XY. Antimüllerian hormone was not detectable.

Gynecologic examination under general anesthesia revealed a normal vagina and cervix. Coeloscopy was performed and did not find wolffian structures, whereas atrophic uterus, tubes, and two adnexa were seen. Macroscopically, these latter looked like ovaries. The girl underwent a bilateral gonadectomy because of the high risk of gonadoblastoma in 46,XY females. The excised gonad from the left side consisted of fibrous tissue without follicles. The right gonad contained spindle cell stroma associated with rete and tubular structures and immature Sertoli cells, which reinforced the diagnosis of partial gonadal dysgenesis. In addition, a gonadoblastoma was identified.

Her plasma estradiol level before surgery was higher than after surgery (<10 pg/mL). Obesity, because it increases androgen aromatization, may have been implicated in the patient's feminization, although estradiol synthesis by the gonadoblastoma itself cannot be ruled out.

Methods

Genomic DNA was prepared from the patient's and father's peripheral blood lymphocytes with the QIAamp Blood Kit (Qiagen, Valencia, CA). Primer pairs RYFW 5'-TTTCGAACTCTGGCACCTTT-3' and SRYRV 5'-AAAGTGAGGGCTGTAAGTTATCG-3' amplified a 739-bp fragment encompassing the HMG box of the SRY gene. The amplification reactions were performed with 100 ng of genomic DNA, 24 µL of Taq PCR Master Mix Kit (1.5 mM MgCl₂, 200 µM of each dNTP; Qiagen), 24 µL of H₂O, and 1 µL of each primer. Amplification was performed

for 39 cycles (30 seconds at 94°C, 1 minute at 58°C, 1 minute 30 at 72°C) and terminated with incubation for 6 minutes at 72°C. The polymerase chain reaction product was purified, and both strands were sequenced directly using the ABI Prism 310 Capillary Sequencer (Applied Biosystems, Foster City, CA) and the following internal primers: xes3 5'-GAGAATCCCAGAATGCGAAA-3' and xes5 5'-GCCATTTTTCGGCTTCAGTA-3'.

RESULTS

The clinical and biological characteristics of our patient were compared with those of 46,XX controls (Table 1).

A new point mutation within the HMG box of the SRY gene was identified in the patient: thymine was replaced by adenine at position +385 in codon 129, resulting in the replacement of the amino acid tyrosine (TAT) by asparagine (AAT). This point mutation has never been described previously. The sequence data from the patient's father did not reveal the presence of the mutation (Fig. 1).

DISCUSSION

The 46,XY female is a rare but not exceptional cause of adolescent primary amenorrhea. Over the last 5 years, seven of the 63 adolescent girls we have managed for primary amenorrhea exhibited a 46,XY karyotype. In addition to complete (or partial) XY gonadal dysgenesis related to a SRY gene mutation, 46,XY sex reversal may occur in association with renal abnormalities, due to a WTI gene mutation (3), adrenal insufficiency (associated with an SF1 gene mutation) (4), or campomelic dysplasia (alteration of the SOX9 gene) (5). Evidence of altered SRY sequence has been reported in only 15% to 20% of the cases of 46,XY gonadal dysgenesis (6).

TABLE 1		
Clinical and biological characteristics of patient compared with 46,XX controls.		
Characteristic	Patient	Control (n = 7)
Age	16	16 ± 1
Body mass index	30	19 ± 1.5
Breast development	B3 ^a	B5 ^b
Pubic hair	P2–P3 ^a	P5 ^b
FSH (mU/mL)	74	3.5 ± 1.2
LH (mU/mL)	20	2 ± 0.9
Testosterone (ng/mL)	0.3	0.2 ± 0.1
AMH	Undetectable	Undetectable
Note: AMH, antimüllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.		
^a Tanner III scale.		
^b Tanner V scale.		
Paris. 46,XY primary amenorrhea. Fertil Steril 2007.		

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