Supplemental data

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Supplemental Methods

Treatment, and follow-up strategies
As reported previously (1), all patients underwent total thyroidectomy (TT), subtotal thyroidectomy, or lobectomy with or without node dissection. Prophylactic central node dissection was introduced at Seoul National University Hospital (SNUH) in 2003 and has been performed in most patients with PTC ≥ 1 cm since 2007. The presence of lung metastasis was evaluated by radiological examinations (^{131}I whole-body scans [WBSs] and/or chest computed tomography [CT]). Postoperative ^{131}I therapy was provided for patients harboring tumors > 1 cm or locoregional and/or lung metastasis. The timing and number of the ^{131}I doses administered were individualized. After completing the initial therapy, patients were followed up with a clinical examination, measurements of serum thyroglobulin and anti-thyroglobulin antibody levels, and neck ultrasonography. ^{131}I WBS, CT, and positron emission tomography were performed if indicated.

Disease outcomes
Disease outcomes were categorized as no evidence of disease (NED), biochemical disease (BCD), and structural disease (SD, persistent or recurrent) based on the follow-up findings (2). NED was defined as the absence of structural abnormalities on imaging and an undetectable serum thyroglobulin level (suppressed or stimulated) for 12 months or longer until the last follow-up. BCD was defined as a detectable, suppressed, or stimulated thyroglobulin level in the absence of structural abnormalities on imaging. SD was defined as the presence of structural abnormalities. Stable and progressive disease was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (3).

DNA and RNA sequencing
Targeted sequencing of cancer-related genes was performed using the FRIST pancancer panel v3 developed at SNUH; this panel includes all exons and some introns of 188 and 71 genes, respectively, known to be important in tumorigenesis (4). All sequencing libraries were sequenced on the Illumina HiSeq platform as paired-end reads. The sequencing reads were aligned to the reference human genome (hg19) using the Burrows–Wheeler aligner (5) and the STAR aligner (6) for DNA and RNA, respectively. WGS and target sequencing followed the Genome Analysis Toolkit (GATK) best practices pipeline until the bam file was created using SAMtools (7), Picard (http://broadinstitute.github.io/picard/), and GATK (8). The average coverage for WGS was 34–50× for blood DNA and 75× for tumor DNA.

Variant detection
Somatic SNVs and short indels were detected by WGS and targeted sequencing using paired calls implemented in GATK MuTect2, annotated using ANNOVAR (9), and selected via several stages of in-house filters that consider the variant allele count and frequency, the possibility of an oxoG error (10) or strand bias, and the frequency in a normal population, such as the 1,000 Genomes Project (http://www.1000genomes.org), Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/), and NLHBI Exome Sequencing Project (ESP) (http://evs.gs.washington.edu/EVS/).

Structural variation detection
To detect the somatic copy number alteration (CNA) in the WGS data, the R package HMMcopy was used to count the number of reads with a fixed window size of 1,000 and to normalize the counts considering the GC content and average mappability of each bin. The log2 ratio was obtained from the normalized counts of tumor tissue and blood and was segmented using the R package DNAcopy. The targeted sequencing data were analyzed for CNA and SV according to the unique analysis pipeline at SNUH.

Fusion gene mutation analysis
Gene fusion was screened using STAR fusion, followed by manual review of chimeric reads using the Integrative Genomics Viewer (11), and the final call was determined by confirming the expression of the genes involved in fusion.

Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC)
NTRK and *RET* rearrangements were examined by FISH using a break apart probes for the *NTRK1* and *RET* loci (ZytoVision, Bremerhaven, Germany) and *NTRK3* loci (Abnova, Taipei, Taiwan).(12, 13) IHC was performed using a BRAF V600E mutation-specific antibody (Ventana Medical Systems, Inc., Tucson, AZ, USA), an NRAS Q61R antibody (Bio SB, Santa Barbara, CA, USA), a monoclonal mouse anti-human ALK antibody (Novocastra,

Newcastle Upon Tyne, UK), and a monoclonal rabbit anti-human pan-Trk antibody (Cell Signaling Technology, Danvers, MA, USA).(14, 15)

Thyroid differentiation score

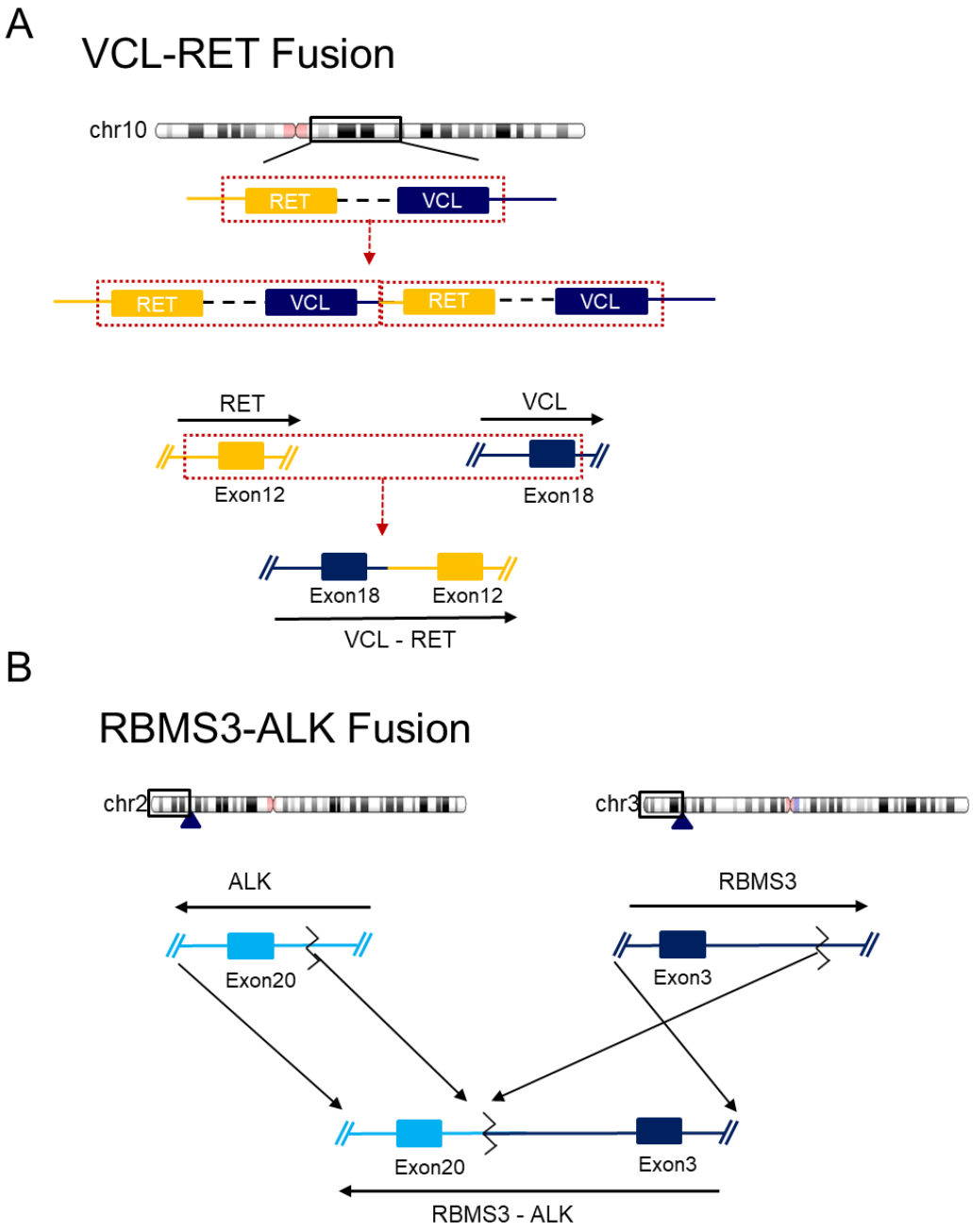
For the Ensembl gene set, the HTSeq-Count was used to count the number of reads mapped to each gene, and these counts were subsequently converted to RPKM and log2 values, respectively. The median-centered log2 values were applied to display the heatmap and to obtain the thyroid differentiation score (TDS) and ERK score according to previous studies (16, 17)

