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Pan-Trk Immunohistochemistry Is an Efficient and Reliable Screen for the Detection of *NTRK* Fusions

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Abstract

Background—Activating neurotrophic tyrosine receptor kinase (*NTRK*) fusions, typically detected via nucleic acid based assays, are highly targetable and define certain tumors. Here, we explore the utility of pan-TRK immunohistochemistry (IHC) to detect *NTRK* fusions.

Design—*NTRK* rearrangements were detected prospectively using MSK-IMPACT, a DNA-based next generation sequencing assay. Transcription of novel *NTRK* rearrangements into potentially functional fusion transcripts was assessed via Archer Dx fusion assay. Pan-Trk IHC testing with mAb EPR17341 was performed on all *NTRK* rearranged cases and 20 cases negative for *NTRK* fusions on Archer.

Results—Of 23 cases with *NTRK* rearrangements, 15 had known activating fusions. Archer detected fusion transcripts in 6 of 8 novel *NTRK* rearrangements of uncertain functional significance. Pan-Trk IHC was positive in 20 of 21 cases with *NTRK* fusion transcripts confirmed by Archer. The discordant negative case was a mismatch repair-deficient colorectal carcinoma with an *ETV6-NTRK3* fusion. All 20 additional Archer-negative cases had concordant pan-TRK IHC results. Pan-Trk IHC sensitivity and specificity for transcribed *NTRK* fusions was 95.2% and 100%, respectively. All positive IHC cases had cytoplasmic staining while the following fusion partner-specific patterns were discovered: all 5 *LMNA-NTRK1* fusions displayed nuclear membrane accentuation, all 4 *TPM3/4* fusions displayed cellular membrane accentuation, and half (3/6) of *ETV6-NTRK3* fusions displayed nuclear staining.

Conclusion—Pan-Trk IHC is a time- and tissue-efficient screen for *NTRK* fusions, particularly in driver-negative advanced malignancies and potential cases of secretory carcinoma and congenital fibrosarcoma. Pan-Trk IHC can help determine whether translation occurs for novel *NTRK* rearrangements.

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INTRODUCTION

Neurotrophic tyrosine kinase receptor (*NTRK*) is a family of 3 proto-oncogenes including *NTRK1*, *NTRK2*, and *NTRK3* which encode Trk A, Trk B, and Trk C proteins, respectively. The latter are involved in biological processes such as neuronal survival, differentiation, and plasticity under physiological circumstances. In various cancers, oncogenic fusions involving the kinase domain of *NTRK1*, 2, or 3 are present. Recently, detecting *NTRK* fusions has become increasingly important as the Trk inhibitor Entrectinib has received FDA approval for patients with *NTRK* fusions and Trk inhibitors have demonstrated that patients a high response rate for patients with *NTRK* fusions.^{1–6}

Screening *NTRK* fusions is usually done on a molecular level and can be achieved with next generation sequencing (NGS) of DNA, or targeted RNA testing. However, molecular analyses are still expensive, comparable time-consuming and sampling error or nucleic acid degradation can pose a technical risk. Immunohistochemistry is a well established method, usually less expensive and fast compared to current molecular tests. Here, we investigate pan-Trk immunohistochemistry (IHC) as a faster and more tissue-efficient method to identify *NTRK* fusions.

METHODS

Case Selection and NGS Screening

After approval by our institutional review board, all patients with solid cancers with *NTRK1*, 2 or 3 rearrangements detected by MSK-IMPACT were included for further RNA/IHC evaluation. MSK-IMPACT is a hybridization-based NGS assay which interrogates all exons and select introns and promoters of 410 genes (including *NTRK1*, 2, and 3) for the detection of fusions, mutations, and copy number alterations in formalin-fixed paraffin embedded tumor tissue against matched normal blood. Both MSK-IMPACT and Archer are clinically validated and performed in a CLIA approved laboratory. Probes for introns 3, and 7 to 12 of *NTRK1*, and intron 15 of *NTRK2* are included in MSK-IMPACT to detect rearrangements involving these two genes. In addition, probes for *ETV6* introns 4 and 5 are included to detect *ETV6-NTRK3* rearrangements. Other introns affected by *NTRK* rearrangements could not be included because they are too large for a DNA-based capture approach (approximate upper limit: 25kb).

