**A de novo missense mutation in the 4th zinc finger of the WT1 gene causes 46,XY and 46,XX DSD in two sibs**

Rita Bertalan MD PhD, Baldzs Gellén MD PhD, Caroline Eozenou PhD, Kenneth McElreavey PhD, Anu Bashamboo PhD

1. Semmelweis University, Budapest, Hungary, 2. University of Szeged, Szeged, Hungary, 3. Inisitut Pasteur, Paris, France

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**Sister 46,XX ovotesticular DSD**

- Hungarian girl born with Prader IV intersex genitalia
- Karyotype: 46,XX, SRY-negative
- Hormonal androgen levels were elevated and congenital adrenal hyperplasia was excluded.
- At three months of age explorative laparotomy identified the uterus and two macroscopically undifferentiated gonads.
- Histology identified testicular tissue in both gonads.
- At six months of age she had a feminization genitoplasty.
- At age of 12 revealed adrenal hyperplasia was excluded.
- Identified a uterus and two macroscopically undifferentiated gonads.
- A de novo missense heterozygote mutation of the highly conserved fourth zinc-finger of WT1 (Wilms' Tumor Suppressor I) (p.Arg495Gly) was revealed by exome sequencing in both sibs.
- Normal ploidy was established by qPCR. There were no other potentially pathogenic mutations in known sex-determining genes.

**Brother 46 XY, DSD: Meacham syndrome**

- Her brother was born 14 years later.
- At birth; male external genitalia, but testes were not palpable.
- Emergency surgery for a diaphragmatic hernia.
- Karyotype was 46,XY, SRY positive.
- At 2 years of age laparoscopy revealed a rudimentary testis on the right side, orchidectomy was performed on the left side.
- Histology: not find any testicular tissue only pieces of funiculus spermaticus and epididymis tissue.
- At age 9 his FSH: 0.6 IU/L, LH <0.11 IU/L, Te < 0.43 nmol/L, E2 < 92 pmol/l hormone levels were in prepubertal range.

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**WT1 gene structure**

- Two different isoforms of WT1 (+KTS and -KTS) have distinct functions during gonad development. The -KTS isoform binds the promoter of SRY and NR5A1, whilst +KTS binds RNA and increases the stability of SRY transcript.

**WT1 gene mutations**

In the human:

- Heterozygous gene deletions: WAGR syndrome (Wilms' tumor, aniridia, genitourinary anomalies, and intellectual disability (1))
- Heterozygous missense mutations:
  - Denys-Drash syndrome: gonadal dysgenesis, nephropathy, and Wilms tumor (2,3)
  - Meacham syndrome: congenital diaphragmatic abnormalities, genital defects and cardiac malformations (4)
  - Donor splice site mutations at the exon 9 (with a change in the ratio of the KTS+/KTS– ratios): Fraser syndrome: cryptophthalmos, syndactyly, and abnormalities of the genitalia and urinary tract (5)

**Gonadal dysgenesis had been associated with the 46,XY, Eozenou has identified first time the same mutation in WT1, associated with 46,XX TDSD (6)**

**Conclusion I**

This is the first time that mutation has been identified in the last zinc finger of WT1, in a girl with ovotesticular DSD and her brother with 46,XY gonadal dysgenesis and hernia diaphragmatic.

**References**

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6. Eozenou et al., DOI: 10.3252/pso.eu.57ESPE.2018
7. Bandiera et al., 2015, Mol and Cell Endo

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**Conclusion II**

These cases confirm that mutations involving WT1 can impact on the development of both the testis and the ovary and that WT1 mutations can result in Meacham syndrome.

**References**

1. Gessler et al., 2007, Am J Med Genet A
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