Real-time quantitative polymerase-chain reaction

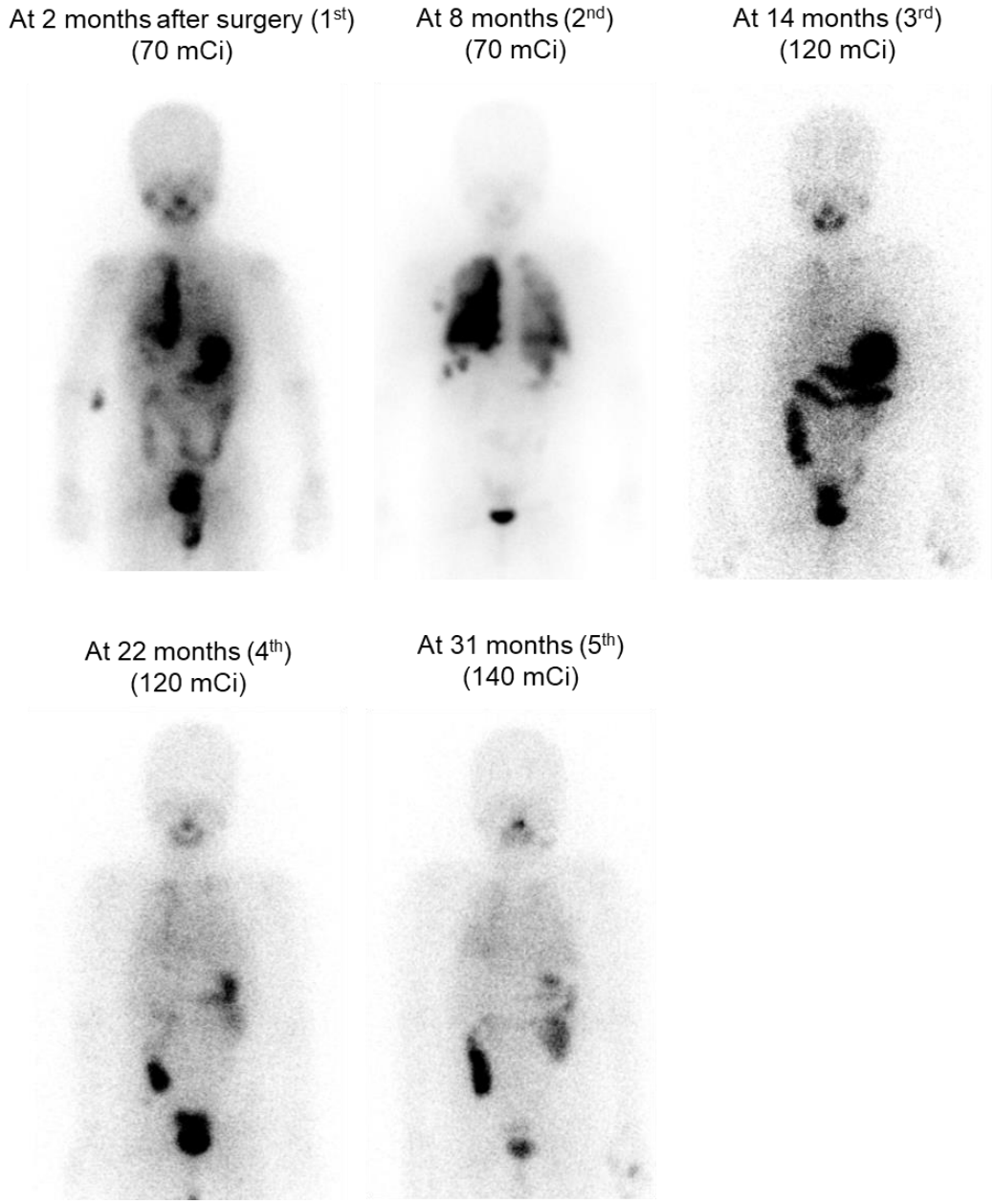
RNA from cell lines or fresh frozen tissues was extracted using the RNeasy Mini kit (Qiagen, Hilden, Germany) or Trizol (Life Technologies, Carlsbad, USA). RNA was assessed for quality and concentration using the 2100 Bioanalyzer (Agilent Technologies Inc., Palo Alto, CA). To confirm mRNA expression of NTRK1, 1,000 ng RNA was reverse-transcribed into cDNA using the PrimeScript™ First-strand cDNA Synthesis Kit (TaKaRa Bio Inc., Seoul, Korea). Reverse-transcribed cDNAs were quantified using TB Green Premix Ex Taq™ II (Tli RNaseH Plus, TaKaRa Bio). The levels of overexpression in $Nthy^{TPR\text{-}NTRK}$ cells were similar to those in NTRK fusion cancer when we compared the NTRK mRNA levels among $Nthy^{WT}$, normal thyroid tissue, $Nthy^{TPR\text{-}NTRK}$ cells, and thyroid cancer tissue harboring *TPR-NTRK* fusion.

Supplemental Figures

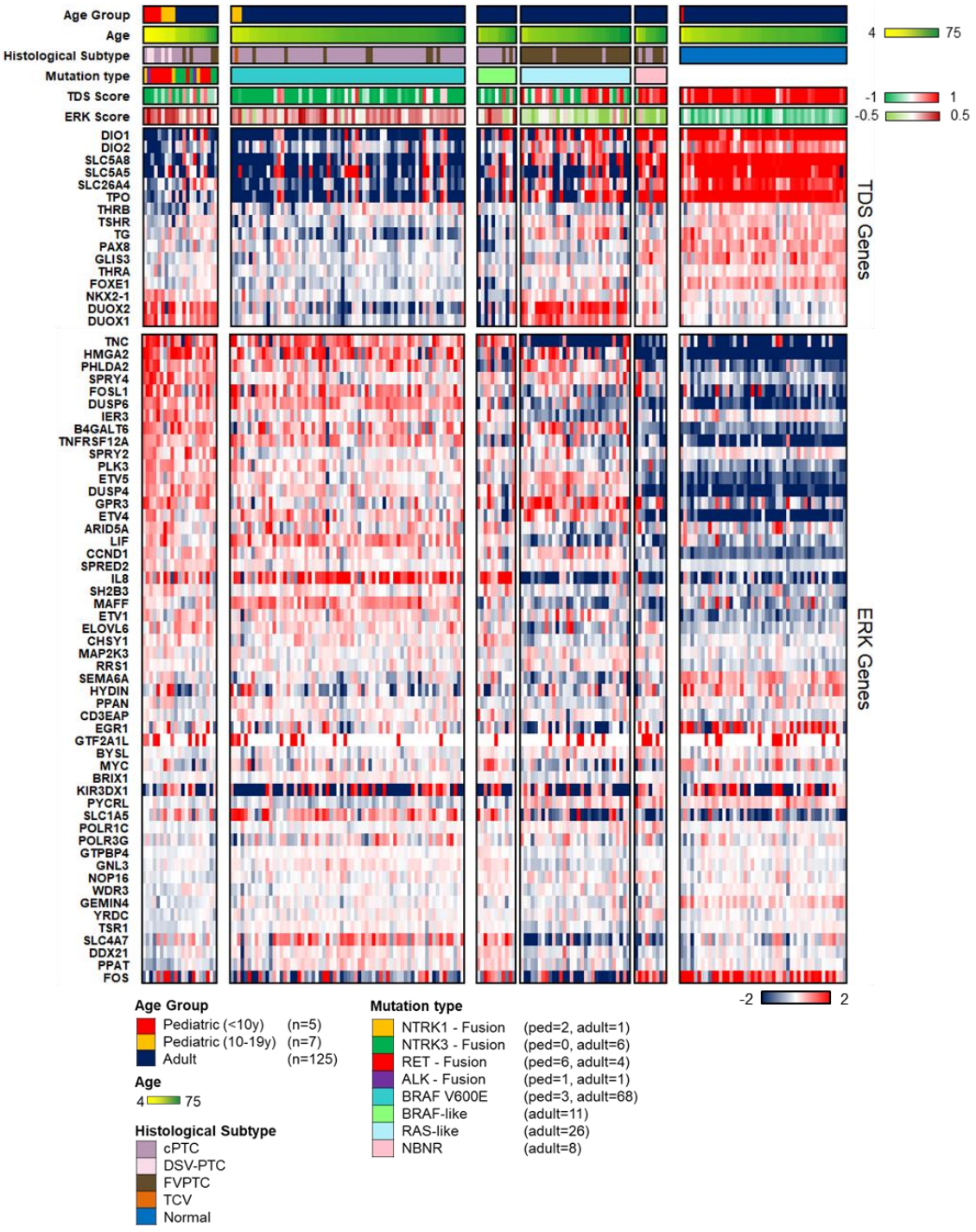
Supplemental Figure 1. Schematic representation of the VCL-RET and RBMS3-ALK fusions**.** Several fusions were identified in the COSMIC database among the tumors of 24 children with fusion oncogenes investigated by targeted or RNA sequencing, including *ETV6-NTRK3, TPM3-NTRK1, CCDC6-RET, NCOA4-RET, RET-NCOA4, TRIM24-RET, ERC1-RET, KTN1-RET, EML4-ALK and STRN-ALK*. We also confirmed *TPR-NTRK1* and *ANK3-RET* fusion in previously published reports (3, 18). However, to our knowledge, *VCL-RET* and *RBMS3-ALK* fusions have not previously been reported in thyroid cancer. Confirming chimeric reads by manual review allowed for identification of fusion breakpoints. (A) Schematic representation of the fusion of genes *VCL* and *RET* by duplication: in-frame fusion between chromosome 10 containing exons 1 to 18 of *VCL* and exons 12 to 19 of *RET*. (B) Schematic representation of the fusion of genes *RBMS3* and *ALK* by translocation: in-frame fusion between *ALK* exon20 and *RBMS3* exon3.



