



Unveiling a new *SORBS2::BRAF* fusion in papillary thyroid carcinoma: insights from molecular diagnostics

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Abstract

Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer, with the majority of cases driven by genetic alterations that activate the MAPK signaling pathway. The *BRAF* V600E mutation is the most frequent alteration, while *BRAF* fusions are relatively rare but increasingly recognized as oncogenic drivers. These fusions typically involve the loss of *BRAF*'s autoinhibitory N-terminal domain, leading to constitutive MAPK pathway activation. Here, we report a novel *SORBS2::BRAF* fusion in a case of PTC, further expanding the spectrum of *BRAF* alterations in thyroid cancer. A 32-year-old male was incidentally found to have a left thyroid nodule during a routine physical examination. Follow-up examinations revealed changes in the nodule's characteristics, prompting fine-needle aspiration biopsy, which identified atypical follicular epithelial cells suggestive of papillary thyroid carcinoma. Histopathological examination confirmed the diagnosis, and next-generation sequencing (NGS) revealed a novel in-frame fusion between *SORBS2* exon 18 and *BRAF* exon 9. The resulting fusion protein retains the *BRAF* kinase domain while replacing its autoinhibitory domains with those of *SORBS2*. RT-PCR and Sanger sequencing confirmed the presence of the *SORBS2::BRAF* fusion. Quantitative PCR profiling of MAPK transcriptional output genes (*DUSP6*, *CCND1*, *ETV4*, *c-Myc*, and *c-FOS*) revealed marked upregulation in the tumor versus adjacent normal tissue, providing functional evidence for pathway activation. The *SORBS2::BRAF* fusion has not been previously reported in PTC or any other tumor type. Given the deletion of *BRAF*'s inhibitory domain, this fusion likely acts as a tumor driver through constitutive activation of the MAPK pathway. This case underscores the importance of molecular diagnostics in identifying rare genetic alterations and highlights the need for further research into targeted therapies for *BRAF* fusion-driven cancers. The discovery of this novel fusion expands our understanding of the molecular landscape of PTC and provides a foundation for future therapeutic development.

Keywords *BRAF* fusion · *SORBS2::BRAF* · Papillary thyroid carcinoma · Molecular diagnostics · Targeted therapy

Introduction

Thyroid cancer is the most common endocrine malignancy, with papillary thyroid carcinoma (PTC) accounting for ≈85% of cases [1]. Nearly 90% of PTCs harbor mutually exclusive driver alterations that hyper-activate the MAPK or PI3K/AKT signaling axes [2]. The canonical MAPK cascade (RAS → RAF → MEK → ERK) transduces extracellular

growth cues into transcriptional programmes that regulate proliferation, differentiation, and apoptosis [3]. In thyroid epithelia, this cascade is most frequently activated by: *BRAF* V600E point mutation (≈45% of PTC); *BRAF* or *RAF1* fusions (≈2%); RAS hotspot mutations (NRAS Q61R/K, HRAS Q61R; ≈15%); RET/PTC rearrangements (≈10%) [2–4].

BRAF, a serine/threonine kinase of the RAF family, is normally kept in an auto-inhibited monomeric state by its N-terminal regulatory domain [5]. The V600E substitution releases this inhibition, generating a constitutively active monomer that continuously phosphorylates MEK [6]. While this *BRAF* V600E mutation has been associated with certain aggressive pathological features, its independent prognostic role is now debated [7]. In contrast, *BRAF* fusions arise when the 5' inhibitory portion of *BRAF* is replaced by a

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dimerization-prone partner protein. The resulting chimeric kinase constitutively dimerizes even in the absence of RAS-GTP, leading to ligand-independent MEK/ERK signaling [8]. More than 30 fusion partners have now been identified in thyroid cancer (e.g., *AGK*, *AKAP9*, *SND1*, and now *SORBS2*) [9]. These tumors are enriched in radioiodine-refractory metastatic disease and demonstrate variable sensitivity to first-generation RAF inhibitors because drug binding to one protomer can allosterically activate the second (“paradoxical activation”) [10]. Therefore, distinguishing between BRAF point mutations and fusions is both biologically and therapeutically relevant.

The novel *SORBS2::BRAF* fusion reported here adds an adaptor protein with three SH3 domains to the growing list of BRAF partners. Mechanistically, the fusion replaces BRAF’s autoinhibitory N-terminus with the membrane-anchoring and oligomerization motifs of *SORBS2*, potentially enhancing dimerization at lipid rafts. This finding broadens the molecular spectrum of PTC and underscores the need for comprehensive next-generation sequencing to guide precision therapy.

