Received: 31 May 2021 | Accepted: 30 July 2021

DOI: 10.1002/ccr3.4706

Clinical Case Reports Open Access WILEY

CASE REPORT

A novel *SRY* pathogenic variant from a 46,XY female harboring a nonsense point mutation (G to A) in position 293

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Funding information
The Research Funds of the Sichuan Provincial Commission of Health and Family Planning, Government of China (No. 16PJ385)

Abstract

46,XY female is a genetic disorder characterized by gonad gender not consistent with chromosomal sex. The *SRY* gene mutation is a common cause of 46,XY reversal type 1 (OMIM: 400044). Peripheral blood was collected from a 46,XY female patient and her father. Sex chromosomes were confirmed by karyotype analysis and fluorescence in situ hybridization (FISH) detection of the specific probe of sex chromosomes with cultured lymphocytes. After extracting blood genomic DNA, *SRY* characteristic fluorescence peak was detected by quantitative fluorescence PCR (QF-PCR) method. Whole exome was sequenced with NGS, and *SRY* gene was sequenced by Sanger sequencing, respectively. The chromosomes X and Y of the patient were confirmed by karyotype of 46,XY, and FISH specific probe of chromosome X and Y. *SRY* specific fluorescence peak was observed by QF-PCR. The whole-exome sequencing results showed chrY: 2655352(GRCh37): c.293G>A hemizygote mutation, confirmed by Sanger sequencing. The de novo mutation resulted in the mRNA encoding the tryptophan codon of 98 (UGG) change into a termination codon (UAG) (P.Trp98ter), and the translation process was terminated prematurely. The discovery of this novel mutation in the *SRY* gene helps elucidate the molecular mechanism of 46,XY female sex reversal and enriches such patients' genetic mutation spectrum.

KEYWORDS

46,XY female, next-generation sequencing, nonsense mutation, pathogenic variant, sex determining region Y

1 | INTRODUCTION

46, XY female is a genetic disorder characterized by gonad gender not consistent with chromosomal sex, which is caused by an abnormality of sexual differentiation. The patient's chromosome karyotype is 46,XY, and the clinical manifestations are female appearance. The majority of patients are nonsyndromic, and abnormal phenotypes only exist in the reproductive system; abnormal gonad of 20%–30% of patients may deteriorate into the gonadal tumor. They inherited from their parents in an autosomal dominant, autosomal recessive, X-linked, or Y-linked manner, but most of them acquired by spontaneous mutation.

In 1959, the study of Jacobs P.A and Ford C.E showed for the first time that the determinant of male sex in humans is the chromosome Y[1,2]. Only until 1990, Sinclair AH et al.[3] cloned the *SRY* gene mapping to Yp11.3. *SRY* acts as a switch for male sexual differentiation by regulating other genes' expression, so it is considered the best candidate gene for testis-determining factor (TDF) and a significant inducer of testis development in mammals.[4]

SRY gene is only briefly expressed in the primary gonadal tissue of early embryo in a manner of tissue and temporal specificity, leading to the differentiation of the primary gonadal tissue into testicular tissue. *SRY* gene mutation is a common cause of 46,XY reversal type 1 (OMIM: 400044)[5–7] and about 10%–15% of 46,XY female sex reversal patients with complete or partial gonadal dysplasia associated with loss of function mutation of *SRY* gene[8–12]. In the complicated biological process of sexual determination and differentiation, the *SRY* gene is the core role of many genes in a concert performance in an orchestrated way.[13] Therefore, it is of great significance to study the SRY gene to understand the physiological mechanism of human sex determination and the pathological mechanism of sex reversal. In this study, we proceed with a molecular genetic analysis of the *SRY* gene in a 46,XY female patient, expect to find out the pathogenic genetic factors.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

The research was approved by the Institutional Committee for the Protection of Human Subjects (Institutional Review Board of Sichuan Provincial Hospital for Women and Children), and the patient's parents signed the informed consent.

2.2 | Sample collection

Peripheral blood was collected from the patient and her parents and anticoagulated with heparin sodium and EDTA-Na_2, which store at 4℃ for use.

