Application of genomics to identify therapeutic targets in recurrent pediatric papillary thyroid carcinoma

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Abstract Children with papillary thyroid carcinoma (PTC) may relapse despite response to radioactive iodine (RAI). Two children with multiply relapsed PTC underwent whole-genome and transcriptome sequencing. A *TPM3-NTRK1* fusion was identified in one tumor, with outlier *NTRK1* expression compared to the TCGA thyroid cancer compendium and to Illumina BodyMap normal thyroid. This patient demonstrated resolution of multiple pulmonary nodules without toxicity on oral TRK inhibitor therapy. A *RET* fusion was identified in the second tumor, another potentially actionable finding. Identification of oncogenic drivers in recurrent pediatric PTC may facilitate targeted therapy while avoiding repeated RAI.

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INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most commonly diagnosed thyroid cancer in childhood (Greco et al. 2010). Compared to adults, children are more likely to present with advanced local disease as well as widespread metastases. The treatment of locally invasive pediatric PTC is complete surgical excision followed by radioactive iodine (RAI) ablation (Parisi et al. 2016). Although overall survival is excellent, the recurrence rate remains high at 40% and some children have multiple relapses, requiring additional surgeries and repeated RAI (Parisi et al. 2016). There are significant acute and late effects associated with RAI (Rubino et al. 2003; Florenzano et al. 2016), which are increased in patients who receive higher cumulative doses (Rubino et al. 2003; Fard-Esfahani et al. 2014).

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Activating point mutations and oncogenic fusions in *NTRK*, *RET*, *RAS*, and *BRAF* have been identified in PTC (Beimfohr et al. 1999; Xing et al. 2013; Khotskaya et al. 2017). Compared with adults, pediatric PTC are more likely to have fusion proto-oncogenes, which are associated with more aggressive and disseminated disease (Prasad et al. 2016). *NTRK1/3* fusion oncogenes (located on Chromosome 1) are rare in adult PTC (Fig. 1A; Nikiforov and Nikiforova 2011; The Cancer Genome Atlas Research Network 2014) but described in up to 26% of pediatric PTC (Prasad et al. 2016). *RET* gain of function mutations (located on Chromosome 10) (Fig. 1B) have been described in many endocrine cancers, and more

Figure 1. *TPM3-NTRK1* and *RET-CCDC6* oncogenic fusions with exon numbers and protein domains. (A) *TPM3-NTRK1* fusion. Chr 1, Chromosome 1; B1, breakpoint that falls into *TPM3*; B2, breakpoint that falls into *NTRK1*; T1, transcript of *TPM3* (ENST00000368530); T2, transcript of *NTRK1* (ENST00000368196). The numbers on T1 and T2 indicate exons. Pfam domains and accession IDs are labeled beneath the transcripts. (B) *RET-CCDC6* fusion. Chr 10, Chromosome 10; B1, breakpoint that falls into *RET*; B2, breakpoint that falls into *CCDC6*; T1, transcript of *RET* (ENST00000355710); T2, transcript of *CCDC6* (ENST00000263102).

than 10 activating *RET* fusions have been identified in thyroid cancers (Menicali et al. 2012; Accardo et al. 2017).

The identification of recurrent oncogenic drivers in aggressive PTC presents the opportunity for targeted therapy. An adult phase I study in *NTRK* fusion driven malignancies and advanced disease have demonstrated partial responses in the first three evaluable patients with minimal toxicity (American Association for Cancer Research 2016). An ongoing pediatric phase I/II trial of a pan-*TRK* inhibitor, larotrectinib, has demonstrated tumor responses across histologic cancer types in *TRK*-fusion driven cancers (NCT02637687) (Laetsch et al. 2017).

There is also evidence to support a role for oral *RET* inhibitors in thyroid cancer. In a phase 1 study in adults with RAI-refractory differentiated thyroid cancer, 53% had a response by RECIST to cabozantinib, an oral multikinase inhibitor for *RET*, *MET*, and *VEGFR2* (Cabanillas et al. 2014). Cabozantinib is FDA-approved in adults with metastatic medullary thyroid carcinoma and renal cell carcinoma (Food and Drug Administration 2016). A pediatric phase I study was recently completed, with a phase II expansion currently accruing patients with refractory solid tumors, including medullary thyroid carcinoma (NCT01709435 and NCT02867592) (Akshintala and Children's Oncology Group 2017).