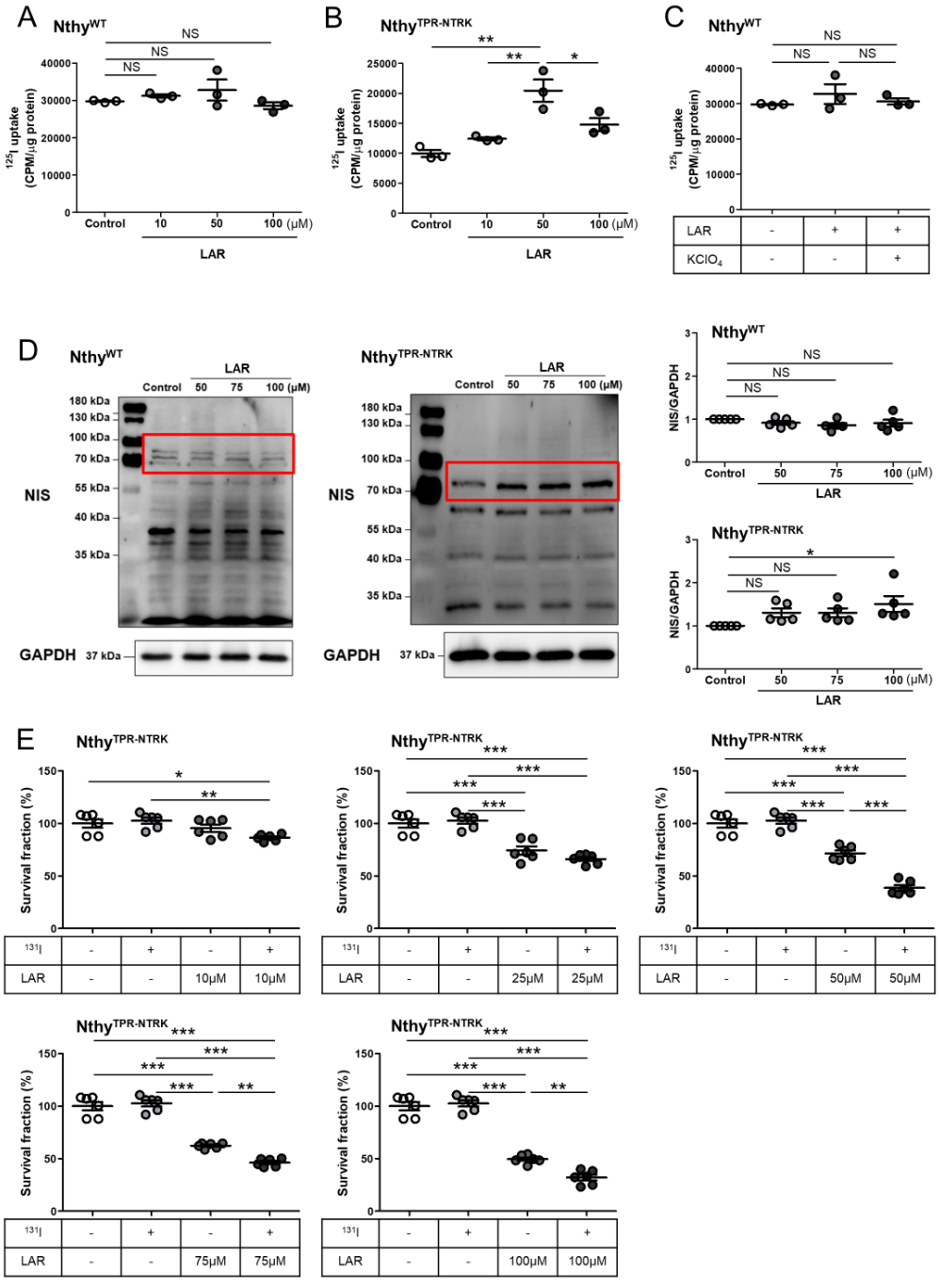
Supplemental Figure 2. A 9-year-old boy (P11) with an *ERC1-RET* fusion resulting in progressively decreased uptake of radioactive iodine during repeated high-dose ^{131}I therapy. All images are anterior-view images obtained at 2 days after ^{131}I administration.



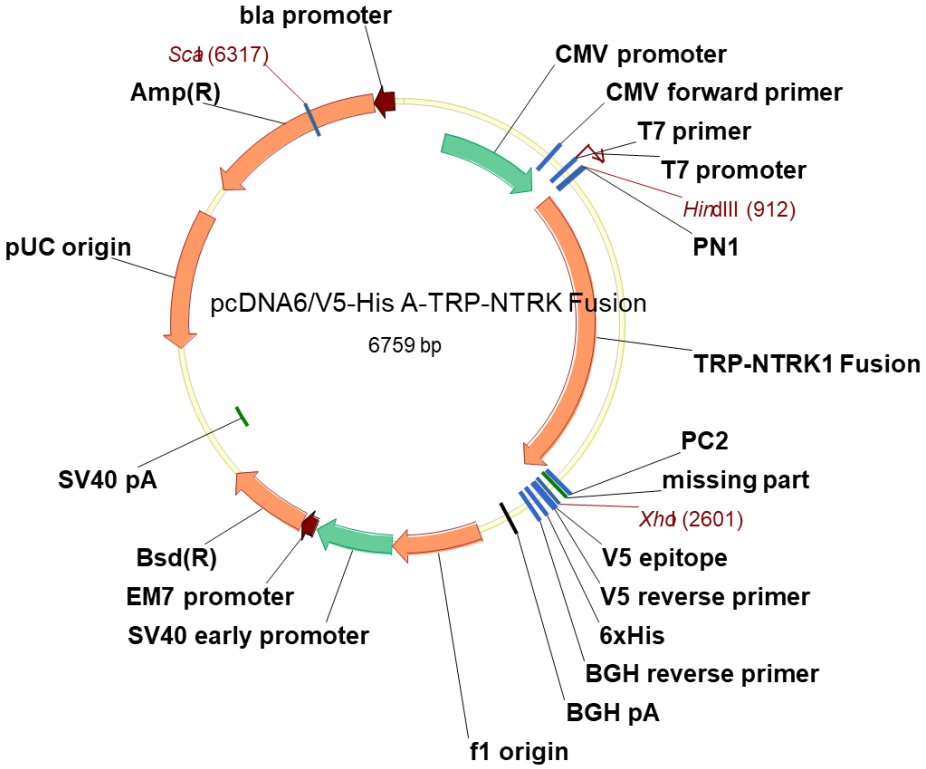
Supplemental Figure 3. Transcriptome data from 12 pediatric and 125 adult PTCs. The data was included in patient age, histological subtype, molecular subtype, TDS score, ERK score, the expression profile of 16 TDS genes and 52 MARK signaling pathway genes.



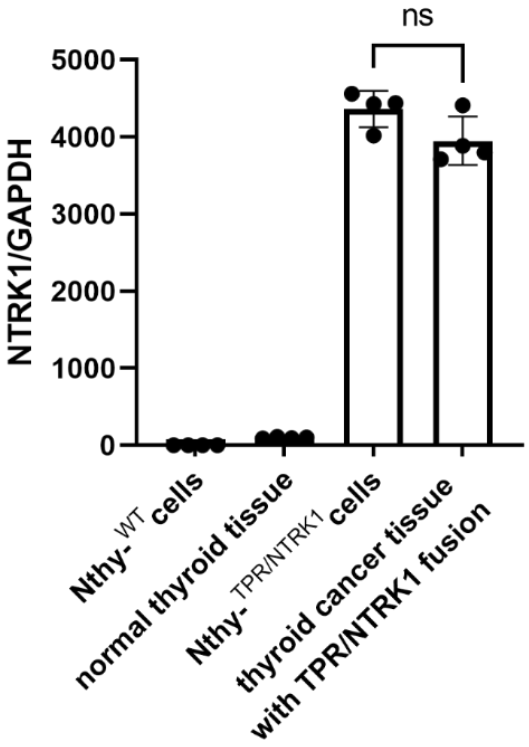
Supplemental Figure 4. *In vitro* effects of larotrectinib on radioiodine uptake capacity and cell growth. (A and B) ^{125}I uptake at baseline and after larotrectinib treatment (10, 50, and 100 μM) in Nthy^{WT} (A) and Nthy$^{TPR\text{-}NTRK}$ cells (B). (C) ^{125}I uptake in Nthy^{WT} cells at baseline and after treatment with larotrectinib (50 μM) and larotrectinib (50 μM) + KClO4. (D) Western blots of NIS (fully glycosylated) in Nthy^{WT} and Nthy$^{TPR\text{-}NTRK}$ cells at baseline, and after larotrectinib treatment (50, 75, and 100 μM). Figure 4C included western blots of NIS at baseline, and after larotrectinib treatment (50 μM only). (E) The colony-forming ability of Nthy$^{TPR\text{-}NTRK}$ cells at baseline, and after ^{131}I therapy alone (100 μCi), larotrectinib treatment alone (10, 25, 50, 75, and 100 μM), and a combination of both therapies. LAR, larotrectinib; NS, not significant; *, p <0.05; **, p <0.01; ***, p <0.001 using One-way ANOVA with Bonferroni's multiple-comparison test. All data are expressed as mean ± SD.



Supplemental Figure 5. The human TPR-NTRK1 expression vector constructed by subcloning the corresponding cDNA into a pcDNA6/V5-His A expression vector (ThermoFisher).