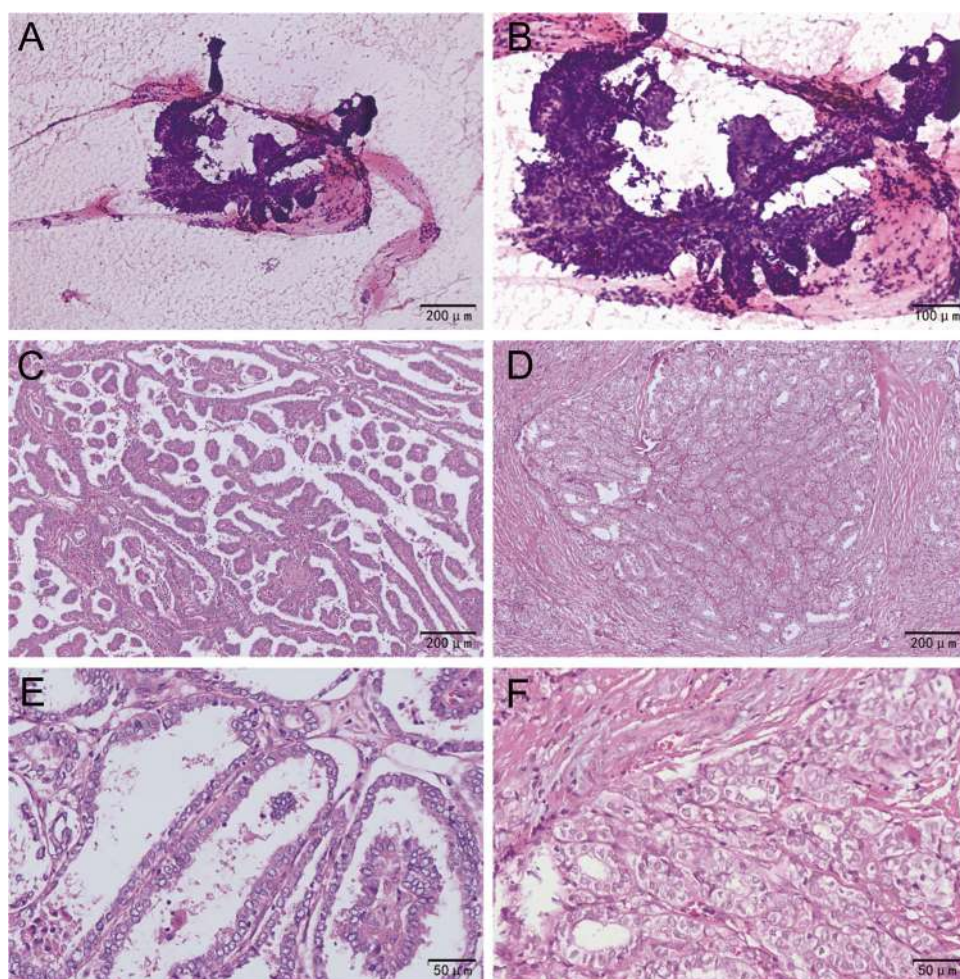
Case presentation

Clinical findings

A 32-year-old male patient was incidentally found to have a left thyroid nodule during a routine physical examination two years prior. An ultrasound evaluation revealed a 16 mm × 13 mm solid, hypoechoic nodule in the lower pole of the left lobe, characterized by irregular margins, fine punctate strong echogenic foci consistent with microcalcifications, and an elasticity score of 4. Fine-needle aspiration biopsy on the left-side nodule identified a small number of follicular epithelial cells, some of which exhibited significant atypia, consistent with papillary thyroid carcinoma (Fig. 1A, B). Based on these features, it was classified as C-TIRADS 6 (highly suspicious for malignancy). The ultrasound also identified a 12 mm × 8 mm mixed cystic-solid nodule in the right lobe, which had smooth margins and no high-risk features, classified as C-TIRADS 3.