We describe whole-genome and transcriptome sequencing in two children with RAI-refractory PTC and document radiographic improvement in a patient with an oncogenic *TPM3-NTRK1* fusion following *TRK* inhibitor therapy.

RESULTS

Case 1

A previously healthy 12-yr-old boy presented with a painless right neck mass without constitutional symptoms, no family history of cancer, no radiation exposure, endocrinopathies or underlying syndromes. An ultrasound showed a large, heterogeneous solid mass arising from the right thyroid lobe, extending into the isthmus with localized lymphadenopathy. A total thyroidectomy confirmed PTC involving the right lobe and microscopic involvement of the isthmus and left lobe. Surgical margins were positive with multiple involved lymph nodes. Postoperatively, he received 100 mCi of I^{131} RAI and was maintained euthyroid with thyroid hormone replacement.

One year later, his thyroglobulin levels rose and imaging confirmed relapse within the neck, thyroid bed and paratracheal lymph nodes, along with new bilateral pulmonary nodules. He underwent cervical debulking surgery and received an additional 150 mCi of I^{131} RAI. Follow-up I^{131} imaging demonstrated progression of multiple bilateral, small pulmonary nodules with active uptake in several neck and thyroid bed lymph nodes. Repeat neck and chest CT two months following repeat RAI revealed progression of innumerable pulmonary metastatic nodules. The patient was enrolled in the POG project, and sections from his surgical resection were sent for WGS and transcriptome sequencing. From the sequencing data we identified four somatic nonsynonymous mutations and one indel, none of which have known clinical significance (Table 1). Analysis of sequencing data results revealed a somatic *TPM3::NTRK1*(e8:e9) fusion (Fig. 1A), reported previously in PTC. The same fusion was validated by PCR and was also identified on archival tissue from diagnosis. Furthermore, there was very high *NTRK1* expression in the tumor compared to a normal thyroid tissue from Illumina Bodymap, and to the TCGA thyroid cancer samples (THCA) (Fig. 2A). In addition to *NTRK1*, other genes encoding receptor tyrosine kinases (RTKs) including *PDGFRB* and *EGFR* also show high percentile compared to THCA. In the hedgehog pathway, *GLI1*, *GLI2*, and *GLI3* all show high level of expression (95th–98th percentile compared to THCA).

Table 1. Somatic nonsynonymous small mutations and indels in Patient 1

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP	Genotype	VAF in tumor genome ^a	Note
<i>MUC5B</i>	11	NM_002458.2: c.12272C>G	NP_002449.2: p.Thr4091Arg	Substitution	Missense	rs199736618	het	17%	
<i>BAZ2B</i>	2	NM_013450.2: c.197C>T	NP_038478.2: p.Ser66Leu	Substitution	Missense		het	26%	
<i>CRIPAK</i>	4	NM_175918.3: c.738G>A	NP_787114.2: p.Met246Ile	Substitution	Missense	rs76723438	het	15%	
<i>DSPP</i>	4	NM_014208.3: c.3139G>A	NP_055023.2: p.Asp1047Asn	Substitution	Missense		het	15%	May be a sequencing artifact
<i>LRRC40</i>	1	NM_017768.4: c.687_691del	NP_060238.3: p.Asn230LeufsTer7	Deletion	Frameshift		het	22%	

HGVS, Human Genome Variation Society; VAF, variant allele frequency; het, heterozygous.

^aWith 58% tumor content in the sequenced sample.

The patient was enrolled on a pediatric phase I/II study (NCT02637687) evaluating an oral, selective pan-TRK inhibitor, larotrectinib (Laetsch et al. 2017). Following two cycles of TRK inhibitor therapy, repeat CT chest demonstrated an overall reduction in number of pulmonary nodules (Fig. 3A,B). Subsequent CT chest after four and six cycles revealed further interval improvement, with excellent functional status (Lansky 100) without any

Figure 2. (A) High *NTRK1* RNA expression in Patient 1 compared to 513 tumor samples from TCGA thyroid (THCA) cohort and 59 matched normal samples. The distributions of *NTRK1* expression in the tumor and normal groups are shown as density curve. The gray line indicates *NTRK1* expression in a normal thyroid sample from Illumina body map. (B) High *RET* RNA expression in Patient 2 compared to 513 tumor samples from TCGA thyroid (THCA) cohort and 59 matched normal samples. The distributions of *RET* expression in the tumor and normal groups are shown as density curve. The gray line indicates *RET* expression in a normal thyroid sample from Illumina body map.

