Clinical and Molecular Characteristics of Russian Patients with 46,XY DSD due to *NR5A1* Gene Mutations.

Natalya Kalinchenko[1] , Evgeniy Vasilyev[2], Vasiliy Petrov[2], Anatoly Tiulpakov[2]

[1]Institute of Pediatric Endocrinology, [2]Department and Laboratory of Inherited Endocrine Disorders, Endocrinology Research Centre, Moscow, Russian Federation.

Background: Steroidogenic factor 1 (encoded by the *NR5A1*gene) is a transcriptional regulator of genes involved in gonadal development and steroidogenesis. Mutations in *NR5A1* have been identified among the most frequently identified genetic causes of disorders of sex development (DSD).

Objective: To report the clinical phenotype of 31 patients associated with 17 novel and 9 previously described *NR5A1* sequence variants identified in Russian patients with 46,XY DSD.

Methods: Molecular genetic analysis using a custom Ion AmpliSeq next generation sequencing 'DSD' panel was performed in 280 subjects with DSD 46,XY. NGS results were confirmed by Sanger sequencing.

Results: Among 280 patients with 46, XY DSD *NR5A1* variants were found in 31 patients (11%).
We identified 28 pathogenic variants, including 17 novel (Table 1) and 11 previously reported. 27 patients presented with abnormal genitalia at birth, 7 of whom had only slightly enlarged clitoris and gonads in labia majora. 11 patients were assigned at birth as males. 3 patients with completely female external genitalia at birth were diagnosed at puberty due to profound masculinization. None of them had Mullerian derivatives. The previously described NR5A1allelic variants c.102+1G>T and R313C were identified in two of them and a novel H24Q mutation was found in the third one. The mutation R313C was also found in the other three patients with severe undervirilized external genitalia (EMS 3-5). Only 1 of the patients showed transient adrenal insufficiency during infancy. Four of our patients, who were registered as males went through puberty with normal spontaneous virilization, adequate testes volume and penile enlargement. Two of them (age 14 and 15 y) at present have gonadotropin levels within normal range, and the other two (21 y and 25 y) showed slightly elevated FSH level, upper normal level of LH and lower normal level of testosterone. DNA analysis in these 4 cases showed 2 previously described (R84H and R313H) and 2 novel (G321V and c.951delC) variants in *NR5A1* gene. Among 20 patients with female assignment at birth 18 underwent bilateral gonadectomy and in 2 cases gonads were left for the follow-up. During laparoscopic procedure Mullerian derivates were found in four patients. Most our patients are still in prepubertal age and will be followed further.

Table 1 Cases with novel mutations in the *NR5A1* gene.

	Sex	External genitalia	Mullerian derivatives	Mutation	Testis position	puberty
1	f	Prader 3	no	E425_V426del	inguinal	
2	f	Prader 4		c.1139-1G>T	in labia majora	
3	f	Prader 3	uterus remnant	P224L	inguinal	
4	m	EMS* 7	no		inguinal|/ in scrotum	
5	m	EMS 9	no	G321V	in scrotum	normal
6	f	Prader 2	no	L245fs	inguinal	
7	f	Prader 3		c.245-1G>T	inguinal	
8	f	Prader 2	uterus remnant	N385fs	inguinal	
9	f	Prader 3		L245fs	in labia majora	
10	m	EMS 7		Y25X	in scrotum	
11	f	Prader 3		G35D	inguinal	
12	f	Prader 4	uterus remnant	S342L	in labia majora	
13	f	Prader 3	no	T335P	inguinal	
14	m	EMS 8		Y197X	in scrotum	
15	f	Prader 4	no	c.103-3C>A	in labia majora	
16	f	Prader 2		H24D	in labia majora	
17	f	normal	uterus remnant	H24Q	inguinal	masculinization

***External musculinization score**

Conclusion. Mutations in NR5A1 gene were found in 11% cases of 46 XY DSD and 17 novel pathogenic variants were identified in our cohort. Our results contribute to the better understanding of diverse phenotypes associated with alterations in the *NR5A1* gene.

References

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