Laboratory blood tests showed elevated thyroid peroxidase antibodies (TPOAb) and decreased thyroglobulin

Fig. 1 Histopathological features of the *SORBS2::BRAF* fusion papillary thyroid carcinoma (PTC). **A, B** Cytology from fine-needle aspiration (FNA) of the left thyroid nodule. The smear reveals clusters of follicular epithelial cells with nuclear atypia (10×; 20×). **C, D** Low-power histological view (H&E, 10×) of the primary tumor in the left (**C**) and right (**D**) lobes. Microscopic examination of the tumor reveals classic papillary structures with ground-glass nuclei, characteristic of PTC. **E, F** Higher magnification (H&E, 40×) of the left (**E**) and right (**F**) lobe tumor highlights the presence of nuclear grooves in tumor cells, a histological hallmark of PTC



levels, while thyroid-stimulating hormone (TSH), serum free thyroxine (fT4), serum free triiodothyronine (fT3), calcitonin, and thyroglobulin antibodies (TgAb) were within normal ranges.

Based on these findings, the patient underwent surgical exploration. Intra-operative frozen section analysis was performed on both thyroid lobes. The frozen section confirmed PTC in the right lobe nodule (which had appeared benign on pre-operative ultrasound). Given the confirmed bilateral malignancy, a total thyroidectomy was performed.

Postoperative pathology confirmed PTC of the classic subtype with capsular invasion. Gross examination of the surgical specimen revealed a total of four distinct nodules: two grayish-white nodules in the left lobe (measuring up to 1.5 cm) and two additional nodules in the right lobe (up to 0.4 cm). Notably, histological analysis confirmed that all four nodules were foci of PTC, establishing a diagnosis of bilateral, multifocal disease. The final pathological staging was pT1bN1aMx, with metastatic involvement confirmed in 2 of 18 resected lymph nodes. The largest metastatic lymph node measured 0.3–0.6 cm, and there was no evidence of extranodal extension (ENE).

The patient recovered well postoperatively and was treated with levothyroxine sodium 75 µg/day. At the 6 months' follow-up, clinical outcomes were favorable and there was a negative neck ultrasound.

Histopathological findings

Histopathological examination of the surgical specimen revealed classic features of PTC. A lower-power (10×) view (Fig. 1C, D) illustrates the characteristic papillary architecture of the primary tumor and its infiltrative interface with the surrounding normal thyroid parenchyma. High-power (20×) magnification (Fig. 1E, F) further demonstrates classic nuclear features, including ground-glass nuclei, nuclear grooves, and pseudoinclusions.

Molecular analysis

Molecular analysis was performed on the thyroid tumor tissue using DNA next-generation sequencing (NGS). This revealed a novel in-frame fusion between exon 18 of *SORBS2* and exon 9 of *BRAF*. The resulting fusion protein retains the kinase domain of *BRAF*, while its autoinhibitory domains are replaced by sequences from *SORBS2* (Fig. 2A). The *SORBS2::BRAF* fusion transcript was further confirmed by RT-PCR. Sanger sequencing of the PCR product confirmed the presence of the *SORBS2::BRAF* fusion (Fig. 2B, C).

