

# Cancer Prone Disease Section

## Mini Review

### Frasier syndrome (FS)

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Published in Atlas Database: May 2007

Online updated version: <http://AtlasGeneticsOncology.org/Kprones/FrasierID10035.html>

DOI: 10.4267/2042/38485

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#### Identity

**Inheritance:** Sporadic occurrence, with possible cases of autosomal dominant inheritance

#### Clinics

##### *Phenotype and clinics*

Clinical presentation usually occurs between 2nd and 3rd decades; most cases at puberty.

- Exceptional cases in younger children; youngest example at 6 months of age.

Male pseudohermaphroditism; phenotypically female patients presenting with amenorrhea.

- XY karyotype:

- Streak (dysgenetic) gonads with gonadoblastoma.

- Normal external female genitalia; clitoris enlargement and ambiguous genitalia may be present.

- Small uterus (often with an inactive/atrophic endometrium) and fallopian tubes.

Nephrotic syndrome with slowly progressing renal disease, resulting in end-stage renal failure.

- Focal and segmental glomerulosclerosis; in later stages of renal disease, only chronic, nonspecific findings may be present in kidney biopsy.

XX karyotype: patients with less severe phenotype, frequently not clinically identified as FS.

- Normal and functioning female genitalia.

- Clinically present only with renal disease.

##### *Neoplastic risk*

Gonadoblastomas are present in virtually all XY patients; usually bilateral.

Germ cell tumors (dysgerminomas) may arise from gonadoblastoma within dysgenetic gonads.

Wilms tumors are exceptional, and in these cases the diagnosis of FS is controversial (differential diagnosis with Denys-Drash syndrome; vide infra).

##### *Treatment*

Prophylactic bilateral gonadectomy (may be laparoscopic if there is no evidence of overgrowth by a germ cell tumor); hysterectomy is not necessary.

The renal disease is usually steroid-resistant, requiring dialysis and renal transplantation.

Chemotherapy may be needed in cases with germ cell tumors.

In XY patients, menstruation can be induced with cyclic hormone replacement therapy; there are reported cases of successful pregnancy following in vitro fertilization procedures in these patients.

##### *Evolution*

The end-stage renal disease is usually the major cause of morbidity in FS patients. The focal and segmental glomerulosclerosis progresses slowly (often for more than 10 years) and leads to terminal renal failure, requiring dialysis therapy and renal transplantation which can result in complications and increased morbidity. There are limited data regarding the clinical outcome after renal transplantation in these patients. The occurrence of germ cell neoplasia in FS patients can affect their prognosis. However, there is no evidence that FS-associated germ cell tumors have a different clinical outcome in comparison with sporadic tumors.

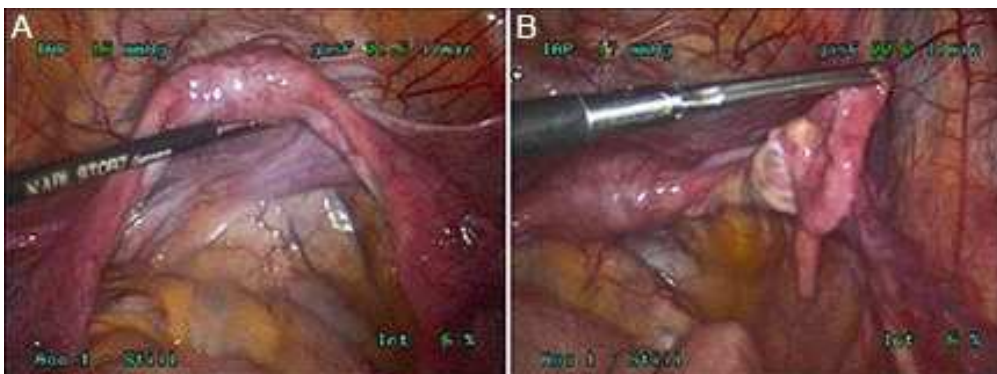


Figure 1. Surgical appearance of the internal genitalia in a patient with Frasier syndrome. A) Small but normally shaped uterus. B) A streak gonad is seen at the tip of the surgical instrument (courtesy of Dr. Masoud Azodi, Yale University School of Medicine).

