

Leukaemia Section

Short Communication

t(12;15)(p13;q25) ETV6/NTRK3 in solid tumors

Jean Loup Huret

jean-loup.huret@atlasgeneticsoncology.org

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Abstract

Review on t(12;15)(p13;q25) in solid tumors, with data on clinics, and the genes involved.

Keywords

Chromosome 12; Chromosome 15; ETV6; NTRK3; Chronic eosinophilic leukemia; Acute myeloid leukemia; B-Lineage Acute lymphoblastic leukemia; Secretory ductal breast carcinoma; Congenital mesoblastic nephroma; Congenital/infantile fibrosarcoma; Papillary thyroid carcinoma; Inflammatory myofibroblastic sarcoma; Secretory carcinoma of salivary glands (mammary analogue); atypical Spitz tumors.

Clinics and pathology

A t(12;15)(p13;q25) ETV6/NTRK3 has been found: 1) in congenital/infantile fibrosarcoma and cellular mesoblastic nephroma (which may be a renal form of infantile fibrosarcoma), 2) in secretory breast (ductal) carcinoma and in its analogue in the salivary glands, 3) in acute leukemias (both myeloid and lymphoid), 4) in papillary thyroid carcinoma, often radiation-associated, 5) in inflammatory myofibroblastic tumor, and, in few cases, in other tumors.

Equivalents of the ETV6/NTRK3 fusion was also found in rare instances in the above mentioned tumors: EML4/NTRK3, MYH9/NTRK3, MYO5A/NTRK3, LMNA/NTRK1, and ETV6/?

Disease

Congenital/infantile fibrosarcoma (WHO/OMS 8814/3) (CIF)

Congenital/infantile fibrosarcoma is a low-grade

malignant spindle cell tumor of the soft tissues that usually presents before the age of 2 years (diagnosed at birth in 40%, before 6 months in 60% of cases, more common in boys than in girls), occurring 1) most often in the extremities and with a good prognosis, at times 2) in the axial skeleton with a somewhat worse prognosis.

Local recurrence is common (10 to 30 % of cases) but metastases are rare. Overall 5-year survival is at least 90% (Farmakis et al., 2014). CIF accounts for 10% of soft tissue tumors in infants.

Cytogenetics

A t(12;15)(p13;q25) ETV6/NTRK3 was found in most cases, but is not found in either infantile fibromatosis, a close but benign entity, or in fibrosarcoma of the adulthood.

The t(12;15) ETV6/NTRK3 is most often accompanied with trisomy or tetrasomy 11 (Knezevich et al., 1998; Rubin et al., 1998; Bourgeois et al., 2000; Punnett et al., 2000; Argani et al., 2001; Dubus et al., 2001; Sheng et al., 2001; Miura et al., 2002; McCahon et al., 2003; Ramphal et al., 2003; Morerio et al., 2004; Nonaka and Sun, 2004; Himori et al., 2005; Rizkalla et al., 2011).

The reciprocal NTRK3/ETV6 fusion product may also be found, with NTRK3 exon 14 fused to ETV6 exon 6 (Dubus et al., 2001).

A t(2;15)(p21;q24) EML4/NTRK3 has also been found in two cases of CIF.

One was a 9-mo-old male patient with recurrent congenital fibrosarcoma and a history of left upper extremity hemimelia without other congenital anomalies.

Exon 2 of EML4 was fused to exon 14 of NTRK3 (Tannenbaum-Dvir et al., 2015; Church et al., 2018).

A congenital infantile fibrosarcoma was found to harbor a LMNA/NTRK1 gene fusion (Wong et al., 2015).

Disease

Congenital Mesoblastic Nephroma (WHO/OMS 8960/1) (CMN)

Congenital mesoblastic nephroma is the most common kidney tumor found in infants younger than 6 months and accounts for 3-5% of all paediatric renal neoplasm. The 5-year event-free survival rate is 95%.

Histopathologically, it consists of spindle cells. There are three histologic subtypes: classic, mixed, and cellular. The cellular subtype is identical to infantile fibrosarcoma and is the form with a t(12;15) ETV6/NTRK3 and trisomy 11 (PDQ Pediatric Treatment Editorial Board, 2019). Cellular mesoblastic nephroma tends to present later in infancy than the classic form, and can exhibit aggressive behavior including metastases (Bayindir et al., 2009). It has been suggested that the cellular subtype represents in fact congenital infantile fibrosarcoma occurring in the kidney (Bayindir et al., 2009; El Demellawy et al., 2016).