2.3 | Case report

The patient, who was raised as a girl, presented at our clinic for the first time at the age of 14 years with primary amenorrhea and absence of secondary sex characteristics. She was 156.5 cm tall, weighed 50.3 kg, and had a BMI of 18.8 kg/m^2. Her clinical manifestations were as follows: no abnormal in mental and motor development, fair and delicate skin, no beard, no Adam's apple, grade 2 development of both breasts, no pubic hair, no axillary hair, normal vaginal length, and no uterus touched by anal examination. Ultrasonography showed a 2.7 × 0.7 × 1.1 muscular echo in the pelvic cavity, which was suspected to be the primary uterus. Neither ovarian and accessories, testicular was found in the abdominal cavity, inguinal region or vulva. Moreover, bilateral adrenals and ureteral bladders abnormalities were not observed. The azoospermia factor (AZF) representative of Y chromosome microdeletion showed no abnormality. Magnetic resonance imaging (MRI) of the pituitary with plain scanning and enhancement showed no obvious abnormalities. The results of laboratory analysis were as follows: Testosterone was 0.10 nmol/L (reference value range was from 0.21 to 2.85), prolactin 1.59 nmol/L (reference value range 0.64–4.45), estradiol 18.35 pmol/L (reference value range 99.46–191.57), luteinizing hormone 22.6 IU/L (reference value range 1.70–8.60), follicle-stimulating hormone 79.82 IU/L (reference value range 1.50–12.40), Anti-Muller-tube hormone <0.43 pmol/L (the reference value range for women is 0.43–128.52), and cortisol 567 nmol/L (reference value range 186.11–627.78). The results of thyroid hormone showed no abnormalities. Her parents were nonconsanguineous, and there was no remarkable family history and genetic disorder history. Both parents were 25 years old when the patient was born, and the mother did not show any abnormalities during pregnancy. The patient was born naturally at 38 weeks and 5 days, with a birthweight of 3,200 g and a length of 50 cm.

2.4 | Analysis of karyotype and fish

Chromosomes were prepared, and karyotype analysis was proceeded by conventional techniques.[14] The chromosomes X and Y were confirmed with probes specific for the centromeres of the chromosomes X and Y[15] (CEP X with spectrum green and CEP Y with spectrum red,from Jinpujia company). The FISH test was performed with lymphocyte cultured as per the manufacturer's instructions.

2.5 | DNA extraction

According to the manufacturer's instructions, blood genomic DNA was extracted from EDTA anticoagulated blood using the Qiagen QIAamp DNA Blood Kit (Qiagen Company). DNA was qualified when the DNA concentration was above 20 ng/uL, and the ratio value of OD260/280 ranged from 1.8 to 2.0, determined by Nanodrop 1C spectrophotometer (Thermo Scientific Company).

2.6 | Detection of the sry gene by QF-PCR

The STR of the SRY gene was detected by a multi-STR of chromosome 13/18/21/X/Y genotyping kit (fluorescence PCR capillary electrophoresis method) (Guangzhou Darui Company) as per the manufacturer's instructions. 10–20 ng DNA was taken for multiple PCR amplification. The forward primer of the SRY gene is 5′-AGTAAAGGCAACGTCCAGGA-3′, and the reverse primer is 5′-TTCCGACGAGGTCGATACTT-3′. The product length of the SRY gene was 248 bp. The 5′ end of the forward primer is labeled with VIC green fluorescence. PCR amplification conditions were as follows: a cycle of 95°C for 5 min; 25 cycles of 95°C for 30 s, 58°C for 40 s, 72°C for 50 s, and a cycle of 72°C for 10 min. Amplification products were detected by capillary electrophoresis with ABI 3500Dx genetic analyzer, and data were analyzed by ABI GeneMapper software.

2.7 | Sequencing of whole exome with NGS

Exome captured sequencing library was produced from NimbleGen SeqCap EZ MedExome kit. All exomes were prepared by fragmenting 1 μg of DNA using sonication technology followed by end-repair and adapter ligation, including incorporating Illumina TruSeq index barcodes. The library was subsequently sequenced by a 2 × 150 bp double-ended method on an Illumina Novaseq 6,000 high-throughput sequencer according to the manufacturer's instructions. The data of sequencing were analyzed by Polyphen-2, SIFT, and Mutation Taster software.

