BRAF V600E-Positive Classical Papillary Thyroid Carcinoma: Integrating Histopathological Diagnosis with Next-Generation Sequencing for Personalized Oncological Management - A Case Report

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Abstract

Background: Papillary thyroid carcinoma (PTC) is the most prevalent thyroid malignancy globally, with *BRAF* V600E being its most common somatic driver mutation. This mutation constitutively activates the MAPK/ERK signalling pathway, contributing to aggressive clinicopathological behaviour and radioiodine (RAI) refractoriness.

Case Presentation: We report a 40-year-old female who presented with a thyroid nodule and was histopathologically diagnosed with classical PTC. Formalin-fixed paraffin-embedded (FFPE) tissue was subjected to targeted next-generation sequencing (NGS) using the oncoReveal™ Solid Tumor v2 Panel (48 genes) on the Illumina NextSeq™ 1000 platform. NGS revealed a pathogenic somatic *BRAF* c.1799T>A (p.Val600Glu) single nucleotide variant (SNV) in exon 15.

Conclusion: This case illustrates the complementary roles of histopathology and NGS in the WHO 2022 molecular classification framework for PTC. The identification of a pathogenic *BRAF* V600E mutation confirms molecular diagnosis, supports RAI-refractoriness risk assessment, and enables eligibility for Dabrafenib/Trametinib combination therapy, exemplifying precision oncology in thyroid cancer.

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1.Introduction

Thyroid cancer is the seventh most common malignancy worldwide, with an estimated 821,214 new cases and 47,507 deaths recorded globally in 2020 according to GLOBOCAN data. Papillary thyroid carcinoma (PTC) constitutes approximately 80–85% of all thyroid malignancies and represents the most frequent endocrine malignancy overall. Although PTC generally carries a favourable prognosis with a 10-year survival rate exceeding 90%, a clinically significant subset demonstrates aggressive behaviour characterised by extrathyroidal extension, lymph node metastasis, distant metastasis, and resistance to radioactive iodine (RAI) therapy.[1]

The *BRAF* V600E mutation, arising from a thymine-to-adenine transversion at nucleotide position c.1799 (T>A) in exon 15 of the *BRAF* gene, is the most common somatic genetic alteration in PTC, present in approximately 40–50% of cases. This mutation leads to constitutive, ligand-independent activation of the MAPK/ERK signalling cascade, driving uncontrolled tumour cell proliferation, dedifferentiation, invasion, and RAI refractoriness.[2] The 2022 WHO Classification of Endocrine and Neuroendocrine Tumours (5th Edition) has

incorporated molecular profiling into the formal classification framework of thyroid neoplasms, stratifying PTC subtypes into *BRAF*-like and RAS-like molecular categories that hold independent prognostic and therapeutic significance.[3]

The clinical translation of genomic data through next-generation sequencing (NGS) has transformed the management landscape for patients with advanced thyroid cancer. Routine molecular profiling enables identification of actionable driver mutations, guides eligibility for targeted therapies, facilitates risk stratification, and informs prognosis. For *BRAF* V600E-positive solid tumours, the combination of Dabrafenib (a selective BRAF kinase inhibitor) and Trametinib (a MEK inhibitor) received FDA tissue-agnostic approval on June 22, 2022, for adult and paediatric patients aged ≥6 years with unresectable or metastatic solid tumours harbouring *BRAF* V600E mutation who have progressed following prior treatment.[4]

This case report presents a 40-year-old female with histopathologically confirmed classical PTC in whom targeted NGS identified a pathogenic *BRAF* c.1799T>A (p.Val600Glu) mutation. The case is discussed in the context of the WHO 2022 molecular classification, clinicopathological correlations, and the evolving paradigm of NGS-guided personalised management in thyroid cancer.