Supplemental Figure 6. Relative expression by real-time PCR (qPCR) of NTRK1 genes among Nthy^{WT} cells, normal thyroid tissue, Nthy$^{TPR\text{-}NTRK}$ cells, and thyroid cancer tissue with a TPR-NTRK fusion



Supplemental Tables

Supplemental Table 1. Genetic analysis performed in available tumor tissue of 106 patients

ID	Age	Sex	RT history	PTC subtypes	Genetic alterations	NGS	WGS	Targeted seq	RNAseq	BRAF seq or IHC	RAS seq	DICER1 seq	TERT seq	RET FISH	TRK FISH	TRK IHC	ALK IHC	RAS IHC
1	4.3	F	Neg	cPTC	*TPR-NTRK1*	Suc	TPR-NTRK1	*TPR-NTRK1*	*TPR-NTRK1*	Neg	ND	ND	Neg	ND	Pos	ND	ND	ND
2	5.2	F	Neg	FVPTC, infiltrative	*ETV6-NTRK3*	Suc	ND	*ETV6-NTRK3*	*ETV6-NTRK3*	Neg	ND	ND	Neg	Fail	Pos	Neg	Neg	Neg
3	10.3	F	Neg	FVPTC, infiltrative	*ETV6-NTRK3*	Suc	ND	*ETV6-NTRK3*	Neg	Neg	Neg	Neg	Neg	ND	ND	ND	ND	ND
4	14.2	F	Neg	cPTC	*TPM3-NTRK1*	Suc	ND	*ND*	*TPM3-NTRK1*	Neg	ND	ND	Neg	Neg	ND	Pos	Neg	ND
5	5.1	F	Neg	cPTC	*VCL-RET*	Suc	ND	*VCL-RET*	Neg	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
6	6.4	M	Neg	DSV-PTC	*NCOA4-RET*	Suc	ND	*NCOA4-RET*	*NCOA4-RET*	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
7	7.1	F	Neg	DSV-PTC	*TRIM24-RET*	Suc	ND	Fail	*TRIM24-RET*	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
8	7.4	F	Neg	DSV-PTC	*CCDC6-RET*	Suc	ND	ND	*CCDC6-RET*	Neg	ND	ND	Neg	Pos	ND	Neg	Neg	Neg
9	7.6	F	Neg	cPTC	*RET-NCOA4*	Suc	ND	*RET-NCOA4*	Neg	Neg	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
10	7.8	M	Pos	cPTC	*NCOA4-RET*	Suc	ND	Fail	*NCOA4-RET*	Neg	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
11	9.0	M	Neg	DSV-PTC	*ERC1-RET*	Suc	ND	*ERC1-RET*	ND	Neg	ND	ND	ND	ND	ND	ND	ND	ND
12	9.6	M	Neg	cPTC	*TRIM24-RET*	Suc	ND	Fail	*TRIM24-RET*	Neg	ND	ND	Neg	ND	ND	ND	ND	ND

13	9.9	M	Neg	DSV-PTC	*NCOA4-RET*	Suc	ND	*NCOA4-RET*	Neg	Neg	ND	ND	Neg	Pos	ND	Neg	Neg	Neg
14	10.1	F	Neg	cPTC	*NCOA4-RET*	Suc	ND	*NCOA4-RET*	ND	Neg	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
15	10.3	F	Neg	DSV-PTC	*CCDC6-RET*	Suc	ND	*CCDC6-RET*	ND	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
16	10.4	F	Neg	DSV-PTC	*NCOA4-RET*	Suc	ND	*NCOA4-RET*	*NCOA4-RET*	Neg	ND	ND	Neg	Pos	ND	Neg	Neg	ND
17	10.5	F	Neg	DSV-PTC	*CCDC6_RET*	Suc	ND	*CCDC6_RET*	ND	Neg	ND	ND	Neg	Pos	ND	Neg	Neg	Neg
18	13.3	F	Pos	cPTC	*CCDC6-RET*	Suc	ND	*CCDC6-RET*	*CCDC6-RET*	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
19	13.7	F	Neg	DSV-PTC	*ANK3_RET*	Suc	ND	*ANK3_RET*	*ANK3_RET*	Neg	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
20	14.3	F	Neg	DSV-PTC	*KTN1-RET*	Suc	ND	*KTN1-RET*	ND	Neg	ND	ND	Neg	Pos	ND	Neg	Neg	ND
21	14.5	F	Neg	cPTC	*CCDC6-RET*	Suc	ND	*CCDC6-RET*	ND	Neg	ND	ND	Neg	Pos	ND	Neg	Neg	Neg
22	16.1	M	Neg	cPTC	*CCDC6-RET*	Suc	ND	*CCDC6-RET*	ND	Neg	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
23	16.1	F	Neg	DSV-PTC	*CCDC6-RET*	Suc	ND	*CCDC6-RET*	ND	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
24	17.2	F	Neg	cPTC	*CCDC6_RET*	Suc	ND	*CCDC6-RET*	ND	Neg	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
25	18.9	F	Neg	DSV-PTC	*CCDC6-RET*	Suc	ND	*CCDC6-RET*	ND	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
26	4.5	F	Neg	DSV-PTC	*STRN-ALK*	Suc	ND	*STRN-ALK*	*STRN-ALK*	Neg	ND	ND	Neg	Neg	ND	Neg	Pos	Neg
27	8.9	F	Neg	cPTC	*EML4-ALK*	Suc	ND	*EML4-ALK*	*EML4-ALK*	Neg	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
28	12.1	F	Neg	cPTC	*ALK**	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Pos	Neg

29	15.6	F	Neg	cPTC	*RBMS3-ALK*	Suc	ND	*RBMS3 -ALK*	ND	Neg	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
30	15.9	F	Neg	cPTC	*ALK**	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	ND	ND	Neg	Pos	Neg
31	18.1	F	Pos	cPTC	*ALK**	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Pos	Neg
32	11.3	M	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
33	12.2	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	ND	ND	Neg	Neg	Neg
34	12.5	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
35	12.9	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	ND	ND	ND	ND	ND
36	13.1	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	ND	ND	ND	ND	ND	ND
37	13.5	F	Neg	PTC, tall cell variant	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
38	13.9	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
39	13.9	F	Neg	N/A	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	ND	ND	ND	ND	ND
40	14.3	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
41	14.5	F	Pos	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
42	14.5	F	Neg	PTC, tall cell variant	*BRAF^{V600E}*	ND	ND	ND	*ND*	Pos	ND	ND	Neg	ND	ND	ND	ND	ND
43	15.0	M	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
44	15.2	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	ND	ND	ND	ND	ND
45	15.4	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
46	15.7	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	ND	ND	ND	ND	ND
47	15.8	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
48	15.9	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
49	16.0	M	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
50	16.1	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
51	16.2	F	Neg	cPTC	*BRAF^{V600E}*	Suc	ND	ND	*BRAF^{V600E}*	Pos	ND	ND	Neg	ND	ND	ND	ND	ND
52	16.6	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
53	16.7	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
54	16.7	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	ND	ND	ND	ND	ND

55	16.8	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
56	17.1	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	ND	ND	ND	ND	ND	ND
57	17.3	F	Neg	cPTC	*BRAF^{V600E}/TERT C228T*	ND	ND	ND	ND	Pos	ND	ND	Pos	Fail	ND	Neg	Neg	Neg
58	17.3	F	Neg	PTC, Hobnail variant	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
59	17.6	M	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Neg	ND	Neg	Neg	Neg
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62	18.1	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
63	18.7	F	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
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66	19.2	M	Neg	cPTC	*BRAF^{V600E}*	ND	ND	ND	ND	Pos	ND	ND	Neg	Fail	ND	Neg	Neg	Neg
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73	9.0	F	Neg	cPTC	*TERT C228T*	Suc	ND	Fail	Neg	Neg	ND	ND	Pos	Neg	ND	Neg	Neg	Neg
74	12.4	F	Neg	cPTC	*DICER1 c.5378delA, p.E1793fs*	Fail	ND	Fail	Fail	Neg	Neg	*c.5378 delA, p.E1793fs*	Neg	Fail	ND	Neg	Neg	Neg
75	16.1	F	Neg	FVPTC, encapsulat	*DICER1 c.5113 G>A, p.E1705K*	Fail	ND	Fail	Fail	Neg	Neg	*c.5113 G>A,*	Neg	Neg	ND	Neg	Neg	Neg

				ed invasive								*p.E1705K*						
76	17.7	F	Neg	cPTC	*DICER1 c.5113 G>A, p.E1705K*	Fail	ND	Fail	Fail	Neg	Neg	*c.5113 G>A, p.E1705K*	Neg	Fail	ND	Neg	Neg	Neg
77	19.0	M	Pos	cPTC	*DICER1 c.5126 A>G, p.D1709G, LOH chr14q, chr16q, chr21, chr22*	Suc	ND	*DICER1 c.5126 A>G, p.D1709G,*	ND	Neg	ND	*c.5126 A>G, p.D1709G*	Neg	ND	ND	ND	ND	ND
78	19.6	F	Neg	cPTC	*DICER1 c.5437 G>A, p.E1813K*	Suc	ND	*DICER1 c.5437 G>A, p.E1813K*	ND	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
79	11.5	M	Pos	cPTC	*FGFR1 amp*	Suc	ND	*FGFR1 amp*	ND	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
80	17.7	M	Pos	cPTC	*EGFR amp*	Suc	ND	*EGFR amp*	ND	Neg	ND	ND	Neg	ND	ND	ND	ND	ND
81	10.8	F	Neg	cPTC	Neg	Suc	ND	Neg	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
82	11.3	F	Neg	cPTC	Neg	Suc	ND	Neg	Fail	Neg	ND	Neg	Neg	Neg	ND	Neg	Neg	Neg
83	11.3	F	Neg	cPTC	Neg	Suc	ND	Neg	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
84	12.5	M	Neg	cPTC	Neg	Suc	ND	Neg	Fail	Neg	ND	Neg	Neg	Neg	ND	Neg	Neg	Neg
85	12.7	F	Neg	cPTC	Neg	Suc	ND	Neg	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
86	13.5	F	Neg	PTC, solid	Neg	Suc	ND	Neg	Fail	Neg	ND	Neg	Neg	Neg	ND	Neg	Neg	Neg
87	13.8	F	Neg	cPTC	Neg	Suc	ND	Neg	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
88	15.0	F	Neg	FVPTC, infiltrative	Neg	Suc	ND	Neg	Fail	Neg	ND	Neg	Neg	ND	ND	ND	ND	ND

