

Solid Tumour Section

Short Communication

Kidney: Renal cell carcinoma with inv(X)(p11q12) NONO/TFE3

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Abstract

Review on Renal cell carcinoma with inv(X)(p11q12) NONO/TFE3, with data on clinics, and the genes involved.

Keywords: Renal cell carcinoma; chromosome X; NONO; TFE3; MiT family

Identity

Other names

NONO-TFE3 renal cell carcinoma

Classification

This renal cell carcinoma belongs to the family of Xp11 translocation renal carcinomas. Xp11 translocation renal cell carcinomas (RCCs) harbor gene fusions involving TFE3 transcription factor. The t(6;11) RCCs harbor a specific MALAT1 (Alpha) - TFEB gene fusion. TFEB and TFE3 belong to the same MiT subfamily of transcription factors. Because of similarities at the clinical, morphologic, immunohistochemical, and genetic levels, the Xp11 translocation RCCs and t(6;11) RCCs are currently grouped together under the category of MiT family translocation renal cell carcinoma.

Clinics and pathology

Etiology

Unclear

Epidemiology

Fewer than 10 cases reported in the literature, median age is 36 years.

Pathology

NONO-TFE3 RCCs frequently have papillary architecture and clear cells with subnuclear vacuoles.

Rare Xp11 translocation perivascular epithelioid cell tumors (PEComas) harbor the same gene fusion.

Treatment

Surgical excision.

Evolution

Unknown.

Cytogenetics

Cytogenetics Morphological

inv(X)(p11.2q12).

Genes involved and proteins

TFE3 (transcription factor E3)

Location Xp11.23

DNA / RNA

The TFE3 gene includes a 5' untranslated region, 8 exons, and a 3' untranslated region.

Protein

TFE3 is a transcription factor with a basic helix-loop-helix DNA binding domain and a leucine zipper dimerization domain. TFE3 contains a nuclear localization signal, encoded at the junction of exons 5 and 6, which is retained within all known TFE3 fusion proteins.

TFE3 protein is 575 amino acids, and is ubiquitously expressed. TFE3, TFEB, TFEC and MITF comprise the members of the microphthalmia transcription factor subfamily, which have homologous DNA binding domains and in fact bind to a common DNA sequence. These four transcription factors may homo- or heterodimerize to bind DNA, and they may have functional overlap.

NONO (non-POU domain containing, octamer-binding)

Location Xq13.1

Protein

NONO is a 471 amino acid protein with several distinctive domains. From N-terminus to C-terminus, it has :

- 1) an N-terminal basic region composed entirely of Proline, Glutamine, and Histidine,
- 2) a pair of RNA recognition motifs,
- 3) a helix-turn helix domain followed by a series of charged amino acids that likely forms a DNA-binding unit,
- 4) a short C-terminal Proline-rich region.

SFPQ and NONO are highly homologous and related proteins. NONO has a region of 320 amino acids with a 71% identity and a 7% similarity to a 320 amino acid region within PSF. Both proteins have both DNA and RNA binding domains, which underlies their multifunctionality. Indeed, these proteins have been implicated in both transcriptional activation and splicing. Both proteins are known to bind to the DNA binding domains of nuclear hormone receptors (such as the thyroid hormone receptors and the retinoid X receptors), and modulate transcriptional activation. These proteins bind to each other, select the same optimal RNA sequence from RNA pools, and have been associated with spliceosomes. Both have been shown to bind to the C-terminal domain of RNA polymerase II, where they may couple pre-mRNA splicing and RNA processing.

SFPQ and NONO enhance Topoisomerase I cleavage of DNA, and induce its jumping to other DNA helices after cleavage.

Finally, both have been shown to bind and retain defective and hyperedited mRNAs within the nucleus, preventing translation of mutated proteins.

Result of the chromosomal anomaly

Hybrid Gene

Description

5' NONO - 3' TFE3

Fusion Protein

Description

The *inv(X)(p11.2q12)* results in fusion of virtually the entire sequence of NONO/p54nrb with the C-terminal portion of the TFE transcription factor that contains the basic helix-loop-helix (bHLH) DNA binding domain and Leucine Zipper domain.

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