Downstream hotspot mutations in *KRAS/NRAS* (codons G12, G13, Q61, K117, A146), and *BRAF* (codon G466, G469, V600), which are readily detect via MSK-IMPACT, were recorded.

Archer RNA Testing

NTRK-rearranged cases with available material were sent for RNA-based tested with Archer to assess specific novel *NTRK1*, 2, and 3 rearrangements for the production of *NTRK* fusion transcripts.

Pan-Trk IHC

IHC staining for Trk A, B, and C expression was performed with pan-Trk monoclonal antibody (mAb) clone EPR17341 (Abcam, Cambridge, MA). The antibody is reactive to a homologous region of Trk-A, -B, and -C near the C terminus, and the exact sequence is proprietary. This commercial antibody is not FDA approved for clinical use to our best knowledge. Testis tissue, ganglia of the colonic plexus submucosus and cortical brain tissue were used as positive control tissues. EPR17341 was used at 6ug/ml. All assays were performed on a Leica-Bond-3 (Leica, Buffalo Grove, IL) automated stainer platform using a heat based antigen retrieval method and high pH buffer solution (ER2, Leica). Non-neoplastic lymphocytes, hepatocytes, colorectal epithelium, alveolar epithelium, and renal cortex were used as negative external controls. All available cases with *NTRK* rearrangements on MSK-IMPACT as well as 20 consecutive tumors without evidence of *NTRK* fusion on Archer were stained.

RESULTS

MSK-IMPACT and Archer Results

A total of 23 cases with *NTRK* rearrangements detected on MSK-IMPACT and sufficient material for immunohistochemistry were identified. Fifteen *NTRK* rearrangements were previously described in the literature while 8 were novel. Of these cases, Archer RNA testing was performed and positive for a fusion transcript in 10 of 15 cases with known Archer fusion (5 cases of known *NTRK* fusion detected by MSK-IMPACT were not tested via Archer) and 6 of 8 novel *NTRK* rearrangements while 2 of 7 novel *NTRK* rearrangements did not produce a fusion transcript.

The fusion cohort consisted of 5 colorectal carcinomas (2 *LMNA-NTRK1* fusions, 2 *TPM3-NTRK1* fusions, and 1 *ETV6-NTRK3* fusion), 4 mammary analogue secretory carcinomas (MASCs)/secretory carcinoma of salivary gland with *ETV6-NTRK3* fusions, 3 glioblastomas (1 *EML4-NTRK3* fusion, 1 novel *AFAP1-NTRK3* fusion, and 1 novel *BCR-NTRK2* fusion), 2 lung adenocarcinomas (1 *IRF2BP2-NTRK1* fusion and 1 *TPM3-NTRK1* fusion), 2 sarcomas (1 novel *TPM4-NTRK3* fusion and 1 *LMNA-NTRK1* fusion), 2 melanomas (1 novel *TRIM63-NTRK1* fusion and 1 novel *TRAF2-NTRK2* fusion), 1 gallbladder carcinoma with an *LMNA-NTRK1* fusion, 1 secretory carcinoma of breast with an *ETV6-NTRK3* fusion, and 1 appendiceal carcinoma with an *LMNA-NTRK1* fusion. All above listed cases with *NTRK* fusions were negative for hotspot mutations in *KRAS*, *NRAS*, *BRAF* (see Methods) as well as negative for other (non-*NTRK*) activating fusions (via Archer testing). Two additional cases with *NTRK* rearrangements were also identified via MSK-IMPACT and were negative for fusion transcripts on Archer: a lung adenocarcinoma with an *NTRK1* exon 5-*P2RY8* exon 2 rearrangement, and a glioblastoma with an *NTRK3* exon 14-*ZNF710* exon 1 rearrangement (Table 1).