2.8 | *SRY* point mutation was verified by PCR combined with sanger sequencing

Sanger sequencing was adopted to verify the results of point mutations of the SRY gene after high-throughput sequencing. First, a 10 ng DNA template was taken for PCR amplification with a pair of specific primers (Forward Primer: 5′-GCATTCATCGTGTGGTCT-3′, Reverse primer: 5′-TTCTTCGGCAGCATCTTC-3′, primers were synthesized by Shanghai Biotechnology Company). Amplification conditions were as follows: a cycle of 95°C for 10 min; 35 cycles of 95°C for 30 s,58°C for 30 s,72°C for 30 s, and a cycle of 72°C for 7 min. The length of the product was 229 bp. Second, the PCR products were purified by ExosAP-IT. Third, sequencing PCR amplification was performed with purified PCR products. Amplification conditions were as follows: a cycle of 96°C for 1 min; 35 cycles of 96°C for 10 s, 50°C 5 s, and 60°C 4 min. Fourth, sequencing PCR products were purified with BigDye XTerminator Bead. Purified sequencing PCR products were detected by capillary electrophoresis with ABI 3500Dx genetic analyzer, and the sequencing data were analyzed by ABI Sequencing Analysis 5.2 software. The experimental operations were performed by referring to BigDye Direct Cycle Sequencing Kit and BigDye X-Terminator Purification Kit (Life Technologies Corporation) instructions.

2.9 | The online database resources used for analysis

The online database resources used for analysis mainly include the following: OMIM (https://omim.org/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), ClinGen (https://dosage.clinicalgenome.org/), Decipher (https://decipher.sanger.ac.uk/), HGMD (http://www.hgmd.cf.ac.uk/ac/index.php), gnomAD (https://gnomadhome.com/), UCSC (http://genome.ucsc.edu/index.html), SIFT (http://sift.jcvi.org), Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/), MutationTaster (http://www.mutationtaster.org/).

3 | RESULTS

3.1 | Confirmation of sex chromosomes

The sex chromosomes of the patient were confirmed as 46,XY by chromosomal karyotyping analysis of metaphase lymphocytes and FISH analysis of the specific fluorescence signal of X and Y chromosomes in interphase and metaphase lymphocytes. The chromosome karyotype of the patient, as shown in Figure 1. Figure 2 showed the result of FISH on the metaphase chromosomes. The sex chromosomes of the parents were consistent with their gender, and no abnormalities were observed.

3.2 | Results of sry gene measured by QF-PCR

The patient and her father's father-son relationship was proved by comparing STR loci of chromosomes. A specific SRY fluorescence peak, green fluorescence-labeled and length of 248 bp, was observed in the patient's electropherogram of sex chromosomes, as shown in Figure 3.