A t(12;15) ETV6/NTRK3, most often accompanied with trisomy or tetrasomy 11, or a fusion ETV6/NTRK3 has been found in more than 40 cases; some cases were mixed forms; none was classical form (Rubin et al., 1998; Knezevich et al., 1998; Argani et al., 2000; Ramachandran et al., 2001; Watanabe et al., 2002; Henno et al., 2003; Anderson et al., 2006; Bayindir et al., 2009).

Cytogenetics

Although the t(12;15)(p13;q25) ETV6/NTRK3 was found in most cases, a t(2;15)(p21;q24) EML4/NTRK3 has also been found in one case of CMN (Church et al., 2018).

Disease

Breast Ductal carcinoma - Secretory breast carcinoma subtype (WHO/OMS 8502/3) (SBC)

Secretory breast carcinoma is a rare (less than 0.15% of all breast cancers) subtype of breast ductal carcinoma (but the most common breast cancer in the pediatric population), with a distinct morphology: eosinophilic secretion and positive periodic acid-Schiff (PAS) secretions are seen, immune-positivity for S100 and mammaglobin, most often triple negativity (ESR1/2-, PGR-, ERBB2-) and an excellent prognosis in children and adolescents. It occurs in both children and adults with a wide age range from 3 to 83 years. Most reported cases are in young women, with a median age of 25 years. There are only 120 cases published in literature, including 32 in male

patients. Breast secretory carcinoma is a slow-growing, low-grade subtype of infiltrating ductal carcinoma.

The disease seems slightly more aggressive in adults (Vasudev and Onuma 2011; Ghilli et al., 2018).

Cytogenetics

A t(12;15)(p13;q25) ETV6/NTRK3 was found in most cases (Tognon et al., 2002; Diallo et al., 2003; Stransky et al 2014).

Genes

ETV6/NTRK3 chimeric product can transform normal mouse mammary epithelial cells.

Fusion was between ETV6 nucleotide 1033 and NTRK3 nucleotide 1601 as previously shown for sarcoma-associated fusions (Knezevich et al., 1998). This differs from the ETV6/NTRK3 gene fusion reported in a case of acute myeloid leukemia, in which ETV6 exon 5 was not present in the fusion (Eguchi et al., 1999).

The rare secretory breast carcinomas with metastases, more aggressive tumors, showed amplification of the 16p13.3 locus, a TERT promoter mutation and loss of 9p21.3 locus (Hoda et al., 2019).

Disease

Mammary analogue secretory carcinoma of salivary glands (MASC)

A t(12;15)(p13;q25) ETV6/NTRK3 was found in salivary gland tumors (mostly from the parotid gland) with histo-morphologic and immune-histochemical features reminiscent of secretory carcinoma of the breast, with eosinophilic secretion, positivity for PAS, S-100 protein and mammaglobin (Skálová et al., 2010; Chiosea et al., 2012; Connor et al., 2012; Skálová et al., 2014; Pinto et al., 2014). More than 250 cases have been described (review in Skálová et al., 2017). Mean age was 47 years (14-78 years), there is a slight male predominance. MASC mimics other salivary tumors, most often adenocarcinoma, not otherwise specified and acinic cell carcinomas.

MASC usually behaves indolently, but like other low-grade salivary gland carcinomas, there is some loco-regional recurrence and distant metastases (Skálová et al., 2017).

Cytogenetics

A t(12;15)(p13;q25) ETV6/NTRK3 was found in most cases.

A few cases where ETV6 was fused with an unknown partner different from NTRK3 were described; these may behave more aggressively (Ito et al., 2015; Skálová et al., 2016).

Disease

Thyroid: Papillary thyroid carcinoma (WHO/OMS 8260/3) (PTC)

In an analysis of 62 radiation-associated papillary thyroid carcinomas post-Chernobyl (iodine-131 exposure), 9 (14.5%) of PTCs harbored ETV6/NTRK3 rearrangement; ETV6/NTRK3 fusion was the second most common rearrangement type after "RET/PTC". Further screening of 151 sporadic PTCs revealed three positive cases, resulting in a prevalence of 2%. The majority of post-radiation-associated PTCs with ETV6/NTRK3 rearrangement were classified as the follicular variant of PTC (Leeman-Neill et al 2014). In a study of 496 papillary thyroid carcinoma without radiation exposure, and classified as low risk, 5 cases (three "classical", one "follicular") presented with an ETV6/NTRK3 rearrangement. Ages and sex: were: 41/F, 36/F, 23/F, 17/F) (The Cancer Genome 2014). Another genome sequencing study from "The Cancer Genome Atlas" (TCGA) found 6 such cases (Stransky et al 2014).