Comparison of Pan-Trk In Situ Protein Expression versus Molecular Analysis

Immunohistochemical analysis of Pan-Trk IHC was concordant with Archer RNA testing in 21 of 22 cases. Positive immunostaining was seen in 15/16 cases with known *NTRK* fusions and 5 novel *NTRK* rearrangements, which were positive for fusion transcripts. Two cases

with *NTRK* rearrangements and negative Archer fusion testing results were also negative by immunohistochemistry. There was only one discordant case of a fusion-positive colorectal carcinoma with a *ETV6-NTRK3* fusion, which did not show any immunostaining with mAb EPR17341. An additional 20 consecutive cases of various tumors without *NTRK* fusions (*NTRK* fusion negative confirmed by Archer), were also negative by immunohistochemistry for EPR17341. These negative cases included 11 lung adenocarcinomas, 2 uterine leiomyosarcomas, 1 osteosarcoma, 1 low grade fibromyxoid sarcoma, 1 melanoma, 1 inflammatory myofibroblastic tumor, 1 intrahepatic cholangiocarcinoma, 1 alveolar soft part sarcoma, and 1 synovial sarcoma. These findings yielded a sensitivity of 95.2%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 96%.

There was no immunostaining present in non-neoplastic lymphocytes, hepatocytes, colorectal epithelium, alveolar epithelium, and renal cortex while testes tissue (which does express Trk when wild type) served as a positive external control.

Pan-Trk Staining Patterns

MAb EPR17341 displayed cytoplasmic labeling in all immunohistochemical positive cases. In addition to cytoplasmic immunoreactivity, staining patterns associated with specific *NTRK* fusion partners were observed. Three of 6 (50%) *ETV6-NTRK3* fusions cases and the single case of *EML4-NTRK3* had nuclear staining (Figure 1). All 5 *LMNA-NTRK1* fusion cases showed staining of the nuclear membrane (Figure 2). All 4 *TPM3/4-NTRK1/3* fusions and the single case of *TRAF2-NTRK2* displayed membranous immunostaining of most tumor cells (Figure 3).

DISCUSSION

In the present study, we analyzed various types of molecularly pre-typed cases of *NTRK1-3* fusions by immunohistochemistry employing a reagent reactive with Trk-A, -B, and -C. While *NTRK* fusions are collectively becoming more frequently identified, they remain rare in each individual cancer type (with the exception of very specific entities such as secretory carcinoma of salivary gland/MASC, secretory carcinoma of breast, and congenital fibrosarcoma). Our cohort represents one of the largest studies of *NTRK* fusion-positive cancers assembled to date. We show that *NTRK* fusions occur largely in mutual exclusivity of the most common driver mutations in *KRAS*, *NRAS*, and *BRAF*, and that IHC with mAb EPR17341 detects approximately 95% of positive cases and is 100% specific for *NTRK* fusions. Further, we demonstrate that staining pattern is indicative for some of the most common *NTRK* fusion partners: *LMNA1*, *TPM3/4* and *ETV6*. This high specificity reflects the very restricted expression of native *NTRK* proteins in adult tissues, namely in as smooth muscles, testes, and neural components.⁷⁻⁹ Indeed, in these tissues, the physiologic expression of wild type *NTRK* proteins limits the usefulness of the IHC assay.

The current widely used methods used to detect *NTRK* fusions include DNA-based next generation sequencing, targeted panels using RNA, and fluorescence in situ hybridization (FISH). All 3 methods have advantages and drawbacks: while DNA-based next generation sequencing can precisely characterize some fusions as well as give information about other genomic events, the turnaround time can be several weeks and fusions may be missed due to

difficulty tiling entire introns (either because of their size or because of the presence of repetitive regions); RNA-based targeted panels can precisely characterize fusion transcripts yet have turnaround time of at least a week and depend on the availability of sufficient RNA of adequate quality. FISH detection is comparably fast but does not answer the question of whether a specific rearrangement results in a transcribed (oncogenic) fusion or which partner gene is involved. Immunohistochemical analysis for Trk confers several benefits such as quick turnaround time, limited material required, only transcribed and translated fusions are detected rather than all DNA-level rearrangements, high sensitivity and specificity, and lower cost than other methods. Furthermore, immunohistochemistry allows for a spatial assessment of the potential presence of the fusion protein. This may have implications for therapeutic approaches such as immunotherapy in which extent of antigen presence may be an important factor.