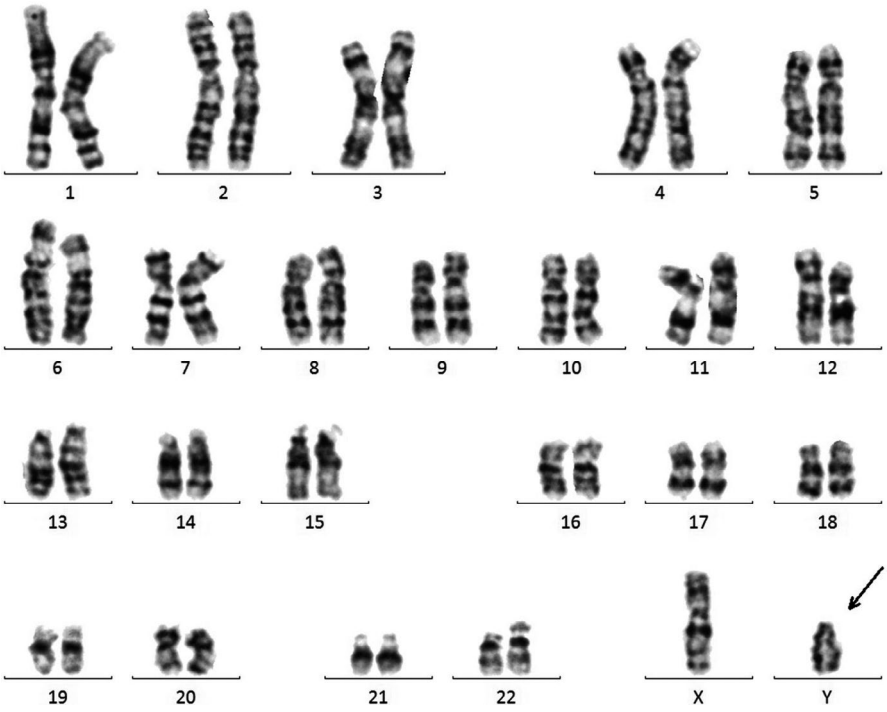

FIGURE 1 Chromosome karyotype diagram of 46, XY female patient. The arrow shows the Y chromosome

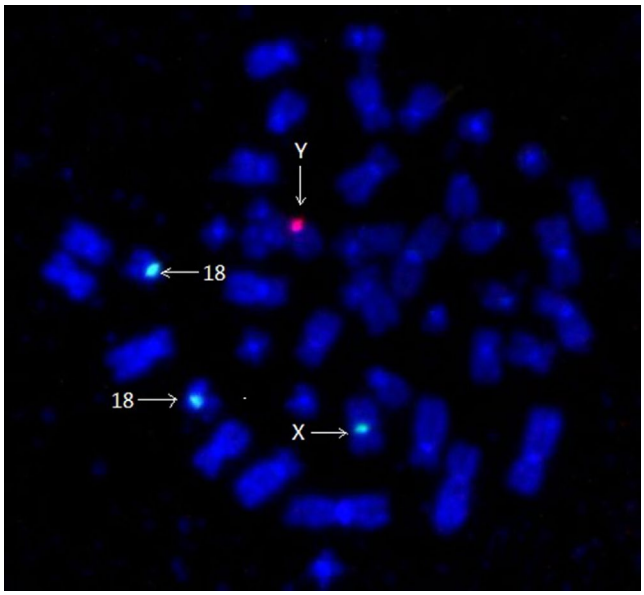

FIGURE 2 FISH picture of the patient in metaphase chromosomes. The chromosomes X, Y, and 18 are labeled by green, red, and blue signal, respectively, as the arrow indicated

3.3 | Results of exome high-throughput sequencing

The sequencing data volume was 17.61G, coverage rate 99.82%, specificity 70.98%, homogeneity 91.45%, >30X accounted for 92.17%, and average depth 161.44X. The data meet WES quality requirements. The gene mutation (HGVS) of chrY:2655352 (GRCh37) and SRY gene c.293G>A (p. Trp98ter) was found after analyzing the sequencing data with relevant software.

3.4 | Verification of mutation point in SRY gene by sanger sequencing

The SRY gene c.293G>A verified by Sanger sequencing was consistent with high-throughput sequencing. Furthermore, this patient base was different from his father's c.293G; namely, the patient's mutation was a de novo mutation not inherited from his father. The results of sequencing are shown in Figure 4.

3.5 | The result of the analysis of the mutation site

The analysis of multiple online databases and software shows that the hemizygote mutation of SRY gene c.293G>A located in the exon region is a nonsense mutation, resulting in the protein-coding termination position of tryptophan 98(p. Trp98ter). According to the ACMG genetic variation (2015 edition), the mutation is judged as pathogenic variation (PVS1+PS2+PM2+PP4). The pathogenic variation including in causing impaired protein function (PVS1), a de novo mutation with the disease and no family history (PS2), the mutation occurs at a shallow frequency in the average population (PM2), and the clinical phenotype is highly consistent with 46,XY reversal (PP4). After querying multiple databases

