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Three Cases of NR5A1 Gene Mutations in DSD Patients

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Introduction:

Mutations in the NR5A1 gene, which encodes the steroidogenic factor 1 (SF1), are responsible for different phenotypes of DSD. So far, the apparent genotype–phenotype correlations in patients with NR5A1 mutations have not been found.

Methods:

Clinical examination, hormonal tests, ultrasound, laparoscopy and molecular analysis, including direct and parallel sequencing

Case 1

An 18-month-old 46XY patient brought up as a girl had female phenotype and Prader II virilization.
A small testis was detected in the right labial fold.

Hormonal tests showed: LH 0.25 IU/l, FSH 12.9 IU/l, Testosterone after hCG stimulation was 0.3 nmol/l.
Pelvic ultrasound and laparoscopy (Fig.1) revealed Mullerian structures and abdominal gonad on the left side. Histology is showed on Fig.2

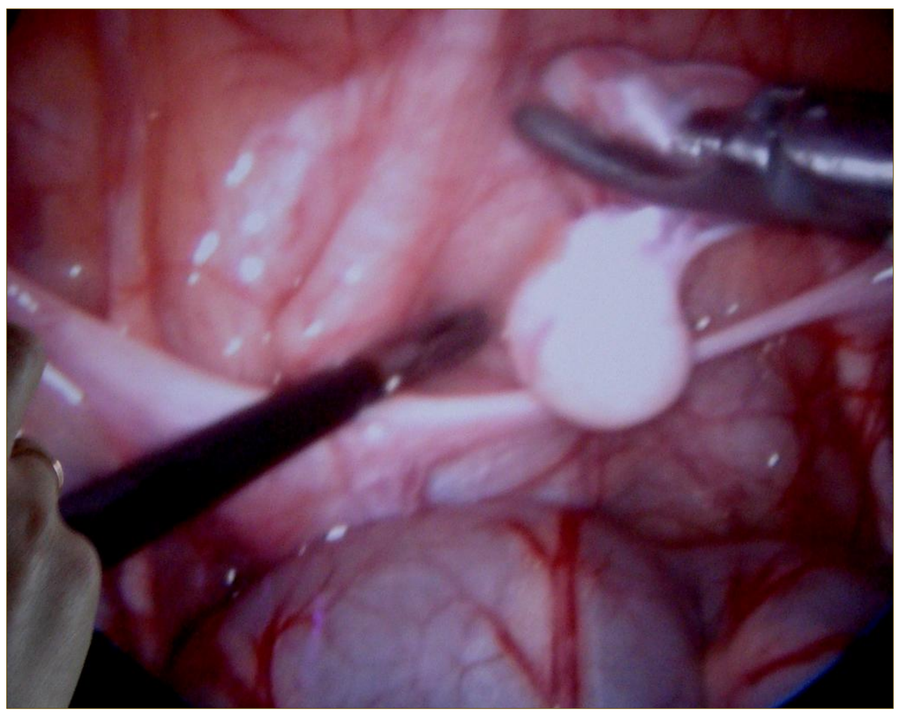

Fig.1. Laparoscopy image of Patient 1 shows uterus, fallopian tubes and a dysgenetic abdominal gonad .