Importantly, specific staining patterns appear to correlate with the subcellular localization of the fusion partners. Tumors with *NTRK1-LMNA* fusions showed a pronounced immunostaining at the nuclear membrane. This is congruent with the biology of *LMNA*, which encodes lamin A/C, a structural component of the inner nuclear membrane. Cases with *TPM3/4* fusions displayed immunostaining of the tumor cell membrane. *TPM3* and *TPM4* both encode tropomyosins that form part of the cytoskeleton in non-muscle cells and were shown to localize to the cell membrane in breast cancer.¹⁰ The protein encoded by *TRAF2* localizes to the cellular membrane as did pan-Trk IHC in the melanoma with the *TRAF2-NTRK2* fusion.¹¹ Half of the present cases with *ETV6-NTRK3* fusions had nuclear staining. *ETV6* encodes a transcription factor, which localizes to the nucleus. Similar staining patterns have been reported for several of these genes when fused to other kinases. For instance, *TPM3-ALK* also shows membranous and nuclear staining, *EML4-ALK* shows cytoplasmic staining, *CD30-ALCL* shows staining of nucleoli and coarse granular cytoplasmic staining.^{12–14}

While overall sensitivity in this cohort was 95%, there was a colorectal carcinoma with an *ETV6-NTRK3* fusion that was negative for pan-Trk IHC. This case was a mismatch repair-deficient colorectal carcinoma with a high mutation load and no other driver mutations. It is not known why this case was discordant, however, it is possible that high mutation load due to mismatch repair-deficiency resulted in mutations within the epitope recognized by the pan-TRK antibody.

The utility of pan-Trk IHC is triple: 1) rapid assessment of driver negative advanced malignancies which may harbor possible *NTRK* fusions to test patients for eligibility for targeted therapy with novel pan-Trk inhibitors 2) assessment of translation as a surrogate for functionality for novel *NTRK* rearrangements detected via NGS and 3) a method to confirm surgical pathology diagnoses in select tumors that are characterized by *NTRK* fusions such as secretory carcinoma of breast, secretory carcinoma of salivary gland/MASC, and congenital fibrosarcoma.^{15–17}

In summary, pan-TRK IHC is a sensitive, specific, and resource-efficient methodology to identify and/ or confirm the presence of *NTRK1-3* fusions. It may also assist in detecting the

fusion partner based on staining pattern. Pan-Trk IHC may serve as an adjunct or alternative to nucleic acid testing for the assessment of *NTRK* fusions.

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Figure 1.

Example of staining pattern for *ETV6-NTRK3* fusion positive case. A) A secretory carcinoma of breast with classic vacuolated cytoplasm (H&E, 100x original magnification) harbored an *ETV6* exon 6-*NTRK3* exon 15 fusion and displays B) strong nuclear and moderate cytoplasmic staining for pan-TRK IHC (pan-Trk IHC clone EPR17341, 100x original magnification, Abcam, Cambridge, MA).

Figure 2.

Example of staining pattern for *LMNA* fusion positive case. A) A moderately differentiated colorectal carcinoma with conventional histology (H&E, 40x original magnification) and an *LMNA* exon 12-*NTRK1* exon 12 fusion displays B and C) diffuse cytoplasmic and nuclear membrane staining for pan-TRK IHC (pan-Trk IHC clone EPR17341, B: 40x and C: 400x original magnification, Abcam, Cambridge, MA).

Figure 3.