2. Case Presentation

2.1 Clinical History

A 40-year-old female presented with a gradually enlarging anterior neck swelling of approximately two years' duration. She denied symptoms of hoarseness, dysphagia, or cervical lymphadenopathy on clinical examination. Thyroid function tests revealed a euthyroid state. Neck ultrasonography demonstrated a hypoechoic, irregular solid nodule in the thyroid gland with internal microcalcifications, raising strong suspicion for malignancy (TIRADS category 5). The patient underwent total thyroidectomy with radical neck dissection following a confirmed fine needle aspiration cytology (FNAC) report of suspicious for malignancy (Bethesda Category V). Post-operative clinical staging workup, including chest imaging, was performed, and no distant metastasis was identified at the time of diagnosis.

2.2 Histopathological Examination

Gross examination of the thyroidectomy specimen revealed a firm, greyish-white nodule measuring approximately 2.5 × 2.0 cm with ill-defined margins and no apparent capsule. Microscopically, the tumour demonstrated characteristic features of classical PTC across three representative high-quality haematoxylin and eosin (H&E)-stained sections examined at low and high magnification.

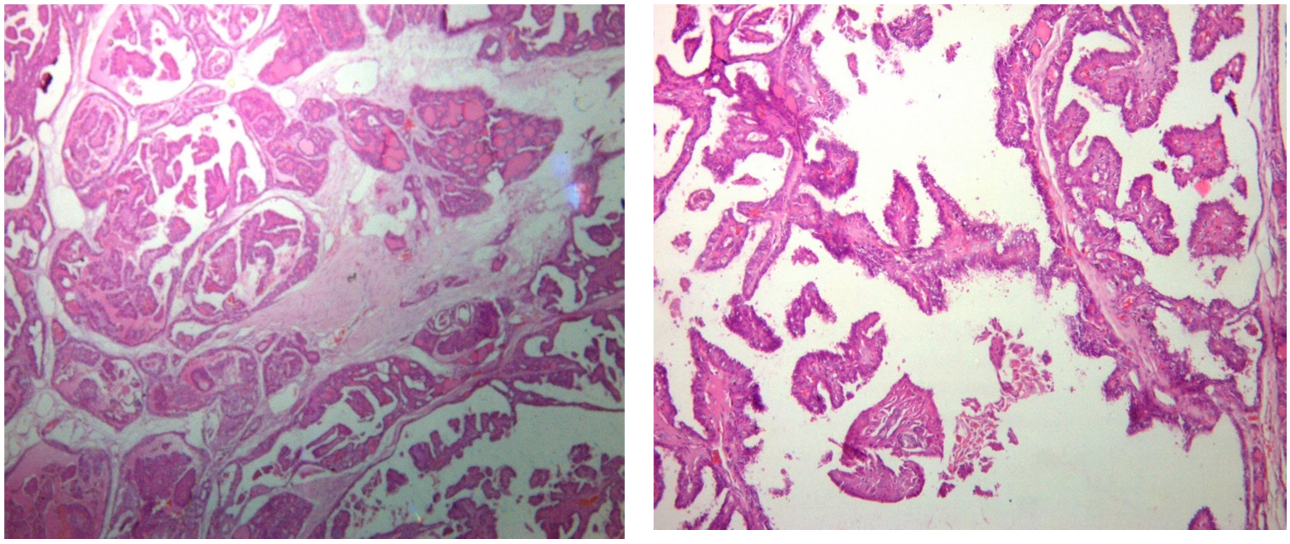

Figure 1. Photomicrograph (H&E, x40) demonstrating the architectural pattern of the tumour. Complex, arborising papillary structures with central fibrovascular cores

