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Review

# ETV6–NTRK3: a chimeric protein tyrosine kinase with transformation activity in multiple cell lineages

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**Abstract**

The *ETV6–NTRK3* (*TEL–TRKC*) gene fusion was discovered by breakpoint analysis of the t(12;15)(p13;q25) translocation associated with congenital fibrosarcoma, a pediatric soft tissue malignancy. *ETV6–NTRK3* (EN) encodes the sterile alpha motif oligomerization domain of the ETV6 (TEL) transcription factor linked to the protein tyrosine kinase domain of the neurotrophin-3 receptor NTRK3 (TRKC). The EN chimeric oncoprotein links to multiple signaling cascades including Ras-MAP kinase and PI3K-AKT through the IRS-1 adapter protein. Recent evidence indicates that a functional insulin-like growth factor 1 receptor axis and higher order polymer formation are essential for EN oncogenesis. EN has been detected in other malignancies, including secretory breast carcinoma. This chimeric oncoprotein is therefore unique in being expressed in tumors derived from multiple cell lineages.


*Keywords:* ETV6–NTRK3; Translocation; Chimeric tyrosine kinase; IRS-1; Tel

**Contents**



*Abbreviations:* EN, ETV6–NTRK3; ETV6, ETS variant gene 6; NTRK3, neurotrophic tyrosine kinase, receptor, type 3; PTK, protein tyrosine kinase; ERK, extracellular signal-regulated kinase; IGFIR, insulin-like growth factor-I receptor; IRS-1, insulin receptor substrate-1; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; PI3K, phosphatidylinositol 3-kinase; PTB, phosphotyrosine binding domain

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## 1. Chimeric protein tyrosine kinases in oncogenesis

Receptor protein tyrosine kinases (PTKs) are a highly regulated family of proteins in normal cells, but these proteins may undergo activating mutations or structural alterations to become oncoproteins in human malignancies. Oncogenic activation of RTKs can result from genetic lesions such as point mutations, deletions, or over-expression by gene amplification (see [1–3]). Alternatively, chromosomal rearrangements leading to the formation of an oncogenic gene fusion can involve receptor PTK or other PTK-encoding genes as fusion partners. In such a scenario, the PTK domain becomes fused to an oligomerization domain contributed by the other fusion partner to create a chimeric oncoprotein. For BCR-ABL and other chimeric PTKs, oligomerization through protein self-association leads to ligand-independent auto- or cross-phosphorylation of the kinase domain. This in turn constitutively activates the PTK domain, resulting in aberrant stimulation of downstream signaling pathways [1]. In almost all instances, generation of these translocation-derived gene fusions appear to represent very early genetic changes suggesting potential etiologic roles in oncogenesis [4].

## 2. The *ETV6* gene as a target of chromosomal translocations

*ETV6* (*TEL*) is a member of the ETS transcription factor gene family and is essential for developmental processes such as hematopoiesis and yolk sac angiogenesis [5]. For reasons that remain unclear this gene is frequently targeted by chromosomal translocations in human malignancies, resulting in the expression of oncogenic *ETV6* gene fusions. Chimeric oncoproteins often contain the sterile alpha motif (SAM; also known as pointed, PNT, or helix-loop-helix, HLH) oligomerization domain of ETV6 fused to either a DNA binding transcription factor such as AML1 [6,7], or more commonly to a PTK domain such as that of PDGFRβ [8], ABL [9,10], JAK2 [11–13], ARG [14,15], or FGFR3 [16]). These chimeric proteins have predominantly been discovered in human leukemias, and expression appears to be sub-type specific [17].

## 3. The ETV6–NTRK3 chimeric oncoprotein

The *ETV6–NTRK3* gene fusion was first identified by cloning of the t(12;15)(p13;q25) translocation in congenital (or infantile) fibrosarcoma [18], a mesenchymal malignancy of very young children (see below). This rearrangement fuses the N-terminal SAM domain of ETV6 to the C-terminal PTK domain of NTRK3 (TrkC), generating a fusion protein that is similar in structure to other ETV6 chimeric PTKs (see Fig. 1). NTRK3 is the transmembrane surface receptor for neurotrophin-3 and is primarily expressed in the central nervous system where it is involved in growth, development, and cell survival of neuronal cells (reviewed in [19]). The ETV6–NTRK3 (EN) fusion protein has potent in vivo and in vitro transforming activity in several cell lineages including fibroblasts [20], hematopoietic cells [21], and breast ep-

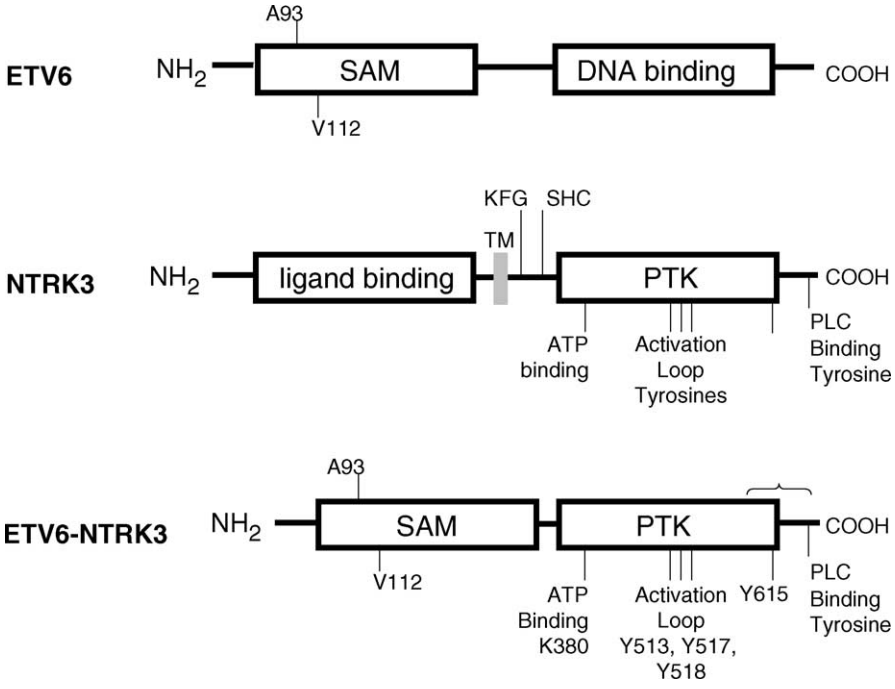


Fig. 1. Schematic diagram of ETV6–NTRK3 (EN) fusion protein, which contains the SAM dimerization domain of ETV6 fused to the protein tyrosine kinase (PTK) domain of NTRK3. Note that EN does not contain the transmembrane domain or SHC and KFG binding sites of wild-type NTRK3. Bracket indicates putative region of IRS-1 binding.