Mutations in NR5A1 can appear in a wide spectrum from hypospadias, uncertain external genital structure, anorchia, gonadal dysgenesis to infertility, and completely female external genital structure. Detecting 'indel' mutations with analysis programs is still a challenging field in next generation sequence analysis. Especially variants greater than 20bp and heterozygous as in this case increase the possibility of giving false negative results in the targeted new generation sequence analysis analysis. In 46, XY DSD cases, even if molecular diagnosis is not made in the targeted NGS panel, repeating the molecular genetic analysis with Sanger sequence analysis in case of clinical strong suspicion may be necessary to make a diagnosis.

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A CASE OF GENDER DEVELOPMENTAL DISORDER WITH DIFFICULTY IN MOLECULAR DIAGNOSIS: NEW VARIANT IN NR5A1 GENE

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INTRODUCTION

Steroidogenic Factor-1" (SF-1); It is encoded by the NR5A1 gene in 9q 33.3 and regulates the transcription of genes involved in steroidogenesis. It is reported that 46 of the variants in this gene constitute 10-20% of XY sex development disorders (DSD).

AIM

We wished to share our experience of a case who presented with ambigus genitalia and was found to have NR5A1 mutation.

RESULTS

The patient admitted because of a swelling in the left groin at one month old. She was raised as female. She was Prader stage 3, single opening, phallus 1 cm, bilateral 0.5x0.5 cm ovoid gonads were palpated in the inguinal region.

Uterus was 12x2.5 mm in ultrasonography and the gonad in the inguinal region was evaluated as testis.

Laboratory values were FSH: 8.99 mIU/ml (N: 0.16- 4.1), AMH: 16.59 ng/ml (N: 39.1 - 91.1) Total testesterone: 50 ng/dl (N: 60 – 400). Serum electrolytes, glucose, ACTH, DHEA-S, 17-0H Progesterone were normal.

She was SRY (+) and XY was detected by QF-PCR. Chromosome analysis was 46XY (20 metaphases)

hCG stimulation test was unresponsive. Male urethra, utriculus, and ureter orifices were observed in cystoscopic examination. With an initial diagnosis of partial gonadal dysgenesis; no mutation was found with the targeted Next-Generation Sequence (NGS) analysis (Trusight One) panel. The gender development disorder council decided to raise the patient as a male with the parents.

	Values	Referance range	
		Male	Female
FSH	**8.99 mIU/ml**	0.16-4.1	0.24-14.2
LH	3.11 mIU/ml,	0.02-7	00.-7
Eastradiol	<20 pg/ml	<20	<20
Total testesterone	50 ng/dl	60-400	<10
Dihidrotestesterone	82.2 ng/dl	12-85	<3
Free testesterone	0.4 pg/ml	0.4-4.8	0.2-0.6
AMH	**16.59 ng/ml**	39.1-91.1	0.0-7.1
ACTH	21.4 pg/ml	6-48	
Cortizol	6.6 µg/dl	2.8-23	
DHEA-S	15.8 µg/dl	5-48	
17-OH Progesterone	0.9 ng/ml	0.13-1.06	

Her identity was changed at the age of 1 year and corrective operations were performed. Heterozygous c.1161_1232delinsGGTGACAAATAAGCAG (p. His387GlnfsTer161) variant was found in the repeated analysis of the NR5A1 gene with Sanger sequence analysis of the patient, who was thought to have SF-1 deficiency clinically. It has been shown that the variant, defined as de novo, can disrupt the protein structure with modeling programs and is pathogenic according to ACGM criteria.

CONCLUSIONS

Mutations in NR5A1 can appear in a wide spectrum from hypospadias, uncertain external genital structure, anorchia, gonadal dysgenesis to infertility, and completely female external genital structure. Detecting 'indel' mutations with analysis programs is still a challenging field in next generation sequence analysis. Especially variants greater than 20bp and heterozygous as in this case increase the possibility of giving false negative results in the targeted new generation sequence analysis analysis. In 46, XY DSD cases, even if molecular diagnosis is not made in the targeted NGS panel, repeating the molecular genetic analysis with Sanger sequence analysis in case of clinical strong suspicion may be necessary to make a diagnosis.

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