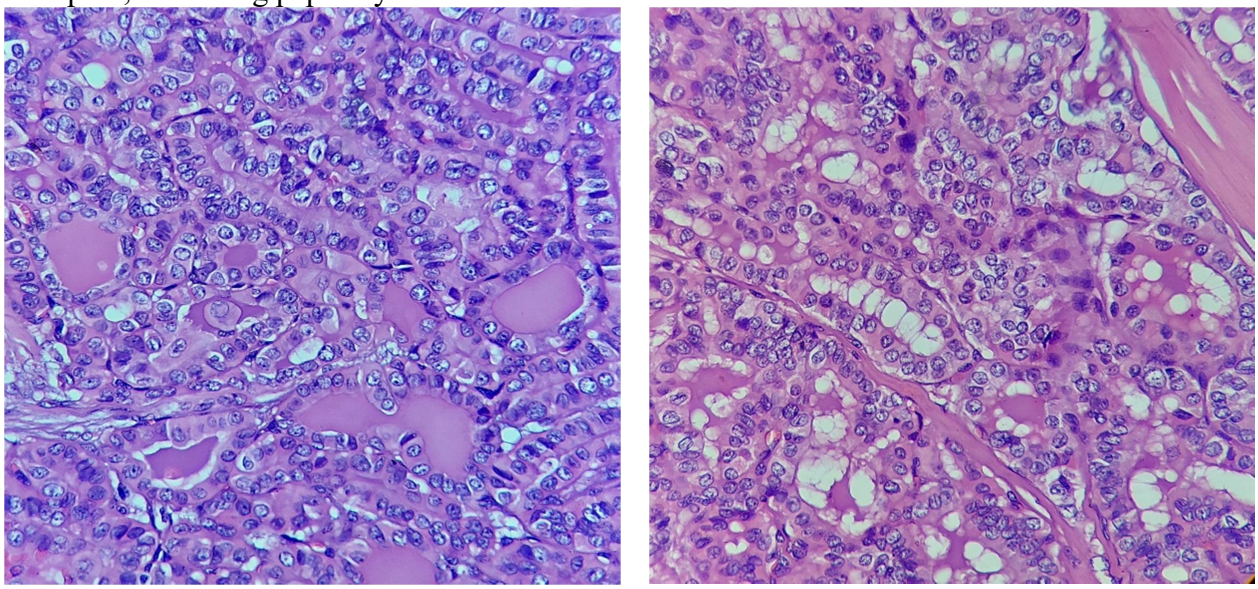

Figure 2**.** Photomicrograph (H&E, ×100) illustrating enlarged, overlapping nuclei with ground-glass ("Orphan Annie eye") nuclear clearing due to margination of chromatin to the nuclear periphery. Nuclear grooves and occasional intranuclear cytoplasmic pseudoinclusions are evident. Colloid-containing follicular structures are present peripherally. These features are consistent with *BRAF* V600E-associated classical PTC morphology.

Papillary thyroid carcinoma (PTC) exhibits a constellation of characteristic histomorphological features that, in combination, are pathognomonic of this entity. The classic architectural hallmark is the presence of branching and arborising papillae with well-formed fibrovascular cores, lined by neoplastic epithelial cells arranged with variable polarity. Foremost among the nuclear features are the iconic ground-glass

("Orphan Annie eye") nuclei — optically clear, enlarged nuclei arising from dispersed chromatin with peripheral margination to the inner nuclear membrane, present in more than 80% of tumour cells — a change considered mechanistically linked to RET proto-oncogene rearrangements. Complementing these are nuclear grooves, representing longitudinal infoldings of the nuclear membrane, and intranuclear cytoplasmic pseudoinclusions (INCIs) - eosinophilic cytoplasmic invaginations into the nucleus that, while not true inclusions, serve as a highly specific confirmatory feature of PTC diagnosis.[5]

3. Molecular Analysis

3.1 Pre-Analytical Considerations

Genomic DNA was extracted from the FFPE tissue block using the QIAGEN QIAamp DNA FFPE Tissue Kit (Germany, CE-marked), which employs silica membrane-based selective binding with optimised lysis conditions to enable efficient purification of degraded FFPE-derived DNA. The extracted DNA input into the assay was 70 ng, exceeding the panel reference threshold of 10–30 ng, ensuring sufficient template for robust library preparation.

