

## Solid Tumour Section

### Review

# Kidney: Nephroblastoma (Wilms tumor)

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## Identity

**Other names:** Nephroblastoma

**Note:** Wilms' tumor, although generally rare, is the most common abdominal malignancy in children. Wilms' tumor cells are believed to derive from pluripotent embryonic renal precursor cells. Thus, Wilms' tumors are linked to the early development of the kidney. While most are isolated sporadic tumors, approximately 10% of cases are associated with genetic syndromes and extrarenal manifestations.

## Classification

According to the staging system employed by the National Wilms' Tumor Study Committee, there are 5 stages of Wilms' tumors.

Stage I: Tumor is limited to the kidney and is completely resected and the renal capsule is intact. The tumor is not ruptured or biopsied prior to removal. Renal sinus vessels shouldn't be involved and there shouldn't be any evidence of the tumor at or beyond the margins of resection. 43% of Wilms' tumor patients fall into this category.

Stage II: Tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. In this stage tumor extends beyond the kidney either by regional extension or the blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor. 23% of Wilms' tumor patients fall into this category.

Stage III: After surgery, residual nonhematogenous tumor is present in the abdominal area. In stage III any of the following criteria may be present:

1-Lymph nodes within the abdominal or pelvic lymph nodes contain the tumor. The tumor has penetrated through the peritoneal surface.

2-Peritoneal surface has tumor implants.

3-Gross or microscopic tumor remains postoperatively.

4-The tumor is not completely resectable due to local infiltration into vital structures.

5-Either before or during the surgery, tumor spillage occurs.

6-The tumor was biopsied (using tru-cut biopsy, open biopsy, or fine needle aspiration) before removal.

7-The tumor is removed in more than one piece.

23% of Wilms' tumor patients fall into this category.

Stage IV: At this stage, lung, liver, bone, brain, etc or lymph node metastases outside the abdominopelvic region are detected. 10% of Wilms' tumor patients fall into this category.

Stage V: Bilateral involvement is detected. Each side should be staged according to the criteria to determine the extent of the disease. 5% of Wilms' tumor patients fall into this category.

## Clinics and pathology

### Phenotype stem cell origin

Wilms' tumor is believed to result from malignant transformation of abnormally persistent renal stem cells that may retain embryonic differentiation potential. Classic Wilms' tumors are triphasic and composed of epithelial, blastemal, and stromal elements. Most tumors have favorable histology but up to 7% of have unfavorable histology with anaplastic changes. Diffuse anaplastic changes generally predict a poor outcome. Wilms tumors with anaplastic changes are called unfavorable histology and require more aggressive treatment.

## Etiology

Wilms tumours are either sporadic or familial (1-2%); it may be associated with hemihypertrophia or genitourinary malformations (10%) and part of a recognized syndrome (2%).

The syndromes predisposing to Wilms tumours are:

- WAGR (Wilms tumour, aniridia, genitourinary abnormalities and mental retardation),
- Denys-Drash syndrome (DDS): mesangial sclerosis, male pseudohermaphroditism and Wilms tumours,
- Beckwith-Weideman (BWS): exomphalos, macroglossia, gigantism and
- Simpson Golabi Behemel syndrome (SGBS): overgrowth, mental impairment, craniofacial anomalies.
- Wilms tumors can also be seen in association with Trisomy 18.

## Epidemiology

Wilms' tumor affects 1 in 10,000 children in North America. Therefore it is the most common pediatric abdominal malignancy and the fourth most common childhood malignancy. 50% of cases occurs before the age of 3 years and 90% before 6 years.

## Clinics

There doesn't seem to be a sex preference concerning the incidence. Sporadic forms are usually unilateral and constitute the majority of cases whereas bilateral or multifocal cases account for 10% of the cases possibly due to a germline mutation.

## Pathology

Wilms tumours show a mimicry of nephrogenesis as the tumour comprises undifferentiated blastemal cells, differentiated epithelial cells and stromal cells; ectopic components, particularly skeletal muscle, are observed in 5-10% of tumours; the presence of identical deletions of WT1 in all components of some sporadic Wilms tumours suggests that the stromal components are neoplastic, raising the possibility that undifferentiated blastema cells are precursors of the stromal and heterologous elements.

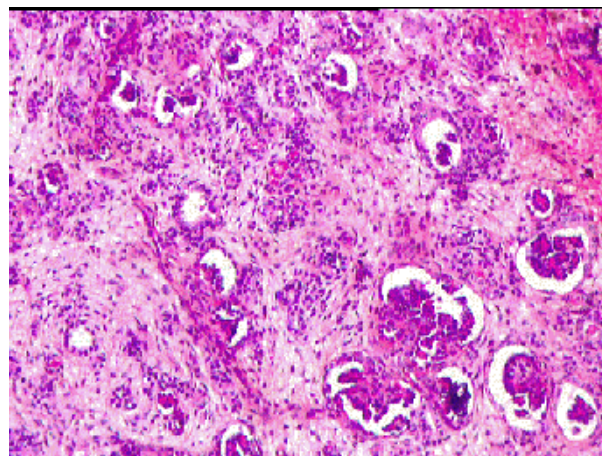
## Treatment

Multimodality therapy including nephrectomy is used for the management of all stages of Wilms' tumor. Chemotherapy has proven beneficial in all stages of the disease and radiation therapy is used to improve the outcome of later stage tumors, including stage II malignancies with diffuse anaplastic changes.

## Prognosis

Wilms' tumor can be classified into favorable and anaplastic histology groups for prognostic purposes. Favorable histology group does not have anaplastic cells in the tumor. Histology is similar to the normal

kidney development. On the other hand, anaplastic histology group indicates either focal or diffused structures. Diffuse anaplasia confers poor prognosis, has chemotherapy resistance and may still be present after preoperative chemotherapy, however; children with stage I anaplastic tumors (Stage I-IV Anaplasia) have an excellent prognosis. Stage V bilateral patients have a 4-year survival rate of 94% for those with the most advanced lesion of stage I or stage II, and 76% for those with the most advanced lesion of stage III.



Blastematosus tissue with some differentiated glomerular structures associated with mesenchymal tissue and tubules. Courtesy Pierre Bedossa.

## Genetics

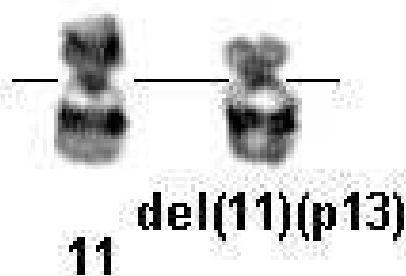
**Note:** This entity is heterogenous at the genetic level.

## Cytogenetics

### Cytogenetics morphological

The observed heterogeneity reflects the complexity of the genetic changes. Trisomies 8, 12, and 18; 11p deletions occur in 20% of cases, trisomy 12 in 25%, del(16q) in 20%; the der(16)t(1;16), also described in a wide range of tumours, is considered a marker of tumour progression.

Recurrent chromosomal abnormalities detected in Wilms' tumor patients are loss of heterozygosity at 1p, 7p and 16q. A study of 67 Wilms' tumor patients detected that 48 (72%) tumors showed an abnormal karyotype. In this study, chromosomal gains were more common compared to chromosomal losses. Hyperdiploidy was seen in 30 cases and hypodiploidy in 4 cases. The most common aneuploidies detected were gains of chromosomes 6, 7, 8, 12, 13, and 18. Rare translocations involving chromosome the 11p13 WT1 gene have been reported associated with desmoplastic small round cell tumors (DSRCT) most often involving the abdominal serosal of young males. These tumors usually have a poor prognosis.



del(11)(p13) G-banding - Courtesy G. Reza Hafez, Eric B. Johnson, and Sara Morrison-Delap Cytogenetics at the Waisman Center.

## Genes involved and Proteins

**Note:** Approximately 10% of Wilms' tumors are bilateral and a small fraction of these are associated with gross congenital syndromes, most often overgrowth syndromes or syndromes associated with hemihypertrophy such as Beckwith-Weidemann syndrome. In most cases of bilateral Wilms' tumors are believed to arise from de novo germ line mutations rather than familial transmission. Genetic defects underlying most cases of Wilms' tumors are not known. However, mutations or deletions in the WT1 gene on 11p13 underlie a subset of Wilms' tumors. Two other familial pre-disposition loci are known. FWT1 (Familial Wilms' tumor 1, aka WT4) maps to 17q12-q21 and FWT2 maps to 19q13.4.

Other genes believed to be involved in Wilms' tumor development are, CTNNB1 (Beta-catenin), IGF2 / H19 (and other imprinted genes on 11p15), GPC3 (Glypican 3; Simpson-Golabi-Behmel gene). Another interesting observation is about Mulibrey nanism (for muscle-liver-brain-eye nanism, MUL). MUL is an autosomal recessive disorder that involves several tissues of mesodermal origin, implying a defect in a highly pleiotropic gene. About 4% of MUL patients develop Wilms' tumour.

