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A novel mutation in the *SRY* gene of a Chinese 46,XY female patient with unilateral mixed germ cell tumor

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Objective *To determine the nosogenetic factors of a 46,XY female with primary amenorrhea and unilateral mixed germ cell tumor.*

Methods *Eight genes associated with 46,XY gonadal dysgenesis were detected in the patient and her parents by target region captured-next generation sequencing.*

Results *An insertion of a single nucleotide (adenine) at the coding site 230 (c. 230_231insA) located in the high mobility group (HMG) domain of SRY was revealed, which led to a truncated protein (p.Lys77fsX27). This mutation was at position 2655414 of the Y chromosome, supported with 127 unique mapped reads, however, this mutation was not found in the in-house dataset of 1 092 controls. Additionally, none of the candidate gene was detected in the patient's parents, which indicated that it is a de novo mutation.*

Conclusion *A novel SRY sporadic mutation due to a single nucleotide insertion at position 230 (c.230_231insA) was identified as the cause of the disease in this patient. Target region captured-next generation sequencing was found to be an effective method for the molecular genetic testing of 46,XY complete gonadal dysgenesis (46,XY CGD).*

Key words: 46,XY complete gonadal dysgenesis (46,XY CGD); *SRY* gene; novel mutation; next generation sequencing (NGS)

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46,XY complete gonadal dysgenesis (46,XY CGD), previously nominated as XY sex reversal[1], is a rare disorder marked by a 46,XY karyotype, normal female external genitalia, completely undeveloped "streak" gonads, no sperm production, and presence of normal Müllerian structures[2]. Patients with this disorder have an increased incidence (about 30%) of gonadoblastoma and germinoma, usually bilateral[3-6]. 46,XY gonadal dysgenesis is a heterogeneous disorder with autosomal, X-, and Y-linked forms[7]. The Y-linked form is caused by mutations or deletions in the *SRY* gene, also called 46,XY sex reversal 1 [*SRXY*1, Mendelian Inheritance in Man (MIM) number: 400044], which is responsible for 15% of the cases of 46,XY CGD[8]. *SRY* encodes a protein with 204 amino acids, which expresses during human embryogenesis at week 7 of gestation in the pre-Sertoli cells, and initiates the development of male gonads. The protein contains a high mobility group (HMG) conserved domain, from amino acid 65 to 130, which has been exhibited to possess sequence-specific DNA binding activity and acts as a transcriptional regulator in the process of sex determination[9-11]. The absence of proper SRY expression, either by absence of the gene (like in case of a deletion), or by inactivating mutations, will embark on a female pathway. Typically, *SRXY*1 is sporadic, although approximately 30% of all identified SRY mutations are inherited[12].

In the present study, a *de novo* truncated mutation in the *SRY* gene was determined in a female patient with 46,XY CGD using the target region captured–next generation sequencing (NGS).

Materials & Methods

Clinical report

A 20-year-old female presented with primary amenorrhea, distension of lower abdomen, and intermittent pain for three months. She was asked for a complete clinical history and underwent a physical examination. Hormone assays showed an elevated FSH (41.51 IU/L) and LH (13.53 IU/L). CT scan of the abdomen revealed a 17 cm × 11 cm mass on the right side of the pelvis without visible gonads. After bilateral gonadectomy, histopathology confirmed the mass to be a mixed germ cell tumor (GCT) and streak gonad on the left side without the tumor.

The woman was 161 cm tall and weighed 55 kg, with a body mass index (BMI) of 21.2 kg/m^2. The external genital was feminine and immature with Tanner stage III breast development and stage II pubic hair. Medroxyprogesterone acetate, known to induce menstrual bleeding, was orally administered (10 mg/d) to the patient for 5 consecutive days. The acytogenetic analysis of cultured peripheral blood lymphocytes showed a 46,XY karyotype without mosaicism.

The familial history of the patient was negative. Her parents and brother showed a normal karyotype and phenotype. Informed consent was obtained from the patient and her