Disease

Inflammatory myofibroblastic tumor/myofibroblastic sarcoma (WHO/OMS 8825/1) (IMT)

Inflammatory myofibroblastic tumor is a rare visceral and soft tissue tumor (commonly seen in the lung), consisting of myofibroblastic spindle cells with inflammatory cells. Local recurrences are seen in about 25% of patient, but metastases are rare. It affects primarily children and young adults, with a slight male predominance. Favorable outcome is documented in most cases.

An ETV6/NTRK3 fusion was found in at least 6 cases of inflammatory myofibroblastic tumor: in a 17-year-old girl and in 2 other cases in a subset of ALK-negative inflammatory myofibroblastic tumors, in a 7-year old child and in a 23-year-old adult patient, and in a 44-year-old female patient (Alassiri et al 2016; Yamamoto et al 2016; Takahashi et al 2018).

Disease

Skin melanocytic tumors (WHO/OMS 8770/1 and 8720/3) and other skin carcinomas

Note

A t(12;15)(p13;q25) ETV6/NTRK3 was found in 4 cases of atypical Spitz tumors (Yeh et al., 2016), a group of cutaneous melanocytic tumors (Murali et al., 2012 <http://atlasgeneticsoncology.org/Tumors/SpitzTumorID6241.html>). Ages and sex were: 2/F, 6/F, 7/M, and 10/F (Yeh et al., 2016).

An ETV6/NTRK3 fusion was also detected in a skin melanoma in massive data sets from genome

sequencing studies from the TCGA (Stransky et al 2014).

A secretory carcinoma of the skin mimicking secretory carcinoma of the breast and the and secretory carcinoma salivary gland was found to harbor an ETV6/NTRK3 fusion gene (Huang et al., 2016)

Cytogenetics

Other cases presented with the following translocations/genes fusions: MYH9/NTRK3 and MYO5A/NTRK3. In all those cases, NTRK3 fusions constitutively activated the RAS/RAF/MAPK, PI3K/AKT/MTOR and PLCG pathways in melanocytes (Yeh et al., 2016).

Disease

Brain tumors (WHO/OMS 9425/3 9401/3)

Note

In a series of 149 pediatric low-grade gliomas, an ETV6/NTRK3 fusion was found in a 13-year-old girl with a pilomyxoid astrocytoma (Zhang et al 2013).

An ETV6/NTRK3 fusion was also found in a high grade astrocytoma (massive data from genome sequencing) (Wu et al 2014).

Cytogenetics

The reciprocal NTRK3/ETV6 fusion product was also found (Zhang et al 2013).

Disease

Colon adenocarcinoma (WHO/OMS 8140/3)

At least 4 cases of colorectal carcinoma were found to have an ETV6/NTRK3 fusion, in massive data from genome sequencing studies from the TCGA (Seshagiri et al 2012; Stransky et al 2014; Hu et al 2018).

Disease

Sinonasal adenocarcinoma

Two cases of low grade sinonasal adenocarcinoma were found to have the t(12;15)(p13;q25) ETV6/NTRK3 (Andreasen et al 2017).

Cytogenetics

Another case presented with ETV6 fused to an unknown partner (Andreasen et al 2017).

Genes involved and proteins

ETV6 (*ets variant 6*)

Location 12p13.2

Protein

ETV6 is a strong transcriptional repressor. ETV6 is a 452 amino acid member of the ETS family (signal-dependent transcriptional regulators, mediating cell proliferation, differentiation and tumorigenesis). The

ETV6 protein contains two major domains, the HLH (helix-loop-helix) and ETS domains. The N-term HLH domain, also referred to as the pointed or sterile alpha motif domain, is responsible for hetero- and homo-dimerization. The C-term ETS domain is responsible for sequence specific DNA-binding and protein-protein interaction. A central domain, called internal domain, is involved in the recruitment of a repression complex including NCOR1, NCOR2, and SIN3A (Braekeleer et al., 2014 <http://atlasgeneticsoncology.org/Genes/ETV6ID38.html>).

