Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Mini Review

WT1 (Wilms' tumor suppressor gene)

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Identity

HGNC (Hugo): WT1

Location: 11p13

Local order: Cen- RAG1/2-CAT-CD59-WT1-RCN-PAX6-FSHB -tel.

DNA/RNA

Description

10 exons spanning 48 kb of genomic DNA.

Transcription

3 kb mRNA; four alternative splice forms: +/- exon 5 and alternative splice donor sites at exon 9.

Protein

Description

Four major isoforms (429-449 aa) due to alternative splicing; there are eight minor isoforms resulting from different initiation sites (upstream CTG: 502-522 aa, downstream ATG: 303-323 aa).

Expression

Kidney, spleen, mesothelia.

Localisation

Nuclear staining, either diffuse or in speckles, depending on isoform and mutations.

Function

Zinc finger transcription factor (4 C2H2-type fingers).

Homology

p1, Egr-1.

Mutations

Germinal

Various types of mutations, mostly affecting zinc fingers in exons 7-10. (WAGR syndrome, genito-urinary (GU) anomalies, Denys-Drash-syndrome, Frasier syndrome; see below).

Somatic

Biallelic inactivation in Wilms' tumors (<15%) and some mesotheliomas and granulosa cell tumors.

Implicated in

Wilms' tumor

Disease
Nephroblastoma of childhood.

Prognosis
Good with treatment according to NWTS or SIOP.

Cytogenetics
11p13 deletions/translocations can be seen in some cases.

Oncogenesis
Up to 15% of tumors show mainly biallelic inactivation of WT1 through deletion or mutation.

Desmoplastic small round cell tumor (DSRCT)

Prognosis
Poor.

Cytogenetics
Translocations, t(11;22)(p13;q12).

Abnormal protein
With EWS: EWS-WT; in frame fusion of EWS exons 1-7 and WT1 exons 8-10.

Denys-Drash syndrome (DDS)

Disease

Defined by: mesangial sclerosis with kidney failure (age 2 yrs), gonadal dysgenesis, risk of Wilms' tumors.

Prognosis

Kidney failure at age 0-5 years.

Hybrid/Mutated gene

Dominant negative mutations, especially missense mutations within the zinc fingers (aa 394 Arg -> Trp) but very few nonsense mutations.

Oncogenesis

High risk of Wilms' tumor development.

Frasier syndrome

Disease

Defined by: complete gonadal dysgenesis, focal glomerular sclerosis, gonadoblastoma; in karyotypic females the syndrome may be limited to focal glomerular sclerosis with regular gonadal development and function.

Prognosis

Kidney failure at age 10-30 years.

Hybrid/Mutated gene

Heterozygous point mutations of alternative splice donor site in exon 9 with imbalance of WT1 isoform ratio.

Oncogenesis

Gonadoblatoma may occur within streak gonads.

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