89	16.0	M	Neg	cPTC, FVPTC	Neg	Suc	ND	Neg	Fail	Neg	ND	Neg	Neg	ND	ND	ND	ND	ND
90	17.0	F	Neg	cPTC	Neg	Suc	ND	Fail	Neg	Neg	Neg	Neg	ND	ND	ND	ND	ND	ND
91	18.0	M	Neg	FVPTC, encapsulated invasive	Neg	Suc	ND	Neg	Fail	Neg	ND	Neg	Neg	Neg	ND	Neg	Neg	Neg
92	10.9	F	Neg	DSV-PTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Fail	ND	Neg	Neg	Neg
93	11.7	F	Neg	PTC, solid variant	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Fail	ND	ND	ND	ND
94	12.0	M	Neg	FVPTC, encapsulated invasive	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	ND	ND	ND	ND	ND
95	12.4	F	Neg	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
96	13.0	M	Pos	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	ND	ND	ND	ND	ND
97	13.7	M	Neg	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Fail	ND	Neg	Neg	Neg
98	14.0	F	Pos	cPTC, PTC, solid variant	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	ND	ND	ND	ND	ND
99	14.4	F	Neg	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
100	14.5	F	Neg	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Fail	ND	Neg	Neg	Neg
101	16.2	F	Neg	FVPTC, infiltrative	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Fail	ND	Neg	Neg	Neg
102	16.3	F	Neg	FVPTC, infiltrative	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
103	16.6	F	Neg	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
104	17.5	F	Neg	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
105	18.3	M	Neg	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Neg	ND	Neg	Neg	Neg
106	18.4	F	Neg	cPTC	Fail	Fail	ND	Fail	Fail	Neg	Neg	Neg	Neg	Fail	ND	Neg	Neg	Neg

* Fusions where no 5′ partner specified

RT, radiation therapy; NGS, next generation sequencing; WGS, whole genome sequencing; seq, sequencing, IHC, immunohistochemistry; FISH, *fluorescence in situ hybridization ;* Suc, success; Neg, negative; ND, not done; Pos, positive*;* cPTC, classic PTC; FVPTC, follicular variant PFC; DSV-PTC, diffuse sclerosing variant PTC; amp, amplification

Supplemental Table 2. Genetic alterations according to age at diagnosis

Age	Fusion			Point mutation				Amplification	Identified	No driver identified
	TRK	*RET*	*ALK*	*BRAF* ^{V600E}	*TERT*	*DICER1*	*RAS*			
<10 years (n = 14)	2	9	2	0	1	0	0	0	14	0
10-14.9 years (n = 40)	2	8	1	11	0	1	0	1	24	16
15-19.9 years (n = 52)	0	4	3	30	1*	4	0	1	42	10
Total, n (detected/evaluated)	4/90	21/70	6/90	41/106	2([a])/102	5/66	0/94	2/45	80/106	26/106
Total, % (detection)	4.4	30	6.7	38.7	2.0	7.6	0	5.0	75.5	24.5

[a]Coexist with *BRAF*^{V600E} (1.0%)

Supplemental Table 3. Breakpoint of fusion gene mutations identified from 28 patients

ID	GeneA_GeneB	Targeted sequencing	RNA sequencing	5' Partner gene			3' Partner gene		
				Gene Name	Last Observed Exon	Inferred Breakpoint	Gene Name	First Observed Exon	Inferred Breakpoint
1	*TPR-NTRK1*	Positive	Positive	TPR	Exon21	chr1:186,317,649	NTRK1	Exon10	chr1:156,844,312
2	*ETV6-NTRK3*	Negative	Positive	ETV6	Exon4	-	NTRK3	Exon14	-
3	*ETV6-NTRK3*	Positive	Negative	ETV6	Exon4	chr12:12,019,359	NTRK3	Exon14	chr13:88,636,734
4	*TPM3-NTRK1*	ND	Positive	TPM3	Exon7	-	NTRK1	Exon10	
5	*VCL-RET*[a]	Positive	Negative	VCL	Exon18	chr10:75,870,829	RET	Exon12	chr10:43,610,293
6	*NCOA4-RET*	Positive	Positive	NCOA4	Exon8	chr10:51,582,992	RET	Exon12	chr10:43,611,619
7	*TRIM24-RET*	Fail	Positive	TRIM24	Exon9	-	RET	Exon12	-
8	*CCDC6-RET*	ND	Positive	CCDC6	Exon1	-	RET	Exon12	-
9	*RET-NCOA4*	Positive	Negative	RET	Exon11	chr10:43,610,159	NCOA4	Exon8	chr10:51,584,672
10	*NCOA4-RET*	Fail	Positive	NCOA4	Exon8	-	RET	Exon12	-
11	*ERC1-RET*	Positive	ND	ERC1	Exon18	-	RET	Exon12	-
12	*TRIM24-RET*	Fail	Positive	TRIM24	Exon9	-	RET	Exon12	-
13	*NCOA4-RET*	Positive	Negative	NCOA4	Exon8	chr10:51,582,527	RET	Exon12	chr10:43,611,276
14	*NCOA4-RET*	Positive	ND	NCOA4	Exon8	chr10:51,584,750	RET	Exon12	chr10:43,611,312
15	*CCDC6-RET*	Positive	ND	CCDC6	Exon2	chr10:61,641,920	RET	Exon12	chr10:43,610,676
16	*NCOA4-RET*	Positive	Positive	NCOA4	Exon8	-	RET	Exon12	
17	*CCDC6_RET*	Positive	ND	CCDC6	Exon2	chr10:61,638,687	RET	Exon12	chr10:43,610,820
18	*CCDC6-RET*	Positive	ND	CCDC6	Exon2	chr10:61,627,804	RET	Exon12	chr10:43,611,457
19	*ANK3_RET*	Positive	ND	ANK3	Exon2	chr10:62,451,714	RET	Exon11	chr10:43,610,112
20	*KTN1-RET*	Positive	ND	KTN1	Exon12	chr14:56,105,452	RET	Exon12	chr10:43,611,421
21	*CCDC6-RET*	Positive	ND	CCDC6	Exon2	chr10:61,649,689	RET	Exon12	chr10:43,611,478
22	*CCDC6-RET*	Positive	ND	CCDC6	Exon2	chr10:61,661,536	RET	Exon12	chr10:43,610,671
23	*CCDC6-RET*	Positive	ND	CCDC6	Exon2	chr10:61,618,874	RET	Exon12	chr10:43,610,001
24	*CCDC6_RET*	Positive	ND	CCDC6	Exon2	chr10:61,660,861	RET	Exon12	chr10:43,610,186
25	*CCDC6-RET*	Positive	ND	CCDC6	Exon2	chr10:61,627,124	RET	Exon12	chr10:43,611,275
26	*STRN-ALK*	Positive	Positive	STRN	Exon3	chr2:37,132,992	ALK	Exon20	chr2:29,446,975

27	*EML4-ALK*	Positive	Positive	EML4	Exon13	chr2:42,527903	ALK	Exon20	chr2:29,448,236
29	*RBMS3-ALK*[a]	Positive	ND	RBMS3	Exon3	chr3:29,572,596	ALK	Exon20	chr2:29,447,452

[a]*VCL/RET* and *RBMS3-ALK* fusion have not been reported in COSMIC or TCGA Fusion Gene database or previous reports.
'- Accurate breakpoint is not known

Supplemental Table 4. Genetic alterations of pediatric PTC patients based on previous studies

Author, date	Age (yrs)	Evaluated (n)	Detection		*Fusion*					*Point mutation*					*Amplification*	Radiation or sporadic	Methods
			n	%	*RET*	*NTRK*	*ALK*	*BRAF*	*PPARG*	*BRAF* ^{V600E}	*RAS*	*DICER1*	*TERT*	*Others*			
Fugazzola L, 1995 (19)	1-8	6	4	66.7	4	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	Radiation	Southern blot
Williams, G.H. 1996 (20)	7-14	21	10	47.6	10	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Sporadic	RT-PCR
Nikiforov, Y.E. 1997 (21)	5-18	38	33	86.8	33	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Radiation	RT-PCR
	5-18	17	12	70.6	12	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Sporadic	RT-PCR
Motomura, T. 1998 (22)	9	1	1	100	1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Sporadic	RT-PCR
	10-14	9	2	22.2	2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Sporadic	
Thomas, G.A. 1999 (23)	6-18	67	37	55.2	37	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Radiation	RT-PCR
Fenton, C., 1999 (24)	6-9	2	0	0.0	ND	ND	ND	ND	ND	ND	0	ND	ND	ND	ND	Sporadic	nested PCR
	10-21	29	2	6.9	ND	ND	ND	ND	ND	ND	2	ND	ND	ND	ND	Sporadic	
Santoro, M., 2000 (25)	<15	106	36	34.0	36	ND	ND	ND	ND	ND	0	ND	ND	ND	ND	Radiation	RT-PCR
Fenton, C.L. 2000 (25)	6-9	1	1	100	1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Sporadic	RT-PCR
	10-21	32	14	43.8	14	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Sporadic	
	10-21	1	1	100	1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Radiation	