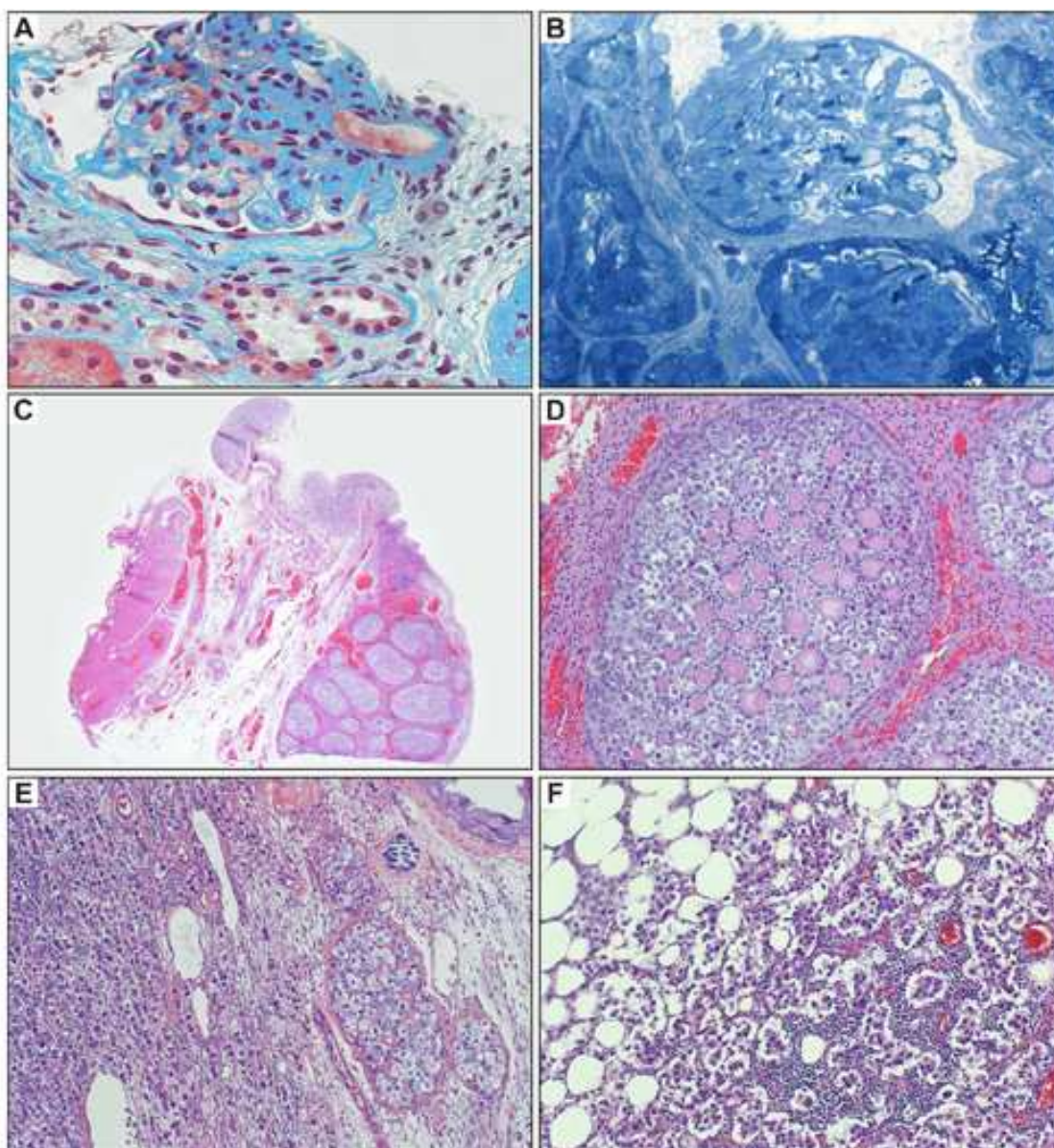


Figure 2. A-B: Kidney biopsy showing focal and segmental glomerulosclerosis (FSGS). A: Masson trichrome stain (400X). B: Semi-thin section stained with toluidine blue (400X). C-D: Gonadectomy specimens. C: Streak gonad with gonadoblastoma (H & E 40X). D: Gonadoblastoma nodule displaying Call-Exner body-like structures, surrounded by Leydig-like cells (H & E 200X). E-F: Histological aspect of dysgerminoma arising in gonadoblastoma. E: Gonadectomy specimen showing both, gonadoblastoma and dysgerminoma (H & E 100X). F: Peritoneal metastasis of dysgerminoma (H & E 200X).