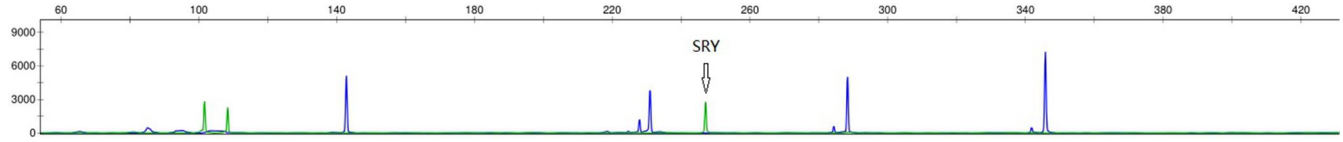

FIGURE 3 The electrophoretogram of sex chromosomes of the patient. Specific SRY fluorescence peak, green fluorescence-labeled, and length of 248 bp were observed in the electrophoretogram of sex chromosomes

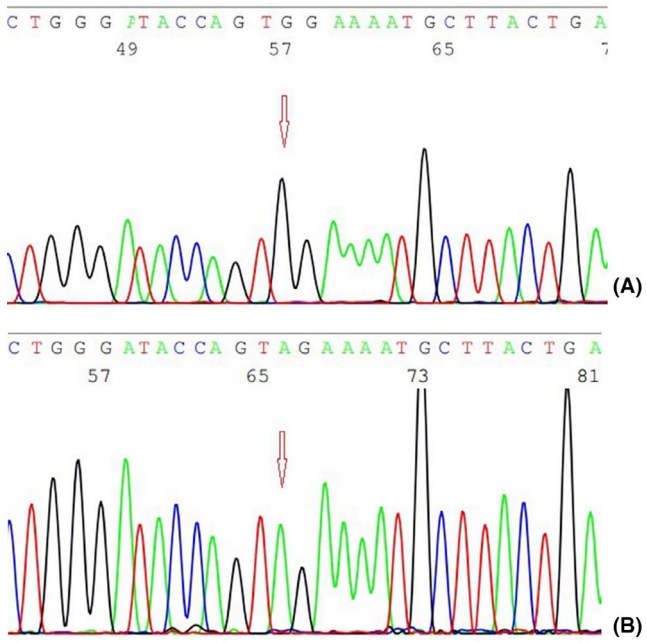

FIGURE 4 Sequence diagram of SRY gene by Sanger sequencing. The base of c.293 in the father's SRY gene sequence is G, and the patient is A, as shown in ⓐ and ⓑ indicated by the arrow, respectively

and previous literature, the SRY gene of c.293G>A (p. Trp98ter) mutation has not been reported, so it is a novel mutation.

4 | DISCUSSION

The SRY gene's mRNA full length is 828 bp (NM_003140. 3) with a single exon and coding protein containing 204 amino acids (NP_003131. 1). SRY protein contains an important domain, high mobility group box (HMG box), binding with DNA sequence.[5,11] HMG box, including 72 amino acids (from codon 59 to codon 130), a particular 3D structure of the "L" shaped consisted of three α-screw, is the structural basis of Sry binding activity. SRY gene sequence is highly conserved among mammals. If a base replacement, mutation, translocation, or deletion happens in the SRY gene of a 46,XY male, the SRY protein activity would be reduced or even inactivated, and he would be phenotypic of 46,XY female. HMG box is a hot spot mutation region of the *SRY* gene, and most of the mutations occurred in this region previously.

Our study analyzed the whole-exome sequence of a 46,XY female patient. The *SRY* c.293G>A (p. Trp98ter) was a nonsense mutation, also located in the HMG box. It was a pathogenic mutation judged by the 2015 ACMG standard. The patient's mutation was a de novo mutation because of nonpaternal origination by comparing their *SRY* gene sequences. The c.293 loci of *SRY* gene mutation has not been found in some online databases such as OMIM, HGMD, and reported literature, so the mutation of *SRY* gene c.293G>A (p. Trp98ter) is a novel one.

