A CASE OF GONADAL DYSGENESIS DUE TO A NOVEL HOMOZYGOUS MUTATION IN NR5A1 GENE

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Conclusion:

We identified a novel homozygous mutation in the SF1 gene causing sex reversal with normogonadotropic hypogonadism and low adrenal androgens.

Background:

Steroidogenic factor (SF1, NR5A1) regulates multiple genes known to be involved in gonadal development, adrenal development, steroidogenesis, and gonadotroph development (1, 5). Heterozygous mutations in the NR5A1 gene have been described in association with mild to severe gonadal dysgenesis with or without adrenal failure (2, 3, 4). Homozygous mutations are rare and have also been described in association with gonadal dysgenesis with or without adrenal failure (6).

Case report:

History

We report a 18-year-old patient of normal female phenotype with absent breast development and primary amenorrhea. Stage of puberty was Tanner B1, PH 3. There was no axillary hair.
Karyotyping had been performed before presentation and revealed 46, XY. Pelvic ultrasound showed no mullerian structures and no gonads.

Clinical Course and Procedures

Substitution with estradiol was initiated and the dosage was increased over one year up to 2mg per day. Under treatment, our patient showed normal breast developement.
Because of low adrenal androgens, ACTH test was performed, which showed normal results for cortisol response (see laboratory results).
The patient decided to have vaginoplasty, and gonadectomy as well, because of tumor risk in complete gonadal dysgenesis. Surgery was performed without complications.

Laboratory Results

	E2 ng/l	Testo µg/l	LH IU/l	FSH IU/L	AMH µg/l	Inhibin B ng/l	Androstendion µg/l	DHEAS µg/dl	ACTH pg/ml	Cortisol µg/dl
Patient	<5,0	<0,025	6,58	34,8	<0,01	<10	<0,30	29,4	41,2	13,30 (basal) 22,8 (stimulated)
Father (age 59y)	20,7	3,44	5,77	5,08	3,35	77	1,14	279,0	31,4	6,06
Reference Range Females	12,4-341	0,084-0,481	2,4-95,6	3,5-21,5	1,22-11,7	15-200	1,3-4,3	65,1-368,0	7,2-63,3	2,47-19,5
Reference Range Males	7,4-42,6	1,88-8,82	1,7-8,6	1,5-12,4	1,43-11,6	95-323	1,3-4,3	70,2-492	7,2-63,3	2,47-19,5

Molecular genetics: Genetic examination was performed and revealed a novel homozygous mutation in the NR5A1 gene (c.1048C>T; p.Arg350Trp). This mutation has an allele frequency of < 0,0001 according to ExAC and gnomAD and has, to our knowledge, not been described in the literature. Prediction programs for a possible pathogenicity SIFT and PolyPhen classify this mutation as "deleterious" and "probably damaging". Both parents and one half-brother are heterozygous for this mutation and phenotypically normal and healthy.

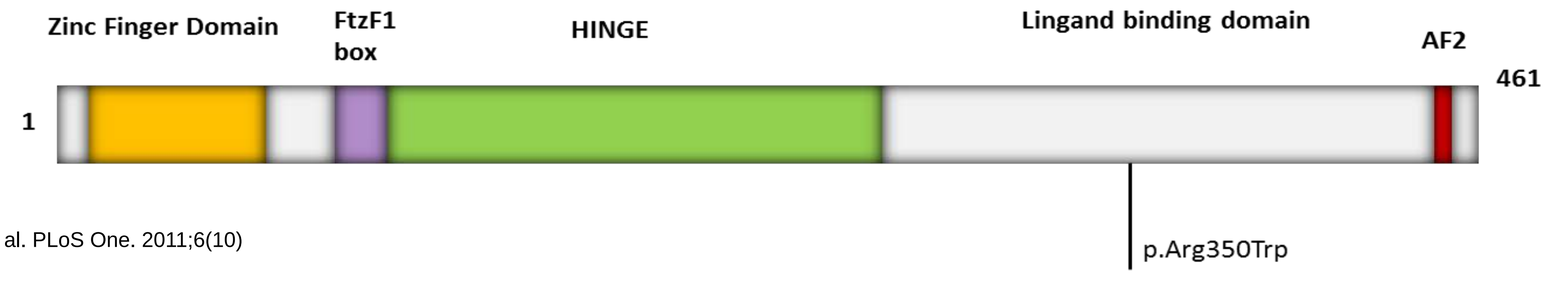

Figure adapted from Allali S et al. PLoS One. 2011;6(10)

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Disclosure Statement:

The authors have nothing to disclose