## Genes involved and Proteins

### WT1 (Wilms Tumor 1)

**Location:** 11p13

#### DNA/RNA

Description: 10 exons; spans approximately 50 kb. Encodes 4 zinc finger domains.

Transcription: Alternative splicing in two different sites (exons 5 and 9) leads to variable insertion of exon 5 and/or insertion of 9 nucleotides in exon 9, resulting in transcription of four different isoforms.

#### Protein

Description: Transcription factor: contains 4 zinc finger domains.

Four different isoforms, ranging from 52 to 54 kDa (429-449 aminoacids).

Alternative splicing in exon 9: variable insertion of aminoacids lysine (K), threonine (T) and serine (S) between 3rd and 4th zinc fingers results in either +KTS or -KTS isoforms.

Expression: During embryonal life, the WT1 protein is mainly expressed in the metanephros and developing kidney, gonadal ridges, coelomic surfaces, heart, spleen, liver, thymus, uterus and muscles of the abdominal wall.

An adequate ratio of +KTS/-KTS expression is essential for the wild type function of WT1.

Localisation: Nuclear (transcription factor function).

Function: WT1 functions mainly as a transcription factor, with many different downstream target genes; a post-transcriptional regulatory function of some target mRNAs has been also proposed.

In mammalian embryos, expression of the -KTS isoform induces gonadal ridge formation through proliferation of the coelomic epithelium, resulting in the bipotential gonad.

In XY individuals, expression of the +KTS isoform will activate the transcription of the SRY gene located on Y chromosome, which induces the expression of anti-mYllerian hormone by the developing Sertoli cells. Expression of the anti-mYllerian hormone in the developing testis results in formation of seminiferous cords, allowing sex-specific gonadal development, and regression of mYllerian structures (which give rise to the female genitalia).

During early kidney development in mammal embryos, the -KTS isoform promotes proliferation of the primordial mesenchyme, epithelial-mesenchymal interactions and ureteric bud branching. In later phases of kidney development, expression of +KTS leads to differentiation of podocytes and glomerular capillaries.

#### Mutations

Most of the WT1 gene mutations in FS are located in positions 2, 4, 5 or 6 of the second splice donor site in intron 9.

These mutations lead to a decrease in the +KTS isoform, affecting the zinc fingers' DNA binding affinity.

A decrease in +KTS is in keeping with the phenotype observed in FS, in which there seems to be a defect in antimüllerian hormone expression resulting in abnormal genital development in XY individuals. Also, defective expression of this isoform could explain the glomerular lesion observed in FS.

## To be noted

The classical clinical picture of FS is that of a phenotypically female adolescent patient presenting with either amenorrhea or nephrotic syndrome, or both. However, the clinical presentation may be atypical, with cases occurring at earlier ages or in XX patients, resulting in the presence of only renal disease. These atypical cases must be differentiated from sporadic forms of nephrotic syndrome, and from other entities such as Denys-Drash syndrome (DDS), which is also related to WT1 mutations but features rapidly progressive renal disease at earlier ages. It is important to establish a differential diagnosis between FS and DDS, since they carry different tumor risks requiring specific clinical management: while in FS there is an increased risk for the development of gonadal neoplasms, in DDS there is an increased risk for the development of Wilms tumors; while FS mutations affect a splice site in intron 9, DDS results from missense mutations in exons 8 and 9 of WT1. In these atypical cases, molecular analysis may be of extreme importance to reveal the specific genetic defect in the WT1 gene, allowing an accurate diagnosis.

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*This article should be referenced as such:*

Cajaiba MM, Reyes-Múgica M. Frasier syndrome (FS). *Atlas Genet Cytogenet Oncol Haematol*.2008;12(1):81-84.

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