Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

NTRK2 (neurotrophic tyrosine kinase, receptor, type 2)

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Published in Atlas Database: December 2007

Online updated version: http://AtlasGeneticsOncology.org/Genes/NTRK2ID41589ch9q21.html
DOI: 10.4267/2042/38553

Identity

Hugo: NTRK2
Other names: GP145-TrkB; TRKB; Trk-B
Location: 9q21.33
Local order: NTRK2 is located between solute carrier family 28, sodium-coupled nucleoside transporter member 3 (SLC28A3) and ATP/GTP binding protein 1 (AGTPBP1).

DNA/RNA

Table 1: NTRK2 exons and size (bp).

Description

NTRK2 gene is comprised between 86,473,286-86,828,325 bp of chromosome 9, with plus strand orientation. The start codon is located on exon 5. Alternative stop codons are placed on terminal exons 16, 19 and 24.

Transcription

According to AceView (NCBI), six alternative promoters may control transcription of the complex NTRK2 locus. There are at least 18 mRNA variants supported by cDNA clones, potentially encoding 12 complete proteins. Variants may include 8 different terminal exons with alternative polyadenylation sites. Truncation at the 5' end or 3' end, alternative splicing, intron retention, occurrence of 5 cassette exons, and different exon boundaries introduce additional differences.
Five confirmed mRNA variants (a, b, c, d, e) are reported (NCBI accessions: NM_006180.3; NM_001007097.1; NM_001018064.1; NM_001018065.1; NM_001018066.1). The mRNA variant (a) encodes the full-length protein; variant (c) is slightly shorter excluding the small internal exon 17. Of particular importance are the truncated isoforms lacking the catalytic tyrosine kinase domain generated by the inclusion of alternate terminal exon 16 (b) or exon 19 (d) and (e).

Pseudogene

None.

Protein

Note: Three TrkB isoforms are reported by UniProt/Swiss-Prot:
1. The long isoform TrkB, including the tyrosine kinase domain (ID Q16620-1; variant c).
2. The truncated isoform TrkB-T1 lacking the tyrosine kinase domain (ID Q16620-2; variant b).
3. The truncated isoform TrkB-T-Shc lacking the tyrosine kinase domain but retaining the Shc site (ID Q16620-3; variant e).

Description

The unprocessed precursor of the full-length TrkB (a) consists of 838 AA. Variant (c) excludes 16 AA of unknown function, located downstream of the transmembrane segment.
The N-terminal portion (AA 32-430) is potentially extracellular and includes several N-glycosylation sites (AA 67, 121, 254). It follows a single transmembrane segment (AA 432-454). The C-terminal portion is cytosolic (AA 455-822) and comprises the Protein Kinase domain. This region includes the ATP binding site (AA 544-552) and several sites of autophosphorylation such as Tyr-516/702/706/707/817 (AA position refers to variant c).
The truncated Trkb-T1 (b) is composed of 477 AA. TrkB-T-Shc variants d and e consist of 553 AA and 537 AA, respectively. Truncated isoforms TrkB-T1 and TrkB-T-Shc include C-terminal sequence variations of 10 and 9 AA, respectively.

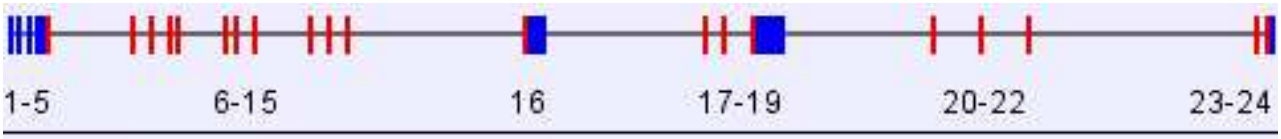
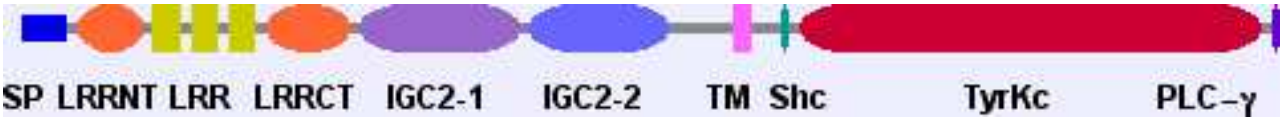


TABLE 1.

EXON	SIZE	EXON	SIZE	EXON	SIZE
1a	194	5a	584	14	101
1b	22	5b	351	15	100
2a	122	6	75	16	5161
2b	89	7	72	17	48
2c	100	8	69	18	189
3a	360	9	155	19	6110
3b	261	10	137	20	131
3c	165	11	133	21	173
4a	454	12	306	22	235
4b	192	13	36	23	159
				24	2339

Figure 1: The horizontal bar represents NTRK2 gene (355,039 bp). Vertical bars depict the exons 1-24 (red: translated regions, blue: 5' and 3' UTR regions).



