

NTRK3

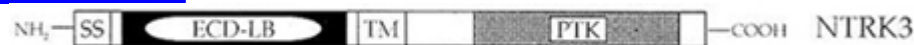
Identity

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|-------------|---|
| Other names | TrkC Neurotrophin 3 Receptor |
| Hugo | NTRK3 |
| Location | 15q25 |

DNA/RNA

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| 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



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.

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| 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. |
| 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

Entity [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.

Entity Congenital Fibrosarcoma (CFS) and Congenital Mesoblastic Nephroma-cellular 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).



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.

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. ETV-6-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 Carinoma counterparts, which do not harbor the ETV6-NTRK3 gene fusion.

Entity [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. This additional copy of chromosome 11 is not found in secretory breast carcinoma. Finally, the ETV6-NTRK3 gene fusion was found in

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

External links

| | |
|-----------------------------|--|
| | Nomenclature |
| Hugo | NTRK3 |
| GDB | NTRK3 |
| Entrez_Gene | NTRK3 4916 neurotrophic tyrosine kinase, receptor, type 3 |
| | Cards |
| Atlas | NTRK3ID433 |
| GeneCards | NTRK3 |
| Ensembl | NTRK3 |
| CancerGene | NTRK3 |
| Genatlas | NTRK3 |
| GeneLynx | NTRK3 |
| eGenome | NTRK3 |
| euGene | 4916 |
| | Genomic and cartography |
| GoldenPath | NTRK3 - 15q25 chr15:86321602-86600665 - 15q25.3 (hg17-May_2004) |
| Ensembl | NTRK3 - 15q25.3 [CytoView] |
| NCBI | Genes Cyto Gene Seq [Map View - NCBI] |
| OMIM | Disease map [OMIM] |
| HomoloGene | NTRK3 |
| | Gene and transcription |
| Genbank | AJ224521 [SRS] AJ224521 [ENTREZ] |
| Genbank | AF052184 [SRS] AF052184 [ENTREZ] |
| Genbank | AF058389 [SRS] AF058389 [ENTREZ] |
| Genbank | AY065844 [SRS] AY065844 [ENTREZ] |
| Genbank | BC013693 [SRS] BC013693 [ENTREZ] |
| RefSeq | NM_001007156 [SRS] NM_001007156 [ENTREZ] |
| RefSeq | NM_001012338 [SRS] NM_001012338 [ENTREZ] |
| RefSeq | NM_002530 [SRS] NM_002530 [ENTREZ] |
| RefSeq | NT_086832 [SRS] NT_086832 [ENTREZ] |
| AceView | NTRK3 AceView - NCBI |
| TRASER | NTRK3 Traser - Stanford |
| Unigene | Hs.410969 [SRS] Hs.410969 [NCBI] HS410969 [spliceNest] |
| | Protein : pattern, domain, 3D structure |
| SwissProt | Q16288 [SRS] Q16288 [EXPASY] Q16288 [INTERPRO] |
| Prosite | PS50835 IG LIKE [SRS] PS50835 IG LIKE [Expasy] |
| Prosite | PS00107 PROTEIN KINASE ATP [SRS] PS00107 PROTEIN KINASE ATP [Expasy] |
| Prosite | PS50011 PROTEIN KINASE DOM [SRS] PS50011 |