Figure 3. Pre- and posttherapy CT chest images for Case 1. (A) Axial CT chest image demonstrating a large (6-mm) pulmonary nodule (red arrow) prior to oral TRK inhibitor therapy initiation. At baseline, the patient had progressive innumerable, small pulmonary nodules demonstrated throughout the lungs bilaterally. (B) Coregistered axial CT image following four cycles of oral TRK inhibitor therapy demonstrating resolution of the prior pulmonary nodule (red circle) documented at baseline.

therapy-related toxicity. Currently, the patient is 10 months post initiation of therapy with almost complete resolution of prior innumerable pulmonary nodules, and has excellent functional status.

Case 2

A previously healthy 13-yr-old girl presented with a three-year history of an enlarging right-sided goiter and a neck ultrasound demonstrating enlarged, calcified cervical lymph nodes. Fine needle aspiration was suspicious for PTC and the patient underwent a total thyroidectomy with right radical neck dissection. Pathology confirmed PTC involving both thyroid lobes, the isthmus as well as extensive involvement of regional lymph nodes. The patient underwent I¹³¹ RAI therapy of 100 mCi. Six months postoperatively, neck ultrasound demonstrated enlarging cervical adenopathy and a cervical lymph node excisional biopsy confirmed locally recurrent PTC in two nodes. Thyrogen stimulated positron emission tomography-computed tomography (PET-CT) demonstrated marked 18-fluoro-deoxy-glucose (FDG) avidity in the thyroid bed and right cervical chain, with no evidence of distant disease. The patient underwent a third surgery with a lymph node biopsy and a modified left radical neck dissection. Resected lymph nodes were again positive for PTC and the patient received an additional I¹³¹ RAI treatment.

The patient's tumor at relapse underwent whole-genome and transcriptome sequencing in POG. We identified 23 somatic nonsynonymous small mutations in the genome, none of which have known clinical significance (Table 2). We also found a *CCDC6::RET* (e1:e12) fusion that is frequently reported in PTC (Fig. 1B; Santoro and Carlomagno 2013). In the fused protein, *RET* loses the extracellular part (for ligand binding), but the kinase domain is intact. Such fusion drives the expression and ligand-independent activation of the fused protein (Nikiforov and Nikiforova 2011). In this case, *RET* shows high expression when compared to TCGA thyroid cancer, and normal thyroid tissue from Illumina bodymap (Fig. 2B). As with Patient 1, *PDGFRB*, *EGFR*, *GLI1*, *GLI2*, and *GLI3* all showed high percentile compared to TCGA THCA.

Several receptor tyrosine kinase inhibitors such as cabozantinib, regorafenib, vandetanib, sorafenib, and sunitinib show activity against *RET*. Preclinical study on PTC cell-line with *RET* fusion showed that XL184 (cabozantinib) is more potent in inhibiting cell growth,