The SRY protein binds to the DNA sequence cored by AACAAAG, which can be recognized by T cell–specific DNA binding protein (TCF-1) in a sequence-dependent manner, and regulates its coding controlled genes[16,17]. The binding of SRY and DNA has specific characteristics of sequence and structure.[18] SRY binds to the particular target DNA sequence containing AACAAAG while contacting the minor groove of linear double-helix DNA, resulting in the structural rearrangement of both SRY protein and target DNA and the formation of sharp angle structure. If the target sequence DNA is distorted, the affinity between HMG-1 like protein and distorted site is higher than that of SRY and malformed site. The DNA sequence AACAAAG lost its binding ability to SRY, while the mutation occurred at the critical bases at the second, fourth, fifth, and sixth positions and appeared critical for this interaction. SRY protein activity is too weak to launch the male testicular development, leading to the XY female sex reversal[19,20]. Meanwhile, the change of amino acids in the SRY gene's coding region will prevent Sry protein from binding to DNA or reduce its affinity with DNA by 1 to 3 orders of magnitudes, eventually causing gonadal dysplasia[21,22]. Several nonsense mutations of SRY result in 46, XY female sex reversal reported previously. Such as, the mutation of A>T at base 684 in the open reading frame (ORF) changed lysine (AAG) into termination codon (UAG)[23], a new nonsense mutation of C>T at base 686 turned the glutamine coding codon (CAG) into the terminating codon (TAG).[24] The mutation of c.291C>T (the locus of c.291C>T in that paper is the locus of c.289C>T in NM_003140. 3) transformed glutamine codon (CAG) into termination codon (UAG) (Gln97X).[25]

A new mutation type of SRY gene (c.294G>A) turned the mRNA encoding the UGG of tryptophan 98 to the stop codon (UGA) (Trp98X),[26] and the mutation of c.293G>A also turned the mRNA encoding the UGG of tryptophan 98 to the stop codon (UAG) (Trp98X) in our study. However, the mutant base is different between the mutation of c.293G>A in our research and that of c.294G>A reported by Preeti Paliwal,[26] but both make the mRNA encoding the UGG of tryptophan 98 change into the termination codon (UAG and UGA) (Trp98X), and produce the truncated protein of the same length. Tryptophan at position 98 is located on the second α-helix of the HMG box, and the truncated protein may not be able to bind to DNA, resulting in the loss of function of the mutant. Theoretically, the molecular mechanism of the mutation of c.293G>A leading to the sex reversal of 46,XY females should be the same as that of c.294G>A.

Two different nuclear localization signals (NLSs), nNLS and cNLS, are located at both ends of the SRY HMG box. These two NLSs are also highly conserved in mammals, and their structural integrity is necessary for nuclear localization function[27–29]. Among the above nonsense mutations (including this study), each single-base substitution mutation formed one termination codon in the conservative HMG domain and translated it into a truncated protein of different lengths. All truncated proteins lacking cNLS neither be recognized by the nuclear input receptor protein IMPβ1 nor be located in the nucleus to bind to the target DNA.[30] Therefore, they would be nonfunctional or inactive protein products,[9,17,21] resulting in the male sex determination's failure to be switched. Clinically, the above patients with truncated proteins present 46,XY female phenotype.

Our report provides evidence for a pathogenic role of the SRY gene c.293G>A mutation in 46, XY female individuals and enlarges the spectrum of molecular diagnosis for such condition, which can also be associated with mutation of SRY, a recognized testis-determining gene.

ACKNOWLEDGMENT

This work was supported by the Research Funds of the Sichuan Provincial Commission of Health and Family Planning, Government of China (No. 16PJ385). The authors are grateful to the supporting of colleague of Molecular Genetics and Cytogenetics Group and Suzhou Basecare Medical Corporation Limited.

CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

AUTHOR CONTRIBUTIONS

Dr. Shengfang Qin conceived and designed the study, Xueyan Wang performed genetic counseling, and Yunxing Li was responsible for the patient's evaluation and diagnosis. Qin Shengfang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The article is original, resulting from further research conducted by a patient in the clinic. There is no controversy.

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How to cite this article: Qin S, Wang X, Li Y. A novel *SRY* pathogenic variant from a 46,XY female harboring a nonsense point mutation (G to A) in position 293. *Clin Case Rep*. 2021;9:e04706. https://doi.org/10.1002/ccr3.4706