NTRK3 (neurotrophic tyrosine kinase, receptor, type 3)

Location 15q25.3

Protein

NTRK3 is a transmembrane receptor tyrosine kinase which triggers PI3K/AKT, RAS/RAF/MAPK, and PLCG pathways. NTRK3 is a 839 amino acid protein with a N-term extra-cellular ligand binding domain, a transmembrane domain, and a C-term intracellular tyrosine kinase domain. Ligand for NTRK3 is NTF3 (neurotrophin 3) (Knezevich 2004 <http://atlasgeneticsoncology.org/Genes/NTRK3ID433.html>).

Result of the chromosomal anomaly

Hybrid Gene

Description

In solid tumors, ETV6 exon 5 - NTRK3 exon 15 fusion is the most frequent:

The fusion was exon 4 - exon 14 in most papillary thyroid carcinoma cases, but one exon 5 - exon 14 fusion case was also found (Leeman-Neill et al.,

2014)

The fusion was exon 5 - exon 15 in: secretory ductal breast carcinoma (Tognon et al., 2002), congenital mesoblastic nephroma (Knezevich et al., 1998; Rubin et al., 1998; Argani et al., 2000; Ramachandran et al., 2001; Watanabe et al., 2002; Henno et al., 2003; Anderson et al., 2006; Bayindir et al., 2009), secretory carcinoma of salivary glands (mammary analogue) (Skálová et al., 2010; Skálová et al., 2014), atypical Spitz tumors (Yeh et al., 2016), and also in a case of colon adenocarcinoma (Seshagiri et al., 2012). The classical exon 5 - exon 15 fusion is also found in congenital/infantile fibrosarcoma (Knezevich et al., 1998; Rubin et al., 1998; Bourgeois et al., 2000; Punnett et al., 2000; Argani et al., 2001; Dubus et al., 2001; Sheng et al., 2001; Miura et al., 2002; McCahon et al., 2003; Ramphal et al., 2003; Nonaka and Sun, 2004; Himori et al., 2005), but, also, a fusion NTRK3 exon 14 - ETV6 exon 6 was found in one case (Dubus et al., 2001).

In most leukemia cases, ETV6 exon 5 was fused to NTRK3 exon 15 (Forghieri et al., 2011; Roberts et al., 2014). In one case ETV6 exon 4 was fused to NTRK3 exon 15 (Eguchi: et al., 1999), and in another case, fusion transcripts contain ETV6 exons 1 through 5 fused to NTRK3 exons 13b and 14b or NTRK3 exons 13 through 18 (Kralik et al., 2011).

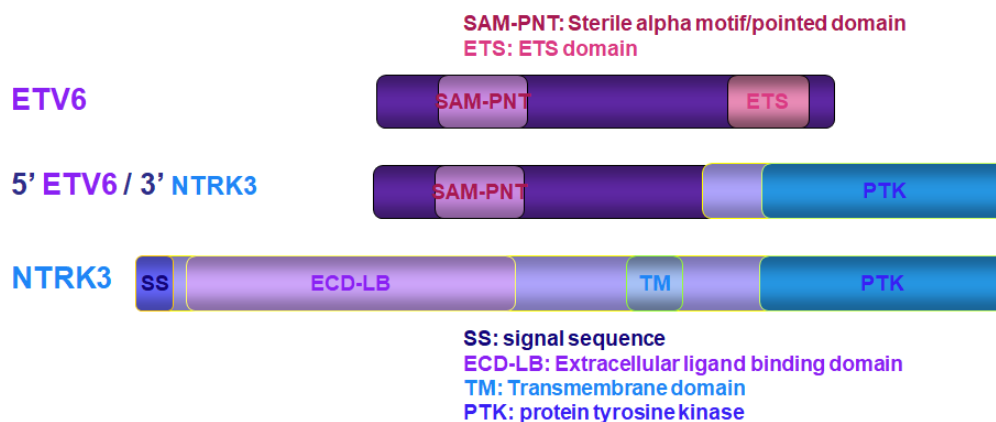
Fusion Protein

Description

The SAM-PNT (sterile alpha motif- pointed) domain of ETV6 is fused to the PTK (Protein Tyrosine Kinase domain) of NTRK3.

Oncogenesis

It leads to dimerization, and induction of CCND1 (cyclin D1) and increased cell cycle progression. ETV6/NTRK3 also leads to constitutive activation of the PI3K/AKT, RAS/RAF/MAPK, and PLCG pathways (Lannon and Sorensen, 2005).



t(12;15)(p13;q25) ETV6/NTRK3

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To be noted

Therapeutic trials with TRK-(tropomyosin receptor kinase) inhibitors are being developed with some remarkable successes (Lange and Lo, 2018).

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