| | |
|--|--|
| Prosite | PROTEIN KINASE DOM [Expasy] PS00109 PROTEIN KINASE TYR [SRS] PS00109 PROTEIN KINASE TYR [Expasy] |
| Prosite | PS00239 RECEPTOR TYR KIN II [SRS] PS00239 RECEPTOR TYR KIN II [Expasy] |
| Interpro | IPR003599 Iq [SRS] IPR003599 Iq [EBI] |
| Interpro | IPR007110 Iq-like [SRS] IPR007110 Iq-like [EBI] |
| Interpro | IPR011009 Kinase like [SRS] IPR011009 Kinase like [EBI] |
| Interpro | IPR001611 LRR [SRS] IPR001611 LRR [EBI] |
| Interpro | IPR000483 LRR Cterm [SRS] IPR000483 LRR Cterm [EBI] |
| Interpro | IPR000372 LRR Nterm [SRS] IPR000372 LRR Nterm [EBI] |
| Interpro | IPR000719 Prot kinase [SRS] IPR000719 Prot kinase [EBI] |
| Interpro | IPR002011 RecepttyrkinsII [SRS] IPR002011 RecepttyrkinsII [EBI] |
| Interpro | IPR001245 Tyr pkinase [SRS] IPR001245 Tyr pkinase [EBI] |
| Interpro | IPR008266 Tyr pkinase AS [SRS] IPR008266 Tyr pkinase AS [EBI] |
| CluSTr | Q16288 |
| Pfam | PF00047 ig [SRS] PF00047 ig [Sanger] pfam00047 [NCBI-CDD] |
| Pfam | PF00560 LRR [SRS] PF00560 LRR [Sanger] pfam00560 [NCBI-CDD] |
| Pfam | PF01462 LRRNT [SRS] PF01462 LRRNT [Sanger] pfam01462 [NCBI-CDD] |
| Pfam | PF00069 Pkinase [SRS] PF00069 Pkinase [Sanger] pfam00069 [NCBI-CDD] |
| Smart | SM00409 IG [EMBL] |
| Smart | SM00082 LRRCT [EMBL] |
| Smart | SM00013 LRRNT [EMBL] |
| Smart | SM00219 TyrKc [EMBL] |
| Prodom | PD000001 Prot kinase [INRA-Toulouse] |
| Prodom | Q16288 NTRK3 HUMAN [Domain structure] Q16288 NTRK3 HUMAN [sequences sharing at least 1 domain] |
| Blocks | Q16288 |
| PDB | 1WWC [SRS] 1WWC [PdbSum], 1WWC [IMB] |
| Polymorphism : SNP, mutations, diseases | |
| OMIM | 191316 [map] |
| GENECLINICS | 191316 |
| SNP | NTRK3 [dbSNP-NCBI] |
| SNP | NM_001007156 [SNP-NCI] |
| SNP | NM_001012338 [SNP-NCI] |
| SNP | NM_002530 [SNP-NCI] |
| SNP | NTRK3 [GeneSNPs - Utah] NTRK3 [SNP - CSHL] NTRK3 [HGBASE - SRS] |
| General knowledge | |
| Family Browser | NTRK3 [UCSC Family Browser] |
| SOURCE | NM_001007156 |
| SOURCE | NM_001012338 |
| SOURCE | NM_002530 |
| SMD | Hs.410969 |
| SAGE | Hs.410969 |
| Enzyme | 2.7.1.112 [Enzyme-SRS] 2.7.1.112 [Brenda-SRS] 2.7.1.112 [KEGG] 2.7.1.112 [WIT] |
| Amigo | function ATP binding |
| Amigo | process cell differentiation |
| Amigo | component integral to plasma membrane |

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|-------------------------|--|
| Amigo | component membrane |
| Amigo | process neurogenesis |
| Amigo | function neurotrophin binding |
| Amigo | process protein amino acid phosphorylation |
| Amigo | function protein kinase activity |
| Amigo | function protein serine/threonine kinase activity |
| Amigo | function receptor activity |
| Amigo | function transferase activity |
| Amigo | function transmembrane receptor protein tyrosine kinase activity |
| Amigo | process transmembrane receptor protein tyrosine kinase signaling pathway |
| Amigo | process transmembrane receptor protein tyrosine kinase signaling pathway |
| PubGene | NTRK3 |
| | Other databases |
| | Probes |
| Probe | NTRK3 Related clones (RZPD - Berlin) |
| | PubMed |
| PubMed | 18 Pubmed reference(s) in LocusLink |

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Medline [9462753](#)

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Cancer Cell 2002; 2(5): 367-376.
Medline [12450792](#)

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[BiblioGene - INIST](#)

Contributor(s)

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