3.2 NGS Panel and Methods

Targeted NGS was performed using the oncoReveal™ Solid Tumor v2 Panel (48 genes), which covers the full coding sequence and associated splice sites of the following genes: EGFR, ALK, BRAF, KRAS, MET, RET, ERBB2, NTRk1, AKT1, CYSLTR2, FBXW7, GNAS, KEAP1, PTEN, SMAD4, DDR2, FGFR1, H3F3A (H3-3A), KIT, PDGFRA, PTPN11, SRSF2, ARAF, FGFR2, HIST1H3B (H3C2), PIK3CA, RAC1, STK11, EIF1AX, FGFR3, HRAS, MAP2K1, PLCB4, RAF1, TERT, CDKN2A, GNA11, IDH1, POLD1, TP53, CTNNB1, ERBB4, GNAQ, IDH2, NRAS, POLE, SF3B1, TSHR.[6]

The panel utilises proprietary SLIMamp® (Stem-Loop Inhibition Mediated Amplification) technology. In a first PCR reaction (PCR1), SLIMamp® primers amplify regions of interest in a simple, single-tube multiplex reaction. The technology employs tagged primers that form inhibitory stem-loop structures to suppress undesirable amplicons, reducing PCR noise and improving coverage uniformity. In a second PCR reaction (PCR2), sequencing adapters including unique index sequences are introduced into each amplicon. The sample pool is subsequently purified using the oncoReveal™ Solid Tumor v2 Panel Library Clean protocol.[6]

The purified library pool was sequenced on the Illumina NextSeq™ 1000 System (Illumina, USA), which employs super-resolution optics delivering highly accurate imaging data with enhanced resolution and sensitivity. Bioinformatic analysis and secondary variant calling were performed using the Pillar® Biosciences PiVAT® Platform v1.3.0 (February 2025), a validated cloud-based variant analysis and reporting solution offering streamlined sample-to-report processing.[7]

3.3 Quality Metrics

All sequencing quality metrics exceeded the established reference thresholds:

Table I: Quality metrics of the case

Quality Parameter	Reference Level	Achieved Value
DNA Input (ng)	10–30	70
Mean ROI Coverage	≥3,500×	5,160×
Mapping Rate (%)	≥90	99.83
Q≥30 (%)	≥75	94.08
On-Target Ratio (%)	≥90	98
Total Number of Reads	—	3,150,310
Mapped Reads	—	3,144,886
NTC Mean Insert Size (bp)	—	151

The high mapping rate (99.83%), excellent Q≥30 score (94.08%), and mean coverage depth of 5,160× ensure reliable variant calling with minimal risk of sequencing artefacts, particularly important for FFPE-derived samples.

3.4 Alteration Details

Table II: Alteration etails of the case

Gene	Nucleotide Change	Amino Acid Change	Alteration Type	Exon	Allele Frequency	Clinical Significance
BRAF	c.1799T>A	p.Val600Glu	SNV (Missense)	15	19.87%	Pathogenic

All other genes covered by the 48-gene panel - including EGFR, ALK, KRAS, MET, RET, ERBB2, NTRk1, AKT1, CYSLTR2, FBXW7, GNAS, KEAP1, PTEN, SMAD4, DDR2, FGFR1, H3F3A (H3-3A), KIT, PDGFRA, PTPN11, SRSF2, ARAF, FGFR2, HIST1H3B (H3C2), PIK3CA, RAC1, STK11, EIF1AX, FGFR3, HRAS, MAP2K1, PLCB4, RAF1, TERT, CDKN2A, GNA11, IDH1, POLD1, TP53, CTNNB1, ERBB4, GNAQ, IDH2, NRAS, POLE, SF3B1 — were negative for pathogenic or likely pathogenic variants.

4. Result Interpretation

4.1 Molecular Pathogenesis

The *BRAF* gene encodes a serine/threonine protein kinase that is an integral component of the MAPK/ERK signalling pathway, which governs cell proliferation, differentiation, survival, and migration. Under physiological conditions, wild-type BRAF requires receptor tyrosine kinase stimulation and RAS activation to form homodimers or heterodimers for kinase activation. The V600E substitution, which is a single valine-to-glutamic acid exchange at codon 600 mimics the phosphorylated intermediate state of BRAF, enabling constitutive, RAS-independent, monomeric activation and increasing kinase activity by up to 500-fold.[8] This constitutive BRAF V600E–MAPK/ERK signalling drives downstream hyperphosphorylation of MEK1/2 and

ERK1/2, resulting in: (1) uncontrolled tumour cell proliferation and inhibited apoptosis through ERK-mediated cyclin D1 upregulation; (2) enhanced tumour invasiveness through NF-κB activation and matrix metalloprotease (MMP) upregulation; and (3) transcriptional silencing of thyroid differentiation genes including *NIS*, *TPO*, *TG*, and *TSHR*, resulting in reduced iodine uptake and RAI refractoriness.[8,9]