The predicted domains of TrkB (variant c): Signal Peptide (SP, AA 1-31); Leucine Rich Repeat N-Terminal domain (LRRNT, AA 31-65); Leucine-rich Repeats (LRR, AA 72-93, 96-117, 116-138); Leucine Rich Repeat C-Terminal domain (LRRCT, AA 148-195); Immunoglobulin C-2 Type 1 domain (IGC2-1, AA 197-282); Immunoglobulin C-2-type 2 domain (IGC2-2, AA 295-365); Transmembrane (TM, AA 431-454); the Protein Kinase domain (TyrKc, AA 538-807). In addition the site of interaction with SHC1 (Shc, AA 516) and with Phospho-Lipase C-gamma-1 (AA PLC-gamma, 817) are indicated.

Expression

NTRK2 gene is preferentially expressed in brain, spinal cord, cranial and spinal ganglia. Expression is most prominent in the following brain regions: amygdale, caudate nucleus, cerebellum, choroid plexus, corpus callosum, cortex, hippocampus, hypothalamus and thalamus. In addition, a variety of cranial structures such as eyes, ophthalmic nerves, various facial districts and vestibular system indicate significant expression. Lower expression is described in several other tissues such as heart, kidney, lung, ovaries, pancreas, pituitary gland, prostate, salivary glands, skeletal muscle, spleen, thymus and thyroid.

Isoforms TrkB and TrkB-T1 are expressed in brain as well as in several peripheral areas, whereas TrkB-T-Shc is primarily expressed in brain.

AceView (NCBI) analysis of cDNA clones supports the expression pattern suggested by the evaluation of mRNA described above. In addition suggests elevated expression in several tumor tissues.

Localisation

Neuronal activity promotes TrkB translocation from intracellular vesicles to the plasma membrane where it becomes available for neurotrophins. The N-terminal segment is extracellular and is involved in neurotrophin binding and cell adhesion. A single transmembrane segment is located in the central portion of the polypeptide. The C-terminal segment is intracellular and comprises the protein kinase domain.

Function

TrkB specifically binds brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5. It can also bind neurotrophin-3 with low affinity but it excludes nerve growth factor (NGF). Neurotrophin binding triggers receptor dimerization and consequent trans-phosphorylation of tyrosine residues of the TyrKc domain. Phosphorylated receptor undergoes conformational changes, which promote the recruitment of intracellular substrates such SHC1, PI-3

kinase, and PLC-gamma-1. The signaling cascades consequently activated support neuronal survival during development and following injuries, promote neuronal differentiation and maintenance, control short-term and long-term synaptic activity. TrkB can also form heterodimers with the pan-neurotrophin receptor p75NTR or with truncated TrkB. This influences the establishment of specific connections with signaling pathways.

Homology

TrkB belongs to the large family of protein kinase comprising a conserved kinase domain. It is included in the subfamily of tyrosine protein kinase. For the presence of a highly conserved intracellular TyrKc domain it is most related to growth factor receptors, and particularly to the neurotrophic factor receptors TrkA and TrkC. The homology with tyrosine kinase receptors is extended to the IGC-2 and LRRs domains, however, these are also present in cell-adhesion molecules.

Mutations

Germinal

Heterozygous missense mutations leading to substitution of highly conserved residues have been linked to Obesity, Hyperphagia and Developmental Delay.
Recurrent SNPs of the NTRK2 locus are associated with Eating Disorders (Anorexia and Bulimia nervosa).

Somatic

Tumor-specific mutations in the kinase domain have been identified in Colorectal Cancer cells.

Implicated in

Various diseases

Disease

Obesity, Hyperphagia and Developmental Delay. Neuroblastomas, Pancreatic Ductal Adenocarcinomas, Wilms's tumors, Colorectal Cancer.

Oncogenesis

Overexpression of full-length TrkB is generally associated with malignant transformation. Excessive TrkB signaling through MAPK, PI3K and mTOR pathways support tumor development and metastasis. In highly malignant tumors the overexpression of TrkB enhances angiogenesis and invasive potential by upregulating VEGF and matrix proteases. Furthermore TrkB overcomes apoptosis caused by loss of cell-matrix interactions (anoikis), which is a natural barrier to metastasis.
In contrast with the oncogenic activity of TrkB, the truncated isoforms TrkB-T1 and TrkB-T-Shc, lacking the tyrosine kinase domain, behave as dominant-negative inhibitors and counteract tumor growth.

To be noted

Note: NTRK2 gene is comprised in the region, del(9q), commonly deleted in acute myeloid leukemia, this disease is believed to arise by heterozygous loss of tumor suppressor genes.
Numerous structural abnormalities of the region 9q22 are associated with cancer cases reported by The Cancer Genome Anatomy Project (CGAP).

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This article should be referenced as such:

Gabellini N. NTRK2 (neurotrophic tyrosine kinase, receptor, type 2). Atlas Genet Cytogenet Oncol Haematol.2008;12(4):314-317.