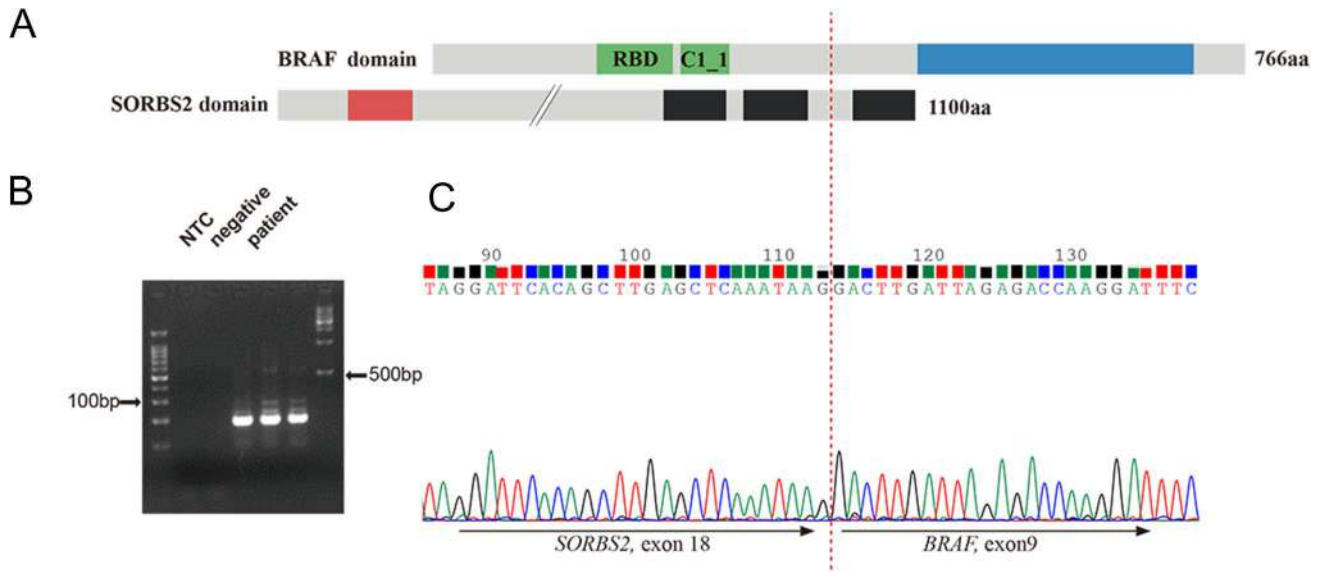
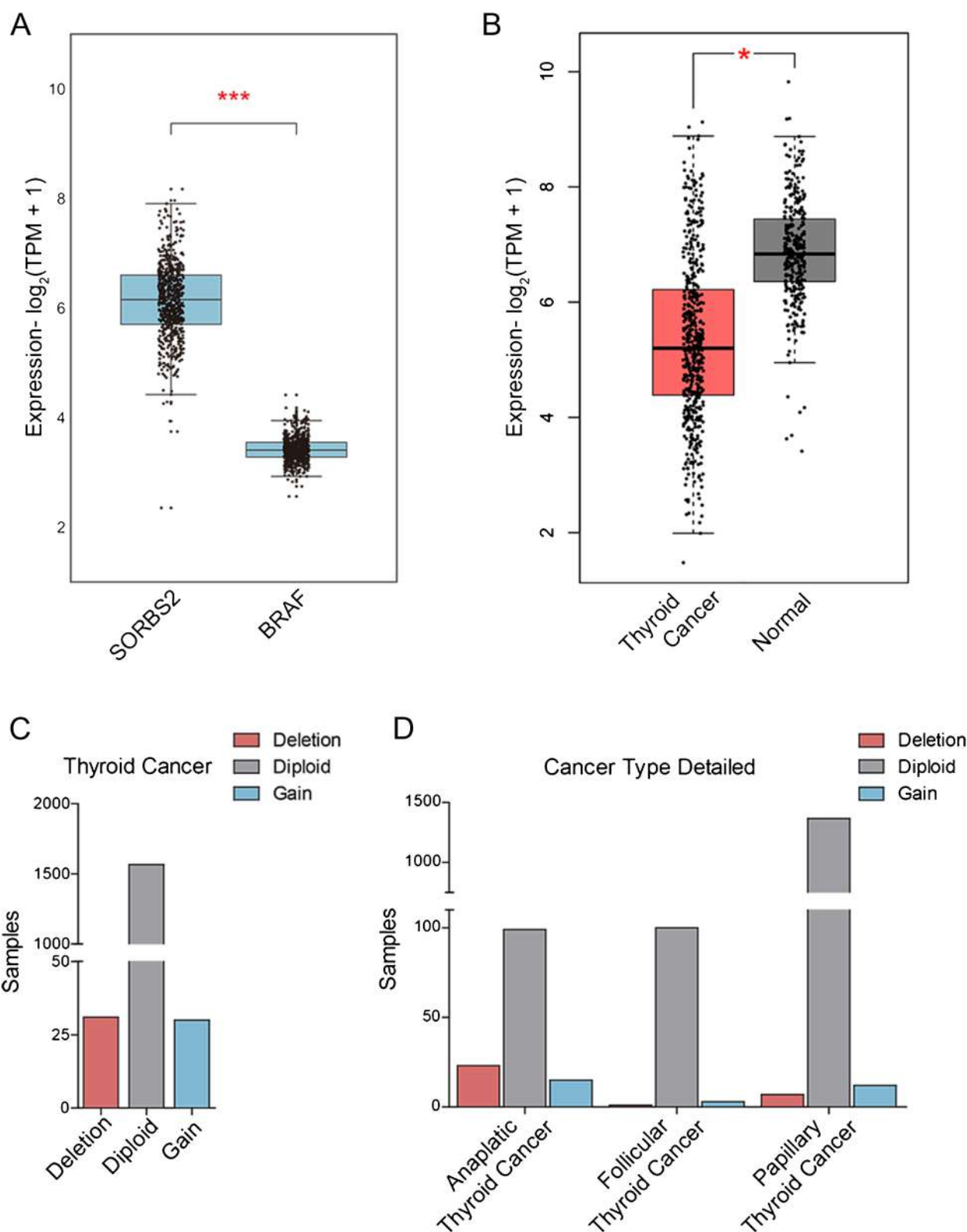


