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Large spectrum of DSD phenotype caused by pathogenic variants in Wilms tumor suppressor gene 1

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Introduction and Objective

The Wilms tumor suppressor gene 1 (*WT1*) plays an essential role in urogenital and kidney development. Heterozygous germline mutations in *WT1* have been classically associated with Denys–Drash (DDS) and Frasier syndrome (FS). Exonic missense mutations in the zinc-finger region are the cause of DDS. Mutations affecting the canonic donor KTS splice site of intron 9 are the cause of FS. New phenotypes, as 46,XX testicular DSD, associated with *WT1* variants have been disclosed with the development of massive parallel sequencing.

The objective of this review is a retrospective analysis of phenotype and genotype correlation of seven patients with pathogenic *WT1* variants.

Methods

Description of seven patients with heterozygous pathogenic variants in *WT1*. The molecular analyses were performed both by Sanger and by massively parallel sequencing targeted DSD-associated gene panel using Illumina Platform.

Results and Conclusions

Five patients, four with 46,XY karyotype and one with 46,XX karyotype, were initially evaluated by atypical genitalia with range chronological age between three to sixteen months. Two 46,XY patients with normal female genitalia and primary amenorrhea at the age of 15. Three 46,XY patients underwent a bilateral gonadectomy, and germ cell tumors (*in situ* gonadoblastoma and unilateral dysgerminoma) were identified in two patients. One showed partial gonadal dysgenesis and the other, complete gonadal dysgenesis. Both of them, presented intronic variants affecting splicing of *WT1* exon 9, the c.1432+4C>T and the c.1432+5G>A, respectively. Two pathogenic *WT1* variants, the c.742A>T (p.Lys248*) and the c.1419T>A (p.His473Gln) were identified in two patients with 46,XY. In those patients, Wilms tumors were diagnosed at early age (four and six months). Nephrotic proteinuria was diagnosed in four of six 46,XY patients. Three of them underwent renal transplantation at seven, eight and 24 years old. The novel c.1453_1456del (p.Arg485Glyfs*14) variant in *WT1* was identified in a 46,XX testicular DSD patient.

Pathogenic allelic variants in *WT1* were associated with a broad spectrum of urogenital abnormalities. In patients with 46,XY gonadal dysgenesis and variants in *WT1* it is mandatory to actively investigate the presence of glomerulopathy. In addition, variants in *WT1* could be the rare cause of 46,XX testicular.

Phenotype and genotype of patients with DSD and pathogenic variants identified in *WT1*

Patient	1	2	3	4	5	6	7
Age at first evaluation	2 yo	13 yo	14 yo	17 yo	4 mo	3 mo	1 yo
External genitalia	atypical	atypical	female	female	atypical	atypical	atypical
Age at proteinuria diagnoses	7 yo	13 yo	1 yo	5 yo	14 yo	8 mo	absent
Renal Biopsy	FSGS*	FSGS*	FSGS*	FSGS*	Multifocal nephroblastoma	Multifocal nephroblastoma	Not performed
Age at renal transplantation	Not performed	24 yo	15 yo	8 yo	Not performed	Not performed	Not performed
Gonadectomy	Not performed	Atrophic testes Bilateral Gonadoblastoma *in situ*	Not performed	Dysgerminoma in right gonad	Performed –testes	Gonadal biopsy –testes without germ cell neoplasm	Bilateral testes with seminiferous tubules containing Sertoli cells with rare germ cells
Karyotype	46,XY	46,XY	46,XY	46,XY	46,XY	46,XY	46,XX
Allelic variant	c.1432+4C>T	c.1432+4C>T	c.1432+5G>A	c.1432+5G>A	c.742A>T (p.Lys248*)	c.1419T>A (p.His473Gln)	c.1453_1456 del (p.Arg485Glyfs*14)

* Focal Segmental Glomerulosclerosis (FSGS)