The thymine-to-adenine transversion at nucleotide position c.1799 (T>A), confirmed in this case, is the defining molecular event of the V600E substitution. The highly specific association of BRAF V600E with PTC is present in approximately 40–50% of cases and its near-exclusive occurrence in papillary and anaplastic thyroid carcinomas underscores its diagnostic utility.[10]

4.2 WHO 2022 Molecular Classification Context

The 5th Edition of the WHO Classification of Endocrine and Neuroendocrine Tumours (2022) represents a paradigm shift in thyroid tumour classification by incorporating molecular profiling alongside morphological criteria. Under this framework, PTCs are broadly categorised into two molecular subtypes with prognostic and therapeutic implications:[3]

BRAF-like tumours: Characterised by *BRAF* V600E mutation or other alterations that strongly activate the MAPK pathway, associated with higher ERK output scores, reduced thyroid differentiation scores (TDS), classical PTC and tall cell PTC morphology, and increased propensity for aggressive clinicopathological features.[11]

RAS-like tumours: Characterised by *RAS* mutations or *RET/PTC* and *NTRK* fusions, associated with lower MAPK signalling (due to ERK negative feedback), higher TDS, follicular variant PTC morphology, and generally more indolent behaviour.[3]

The present case demonstrating classical PTC morphology with pathogenic *BRAF* V600E clearly belongs to the BRAF-like molecular subgroup as defined by the WHO 2022 framework, a designation with direct implications for risk stratification and targeted therapeutic eligibility.

5. Discussion

5.1 Clinical and Prognostic Significance of BRAF V600E in PTC

BRAF V600E mutation in PTC has been extensively studied as a molecular indicator of aggressive behaviour. Multiple studies and meta-analyses have demonstrated associations between *BRAF* V600E and adverse clinicopathological features including larger tumour size, extrathyroidal extension, lymph node metastasis, higher tumour stage, and increased risk of disease recurrence. The mutation is also significantly associated with loss of iodine avidity (P=0.0003), particularly in patients with recurrent PTC.[12]

The clinical significance of *BRAF* V600E extends beyond diagnosis to inform risk stratification. Under the 2015 American Thyroid Association (ATA) guidelines and their 2025 revisions, molecular biomarker testing is explicitly recommended to identify actionable oncogenic driver alterations in patients with radioiodine-refractory differentiated thyroid cancer (RAIR DTC) prior to initiating systemic therapy. The 2025 ATA guidelines specifically endorse NGS-based multigene panel testing as a standard component of management for advanced thyroid cancer, reflecting the growing therapeutic relevance of molecular profiling.[13]

5.2 Radioiodine Refractoriness and BRAF V600E

A key clinical implication of *BRAF* V600E in the present case is its established role as a predictor of RAI refractoriness. The

constitutive activation of BRAF V600E–MAPK/ERK signalling transcriptionally silences the sodium-iodide symporter (*NIS*) gene and other iodine metabolism-related genes (*TPO*, *TG*, *TSHR*, *PDS*), substantially reducing iodine uptake capacity of tumour cells. A 2025 meta-analysis incorporating 2,890 PTC patients found that *BRAF* V600E mutation was strongly associated with loss of iodine avidity (P=0.0003), particularly in recurrent disease (P<0.0001). These findings underscore the importance of preoperative molecular characterisation of PTC, as identification of *BRAF* V600E can stratify patients who are unlikely to benefit from adjuvant RAI therapy and should be considered for alternative targeted approaches.[14]

5.3 Targeted Therapy: Dabrafenib and Trametinib

The identification of *BRAF* V600E in this case carries direct therapeutic implications. Dabrafenib is a selective ATP-competitive inhibitor of BRAF V600-mutant kinase, and Trametinib is a selective MEK1/MEK2 inhibitor acting downstream in the BRAF signalling cascade. The dual combination achieves more complete pathway blockade and delays the emergence of resistance mechanisms compared to single-agent BRAF inhibition.[15]