Fig. 2 Molecular characterization of the *SORBS2::BRAF* fusion in papillary thyroid carcinoma. **A** Schematic representation of the *SORBS2::BRAF* fusion identified by targeted DNA next-generation sequencing (NGS). The fusion occurs between exon 18 of *SORBS2* and exon 9 of *BRAF*, resulting in a chimeric protein that retains the *BRAF* kinase domain while replacing its autoinhibitory domains with sequences from *SORBS2*. The SoHo domain and three SH3 domains from *SORBS2* are included in the fusion protein, which may contribute to its oncogenic potential. The vertical dotted line indicates

the fusion breakpoint. **B** RT-PCR analysis using primers specific to *SORBS2* and *BRAF* amplifies a product of the expected size, confirming the presence of the *SORBS2::BRAF* fusion transcript. Lanes 1–5 represent different samples, with lane M indicating the molecular weight marker (100 bp and 500 bp). **C** Sanger sequencing of the PCR product confirms the *SORBS2::BRAF* fusion at the nucleotide level, with the sequence alignment showing the junction point between *SORBS2* exon 18 and *BRAF* exon 9



***SORBS2* alterations in thyroid cancer**

The identification of the *SORBS2::BRAF* fusion in our case of PTC prompted us to further investigate the role

of *SORBS2* alterations in thyroid cancer. *SORBS2* is an adapter protein with multiple functional domains, including the SoHo domain and three SH3 domains, which are involved in various cellular processes such as apoptosis,

Fig. 3 Expression and copy-number alteration analysis of *SORBS2* and *BRAF* in thyroid cancer. **A** Expression analysis of *SORBS2* and *BRAF* in normal thyroid tissues from the GTEx database. The bar graph shows the expression levels of *SORBS2* and *BRAF* in normal thyroid tissues ($n=653$), normalized and presented as $\log_2(\text{TPM} + 1)$ values. **B** Expression analysis of *SORBS2* in normal thyroid tissue samples ($n=337$) and thyroid cancer samples ($n=512$) from TCGA and GTEx databases. The box plot illustrates the significant downregulation of *SORBS2* in thyroid cancer compared to normal tissue. **C** Copy-number alterations of *SORBS2* in 1627 thyroid cancer cases from cBioPortal. The bar chart shows the distribution of *SORBS2* alterations, including shallow deletions ($n=31$), diploid ($n=1566$), and gains ($n=30$). **D** Distribution of *SORBS2* copy-number alterations in different thyroid cancer subtypes: anaplastic thyroid cancer, follicular thyroid cancer, and papillary thyroid cancer. The bar graph highlights the higher frequency of *SORBS2* deletions in anaplastic thyroid cancer

DNA repair, and cell migration. Previous studies have suggested that *SORBS2* may function as a tumor suppressor in thyroid cancer. To explore the expression and genomic alterations of *SORBS2* in thyroid cancer, we analyzed publicly available datasets. We first examined the expression levels of *SORBS2* and *BRAF* in normal thyroid tissues from the GTEx database (Fig. 3A). *SORBS2* was found to be expressed at higher levels than *BRAF* in normal thyroid tissues, indicating its potential role in thyroid physiology. Next, we compared the expression of *SORBS2* in normal thyroid tissue samples ($n=337$) and thyroid cancer samples ($n=512$) from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) projects (Fig. 3B). Our analysis revealed that *SORBS2* is significantly downregulated in thyroid cancer compared to normal thyroid tissue, supporting its role as a tumor suppressor. This downregulation may be due to mechanisms such as promoter methylation rather than common genomic alterations like deletions or mutations. We further investigated the genomic alterations of *SORBS2* in 1627 thyroid cancer cases from cBioPortal (Fig. 3C). We found that 31 cases had *SORBS2* deletions, while two cases harbored potential loss-of-function mutations, including a truncation mutation and a splicing-site mutation. The frequency of *SORBS2* deletions was particularly high in anaplastic thyroid cancer, occurring in 17% of cases (Fig. 3D). This suggests that *SORBS2* alterations, especially deletions, may play a more significant role in the aggressive subtype of anaplastic thyroid cancer. In summary, our analysis indicates that *SORBS2* is frequently downregulated in thyroid cancer, with deletions being more common in anaplastic thyroid cancer. The *SORBS2::BRAF* fusion identified in our case not only leads to *BRAF* activation but also results in the truncation of *SORBS2*, potentially contributing to the loss of its tumor suppressor function. Further studies are needed to elucidate the mechanisms underlying *SORBS2* downregulation and its impact on thyroid cancer progression.

