Denys-Drash syndrome (DDS)

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Identity

Other names
Drash syndrome
Wilms tumor and pseudo- or true hermaphroditism
Nephropathy, Wilms tumor, and genital anomalies

Note
Meacham Syndrome (OMIM # 608978) is an allelic disorder with some clinical features overlapping plus cardiac and pulmonary malformations.

Inheritance
To date about 150 patients with DDS have been described and its prevalence is largely unknown (Mueller 1994). The inheritance pattern is autosomal dominant, but most reported cases resulted from a de novo mutation in germline cells or in earlier phases of embryonic development as postzygotic somatic event (Coppes et al.1992).

Cytogenetics
Deletion or chromosomal rearrangements of 11p13 critical region are rarely reported: only 1 DDS case was found carrier of 11p13-p12 deletion and none with Frasier Syndrome (Jadresic et al.1991). However cyogenetic deletion involving 11p11 and 11p13 are described in sporadic Wilms Tumor and in Wilms tumor in association to WAGR (Wilms tumor, aniridia, genitourinary anomalies and mental retardation) Syndrome (OMIM #194072).

Genes involved and proteins

<table>
<thead>
<tr>
<th>Gene-phenotype</th>
<th>Denys-Drash syndrome</th>
<th>Frasier Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denys-Drash syndrome</td>
<td>46,XY DSD: gonadal dysgenesis and external ambiguous genitalia (without uterus)</td>
<td>46,XY partial DSD: gonadal dysgenesis and normal external genitalia (with uterus)</td>
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<tr>
<td>Frasier syndrome</td>
<td>Diffuse mesangial sclerosis</td>
<td>Focal segmental sclerosis</td>
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<td>Meacham syndrome</td>
<td>0-3 years</td>
<td>10-20 years</td>
</tr>
<tr>
<td>Mesothelioma, somatic</td>
<td>156240</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome, type 4</td>
<td>256370</td>
<td></td>
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<tr>
<td>Wilms tumor, type 1</td>
<td>194070</td>
<td></td>
</tr>
</tbody>
</table>

Comparison between Denys-Drash and Frasier Phenotypes.
**WT1 (Wilms’ tumor suppressor gene)**

**Location**
11p13

**Note**
WT1 gene encodes for a DNA-binding protein including four zinc-finger motifs at the C-terminus and a proline/glutamine-rich DNA-binding domain at the N-terminus. It acts as transcriptional modulator that has an essential role in the normal development of the urogenital system. This gene has a biallelic, and monoallelic expression from the maternal and paternal alleles in different tissues.

**DNA/RNA**

**Description**
10 exons, extending for 48 kb of genomic DNA.

**Transcription**
Alternative splicing at two sites results in four major different zinc finger protein isoforms (molecular weights of between 52 and 54 kDa).

**Protein**

**Description**
Alternative splicing at the two sites generates 4 different isoforms, respectively either including or excluding exon 5 and including or excluding three amino-acids - lysine, threonine and serine (KTS positive or negative isoforms). The KTS isoforms are highly conserved throughout evolution, indicating a very biological important function.

**Expression**
Kidney, ovary, testis, liver, heart and hematopoietic cells.

**Localisation**
Mainly nuclear, depending on the different isoforms.

**Function**
WT1 mediates transcriptional activation and/or repression of several gene targets. It particular seems to directly synergize with SFI participating to steroidogenesis and in sexual differentiation by regulating expression of the polypeptide hormone Mullerian inhibiting substance. In addition WT1 plays a key role in podocyte gene-expression and subsequently in podocyte differentiation (Nachtigal et al 1998; Lefebvre et al. 2015).

**Mutations**
Denys-Drash WT1 mutations are clustered particularly in the exons encoding ZF2 and ZF3 in and behave as dominant negatives. Most WT1 mutations in rasier patients affect the exon 9 donor splice site resulting in a functional imbalance of WT1 +KTS isoforms, as detected on dysgenetic gonads by RTPCR (Klam et al.1998; Haber et al.1991). In addition transcriptional profiling of mice lacking the WT1 alternative splice isofrom (+KTS) seems to have a more restrictive podocyte set of genes whose expression depends on these alternatively spliced isoforms (Klamt et al 1998; Lefebvre et al. 2015).

**References**


This article should be referenced as such: