Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Solid Tumour Section

Mini Review

Kidney: Nephroblastoma (Wilms tumor)

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Identity

Alias: Wilms tumour

Clinics and pathology

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), DDS (Denys-Drash syndrome: mesangial sclerosis, male pseudohermaphrodism and Wilms tumours), BWS (Beckwith-Weideman: exomphalos, macroglossia, gigantism) and SGBS (Simpson Golabi Behmel syndrome: overgrowth, mental impairment, craniofacial anomalies).

Epidemiology

The most common paediatric cancer of the kidney, affecting $10/10^5$ children; 50% of cases occurs before the age of 3 years and 90% before 6 years.

Clinics

The localization is primarily the kidney; the incidence of bilateral involvement is 5-10%.

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

Stage 1 and 2 are treated with nephrectomy and chemotherapy, radiation therapy is added to tumours of higher staging.

Prognosis

The overall cure rate for unilateral Wilms tumours is 80%; anaplastic tumours (4%) have an unfavorable prognosis.

Genetics

Note

This entity is heterogenous at the genetic level.

Cytogenetics

Cytogenetics Morphological

The observed heterogeneity reflects the complexity of the genetic changes; structural changes at 11p13, 11p15, 1p, 1q and 7p are the most frequently reported, as well as 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.

Genes involved and proteins

Note

- 11p13: 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.

- 11p15: BWS, an overgrowth syndrome, is caused by alterations of 11p15, a region subject to genomic imprinting: loss of 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.

WT1

Location

11p13

DNA / RNA

50 kb, 10 exons.

Protein

Protein tumour zing finger transcription factor expressed during renal and gonadal development; 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).

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 WT; in the donor splice site of intron 9 in Frasier syndrome (pseudohermaphroditism, glomerulopathy, not associated WT).

Somatic mutations

Stop and frameshift mutations in about 10% of WT.

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