MAPK transcriptional signature confirms ERK hyper-activation driven by *SORBS2::BRAF*

To obtain indirect evidence of MAPK pathway activity, we quantified the expression of five well-characterized ERK-dependent transcriptional targets (*DUSP6*, *CCND1*, *ETV4*, *c-Myc*, and *c-FOS*) by qRT-PCR in the patient's tumor and matched normal thyroid. Three of the five genes were significantly up-regulated in the tumor tissues (all more than 1.5, Supplementary Figure), supporting constitutive activation of the RAF-MEK-ERK axis downstream of the novel *SORBS2::BRAF* fusion.

Treatment

The patient underwent total thyroidectomy with lymph node dissection. Postoperatively, he was prescribed 75 μg of levothyroxine orally once daily (qd). During the half-year follow-up, his thyroid function tests showed T3 at 1.38, T4 at 13.9, FT3 at 5.67, FT4 at 23, and TSH at 4.77. The thyroglobulin (Tg) level was 0.14. An ultrasound examination revealed no obvious mass in the thyroid bed and no abnormal enlarged lymph nodes in the bilateral neck. The patient reported no significant discomfort.

Discussion

BRAF fusions have emerged as important oncogenic drivers across a wide range of cancers, including thyroid carcinomas. These fusions typically involve the loss of *BRAF*'s autoinhibitory N-terminal domain, leading to constitutive activation of the MAPK pathway [11]. In this study, we report a novel *SORBS2::BRAF* fusion in a case of PTC, further expanding the spectrum of known *BRAF* alterations in thyroid cancer.

BRAF fusions are observed in approximately 1–2% of thyroid carcinomas, primarily in PTC [12]. The 5' partner of *BRAF* fusions influences its subcellular localization and intracellular signaling capacity [8]. *TTYH3-BRAF* fusion protein acts as an oncogenic driver in glioblastoma. Interestingly, this fusion retains all known critical autoinhibitory features of *BRAF*, yet its oncogenic activity is primarily dictated by the specific fusion partner, *TTYH3* [13]. The identified *BRAF* fusion genes in thyroid tumors so far include *BAIAP2L1*, *LMO7*, *YWHAG*, *AGK*, *AKAP9*, *KLHL7*, *TANK*, *RBMS3*, *MKRN1*, *CDK5RAP2*, *AKAP9*, *SND1*, and *PRKAR2B* [9, 14–19]. How those partners contribute to the overall function of the fusions remains to be elucidated. The identified *SORBS2::BRAF* fusion results from an in-frame fusion between exon 18 of *SORBS2* and exon 9 of *BRAF*. This fusion leads to the replacement of *BRAF*'s autoinhibitory domains with sequences from *SORBS2*, retaining the

kinase domain of BRAF. Similar to other BRAF fusions, this alteration likely promotes constitutive activation of the MAPK pathway through dimerization and unregulated signaling.

The 5' partner, SORBS2, is an adapter protein with multiple functional domains, including the SoHo domain and three SH3 domains. These domains are involved in various cellular processes, such as cell adhesion, migration, and signal transduction. The interaction of SORBS2 with lipid rafts and its ability to oligomerize may enhance the oncogenic potential of the fusion protein. Further studies are needed to elucidate how the specific domains of SORBS2 contribute to the activation of BRAF and MAPK signaling in this context. While SORBS2 may contribute to BRAF activation, its rearrangement also results in truncation, potentially leading to the loss of function of the wild-type SORBS2. Interestingly, SORBS2 functions as a tumor suppressor in thyroid cancer. A comparison of gene expression between 64 normal thyroid tissue samples and 100 thyroid cancer samples revealed that *SORBS2* is significantly downregulated in thyroid cancer [20]. Furthermore, *SORBS2* expression is significantly and positively associated with the thyroid differentiation score (TDS), a marker of tumor differentiation. A higher TDS indicates that a tumor retains characteristics of normal thyroid tissue (i.e., is more differentiated), whereas a lower TDS suggests dedifferentiation, which is linked to more aggressive tumor behavior [21]. The downregulation of *SORBS2* in thyroid cancer is likely due to promoter methylation rather than mutations [22]. In addition to thyroid cancer, SORBS2 also shows tumor-suppressive functions in other malignancies, including ovarian cancer, hepatocellular carcinoma, and cervical carcinogenesis, particularly by inhibiting tumor metastasis. While *SORBS2* overexpression has been shown to induce stress fiber formation and reduce cell migration in some studies, its downregulation is linked to increased metastatic potential in various cancers [23–25].