### WT1

**Location:** 11p13

**Note:** Mutations in the WT1 gene have been identified in patients with Wilms tumor, WAGR syndrome, and Denys-Drash syndrome (DDS), Frasier syndrome, and isolated diffuse mesangial sclerosis (IDMS). There are rare inherited mutations. Coding region mutations of WT1 has been reported as nonsense and missense changes. Constitutional deletion of one copy of the WT1 gene (11p13) is responsible for predisposition to Wilms tumours and for genitourinary malformations in WAGR patients. Constitutional heterozygous intragenic mutations have been described in DDS; WT1 is somatically involved in 10% of the sporadic cases.

### DNA/RNA

The gene spans 50 kbs and has 10 exons. Four transcript variants have also been detected.

Transcript variant A, 2969 bp, lacks exon 5 and the additional sequence coding for KTS at the end of exon 9.

Transcriptional Variant B, 3020 bp, has all 10 exons except the sequence coding KTS at the end of exon 9.

Transcriptional Variant C, 2978 bp, lacks exon 5 but has the additional sequence coding KTS at the end of exon 9.

Transcriptional Variant D, 3029 bp, has all 10 exons and the additional sequence coding KTS at the end of exon 9. This transcript is the longest known compared to all others.

### Protein

55kDa zing finger transcription factor expressed during renal and gonadal development. It can act as an activator of transcription or a transcriptional repressor depending on the cellular context in which it is expressed. It is most commonly considered to function as a tumor suppressor.

Exons 1-6 encode a proline/glutamine rich transcriptional regulation region; exons 7-10 encode the four zinc fingers; two alternative splicing regions allow synthesis of four isoforms showing different binding specificity; WT1 regulates transcription of several genes, including IGF2 and PDGFA ; the WT1-KTS isoforms associate and synergize with SF-1 (steroidogenic factor 1) to promote AMH (anti mullerian hormone or MIS, mullerian inhibiting substance).

Isoforms of WT1 are:

- Isoform A: Translation starts from a CUG codon and also from a downstream, in-frame AUG to generate the same reading frame that is 20 amino acids shorter than the longest isoform D.

- Isoform B: Translation starts from a CUG codon and also from a downstream, in-frame AUG to generate the same reading frame that is 3 amino acids shorter than the longest isoform D.

- Isoform C: Translation starts from a CUG codon and also from a downstream, in-frame AUG to generate the same reading frame that is 17 amino acids shorter than the longest isoform D.

- Isoform D: Translation starts from a CUG codon and also from a downstream, in-frame AUG to generate the longest isoform, 517 amino acids.

### Germinal mutations

Missense mutations of exons 8 and 9 in DDS; in the proximal part of the gene leading to truncated proteins in WAGR, genitourinary malformations and Wilms Tumours; in the donor splice site of intron 9 in Frasier syndrome (pseudohermaphroditism, glomerulopathy, not associated Wilms Tumours).

In germline heterozygous mutations of WT1, renal and genitourinary defects are observed in patients. Arginine to tryptophan transition in exon 3 of WT1 is also associated with DDS as well as exon 2 mutations and N-terminal truncations.

#### Somatic mutations:

Stop and frameshift mutations in about 10% of Wilms Tumours. Aberrant splice forms have also been detected.

**Note:** Other chromosomal regions involved are:

- 11p15 : BWS, an overgrowth syndrome, is caused by alterations of 11p15, a region subject to genomic imprinting: loss of imprinting of IGF2 is the most common defect found; WT1 is rarely implicated solely in sporadic Wilms tumours, but maternal alleles often displays a loss of heterozygosity (LOH) at 11p15, which suggests the existence of a second locus WT2.

- 7p, 17q, 19q : a third locus WT3, at least, is likely, on the grounds of the existence of familial cases of Wilms tumour without 11p13 nor 11p15 involvement; one locus has been identified in 17q in one large Wilms tumours family, and another one in 19q13 in five families; another predisposing gene to Wilms tumours maps to 7p, where constitutional translocations and somatic deletions have been described; in tumours, loss of heterozygosity for 16q has been reported for two different loci: 16q13 and 16q21.

- Xq26 : the gene of SGBS, an overgrowth syndrome, has been cloned at Xq26.

- Mutations of P53 occur in 5% of Wilms tumours and are associated with tumour progression.

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