## Phylogeny

• Member of the Tyrosine Kinase (TK) group, TRK subfamily defined by kinome surveys; paralogs are NTRK2 (TRKB) and NTRK3 (TRKC) (cocco2018ntrkfusionpositivecancers pages 1-3).  
• Orthologs are retained across vertebrates—documented in human, mouse, rat, zebrafish, medaka, stickleback and sea lamprey—consistent with high retention of TRK genes after 1R/2R whole-genome duplications (brunet2016wholegenomeduplications pages 6-7).  
• TRK subfamily clusters with DDR, ROR and MUSK families within RTKs in phylogenetic analyses of 5,181 TK domains (brunet2016wholegenomeduplications pages 3-4).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (unknownauthors2009micrornamediatedregulation pages 26-30).

## Cofactor Requirements

Catalytic activity requires divalent cations (Mg²⁺ or Mn²⁺) for ATP coordination, as observed for receptor tyrosine kinases (unknownauthors2016traf4andcastrationresistant pages 27-27).

## Substrate Specificity

• Intrinsic autophosphorylation targets: Y676, Y680, Y681 (activation loop), Y496 (juxtamembrane NPXY motif), Y791 (C-terminal PLCγ docking site) (cocco2018ntrkfusionpositivecancers pages 3-4).  
• Phospho-Y496 NPXY motif recruits PTB-domain adaptors SHC1 and FRS2, exemplifying preference for substrates containing NPXY around the target tyrosine (cocco2018ntrkfusionpositivecancers pages 3-4).  
• Motif profiling attributed to Yaron-Barir 2024 indicates selectivity for acidic residues at –2 and hydrophobic residues at +1 relative to the phosphorylated tyrosine, although full consensus is not detailed in the excerpt (unknownauthors2020structuralandfunctional pages 25-28).

## Structure

• Single-pass type I membrane protein, 790–796 aa: N-terminal signal peptide → three leucine-rich repeats flanked by cysteine clusters (C1, C2) → two Ig-like domains (Ig1, Ig2) → transmembrane helix → juxtamembrane segment → bilobed tyrosine-kinase domain → short C-terminal tail (cocco2018ntrkfusionpositivecancers pages 3-4).  
• Mature receptor is an N-glycosylated 140 kDa protein; precursor undergoes glycan processing in the secretory pathway (cocco2018ntrkfusionpositivecancers pages 3-4).  
• Kinase domain contains conserved VAIK (β3), HRD (catalytic loop) and DFG (activation loop) motifs; Y674-Y675 (human numbering corresponds to Y676-Y681 region described) lie in the activation loop and participate in the hydrophobic regulatory spine together with the C-helix (unknownauthors2016traf4andcastrationresistant pages 27-27).

## Regulation

Post-translational modifications  
– Autophosphorylation at Y676/Y680/Y681 activates catalytic competence (cocco2018ntrkfusionpositivecancers pages 3-4).  
– Phospho-Y496 creates SHC/FRS2 docking sites initiating RAS-MAPK and PI3K cascades (cocco2018ntrkfusionpositivecancers pages 3-4).  
– Phospho-Y791 recruits PLCγ1 to stimulate DAG/IP₃ signalling (cocco2018ntrkfusionpositivecancers pages 3-4).  
– Lys63-linked polyubiquitination mediated by the E3 ligase CBL facilitates receptor internalisation and down-regulation (unknownauthors2016traf4andcastrationresistant pages 27-27).  
Allosteric and contextual regulation  
– NGF-induced homodimerisation aligns intracellular kinase domains for trans-phosphorylation (unknownauthors2024smallmoleculemodulation pages 11-15).  
– Co-receptor p75NTR modulates ligand affinity, receptor turnover and downstream signalling bias (cocco2018ntrkfusionpositivecancers pages 4-6).  
– Alternative splicing yields isoforms TRKA I, TRKA II and constitutively active TRKA III lacking Ig domains, the latter signalling independently of ligand (cocco2018ntrkfusionpositivecancers pages 6-7).

## Function

• Highest expression in sympathetic, trigeminal and dorsal-root-ganglion neurons and in central cholinergic neurons; limited expression in non-neuronal tissues (unknownauthors2020structuralandfunctional pages 25-28).  
• Primary ligand NGF triggers survival and differentiation; NT-3 supports axonal extension via NTRK1 without affecting survival (unknownauthors2024smallmoleculemodulation pages 11-15).  
• Downstream pathways  
 – SHC/FRS2-GRB2-SOS → RAS-RAF-MEK-ERK regulates neuronal differentiation (cocco2018ntrkfusionpositivecancers pages 4-6).  
 – SHC/GAB1 or direct p85 binding → PI3K-AKT governs cell survival (diaz2016noveloncogenicdrivers pages 34-37).  
 – Phospho-Y791 → PLCγ1 → PKC pathway drives neurite outgrowth (cocco2018ntrkfusionpositivecancers pages 4-6).  
• Interacting partners include SH2B1/2, IRS1/2, GRB2, SHP2 and SRC-family kinases recruited to defined phosphotyrosines (cocco2018ntrkfusionpositivecancers pages 6-7).

## Inhibitors

• Clinically approved pan-TRK inhibitors: larotrectinib and entrectinib bind the kinase domain with nanomolar potency (cocco2018ntrkfusionpositivecancers pages 24-27).  
• Pre-clinical multikinase inhibitors with TRKA activity: CEP-751 and lestaurtinib (cocco2018ntrkfusionpositivecancers pages 6-7).  
• Resistance mutations in the kinase domain emerge under inhibitor pressure, necessitating second-generation compounds (cocco2018ntrkfusionpositivecancers pages 24-27).

## Other Comments

• Loss-of-function missense mutations such as G571R abolish kinase activity and cause congenital insensitivity to pain with anhidrosis (cocco2018ntrkfusionpositivecancers pages 24-27).  
• Oncogenic fusions retaining the kinase domain—TPM3-NTRK1, TPR-NTRK1 and others—drive constitutive signalling in diverse tumours; ETV6-NTRK3 is a well-studied paralogous fusion (cocco2018ntrkfusionpositivecancers pages 20-21).  
• Constitutively active splice variant TRKA III contributes to neuroblastoma pathogenesis (cocco2018ntrkfusionpositivecancers pages 6-7).  
• Over-expression correlates with aggressive behaviour in breast and other solid tumours via MAPK and PI3K pathway activation (cocco2018ntrkfusionpositivecancers pages 6-7).

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