Example of staining pattern for *TPM* fusion positive case. A) A poorly differentiated, microsatellite instability-high colorectal carcinoma (H&E, 100x original magnification) with a *TPM3* exon 10-*NTRK1* exon 9 fusion displays B) cytoplasmic and membranous staining for pan-TRK IHC (pan-Trk IHC clone EPR17341, 100x original magnification, Abcam, Cambridge, MA).

Table 1

Archer and Pan-Trk IHC Characteristics of Solid Cancers with NTRK Rearrangements detected on MSK-IMPACT.

TUMOR TYPE	NTRK GENE	PARTNER GENE	NOVEL	ARCHER	STAINING PATTERN			MEMBRANOUS	NUCLEAR
					CYTOPLASMIC	PERI-NUCLEAR			
APPENDICEAL ADC	<i>NTRK1</i> EXON 12	<i>LMNA</i> EXON 4	NO	POSITIVE	X	X			
COLORECTAL CARCINOMA	<i>NTRK3</i> EXON 15	<i>ETV6</i> EXON 6	NO	POSITIVE					
COLORECTAL CARCINOMA	<i>NTRK1</i> EXON 12	<i>LMNA</i> EXON 12	NO	POSITIVE	X	X			
COLORECTAL CARCINOMA	<i>NTRK1</i> EXON 12	<i>LMNA</i> EXON 8	NO	NT	X	X			
COLORECTAL CARCINOMA	<i>NTRK1</i> EXON 9	<i>TPM3</i> EXON 10	NO	NT	X		X		
COLORECTAL CARCINOMA	<i>NTRK1</i> EXON 10	<i>TPM3</i> EXON 8	NO	POSITIVE	X		X		
GALLBLADDER ADC	<i>NTRK1</i> EXON 12	<i>LMNA</i> EXON 2	NO	NT	X	X			
GLIOBLASTOMA	<i>NTRK1</i> EXON 9	<i>AFAP1</i> EXON 4	YES	POSITIVE	X				
GLIOBLASTOMA	<i>NTRK2</i> EXON 17	<i>BCREXON 1</i>	YES	POSITIVE	X				
GLIOBLASTOMA	<i>NTRK3</i> EXON 14	<i>EML4</i> EXON 2	YES	POSITIVE	X				X
GLIOBLASTOMA	<i>NTRK3</i> EXON 14	<i>ZNF710</i> EXON 1	YES	NEGATIVE					
LUNG ADC	<i>NTRK1</i> EXON 10	<i>IRF2BP2</i> EXON 1	NO	POSITIVE	X				
LUNG ADC	<i>NTRK1</i> EXON 5	<i>P2RY8</i> EXON 2	YES	NEGATIVE					
LUNG ADC	<i>NTRK1</i> EXON 12	<i>TPM3</i> EXON 8	NO	POSITIVE	X		X		
SC OF BREAST	<i>NTRK3</i> EXON 15	<i>ETV6</i> EXON 5	NO	POSITIVE	X				X
SC OF SALIVARY GLAND	<i>NTRK3</i>	<i>ETV6</i>	NO	NT	X				
SC OF SALIVARY GLAND	<i>NTRK3</i>	<i>ETV6</i>	NO	NT	X				
SC OF SALIVARY GLAND	<i>NTRK3</i> EXON 15	<i>ETV6</i> EXON 5	NO	POSITIVE	X				X
SC OF SALIVARY GLAND	<i>NTRK3</i> EXON 15	<i>ETV6</i> EXON 5	NO	POSITIVE	X				X
MELANOMA	<i>NTRK1</i> EXON 10	TRIM63 EXON 8	YES	POSITIVE	X				
MELANOMA	<i>NTRK2</i> EXON 15	<i>TRAF2</i> EXON 9	YES	POSITIVE	X				
SARCOMA	<i>NTRK1</i> EXON 11	<i>LMNA</i> EXON 2	NO	POSITIVE	X	X			
SARCOMA	<i>NTRK3</i> EXON 11	<i>TPM4</i> EXON 6	YES	POSITIVE	X		X		

* ADC=adenocarcinoma, SC= secretory carcinoma, NT= not tested