Rabes, H.M. 2000 (26)	0-14	99	54	54.5	50	4	ND	ND	ND	ND	ND	ND	ND	ND	ND	Radiation	RT-multiplex PCR
Pauws, E. 2001 (27)	9-16	8	0	0	ND	ND	ND	ND	ND	ND	0	ND	ND	ND	ND	Sporadic	SSCP-analysis
Elisei, R. 2001 (28)	<18	25	19	76.0	19	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Radiation	RT-PCR, Southern blot
	<18	25	10	40.0	10	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Sporadic	
Lima, J. 2004 (29)	<18	17	1	5.9	ND	ND	ND	ND	ND	1	ND	ND	ND	ND	ND	Sporadic	SSCP and sequencing analysis
Kumagai A, 2004 (30)	≤15	46	6	13.0	5	ND	ND	ND	ND	1	0	ND	ND	ND	ND	Radiation	PCR, RT-PCR
Penko K, 2005 (31)	10-21	14	7	50.0	ND	ND	ND	ND	ND	7	ND	ND	ND	ND	ND	Radiation (1) sporadic (13)	BRAF (PCR)
Rosenbaum E, 2005 (32)	10-17	20	4	20.0	ND	ND	ND	ND	ND	4	ND	ND	ND	ND	ND	Sporadic	BRAF (PCR)
Espadinha, C, 2009 (33)	5-21	15	1	6.7	ND	ND	ND	ND	ND	1	ND	ND	ND	ND	ND	Unknown	BRAF (PCR)
Sassolas G, 2012 (34)	<20	28	11	39.3	8	0	ND	ND	ND	2	1	ND	ND	ND	ND	Radiation (5) Sporadic (23)	PCR, RT-PCR
Ricarte-Filho JC, 2013 (35)	5-9	2	0	0.0	0	0	0	0	0	0	0	ND	ND	ND	ND	Sporadic (2)	RT-PCR, NGS
	10-23	25	18	66.7	7	2	ND	0	0	7	2	ND	ND	ND	ND	Sporadic (27)	
	10-23	26	25	96.2	15	3	ND	2	1	2	0	ND	ND	2	0	Radiation (26)	

Givens DJ, 2014 (36)	<10	1	0	0.0	ND	ND	ND	ND	ND	0	ND	ND	ND	ND	ND	Unknown	BRAF (PCR)
	10-18	18	7	38.9	ND	ND	ND	ND	ND	7	ND	ND	ND	ND	ND	Unknown	BRAF (PCR)
Henke LE, 2014 (37)	<21	27	17	63.0	ND	ND	ND	ND	ND	17	ND	ND	ND	ND	ND	Sporadic	BRAF (PCR)
Ballester LY, 2016 (38)	10-19	25	15	60.0	5	ND	ND	ND	ND	10	0	ND	ND	1	0	Radiation (2) Sporadic (23)	NGS (cancer panel)
Picarsic JL, 2016 (39)	<10	2	2	100	0	2	0	0	0	0	0	0	0	ND	ND	Sporadic	NGS (cancer panel)
	10-17	16	12	81.3	3	2	0	0	1	3	3	0	0	0	0	Sporadic	
Mitsutake, N. 2015 (40)	9-22	67	54	80.6	7	4	ND	0	ND	43	0	ND	0	ND	ND	Radiation	PCR, RT-PCR
Nikita ME, 2016 (41)	7-18	34	19	55.9	6	ND	ND	ND	3	9	1	ND	ND	ND	ND	Radiation (2), Sporadic (37)	PCR, RT-PCR
Alzahrani AS, 2016 (42)	9-18	52	13	25.0	ND	ND	ND	ND	ND	12	0	ND	1	ND	ND	Unknown	PCR
Prasad ML, 2016 (43)	<10	1	1	100	0	1	0	0	0	0	0	0	0	0	0	Sporadic	NGS (cancer panel)
	10-18	26	25	96.2	6	6	0	0	0	13	0	0	0	0	0	Sporadic	
Gertz, R.J. 2016 (44)	8-18	14	7	50.0	2	ND	ND	ND	ND	5	0	ND	ND	ND	ND	Sporadic	PCR, RT-PCR, FISH
Onder, S. 2016 (45)	0-18	50	15	30.0	ND	ND	ND	ND	ND	15	ND	ND	0	ND	ND	Radiation (3), Sporadic (47)	PCR
	4-10	12	1	8.3	ND	ND	ND	1	ND	ND	ND	ND	ND	ND	ND	Sporadic	RT-PCR, FISH

Cordioli MI, 2016 (46)	10-18	18	2	11.1	ND	ND	ND	2	ND	ND	ND	ND	ND	ND	ND	Sporadic	
Alzahrani AS, 2017 (47)	8-17	79	25	31.6	ND	ND	ND	ND	ND	19	2	0	1	3	0	Unknown	PCR
Cordioli MI, 2017 (48)	<10	12	6	50.0	4	1	ND	1	ND	0	0	ND	ND	ND	ND	Sporadic	PCR, RT-PCR, FISH
	10-19	23	18	78.3	10	2	ND	3	ND	3	0	ND	ND	ND	ND	Radiation (3) sporadic (20)	PCR, RT-PCR, FISH
Oishi, N, 2017 (49)	0-20	81	44	54.3	ND	ND	ND	ND	ND	44	ND	ND	0	ND	ND	Sporadic	PCR (BARF TERT)
Hardee, S. 2017 (50)	0-21	50	24	48.0	ND	ND	ND	ND	ND	24	ND	ND	ND	ND	ND	Unknown	PCR
Mostoufi-Moab, S.2018 (51)	0-18	62	30	48.4	12	ND	ND	ND	2	12	4	ND	ND	ND	ND	Radiation (3) Sporadic (59)	PCR, RT-PCR
Wasserman JD, 2018 (52)	5-18	30	15	40.0	7	ND	ND	ND	ND	5	ND	3	0	ND	ND	Radiation (2), Sporadic(28)	PCR, RT-PCR
Pozdeyev N, 2018 (53)	<10	5	5	100	3	0	2	0	0	0	0	0	0	ND	ND	Unknown	NGS (cancer panel)
	10-19	10	4	40.0	1	0	3	0	0	0	0	0	0	0	0	Unknown	
Huang, M. 2018 (54)	<21	30	16	53.3	ND	ND	ND	ND	ND	16	ND	ND	ND	ND	ND	Unknown	BRAF (PCR)
Sisdelli, L. 2019 (55)	0-18	80	27	33.8	ND	ND	ND	15	ND	12	ND	ND	ND	ND	ND	Radiation (3), Sporadic (77)	PCR, RT-PCR, FISH
	6-9	9	5	55.6	2	2	1	0	ND	0	0	ND	0	0	0		

Pekova B, 2020 (56)	10-19	84	64	79.8	24	15	5	2	ND	18	2	ND	0	1	0	Radiation (2) Sporadic (89)	NGS (RNA and DNA targeted sequencing)
Lee YA et al, this study	4-9	14	14	100	9	2	2	0	0	0	0	0	1	0	0	Radiation (1) Sporadic (13)	PCR, FISH, NGS (cancer panel, RNAseq), IHC
	10-19	92	66	71.7	12	2	4	0	0	41	0	5	1[a]	0	2	Radiation (8) Sporadic (84)	
Pooled analysis (June, 2020)	<10	68	40	58.8	24	8	5	2	0	0	0	0	1	0	0		
	10-23	468	289	61.8	100	32	12	12	2	112	9	5	1[a]	4	2		
	<23	1704	866	50.8	379	47	17	29	7	350	17	8	4(1[a])	7	2		

[a]Coexist with *BRAF*^{V600E}

Supplemental Table 5. Clinicopathological presentation and disease outcome in pediatric PTCs harboring *BRAF*^{V600E}