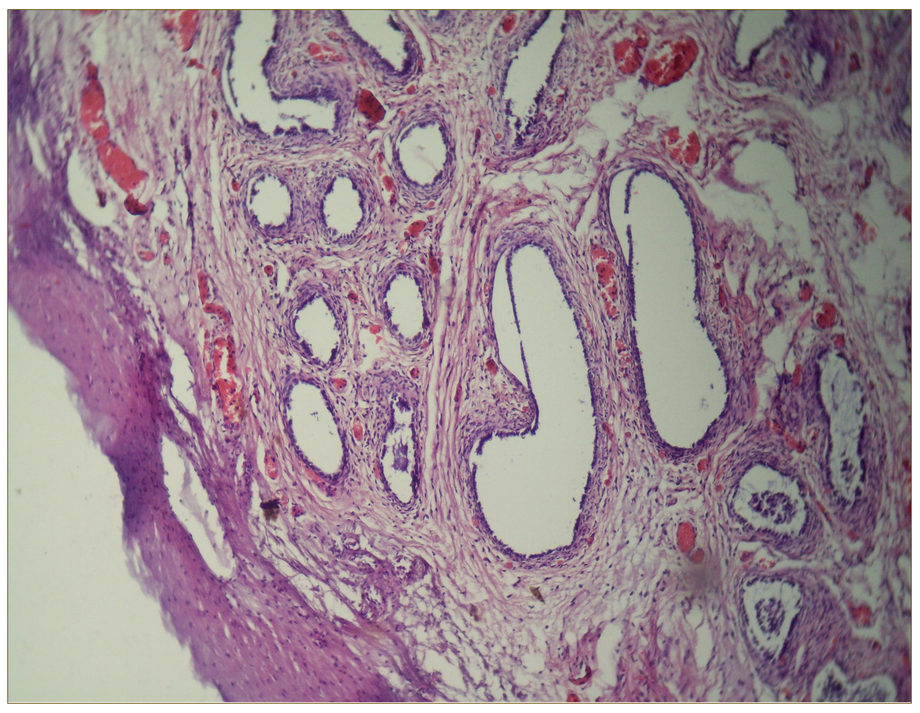

Fig.2 Histology (haematoxylin & eosin X 250) shows wide fibrocystic tubules with atrophic epithelium and calcification. (1). The element of ovarian stroma is shown (2)

Nonsense c.256delA // p.Arg89GlyfsX17 mutation in NR5A1 was detected

Case 2

A 46 XY patient, 5 months old, with ambiguous genitalia.

The left testis was found in labioscrotal fold and the right testis was not palpable.
There was no uterus in pelvic cavity. Urogenital sinus was detected (Fig. 3).

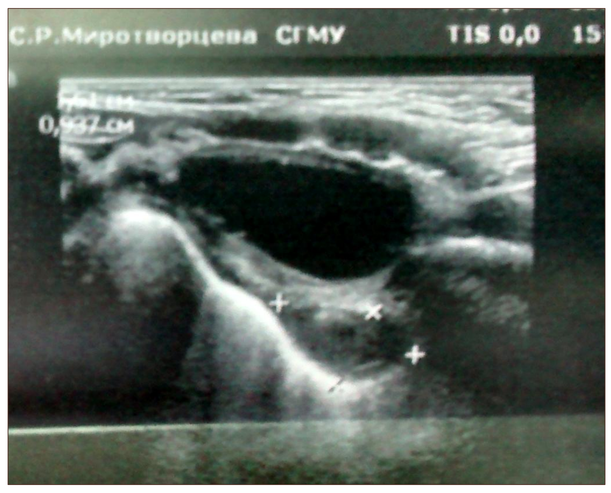

Fig.3 Ultrasound image of Patient 2. demonstrates urogenital sinus

Hormonal tests in mini-puberty showed:

LH 2.2 IU/l, Testosterone – 5.6 nmol/l,
FSH 5.0 IU/l and AMH – 43.8 ng/ml

The patient was assigned as a boy.

Molecular analysis excluded AR gene mutations and revealed heterozygous p.R313C mutation in NR5A1 gene.

Case 3

A 46XY boy, aged 16 months, had small testes in bifid scrotum, severe hypospadias and absent Mullerian structures.

Hormonal tests showed:
LH 2.2 IU/l , FSH 5.0 IU/l
hCG-test: Testosterone – 5.6 nmol/l, DHT – 0.3 nmol/

Mutations in 5ARD2 gene were not found and heterozygous p.S303R mutation in NR5A1 gene was revealed

Conclusions:

All three 46XY patients had heterozygous mutations in NR5A1 without adrenal insufficiency.
One patient had a nonsense mutation displaying female phenotype and severe gonadal dysgenesis with Mullerian structures. Two patients had missense mutations displaying underandrogenization with perinea hypospadias and small testes with impaired Leydig and Sertoli cells - partial gonadal dysgenesis.

Reference:

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