

Gene Section

Mini Review

NTRK3 (neurotrophic tyrosine kinase, receptor, type 3)

Stevan Knezevich

BC Cancer Research Centre (BCCRC), Vancouver, British Columbia, Canada (SK)

Published in Atlas Database: April 2004

Online updated version: <http://AtlasGeneticsOncology.org/Genes/NTRK3ID433.html>

DOI: 10.4267/2042/38068

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.

© 2004 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: TrkC; Neurotrophin 3 Receptor

HGNC (Hugo): NTRK3

Location: 15q25

DNA/RNA

Description

The gene for NTRK3 is located on chromosome 15 q25 and is encoded by 20 exons. Exon 1 codes for the translation initiation codon (ATG) and the signal sequence (SS), while the stop codon is located in exon 18. Exons 1 to 4 encode the Neurotrophin ligand binding domain (also known as the Immunoglobulin-like domain 2). Exons 10 and 11 encode the transmembrane domain while the tyrosine kinase domain is encoded by exons 13-18.

Pseudogene

Variant transcripts exist for NTRK3, which have been termed non-catalytic (NC) as they do not

contain enough sequence to mount an appropriate autophosphorylation event. These have been named NTRK3-NC1 and NTRK3 NC2.

Protein

Description

145 kDa protein, located on plasma membrane with an extra-cellular ligand binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. Ligand for NTRK3 is Neurotrophin 3; after binding to NTRK3, it causes dimerization and autophosphorylation of specific tyrosine phosphates, which in turn act as anchors and activators of downstream molecules such as Shc, PI3-K and PLC-g.

Expression

Primarily in central nervous system tissue with specific emphasis in hippocampus, cerebral cortex, and the granular cell layer of the cerebellum. In addition, there is a minor amount expressed in a variety of other tissues.



The NTRK3 protein is composed of several regions.

Starting at the amino terminus is the signal sequence (SS) responsible for directing the newly translated protein to the cell surface.

Next is the Extracellular Ligand Binding Domain (ECD-LB), which binds Neurotrophin 3 and subsequent homo-dimerization with autophosphorylation of key tyrosine residues.

The transmembrane domain (TM) spans the plasma membrane.

The intracellular portion is composed of the protein tyrosine kinase domain (PTK) which has both the key tyrosines for autophosphorylation as well as tyrosines that are phosphorylated and act as activators of downstream molecules including Shc, PI3-Kinase and PLC-g.

Localisation

Plasma membrane; transmembrane receptor tyrosine kinase.

Function

Tyrosine kinase cell surface receptor responsible for the proliferation and differentiation of neural derived cells.

Homology

Acid sequence is 97% and 98% homologous to the rat and porcine TRKC sequences, respectively.

Implicated in

Medulloblastoma

Note

Over-expression of NTRK3 mRNA was found to be associated with a much favorable prognosis over medulloblastomas with a comparatively low expression of NTRK3.

Congenital Fibrosarcoma (CFS) and Congenital Mesoblastic Nephromacellular variant (cellular CMN)

Disease

CFS and cellular CMN are pediatric tumors of spindle cell origin (mesoblastic origin). CFS primarily presents at birth up to 2 years of age, usually affecting the extremities. Cellular CMN, on the other hand is a pediatric spindle cell tumor of the kidney.

Prognosis

The presence of the ETV6-NTRK3 gene fusion in both CFS and cellular CMN indicate an excellent

prognosis when compared to their histologically similar and more aggressive counterparts.

Cytogenetics

The ETV6-NTRK3 gene fusion is the result of a t(12;15)(p13;q25).