On June 22, 2022, the FDA granted accelerated approval to the Dabrafenib/Trametinib combination as a tissue-agnostic therapy for adult and paediatric patients (≥6 years) with unresectable or metastatic solid tumours harbouring *BRAF* V600E mutation who have progressed on prior therapy, excluding colorectal cancer due to intrinsic resistance. This approval, the result of over 20 years of research into BRAF-mediated tumour biology, was based on objective response data from the BRF117019 (ROAR) and NCI-MATCH basket trials, demonstrating a 41% overall response rate (95% CI: 33–50%) in 131 adults across multiple tumour types.[16]

5.4 NGS-Guided Personalised Management in Thyroid Cancer

The application of targeted NGS in this case exemplifies the evolving standard of molecular characterisation in thyroid oncology. A landmark study from the Princess Margaret Cancer Centre demonstrated that NGS identified actionable alterations in 87% of patients with advanced thyroid cancer, with *BRAF* V600E being the most common alteration in PTC (62%), and that 57% of patients had at least one Level 1 or 2 alteration with an FDA-approved targeted therapy available. These data support the clinical rationale for routine NGS profiling of advanced or high-risk PTC.[17]

The oncoReveal™ Solid Tumor v2 Panel used in this case represents a validated, amplicon-based, clinical-grade NGS workflow that simultaneously interrogates 48 clinically relevant oncogenes in a single FFPE-compatible assay. The SLIMamp® chemistry achieves superior coverage uniformity and detects variants at VAF ≥2.5% from as little as 2.5–10 ng of input DNA, making it particularly suited for FFPE samples where DNA is often degraded or limited. The integration of the PiVAT® bioinformatics platform provides validated, streamlined secondary analysis and reporting from raw sequencing output, enhancing reproducibility and reducing turnaround time which is critical attributes for clinical decision-making.[6,7]

The AMP/ASCO/CAP variant classification framework was applied to contextualise the clinical significance of the detected *BRAF* V600E alteration. Under this four-tiered system:[18]

Tier IA: Variants with strong clinical significance predictive of response to FDA/EMA-approved therapies - applicable to *BRAF* V600E in the context of the tissue-agnostic Dabrafenib/Trametinib indication.

Tier IB: Variants with strong clinical significance based on well-powered studies and expert consensus — applicable to the diagnostic role of *BRAF* V600E in confirming PTC on the molecular level.
The *BRAF* V600E mutation in this case is accordingly classified as Tier IA, representing the highest level of clinical actionability under both therapeutic and diagnostic evidence categories.

5.5 Limitations and Future Directions
Several important limitations should be acknowledged. First, the low VAF of 19.87% warrants careful consideration of tumour purity, and pathological assessment of tumour cellularity in the submitted FFPE block would strengthen confidence in the interpretation. Second, the 48-gene panel employed does not calculate TMB or MSI, which are increasingly relevant biomarkers for immunotherapy eligibility in RAI-refractory disease. Third, gene fusions involving *RET* and *NTRK* which are clinically actionable in thyroid cancer are not detected by this SNV/indel-focused panel, and supplementary RNA-based fusion testing may be warranted in selected cases.[17]

Future directions in NGS-guided thyroid cancer management include the integration of liquid biopsy platforms for non-invasive *BRAF* V600E monitoring and assessment of minimal residual disease, the adoption of broader whole-exome or whole-transcriptome sequencing for comprehensive molecular profiling, and the development of co-mutation-aware predictive models incorporating *BRAF* V600E with *TERT* promoter and *PIK3CA* co-mutations to refine prognosis.[19]

Conclusion
This case illustrates a 40-year-old female with classical papillary thyroid carcinoma harboring a *BRAF* V600E somatic mutation confirmed by high-quality targeted NGS which exemplifies integrated morphomolecular diagnosis. Histopathological features aligned with the WHO 2022 BRAF-like subgroup. Molecular profiling stratified RAI refractoriness risk and enabled eligibility for Dabrafenib/Trametinib targeted therapy, underscoring NGS as indispensable in precision thyroid oncology.

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