Table 2. Somatic nonsynonymous small mutations in Patient 2

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP	Genotype	VAF in tumor genome ^a
<i>TCHH</i>	1	NM_007113.3: c.1030G>C	NP_009044.2: p.Glu344Gln	Substitution	Missense	rs201434724	het	9%
<i>FCGR2A</i>	1	NM_021642.3: c.818T>C	NP_067674.2: p.Leu273Pro	Substitution	Missense		het	14%
<i>CD163L1</i>	12	NM_174941.5: c.2332G>T	NP_777601.2: p.Ala778Ser	Substitution	Missense		het	10%
<i>PRB4</i>	12	NM_002723.5: c.347C>A	NP_002714.2: p.Pro116His	Substitution	Missense	rs59189129	het	14%
<i>DACH1</i>	13	NM_004392.6: c.235G>A	NP_004383.4: p.Gly79Ser	Substitution	Missense	rs200162861	het	20%
<i>PAPLN</i>	14	NM_173462.3: c.2041C>T	NP_775733.3: p.Gln681Ter	Substitution	Stop_gained		het	17%
<i>TPSB2</i>	16	NM_024164.5: c.253G>A	NP_077078.5: p.Ala85Thr	Substitution	Missense	rs202041848	het	17%
<i>EXOC3L1</i>	16	NM_178516.3: c.41C>G	NP_848611.2: p.Ser14Cys	Substitution	Missense		het	17%
<i>ZNF844</i>	19	NM_001136501.2: c.1459T>C	NP_001129973.1: p.Phe487Leu	Substitution	Missense		het	13%
<i>ZNF430</i>	19	NM_025189.3: c.869G>A	NP_079465.3: p.Arg290Lys	Substitution	Missense		het	9%
<i>TRIOBP</i>	22	NM_001039141.2: c.2072T>C	NP_001034230.1: p.Ile691Thr	Substitution	Missense		het	20%
<i>ZNF852</i>	3	XM_001717544.3: c.1477G>A	XP_001717596.3: p.Glu493Lys	Substitution	Missense + splice_region	rs113868900	hom	46%
<i>MUC4</i>	3	NM_018406.6: c.11633T>C	NP_060876.5: p.Leu3878Pro	Substitution	Missense		het	20%
<i>ART3</i>	4	NM_001179.5: c.376C>T	NP_001170.2: p.Arg126Ter	Substitution	Stop_gained		het	20%
<i>PRDM9</i>	5	NM_020227.3: c.1696C>G	NP_064612.2: p.His566Asp	Substitution	Missense		het	12%
<i>MUC21</i>	6	NM_001010909.3: c.743C>T	NP_001010909.2: p.Pro248Leu	Substitution	Missense	rs41288651	het	16%
<i>MUC22</i>	6	NM_001198815.1: c.2969A>C	NP_001185744.1: p.Glu990Ala	Substitution	Missense		het	9%
<i>ZAN</i>	7	NM_003386.1: c.2140C>A	NP_003377.1: p.Pro714Thr	Substitution	Missense		het	10%
<i>MUC12</i>	7	NM_001164462.1: c.5495C>T	NP_001157934.1: p.Thr1832Ile	Substitution	Missense		het	14%
<i>MUC17</i>	7	NM_001040105.1: c.8225G>C	NP_001035194.1: p.Arg2742Pro	Substitution	Missense	rs141347629	het	11%
<i>MUC17</i>	7	NM_001040105.1: c.8990T>C	NP_001035194.1: p.Met2997Thr	Substitution	Missense	rs193142121	het	9%
<i>RPGR</i>	X	NM_001034853.1: c.2808A>T	NP_001030025.1: p.Glu936Asp	Substitution	Missense	rs187844918	het	20%
<i>GCNA</i>	X	NM_052957.4: c.883T>C	NP_443189.1: p.Ser295Pro	Substitution	Missense		het	12%

het, heterozygous; hom, homozygous.

^aWith 35% tumor content in the sequenced sample.

compared to other inhibitors such as sunitinib, vandetanib, and axitinib (Verbeek et al. 2011). Access to cabozantinib may be possible through an early phase pediatric trial (NCT01709435), if this high-risk patient has further relapses.

DISCUSSION

Children with PTC have a high risk of recurrence, which may lead to multiple invasive surgeries and RAI. High cumulative lifetime doses of RAI carries a significant risk of late effects, including secondary malignancies and pulmonary fibrosis (Fard-Esfahani et al. 2014). Recurrent oncogenic drivers are frequently associated with childhood PTC, and tumor genomics may be leveraged to guide molecularly targeted therapy. We document a favorable response to an oral *TRK* inhibitor in an adolescent with multiply relapsed PTC.

These cases highlight the potential clinical utility of using tumor genomics to rationally guide targeted therapy. In the first case, a selective *TRK* inhibitor resulted in rapid and sustained radiographic improvement without toxicity. As the recognition of recurrent, actionable oncogenic drivers in pediatric thyroid carcinoma increases, there is an increasing need for development and access to clinically validated assays for rapid, cost-effective screening in relapsed, or refractory patients. Fusion panel assays may identify a proportion of recurrent actionable fusions, but this approach is not comprehensive and will likely miss other functionally equivalent fusions related to cryptic or noncanonical structural alterations. As the costs of WGS decrease and with improved turnaround times, clinically validated WGS assays may soon be available to facilitate comprehensive genomic analysis to identify potentially actionable oncogenic drivers in relapsed or refractory thyroid carcinoma.