ID	Age (yrs)	Sex	Sporadic or radiotherapy	PTC Subtype	Genetic alteration	Size (cm)	Multi-focality	ETE	LN meta	Distant meta	FU years	Disease outcome (any event)	Disease outcome (at last follow-up)
1	11.3	M	Sporadic	cPTC	*BRAF*^{V600E}	0.6	no	yes	no	no	4.3	NED	NED
2	12.2	F	Sporadic	cPTC	*BRAF*^{V600E}	3	yes	yes	yes	no	19.5	SD	NED
3	12.5	F	Sporadic	cPTC	*BRAF*^{V600E}	0.9	no	yes	no	no	8	NED	NED
4	12.9	F	Sporadic	cPTC	*BRAF*^{V600E}	0.5	no	no	no	no	2.4	NED	NED
5	13.1	F	Sporadic	cPTC	*BRAF*^{V600E}	0.6	no	no	yes	no	7.3	NED	NED
6	13.5	F	Sporadic	PTC, tall cell	*BRAF*^{V600E}	2	no	yes	yes	no	12.4	NED	NED
7	13.9	F	Sporadic	cPTC	*BRAF*^{V600E}	0.2	no	no	yes	no	4.6	Recur	Recur
8	14	F	Sporadic	N/A	*BRAF*^{V600E}	0.8	no	no	yes	no	2	NED	NED
9	14.3	F	Sporadic	cPTC	*BRAF*^{V600E}	2.6	yes	yes	yes	no	11.2	BCD	BCD
10	14.5	F	Radiotherapy	cPTC	*BRAF*^{V600E}	0.6	no	yes	yes	no	8.8	BCD	BCD
11	14.5	F	Sporadic	PTC, tall cell	*BRAF*^{V600E}	0.5	yes	no	no	no	0.9	Ongoing	Ongoing
12	15	M	Sporadic	cPTC	*BRAF*^{V600E}	0.8	no	yes	no	no	8.9	NED	NED
13	15.2	F	Sporadic	cPTC	*BRAF*^{V600E}	0.6	no	no	no	no	3.8	NED	NED
14	15.4	F	Sporadic	cPTC	*BRAF*^{V600E}	1.1	yes	no	yes	no	11	BCD	BCD
15	15.7	F	Sporadic	cPTC	*BRAF*^{V600E}	0.6	no	yes	no	no	3.2	NED	NED
16	15.8	F	Sporadic	cPTC	*BRAF*^{V600E}	2.2	no	no	yes	no	16.6	NED	NED
17	15.9	F	Sporadic	cPTC	*BRAF*^{V600E}	1.6	no	yes	yes	no	1.5	Ongoing	Ongoing
18	16	M	Sporadic	cPTC	*BRAF*^{V600E}	2.4	yes	yes	yes	no	4.9	BCD	BCD
19	16.1	F	Sporadic	cPTC	*BRAF*^{V600E}	0.3	no	no	no	no	7	NED	NED
20	16.2	F	Sporadic	cPTC	*BRAF*^{V600E}	4.1	no	no	yes	no	1.6	Ongoing	Ongoing

21	16.6	F	Sporadic	cPTC	*BRAF*^{V600E}	1.6	no	yes	yes	no	14.5	NED	NED
22	16.7	F	Sporadic	cPTC	*BRAF*^{V600E}	1.7	no	yes	yes	no	18.2	NED	NED
23	16.7	F	Sporadic	cPTC	*BRAF*^{V600E}	0.9	yes	yes	no	no	4.8	NED	NED
24	16.8	F	Sporadic	cPTC	*BRAF*^{V600E}	1.1	yes	yes	NA	no	11.6	NED	NED
25	17.1	F	Sporadic	cPTC	*BRAF*^{V600E}	1.5	yes	yes	yes	no	7.5	NED	NED
26	17.3	F	Sporadic	cPTC	*BRAF*^{V600E} *TERT* ^{C228T}	1.5	no	yes	no	no	9.5	NED	NED
27	17.3	F	Sporadic	PTC, Hobnail	*BRAF*^{V600E}	0.9	no	yes	yes	yes	7.1	NED	NED
28	17.6	M	Sporadic	cPTC	*BRAF*^{V600E}	3	yes	yes	yes	NA	1	NA	NA
29	17.7	F	Sporadic	cPTC	*BRAF*^{V600E}	1.8	no	no	yes	no	7.8	NED	NED
30	18	F	Sporadic	cPTC	*BRAF*^{V600E}	0.7	no	yes	yes	no	7.4	NED	NED
31	18.1	F	Sporadic	cPTC	*BRAF*^{V600E}	NA	no	NA	NA	no	14.9	Recur	Recur
32	18.7	F	Sporadic	cPTC	*BRAF*^{V600E}	0.4	yes	no	no	no	11.3	NED	NED
33	18.8	F	Sporadic	cPTC	*BRAF*^{V600E}	NA	yes	NA	yes	no	18.4	Recur	NED
34	19.1	F	Sporadic	PTC, tall cell	*BRAF*^{V600E}	4.3	no	yes	yes	no	4.5	NED	NED
35	19.2	M	Sporadic	cPTC	*BRAF*^{V600E}	0.7	no	no	yes	no	9.9	NED	NED
36	19.2	M	Sporadic	cPTC	*BRAF*^{V600E}	2.5	no	no	yes	no	17.9	NED	NED
37	19.5	F	Sporadic	cPTC	*BRAF*^{V600E}	NA	NA	NA	NA	no	37.3	Recur	BCD
38	19.5	F	Sporadic	cPTC	*BRAF*^{V600E}	2.6	no	yes	no	no	19.8	Recur	BCD
39	19.7	F	Sporadic	cPTC	*BRAF*^{V600E}	0.7	yes	no	yes	no	7	NED	NED
40	19.8	F	Sporadic	cPTC	*BRAF*^{V600E}	1.4	yes	yes	yes	no	14.4	NED	NED
41	19.8	F	Sporadic	NA	*BRAF*^{V600E}	0.8	no	yes	yes	no	10.3	NED	NED

ETE, extrathyroidal extension; LN, lymph node; meta, metastasis; FU, follow-up; cPTC, classic variant PTC; FVPTC, follicular variant PTC; DSV-PTC, diffuse sclerosing variant PTC; NED, no evidence disease; BCD, biochemical disease; and SD, structural disease.

Supplemental Table 6. Comparison between pediatric and adult patients at SNUH harboring a fusion oncogene *(TRK, RET, or ALK)* and *BRAF*^{V600E}

	Adult PTC patients (Total 125 cases in SNUH)		Fusion *(TRK, RET, or ALK)* pediatric vs. adult patients					*BRAF*^{V600E} pediatric vs. adult patients				
	No. evaluated	Total patients (n = 125)	N	Adult (n = 12)	N	Pediatric (n = 31)	p-value	N	Adult (n = 68)	N	Pediatric (n= 41)	p-value
Age (yrs)	125	47.0 ± 12.9	12	40.6 ± 15.7	29	11.1 ± 4.2	<0.001	68	46.9 ± 12.1	41	16.3 ± 2.3	<0.001
Females, n (%)	125	91 (72.8)	12	10 (83.3)	29	25 (80.6)	1.000	68	50 (73.5)	41	35 (85.4)	0.163
Thyroidectomy (total thyroidectomy/ lobectomy)	125	114/11 (91.2/8.8)	12	12/0 (100/0)	29	30/1 (96.8/3.2)	1.000	68	65/3 (95.6/4.4)	41	38/3 (92.7/7.3)	0.670
LN dissection, total, n (%)	125	9/116 (7.2/92.8)	12	12 (100)	31	28 (90.3)	0.548	68	67 (98.5)	41	33 (82.5)	0.004
Lateral LN dissection, n (%)	125	19 (15.2)	12	5 (41.7)	31	22 (71.0)	0.092	68	11 (16.2)	40	11 (29.7)	0.133
Radioiodine therapy, n (%)	125	69 (55.2)	12	10 (83.3)	31	27 (87.1)	1.000	68	37 (54.4)	40	23 (57.5)	0.842
PTC subtype (classic variant/ diffuse sclerosing variant/ other subtypes), n (%)	125	77/0/48 (61.6/0/38.4)	12	8/0/4 (66.7/0/33.3)	31	16/13/2 (51.6/41.9/ 6.5)	0.634	68	55/0/13 (80.9/0/19.1)	39	35/0/4 (89.7/0/10.3)	0.281
Size (cm)	124	1.5 ± 1.0	12	1.8 ± 0.9	31	2.8 ± 1.5	0.055	67	1.2 ± 0.5	38	1.4 ± 1.0	0.232
Size > 2cm, n (%)	124	26 (21)	12	5 (41.7)	31	20 (64.5)	0.301	67	7 (10.4)	38	10 (26.3)	0.052
Multifocality, n (%)	125	34 (27.2)	12	4 (33.3)	31	14 (45.2)	0.731	68	20 (29.4)	40	13 (32.5)	0.829
Extrathyroidal extension, n (%)	125	59 (47.2)	12	6 (50.0)	31	26 (86.7)	0.020	68	43 (63.2)	38	23 (60.5)	0.836
No/ minimal/ gross, n (%)	125	66/42/17 (52.8/33.6/13.6)	12	6/5/1 (50.0/41.7/8. 3)	31	4/17/9 (13.3/56.7/ 30.0)	0.014	68	25/31/12 (36.8/45.6/1 7.6)	38	15/17/6 (39.5/44.7/1 5.8)	0.752
LN metastasis, n (%)	125	59 (47.2)	12	9 (75.0)	31	29 (93.5)	0.123	68	23 (33.8)	38	26 (68.4)	0.001
Lateral LN metastasis, n (%)	125	15 (12.0)	12	6 (50.0)	31	11 (35.5)	0.492	68	8 (11.8)	35	6 (17.1)	0.546
Distant metastasis, n (%)	125	3 (2.4)	12	1 (8.3)	31	13 (41.9)	0.067	68	1 (1.5)	40	1 (2.5)	1.000
Follow-up years, median (range)	125	7.4 (0.1-13.3)	12	6.3 (1.2-13.2)	31	4.8 (0.9-34.3)	0.443	68	8.0 (0.1-13.3)	41	8.0 (0.6-37.3)	0.070
Disease outcome at any event	112	100/9/3	12	12/0/0	29	6/6/17	<0.001	60	50/8/2	37	27/4/6	0.108

(NED/ BCD/ SD), n (%)		(89.3/8.0/2.7)		(100/0/0)		(20.7/20.7/ 58.6)			(83.3/13.3/3. 3)		(73.0/10.8/1 6.2)	
Disease outcome at last follow-up (NED/ BCD/ SD), n (%)	112	100/9/3 (89.3/8.0/2.7)	12	12/0/0 (100/0/0)	29	8/6/15 (27.6/20.7/ 51.7)	<0.001	60	50/8/2 (83.3/13.3/3. 3)	37	29/7/1 (78.4/18.9/2. 7)	0.607

Data are expressed as means ± standard deviation (means ± SD) or number (%).

