

Supplemental Figure 1

94 unique fusions



20 NTRK as 5' partner



8 curation errors

Remove	Note
NTRK1-LMNA*	Data entry error
NTRK1-NFASC*	Data entry error
NTRK1-TFG*	Data entry error
NTRK1-TPR*	Data entry error
NTRK2-SPECC1L*	Data entry error
NTRK3-TFG*	Data entry error
NTRK1-Fc	Recombinant
NTRK1-CD5	Unlisted

12 properly curated

Keep	Note
NTRK1-TPM3*	w/ Reciprocal
NTRK2-AFAP1*	w/ Reciprocal
NTRK3-ETV6*	w/ Reciprocal
NTRK3-RBPMS*	w/ Reciprocal
NTRK1-DYNC2H1	w/o Reciprocal
NTRK2-LAP3	w/o Reciprocal
NTRK2-RASEF^	w/o Reciprocal
NTRK3-LOXL2	w/o Reciprocal
NTRK3-PEAK1^	w/o Reciprocal
NTRK3-SCAPER^	w/o Reciprocal
NTRK3-ACTR8	w/o Reciprocal
NTRK3-SLC8B1	w/o Reciprocal

* = reciprocal contained in main list
 ^ = result of intrachromosomal deletion

Supplemental Figure 1: Analysis of 5' NTRK fusions found in public fusion databases. 94 unique NTRK fusions were collected from public fusion databases. 20/94 listed an NTRK as the 5' fusion partner. Manual vetting of each manuscript determined 8/20 were curation errors as 6/8 were listed with NTRK as the 3' partner in the paper, but were curated into the database in the reverse orientation. NTRK1-Fc was a recombinantly created protein for experimental purposes and therefore not found in a patient. NTRK1-CD5 was not found within the cited manuscript and was entered into the fusion database in error. 12/20 5' NTRK fusions were found in their cited papers, with 4/12 also having their reciprocal fusion listed. Additionally, 3/8 5' NTRK fusions reported without reciprocal fusions were likely the result of an intrachromosomal deletion.

Supplemental Figure 2

GENE NTRK1 Fusion orientation Patient information Gene Summary Gene Talk

VARIANT LMNA-NTRK1 e11-e10 Variant Summary Variant Talk

EVIDENCE EID8900 Evidence Summary Evidence Talk

Submitted by JasonSaliba Last Modified by ArpadDanos Last Reviewed by JasonSaliba Accepted by ArpadDanos

Detection Method After disease progression with no objective response to therapy, a 75-year-old with metastatic colorectal cancer that spread to the liver displayed elevated NTRK1 expression in both primary tumor and liver metastasis as measured by immunohistochemistry. FISH of the tumor and patient derived xenograft indicated NTRK1 involvement. 5'RACE PCR discovered a novel LMNA-NTRK1 fusion (exon 11 & exon 10) which resulted in the expression of two different fusion splice transcripts (exons 1-10 with exons 10-16 and exons 1-11 with exons 10-16). Fusion expression of both transcripts was confirmed by western blot, and Sanger sequencing revealed the fusion to be in-frame with the kinase domain intact. After 4 weeks of treatment with Entrectinib, CT scan revealed the patient showed a partial response with a 30% reduction of target lesions. This response was maintained for 5 months.

Exons fused

Frame & TKD status

Validation method

Clinical Interpretation

Evidence Level: C - Case Study

Response

Disease: Colorectal Cancer

Associated Phenotype: -

Source: Sartore-Bianchi et al., 2016, J Natl Cancer Inst

PubMed ID: 26563355

Citation

Clinical Trial: -

Evidence Rating: ★★★★★

Revisions Comments Log

Additional Comments
Posted by JasonSaliba 10 months ago

DNA breakpoints LMNA chr1:156,108,559; NTRK1 chr1:156,844,686

DNA breakpoints

Supplemental Figure 2: Screenshot of CIViC Evidence Item 8900 - LMNA-NTRK1. This evidence item was created from data curated from a published manuscript (PMID:26563355) describing a 75 year-old Colorectal Cancer patient found to harbor a LMNA-NTRK1 fusion who responded positively to Entrectinib therapy. Structured fields like the Ontology linked Disease field, Source and PubMed ID fields, and those fields relevant to a clinical interpretation are highlighted. Additionally, information in the Evidence statement relevant to the NTRK fusions SC-VCEP evaluation process describing fusion orientation, exons fused, fusion frame and tyrosine kinase domain (TKD) status, detection and validation methods, patient information, and patient response are highlighted as well. Finally, any breakpoints are listed in the Comments of the Evidence Item.

<https://civicdb.org/events/genes/3983/summary/variants/3225/summary/evidence/8900/summary#evidence>

Supplemental Figure 3

GENE NTRK2 Patient information Gene Summary Gene Talk

VARIANT KANK1-NTRK2 Variant Summary Variant Talk

EVIDENCE EID8653 Evidence Summary Evidence Talk

Submitted by Wan-HsinLin Last Modified by Wan-HsinLin Last Reviewed by JasonSaliba Last Commented On by JasonSaliba

Accepted by JasonSaliba

Fusion orientation
 A case report showing a two-year-old girl with an unusual pilocytic astrocytoma (PA) with both classic- and anaplastic- appearing tumors. A custom NGS panel identified a novel KANK1-NTRK2 fusion in both the classic and anaplastic regions. The KANK1-NTRK2 fusion was also detected in the resected recurrence which was histologically similar to the initial anaplastic region. The KIAA1549-BRAF fusion, the most common genetic alteration in PA, was absent in this case. Different from previously known mechanisms underlying the progression to anaplastic PA, this case lacks NF1 alterations and is radiation-naïve.

Detection Method

Ontology linked Disease
 Disease: Pilocytic Astrocytoma

Citation
 Source: López et al., 2019, Neuropathol. Appl. Neurobiol.
 PubMed ID: 29804288

Clinical Interpretation
 Evidence Level: C - Case Study
 Evidence Type: Diagnostic
 Evidence Direction: Supports
 Clinical Significance: Positive
 Variant Origin: Somatic

Associated Phenotype: -
 Clinical Trial: -
 Evidence Rating: ★★★★★

Revisions Comments Log

Additional Comments
 Posted by Wan-HsinLin about a year ago

The following were not reported: DNA breakpoints, RNA breakpoints, exons fused, if the fusion was in-frame, expressed, and if the tyrosine kinase domain was intact.
 Posted by JasonSaliba about a month ago

Unreported information

Supplemental Figure 3: Screenshot of CIViC Evidence Item 8653 - KANK1-NTRK2. This evidence item was created from data curated from a published manuscript (PMID:29804288) describing a 2 year-old Pilocytic Astrocytoma patient found to harbor a KANK1-NTRK2 fusion. Structured fields like the Ontology linked Disease field, Source and PubMed ID fields, and those fields relevant to a clinical interpretation are highlighted. Additionally, information in the Evidence statement relevant to the NTRK fusions SC-VCEP evaluation process describing fusion orientation, detection method, patient information and patient response are highlighted as well. Finally, in the Comments of the Evidence Item, special notation is made that several evaluation parameters are not reported in the manuscript this evidence was curated from.

<https://civicdb.org/events/genes/3984/summary/variants/3158/summary/evidence/8653/summary#evidence>