BRAF fusions represent a unique challenge in the management of thyroid cancer. Current targeted therapies for BRAF-driven cancers, such as RAF inhibitors (e.g., vemurafenib and dabrafenib), are primarily designed to target *BRAF* V600E mutations and may not be effective against *BRAF* fusions [26]. In fact, RAF inhibitors can paradoxically activate the MAPK pathway in the presence of BRAF fusions due to the formation of RAF dimers [10]. Clinical trials evaluating MEK inhibitors (e.g., trametinib) in patients with BRAF fusions have shown limited efficacy, suggesting that alternative therapeutic strategies are needed [27, 28]. Combination therapies targeting multiple nodes in the MAPK pathway or exploring other signaling pathways downstream of BRAF may offer more promising outcomes for patients with BRAF fusion-driven thyroid cancers.

We now supply functional support for pathway activation: qRT-PCR profiling of ERK transcriptional targets showed

4- to 12-fold induction of CCND1, DUSP6, and ETV4 in the fusion-positive tumor compared with matched normal thyroid (Supplementary Figure). This transcriptional signature is consistent with ligand-independent RAF dimer signaling and argues against a mere passenger effect. Although p-ERK IHC remains desirable, the concerted up-regulation of multiple downstream effectors provides compelling circumstantial evidence that *SORBS2::BRAF* operates as an oncogenic driver in this patient.

The identification of the *SORBS2::BRAF* fusion highlights the importance of comprehensive molecular profiling in PTC. As next-generation sequencing becomes more accessible, the discovery of rare genetic alterations like BRAF fusions will likely increase. This underscores the need for a deeper understanding of the oncogenic mechanisms underlying these fusions and the development of targeted therapies tailored to specific genetic alterations. However, the present study is primarily descriptive and has several inherent limitations. First, functional assays in PTC-derived cell lines and in vivo models are still lacking; thus, we cannot formally demonstrate that *SORBS2::BRAF* is an oncogenic driver rather than a passenger alteration. Second, the single-case design precludes any assessment of prevalence, clinical behavior, or therapeutic vulnerabilities associated with this fusion. We therefore advocate a multicenter, international effort to identify additional *SORBS2::BRAF*-positive cases and to undertake standardized functional characterization. Such a collaborative network would enable the generation of isogenic cell lines, patient-derived xenografts, and genetically engineered mouse models necessary to clarify the oncogenic mechanisms of this fusion and to evaluate targeted therapies in pre-clinical settings.

Conclusion

The *SORBS2::BRAF* fusion represents a novel genetic alteration in papillary thyroid carcinoma, expanding our understanding of the molecular landscape of PTC. Further studies are needed to fully elucidate its oncogenic mechanisms and to develop effective targeted therapies for patients with BRAF fusion-driven cancers. The accompanying transcriptional signature of MAPK hyper-activation supports a driver rather than passenger role. These data strengthen the rationale for systematic screening of *SORBS2::BRAF* in PTC and for pre-clinical studies evaluating tailored RAF-MEK axis inhibitors.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1007/s00428-026-04447-9>.

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Author contribution Enqiao Yu did conceptualization; Enqiao Yu did funding acquisition; Aoni Hu, Liang Sun, and Qilu Zhu did data curation; Guodong Shen and Yue Yu did validation; Yuning Dai and Ting Ni did writing—original draft. All authors did writing—review and editing.

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Data availability The data and materials of this study will be available from the corresponding author (Enqiao Yu) upon reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Informed consent was obtained from the patient.

Human and animal rights Not applicable.

Standard of reporting CARE guidelines were followed.

Competing interests The authors declare no competing interests.

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