LN, lymph node; NED, no evidence disease; BCD, biochemical disease; and SD, structural disease.

Supplemental Table 7. Comparison between pediatric and adult patients in the TCGA database harboring a fusion oncogene *(TRK, RET, or ALK)* and *BRAF*^{V600E}

	Adult PTC patients (Total 485 cases in TCGA database)		Fusion *(TRK, RET, or ALK)* pediatric vs. adult patients					*BRAF*^{V600E} pediatric vs. adult patients				
	No. of evaluated	Total patients (n = 485)	N	Adult (n = 42)	N	Pediatric (n = 31)	p-value	N	Adult (n = 241)	N	Pediatric (n= 41)	p-value
Age (yrs)	485	47.8 ± 15.3	42	38.8 ± 13.5	31	11.1 ± 4.2	<0.001	241	48.0 ± 15.3	41	16.3 ± 2.3	<0.001
Females, n (%)	485	355 (73.2)	42	32 (76.2)	31	25 (80.6)	0.778	241	172 (71.4)	41	35 (85.4)	0.084
Radioiodine therapy, n (%)	325	182 (56.0)	27	12 (44.4)	31	27 (87.1)	0.001	164	88 (53.7)	40	23 (57.5)	0.725
PTC subtype (classic variant / diffuse sclerosing variant / other subtypes), n (%)	485	344/4/137 (70.9/0.8/28.2)	42	37/1/4 (69.8/2.4/9.5)	31	16/13/2 (51.6/41.9/6.5)	0.026	241	194/1/46 (80.5/0.4/19.1)	39	35/0/4 (89.7/0/10.3)	0.173
Size (cm)	485	2.8 ± 1.6	42	2.7 ± 1.3	31	2.8 ± 1.5	0.830	241	2.8 ± 1.7	38	1.4 ± 1.0	<0.001
Size > 2cm, n (%)	484	326 (67.2)	42	28 (66.7)	31	20 (64.5)	1.000	241	156 (64.7)	38	10 (26.3)	<0.001
Multifocality, n (%)	484	222 (45.9)	41	16 (39.0)	31	14 (45.2)	0.636	241	111 (46.1)	40	13 (32.5)	0.124
Extrathyroidal extension, n (%)	485	148 (30.5)	42	10 (23.8)	30	26 (86.7)	<0.001	241	94 (39.0)	38	23 (60.5)	0.014
Lymph node metastasis, n (%)	439	217 (49.4)	41	28 (68.3)	31	29 (93.5)	0.010	221	118 (53.4)	38	26 (68.4)	0.111
Distant metastasis, n (%)	280	7 (2.5)	25	0 (0)	31	13 (41.9)	<0.001	150	4 (2.7)	40	1 (2.5)	1.000
Follow-up years, median (range)	485	2.6 (0.1-14.8)	42	2.7 (0.1-9.7)	31	4.8 (0.9-34.3)	0.006	241	2.9 (0-14.9)	41	8.0 (0.6-37.3)	<0.001
Outcome (disease free/ recurred or progressed), n (%)	471	43 (9.1)	41	40/1 (97.6/2.4)	29	12/17 (41.4/58.6)	<0.001	233	26 (11.2)	37	6 (16.2)	0.410

Data are expressed as means ± standard deviation (means ± SD) or number (%).

Supplemental Table 8. Nucleotide sequences of primers

For direct sequencing		
Gene	**Forward**	**Reverse**
TERT promoter	CCCTTCACCTTCCAGCTC	CAGCGCTGCCTGAAACTC
NRAS 12/13	TACTGTACATGTGGCTCGCC	CCGACAAGTGAGAGACAGGA
NRAS 61	CCAGATAGGCAGAAATGGGC	CCTTCGCCTGTCCTCATGT
HRAS 12/13	CAGTCCTTGCTGCCTGGC	CTCCCTGGTACCTCTCATGC
HRAS 61	GCATGAGAGGTACCAGGGAG	TGATGGCAAACACACACAGG
KRAS 12/13	AAGCGTCGATGGAGGATTT	TGTATCAAAGAATGGTCCTGCA
KRAS 61	CGTCATCTTTGGAGCAGGAA	ACTCCACTGCTCTAATCCCC
BRAF 15	GCTTGCTCTGATAGGAAAATGAG	GATACTCAGC AGCATCTCAGG
DICER1 12	CCTAAATGCAGAACCCGAGA	TGACACATTTTAAAAGATAACAATCA
DICER1 16	TCTTCGGCTTGAAAAACCTG	TCCAAAGTGCTGGAGTCATT
DICER1 20	CTTTTGTGTGTGCGCTTTGT	CTGCAGTCAAAAGGCAGTGA
DICER1 21	GCTGCACATCAAGGTGCTAA	CCATTGGCGAGATTTTGATT
DICER1 23	GCTATGTTTCCCCTCCTTCC	CATAGTCAGCCTCTTCCTTCG
DICER1 24	ACTTCGGATCCCCTCAGATT	CGATGCAAAGATGGTGTTGT
DICER1 25	TGGACTGCCTGTAAAAGTGG	ACACCTGCCAGACTGTCTCC
For RT-PCR		
Fusion gene	**Forward**	**Reverse**
SLC5A5 (NIS)	CTGCCCCACTCCAGTACATGCC	TGACGGTGAAGGAACCCTGAAG
NTRK1	GGTGGAGAAGAAGGACGAAA	TTGTTGAGCACAAGGAGCAG
GAPDH	CAGCCTCAAGATCATCAGCA	TGTGGTCATGAGTCCTTCCA
cDNA cloning		
TPR-NTRK1	TAAAAGCTTATGACTCAAGATTTGAGAGGAGCA	AAACTCGAGTTGCAGCCGGGCGTGCACATCCTT

PCR sequencing was performed with the BigDye Terminator 3.1 cycle sequencing ready reaction kit (Applied Biosystems, Foster City, Calif) and the ABI-Prism 3130xl genetic analyzer (Applied Biosystems).

Supplemental Table 9. Target gene lists of SNUH FIRST cancer panel (version 3)

ABL1	*AKT1*	*AKT2*	*AKT3*	*ALK*	*APC*	*AR*	*ARAF*	*ARID1A*	*ATM*
ATR	*AURKA*	*AURKB*	*AURKC*	*AXL*	*BAP1*	*BARD1**	*BCL2*	*BRAF*	*BRCA1*
CDK6	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CHEK1*	*CHEK2*	*CREBBP*	*CSF1R*	*CTNNB1*
DDR1	*DDR2*	*DICER1*	*DPYD*	*EGFR*	*EIF1AX*	*EMSY*	*EP300*	*EPCAM*	*ERBB2*
ERBB3	*ERBB4*	*ERCC2*	*ERG*	*ESR1*	*ETV1*	*EWSR1*	*EZH2*	*FAM175A*	*FANCA*
FANCC	*FANCD2*	*FANCG*	*FANCI*	*FANCL*	*FANCM*	*FBXW7*	*FGF19*	*FGF23*	*FGFR1*
FGFR2	*FGFR3*	*FGFR4*	*FOXA1*	*GNAQ*	*GNAS*	*GNB2L1*	*HDAC1*	*HRAS*	*IDH1*
IDH2	*IGF1R*	*IGF2*	*IGFBP3*	*INPP4B*	*IRF1*	*JAK1*	*JAK2*	*JAK3*	*JUN*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KIT*	*KMT2D*	*KRAS*	*LATS1*	*LATS2*	*MAP2K1*
MAP2K2	*MAP2K4*	*MAP3K1*	*MAP3K4*	*MAPK1*	*MAPK8*	*MCL1*	*MDM2*	*MET*	*MLH1*
MRE11A	*MSH2*	*MSH6*	*MTOR*	*MUTYH*	*MYC*	*MYCN*	*NF1*	*NF2*	*NFE2L2*
NOTCH1	*NOTCH2*	*NOTCH3*	*NOTCH4*	*NRAS*	*NRG1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUTM1*
PAK2	*PALB2*	*PARP1*	*PARP2*	*PBRM1*	*PDGFB*	*PDGFRA*	*PDGFRB*	*PIK3CA*	*PMS2*
POLD1	*POLE*	*POLQ*	*PPARG*	*PPP2R2A*	*PRKCB*	*PTEN*	*RAD21*	*RAD50*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD54L*	*RB1*	*RelA*	*RET*	*RHEB*	*RICTOR*	*RIT1*
RNF43	*ROS1*	*RPTOR*	*SDHB*	*SETD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SOX2*	*SPOP*
SQSTM1	*SRC*	*SS18*	*STAT1*	*STAT6*	*STK11*	*SUMO1*	*SYK*	*TERT*	*TFE3*
TOP2A	*TP53*	*TP63*	*TSC1*	*TSC2*	*TSHR*	*UGT1A1*	*VHL*	*XRCC2*	*ZBTB16*

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