Hybrid/Mutated gene

ETV6-NTRK3

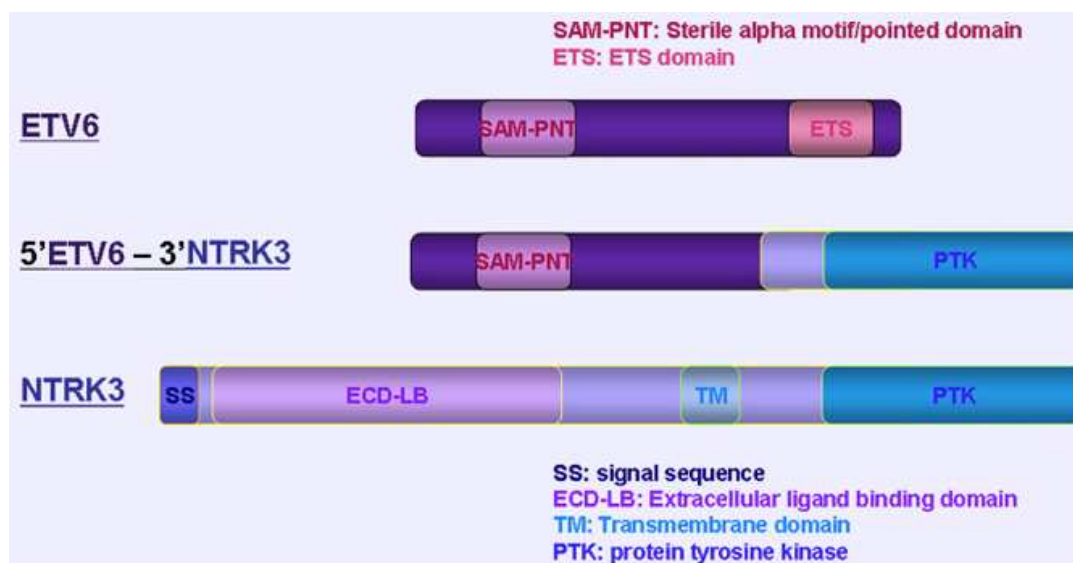
Oncogenesis

Current speculation regarding the oncogenic mechanism of the fusion protein is related to its putative activation of the MAP Kinase pathway with resultant activation of various downstream proteins such as transcription factors. Native NTRK3 requires extracellular ligand binding of Neurotrophin 3 prior to its dimerization and autophosphorylation. ETV6-NTRK3, however, bypasses this requirement as it contains the HLH domain from ETV6 which allows the molecule to dimerize in the absence of Neurotrophin 3 and thus remain in a constitutively activated (phosphorylated) state. Once again, the presence of ETV6-NTRK3 seems to make these particular neoplasms behave more indolent than their aggressive Ductal Carcinoma counterparts, which do not harbor the ETV6-NTRK3 gene fusion.

Secretory Breast Carcinoma (a variant of ductal carcinoma of the breast)

Note

Virtually all cases of CFS and cellular CMN to date have been associated with the ETV6-NTRK3 gene fusion. In addition these malignancies almost always have an additional copy of chromosome 11.



The amino terminus is composed of the first 5 exons from ETV6, which carries the Helix-Loop-Helix Domain (HLH) responsible for dimerization. The remainder of the protein is composed of the Protein Tyrosine Kinase domain from NTRK3. The arrow represents the point at which the ETV6 contribution ends and the NTRK3 contribution begins.

This additional copy of chromosome 11 is not found in secretory breast carcinoma. Finally, the ETV6-NTRK3 gene fusion was found in secretory breast carcinomas of all ages (the youngest case being a 6 year old female).

Disease

Secretory Breast Carcinoma is an epithelially derived breast cancer, as opposed to the mesoblastic CFS and cellular CMN above. It can occur in the pediatric population and much more commonly in adults.

Cytogenetics

The ETV6-NTRK3 gene fusion is the result of a t(12;15)(p13;q25).

Hybrid/Mutated gene

ETV6-NTRK3

Please see above diagrams and explanations for the protein and proposed oncogenic mechanism.

References

Barbacid M. The Trk family of neurotrophin receptors. *J Neurobiol.* 1994 Nov;25(11):1386-403

McGregor LM, Baylin SB, Griffin CA, Hawkins AL, Nelkin BD. Molecular cloning of the cDNA for human TrkC (NTRK3), chromosomal assignment, and evidence for a splice variant. *Genomics.* 1994 Jul 15;22(2):267-72

Segal RA, Goumnerova LC, Kwon YK, Stiles CD, Pomeroy SL. Expression of the neurotrophin receptor TrkC is linked to a favorable outcome in medulloblastoma. *Proc Natl Acad Sci U S A.* 1994 Dec 20;91(26):12867-71

Ichaso N, Rodriguez RE, Martin-Zanca D, Gonzalez-Sarmiento R. Genomic characterization of the human trkC gene. *Oncogene.* 1998 Oct 8;17(14):1871-5

Knezevich SR, Garnett MJ, Pysher TJ, Beckwith JB, Grundy PE, Sorensen PH. ETV6-NTRK3 gene fusions and trisomy 11 establish a histogenetic link between mesoblastic nephroma and congenital fibrosarcoma. *Cancer Res.* 1998 Nov 15;58(22):5046-8

Knezevich SR, McFadden DE, Tao W, Lim JF, Sorensen PH. A novel ETV6-NTRK3 gene fusion in congenital fibrosarcoma. *Nat Genet.* 1998 Feb;18(2):184-7

Menn B, Timsit S, Calothy G, Lamballe F. Differential expression of TrkC catalytic and noncatalytic isoforms suggests that they act independently or in association. *J Comp Neurol.* 1998 Nov 9;401(1):47-64

Tognon C, Knezevich SR, Huntsman D, Roskelley CD, Melnyk N, Mathers JA, Becker L, Carneiro F, MacPherson N, Horsman D, Poremba C, Sorensen PH. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. *Cancer Cell.* 2002 Nov;2(5):367-76

This article should be referenced as such:

Knezevich S. NTRK3 (neurotrophic tyrosine kinase, receptor, type 3). *Atlas Genet Cytogenet Oncol Haematol.* 2004; 8(2):76-78.
