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

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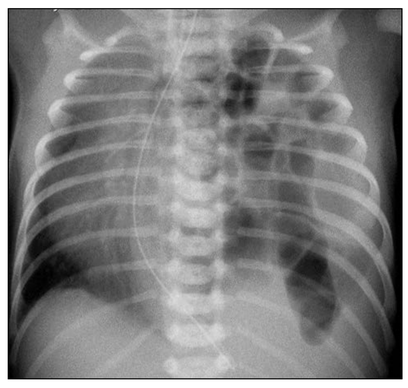
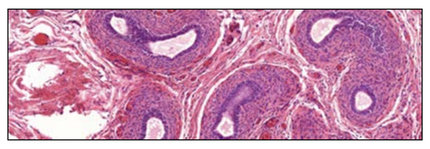
Sister 46,XX ovotesticular DSD

- Hungarian girl born with **Prader IV intersex** genitals
- Karyotype: **46,XX, SRY-negative**
- Hormonal androgen levels were elevated and congenital adrenal hyperplasia was excluded.
- At three months of age explorative laparotomy identified a 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 **ovotestis in both** she underwent a bilateral gonadectomy and histological examination **gonads**

Brother 46 XY,DSD: Meacham syndrome

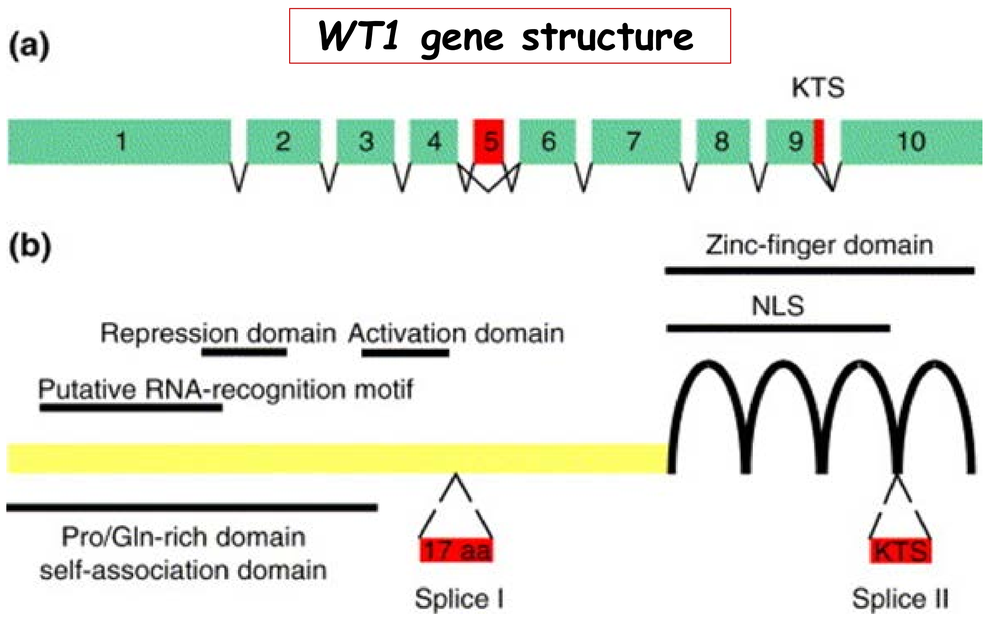




- Her brother was born 14 years later.
- At birth: **male external genitalia, but testes were not palpable**
- Emergency surgery for a **diaphragmatic hernia**
- Karyotype was 46,XY, SRY positive
- At 2 years of age laparoscopy:
  a rudimentary testis on the right side.
  orchidectomy was performed on 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

A *de novo* missense heterozygote mutation of the highly conserved fourth zinc-finger of *WT1* (*Wilms' Tumor Suppressor 1*) (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.

WT1 gene structure



Englert *et al.*, 1998, *Trends in Biochemical Science*

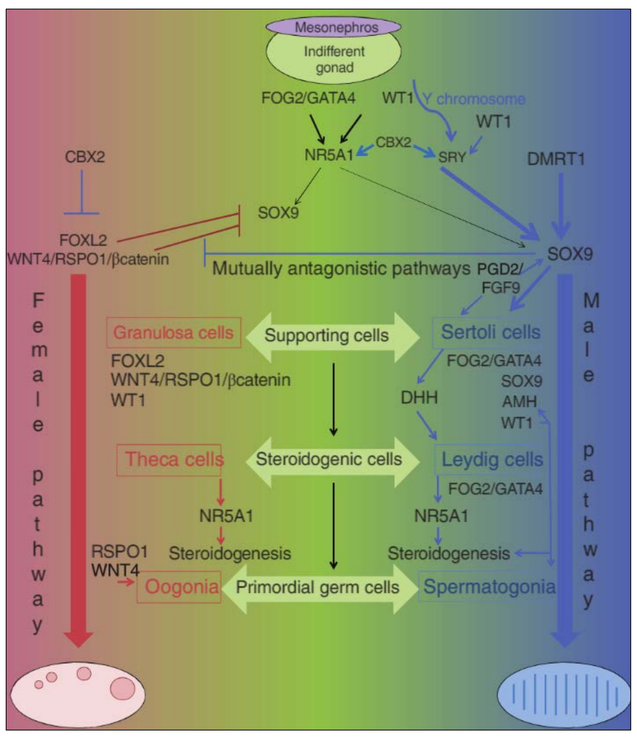
WT1 gene mutations

In the human:

- ***Heterozygous gene deletions*: WAGR syndrome** Wilms' tumor, anirida, 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): **Frasier 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)

Differentation of the gonads and *WT1*

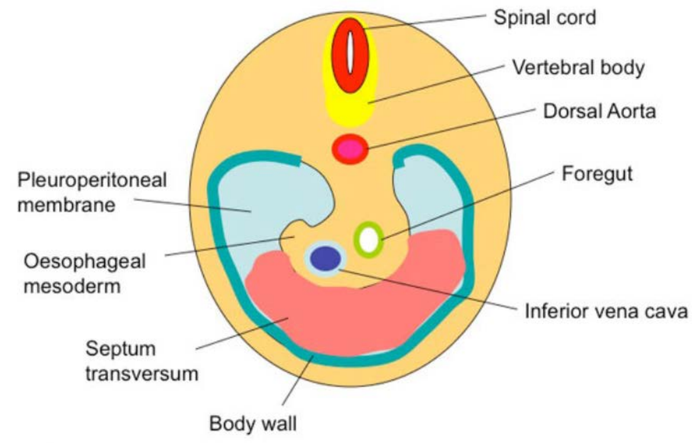


Bashamboo *et al.*, 2017, *Clin Genet*

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 (7).

Genesis of the diaphragm and *WT1*

Congenital diaphragmatic hernia (CDH) is a common class of congenital birth defects, which is associated with significant morbidity and mortality due to associated pulmonary hypoplasia, pulmonary hypertension and heart failure.



https://embryology.med.unsw.edu.au/embryology/index.php/File:Diaphragm_components.jpg

The transient pleuroperitoneal fold arise from the posterior body wall, and appears in late week 4 and is present until week 6. The affected genes identified in CDH patients include transcription factors, such as **GATA4, ZFPM2, NR2F2** and **WT1** and signaling pathway components, including **members of the retinoic acid pathway** (8).

Conclusion I

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

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

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Sex differentiation, gonads and gynaecology or sex endocrinology

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Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018

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