Wilms' Tumor

"The most common renal tumor in children"

Overview

- What is Wilms' Tumor?
- History.
- Cause and proposed mechanisms of tumor development.
- Identification of Wilms' tumor.
- Staging and Cellular classification.
- Treatments.
- Future outlook.

What is Wilms' tumor?

- It is the most common kidney tumor of children.
- Originates within the kidney during early childhood development.
- Occurs with a frequency of 1 in 10,000 live births.
- Average age of diagnosis—3 yrs.
- Average size—0.5 lbs.
- Two types:
    1. Favorable histology.
    2. Unfavorable histology
        --anaplastic and diffuse anaplastic

History


MAX WILMS (1867 - 1918)

- Discovered in 1899 by Max Wilms.
- Establishment of the National Wilms Tumor Study Group (NWTSG).

*Goals: --increase the survival rate of children.

--identify adverse effects of treatments.

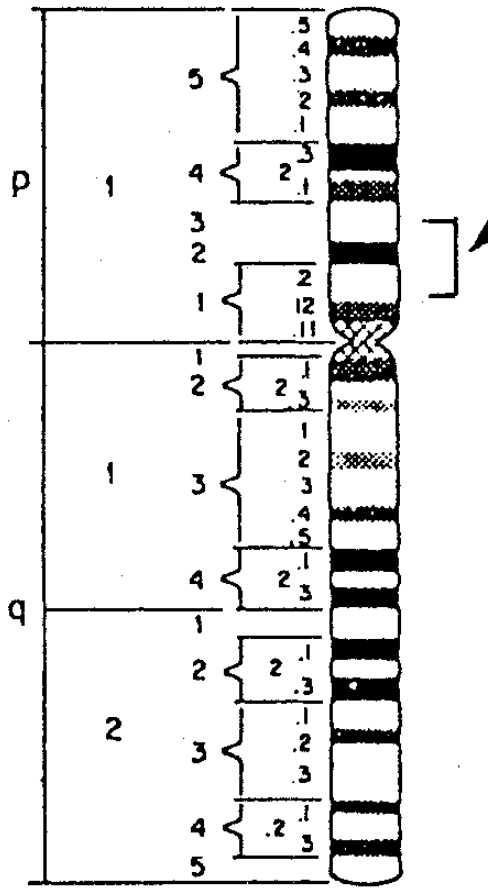
--study long-term effects of treatments.

--study epidemiology and biology of the Wilms tumor.

Cause and proposed mechanisms of tumor development.

- Caused by one or more changes in several genes.
- Two mutations recognized are on chromosome 11p; 11p13 & 11p15.
- Other loci possibly affected: 1p, 7p, 16p, 17p(the p53 suppressor gene), and 19p.
- Possible causes I will look at are:
    1. Mutations in gene WT1
    2. Mutations in gene WT2
    3. Mutations in p53
    4. Mutations in the beta-catenin pathway

Chromosome 11



WT1 mutation

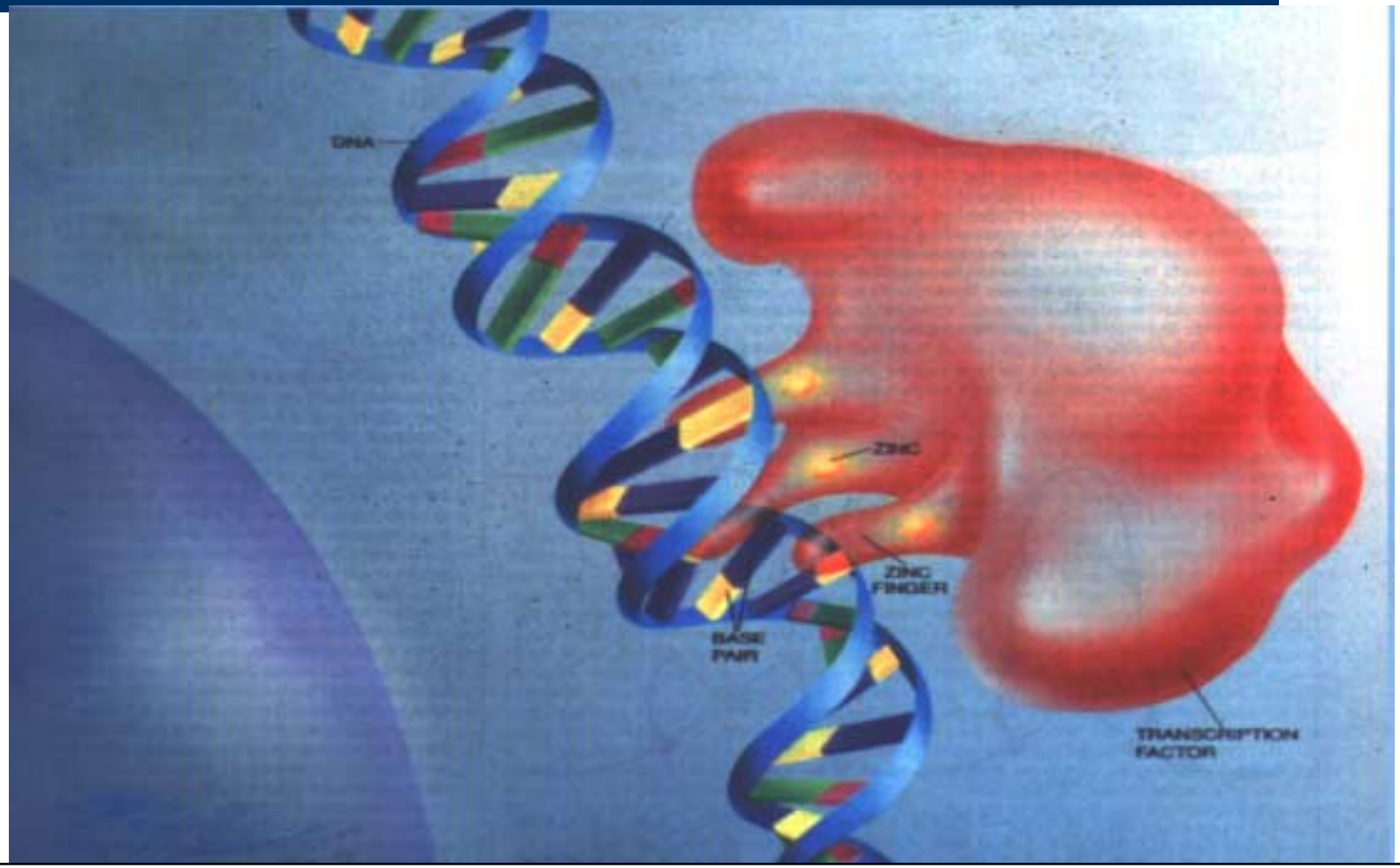
- WT1 functions as a zinc finger transcription factor.