Incorporation of transcriptome data in pediatric sequencing analyses may facilitate a deeper understanding of both oncogenic drivers, as well as treatment resistance, by delineating cellular pathway activation (Laskin et al. 2015). Interestingly, although these patients shared no genomic mutations, several genes such as *PDGFRB*, *EGFR*, *GLI1*, *GLI2*, and *GLI3* are highly expressed in both samples. Given the limited sample size, it is unclear if this observation is by chance, or due to the difference between pediatric and adult thyroid carcinoma cohorts. The challenge in the pediatric setting is the availability of age-matched normal tissue and pediatric cancer reference compendia. With recent acceleration in the availability of genomic sequencing in childhood cancer, it is essential that data sharing initiatives are established and strengthened.

With increasing ability to identify oncogenic drivers in pediatric and adolescent oncology patients who fail upfront therapy, it is essential that we develop strategies to access molecularly guided clinical trials. Despite logistical challenges in pediatric oncology, molecularly guided phase II basket trials and novel trial designs are desperately needed.

Conclusion

Next-generation sequencing may frequently identify therapeutic targets in recurrent pediatric PTC. We demonstrate sustained efficacy of an oral *TRK* inhibitor in a child with multiply relapsed PTC and an oncogenic *TRK* fusion. The incorporation of genomic data in the routine care of relapsed pediatric PTC may help minimize treatment-related morbidity. Collaborative pediatric phase II studies of targeted therapy in PTC are needed to better define efficacy, toxicity and duration of response.

METHODS

Patients were enrolled in the Personalized Onco-Genomics (POG) project at BC Cancer in Vancouver, British Columbia. Tumor biopsies or surgical resections and blood samples were

Table 3. Sequencing coverage

	Tumor sample WGS	Blood sample WGS	Tumor sample RNA-seq coverage
Patient 1	2,221,403,836 reads (84.2-fold)	1,156,446,710 reads (43.8-fold)	205,572,316 reads ^a
Patient 2	2,030,407,160 reads (82.9-fold)	859,662,882 read (33.8-fold)	229,706,898 reads

WGS, whole-genome sequencing.

^aRead length is 75 bases.

collected for paired-end whole-genome and transcriptome sequencing. Whole-genome sequencing (WGS) depth is >80× for tumor samples and >30× for constitutional samples, and transcriptome sequencing depth is approximately 230 M reads in total (115 M read pairs, Table 3). Somatic point mutations, small insertions or deletions (indels), copy-number alterations, structural variants were detected as described before (Jones et al. 2017). Gene expression levels were evaluated using public and in-house transcriptome sequencing data from the Illumina bodymap (www.illumina.com; ArrayExpress ID: E-MTAB-513) and The Cancer Genome Atlas (TCGA, <https://tcga-data.nci.nih.gov/tcga/>). Genes were linked to cancer pathways and drugs to identify potential therapeutic recommendations (Jones et al. 2017).

ADDITIONAL INFORMATION

Data Deposition and Access

As per the consent of POG, we do not share the sequencing data outside of the research group. The two structural variants were deposited to ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) and can be found under accession numbers SCV000693715 (the TPM3-NTRK1 fusion) and SCV000693716 (the CCDC6-RET fusion).

Ethics Statement

Both patients and their guardians provided informed consent/assent for participation in the Pediatric Personalized Oncogenomics project, which is approved by the BC Children's and Women's Research Ethics Board.

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Competing Interest Statement

The authors have declared no competing interest.

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Author Contributions

R.R. participated in case series conception and prepared the first draft of the manuscript with revisions based on coauthor's feedback. S.R.R. participated in case series conception and manuscript preparation and revisions. Y.S. performed the bioinformatics analysis, created the data figures and participated in manuscript preparation and revisions. A.F.L., C.J., J.H., C.A., D.S.H., S.A., R.R., A.J.M., D.D., G.B., S.J.M.J., J.L., and M.A.M. participated in manuscript preparation and revisions. H.N. participated in manuscript revisions and provided imaging for the first case. R.J.D. was responsible for case series conception, manuscript preparation and revisions, and trainee supervision and oversaw completion of the project.

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