  --Amino terminus is rich in proline and glutamine

  --Carboxyl terminus contains four C2H2 zinc finger DNA-binding motifs and a NLS sequence.
- In vivo there are 4 major isoforms that are generated by alternative splicing at two sites. These 4 isoforms are at a constant ratio, which suggest that there functions are independent of each other.
- DNA binding is isoform-dependent.
- WT1 has been shown to be a transcriptional activator or repressor.

Zinc Finger

Zinc Finger



Zinc Finger

Alternative Splicing of WT1

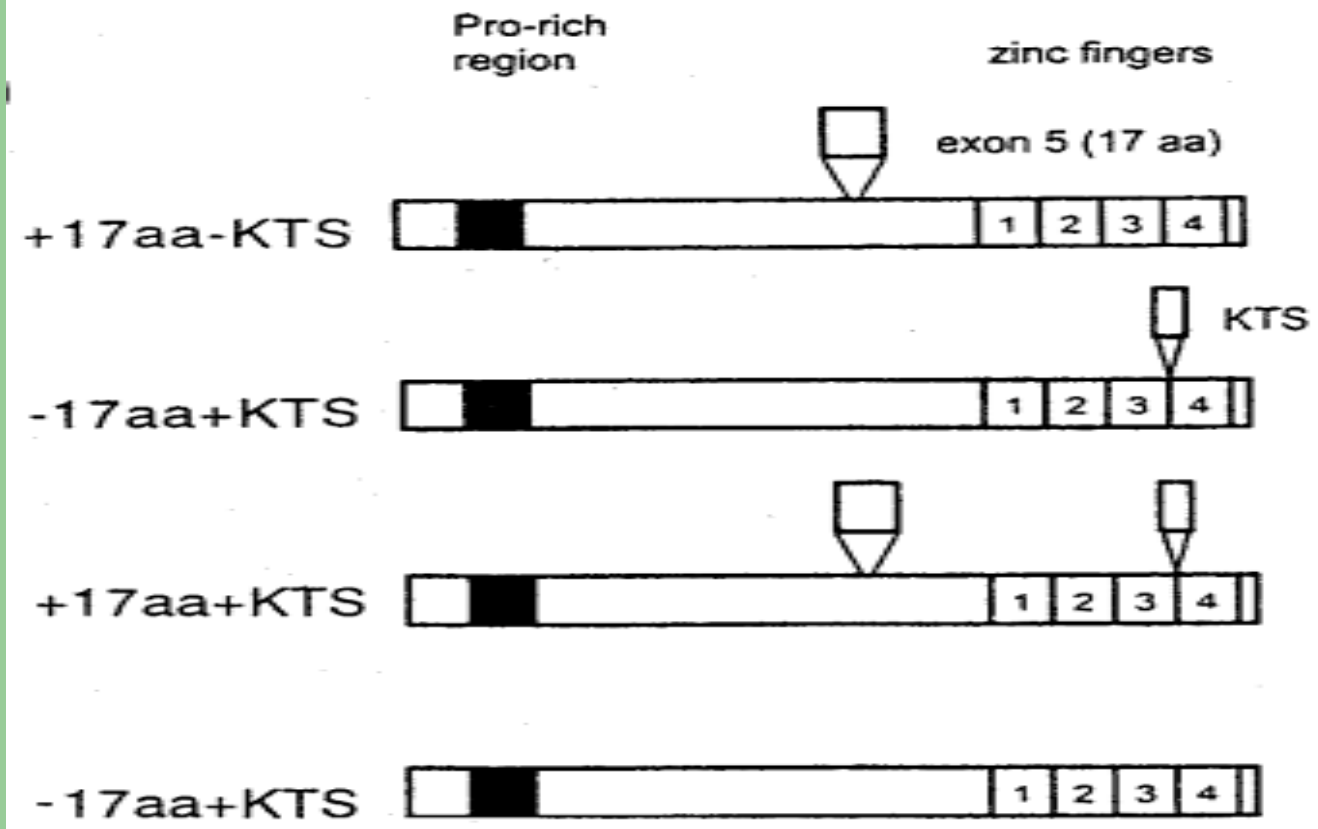


Figure 1 . The four patterns of alternative splicing of the *WTI* gene. The details are explained in the text.

Other mutations found:

- Mutations at 11p15 has now been identified and designated as WT2.
- *B*-catenin mutations were also found associated with Wilms' tumor.

*p*53 identified as a cyclin-dependent kinase (CDK) inhibitor.

Regulation the cell cycle

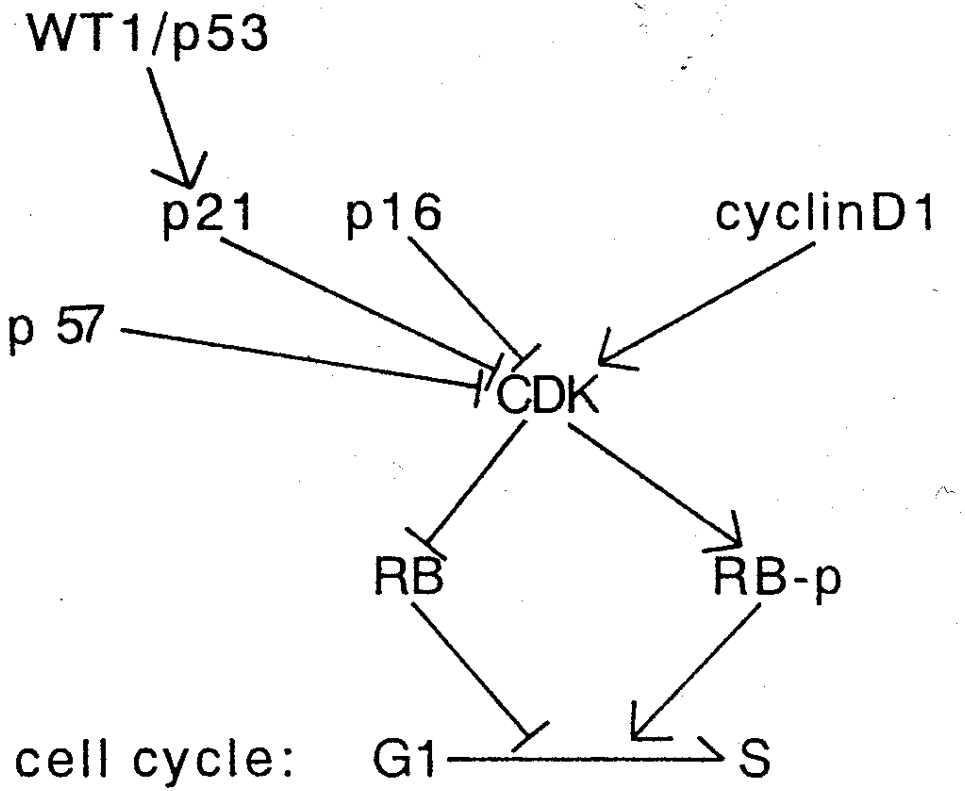


Figure 2. The relation between the proteins that regulate cell cycle progression.

Identification of Wilms' tumor.

- 1st sign is a large lump or swelling in the abdomen.
- 25% also have other symptoms:
  - -stomach pain
  - -fever
  - -blood in the urine
  - -high blood pressure
- Medical history, examination, and imaging testing.
- Surgical removal of the tumor is performed in 95% of the cases.

Staging and Cellular classification.

- Staging of the tumor.
  - Stages 1, 2, 3, 4, & 5.
- 2 prognostic groups on the basis of histology:
  - Favorable histology
  - Unfavorable histology
    - Anaplastic
    - Diffuse anaplastic

Treatments.

- Surgery—complete removal of the tumor and surrounding tissue without tumor rupture.
- Treatments range from:
  - --18 weeks of chemotherapy /no radiation
  - --24 weeks of chemotherapy plus abdominal and whole lung radiation
- Relapse treatment depends on these factors:
  - Site of recurrence
  - Tumor histology
  - Length of remission
  - Initial chemotherapy regimen

Future outlook.

- Amount of chemotherapy and radiation used has decreased over the years.
- Further studies associated with WT1, WT2, b-catenins, etc…
- Discoveries of new mutations that lead to Wilms' tumor.
- Therapies that might use anti-telomerase.
- Study #5 will be finished in 2003.

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