

Genetic Alterations in Thyroid Cancer: Focus on BRAF, RAS and RET/PTC Mutations

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Introduction

Thyroid cancer is the most common endocrine malignancy and its incidence has been steadily rising over the past few decades worldwide. While the majority of thyroid cancers are indolent and have a favorable prognosis, a subset exhibits aggressive behavior, resistance to therapy and poor clinical outcomes. In recent years, the understanding of thyroid carcinogenesis has shifted significantly with the identification of key genetic alterations that drive tumor development and progression. Among the most well-studied mutations are BRAF, RAS and RET/PTC rearrangements, which play pivotal roles in tumorigenesis and hold promise as diagnostic, prognostic and therapeutic markers. The BRAF V600E mutation is highly prevalent in Papillary Thyroid Carcinoma (PTC), the most common histological type and is associated with more aggressive tumor features and recurrence. Similarly, point mutations in RAS genes are more commonly found in follicular-patterned thyroid cancers and may signify a step toward malignant transformation. RET/PTC rearrangements, on the other hand, are primarily implicated in radiation-induced PTC and are particularly prevalent in pediatric populations. The growing body of literature on these mutations has enabled the development of molecular diagnostic tests and targeted therapies, revolutionizing thyroid cancer management. Understanding these alterations not only improves our knowledge of thyroid cancer biology but also enables personalized treatment approaches. Genetic profiling of thyroid nodules can help distinguish benign from malignant lesions, thus reducing unnecessary surgeries. Moreover, the role of these genetic changes in predicting response to targeted therapies has added a new dimension to precision oncology in thyroid cancer. This article explores the molecular landscape of thyroid cancer with a focus on BRAF, RAS and RET/PTC alterations, highlighting their clinical relevance and future implications [1].

Description

The BRAF gene encodes a serine/threonine kinase that plays a critical role in the MAPK signaling pathway, which regulates cell proliferation and differentiation. The most notable mutation, BRAF V600E, results in constitutive activation of the kinase, leading to uncontrolled cell growth and survival. This mutation is identified in approximately 40-60% of Papillary Thyroid Carcinomas (PTC), particularly the classical and tall cell variants and is associated with a higher risk of lymph node metastasis, extrathyroidal extension and disease recurrence. Importantly, BRAF V600E-positive tumors are less likely to concentrate Radioactive Iodine (RAI), which poses challenges in the postoperative management of these patients. Molecular testing for BRAF mutations is now integrated into the routine workup of thyroid nodules with indeterminate cytology. Its presence not only confirms

malignancy in suspicious nodules but also helps guide surgical and therapeutic decisions. BRAF inhibitors, such as vemurafenib and dabrafenib, have shown clinical benefit in patients with advanced or RAI-refractory thyroid cancer harboring this mutation. However, resistance to these therapies can develop, often necessitating combination regimens. Despite its clinical utility, the BRAF mutation alone is not entirely predictive of outcomes, as coexisting genetic alterations may influence tumor behavior. Hence, comprehensive genomic profiling is recommended for a more accurate prognosis. Furthermore, detection of circulating tumor DNA (ctDNA) with BRAF mutations in blood samples represents a promising non-invasive biomarker for disease monitoring. Continued research into BRAF signaling and resistance mechanisms is critical to optimize therapeutic strategies and improve long-term outcomes for patients with BRAF-mutant thyroid cancer [2].

RAS mutations are another major category of genetic alterations implicated in thyroid tumorigenesis. These mutations involve the HRAS, KRAS and NRAS genes, all of which encode small GTPases that activate the MAPK and PI3K pathways, essential for cell cycle progression and survival. Unlike BRAF mutations, RAS alterations are more common in Follicular Thyroid Carcinoma (FTC), follicular variant PTC and poorly differentiated thyroid carcinoma. RAS-mutant tumors often exhibit a more indolent course, though some may progress to more aggressive phenotypes depending on coexisting genetic events. RAS mutations are typically mutually exclusive with BRAF and RET/PTC rearrangements, suggesting distinct molecular pathways of tumor development. Clinically, RAS positivity in thyroid nodules has been associated with increased malignancy risk, especially in nodules with indeterminate cytology. As a result, RAS mutation testing is used as a complementary tool in the preoperative risk assessment of thyroid nodules. However, the presence of RAS alone does not definitively predict malignancy, as it is also found in some benign adenomas. Targeted therapies specifically for RAS-mutant thyroid cancer remain limited, although trials investigating MEK inhibitors and PI3K pathway modulators are ongoing. A key challenge in targeting RAS-driven tumors is the complexity and redundancy of downstream signaling, which often results in resistance to monotherapies. Additionally, the role of RAS mutations in radioiodine refractoriness is an area of active investigation. Overall, while RAS mutations provide valuable diagnostic information, more research is needed to harness their full therapeutic potential in thyroid cancer management [3].

RET/PTC rearrangements represent a distinct class of genetic alterations characterized by the fusion of the RET proto-oncogene with various partner genes, such as CCDC6 (RET/PTC1) and NCOA4 (RET/PTC3). These rearrangements lead to the constitutive activation of RET tyrosine kinase, driving uncontrolled cell proliferation and survival. RET/PTC fusions are predominantly found in papillary thyroid carcinomas, especially those arising after radiation exposure and are more frequent in pediatric and young adult populations. The presence of RET/PTC rearrangements is highly specific for malignancy and their detection can aid in the diagnosis of suspicious thyroid nodules. RET/PTC-positive tumors often exhibit classical histologic features and a favorable prognosis, although aggressive variants have also been reported. Recent advancements in Next-Generation Sequencing (NGS) have improved the detection of RET fusions, enabling more precise molecular classification of thyroid tumors. Therapeutically, RET inhibitors such as

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selpercatinib and pralsetinib have shown impressive efficacy in RET-driven thyroid cancers, including those refractory to conventional treatments. These agents are now approved for uses in advanced RET fusion-positive thyroid cancers, marking a major milestone in precision oncology. Importantly, RET fusions can coexist with other genetic alterations, underscoring the importance of comprehensive molecular testing. Furthermore, ongoing studies are evaluating the use of RET inhibitors in neoadjuvant settings and as part of combination therapies to enhance their efficacy. While RET/PTC rearrangements offer both diagnostic and therapeutic utility, careful interpretation of their presence is required, particularly in the context of tumor histology and clinical behaviour [4].

The integration of molecular genetics into thyroid cancer diagnosis and treatment represents a paradigm shift in the management of this disease. The identification of key genetic mutations BRAF, RAS and RET/PTC has transformed the approach to thyroid cancer from a largely histopathological process to one guided by molecular insights. Genetic testing of Fine-Needle Aspiration (FNA) specimens now enables risk stratification of indeterminate nodules, helping avoid unnecessary surgeries and enabling early intervention for high-risk cases. Moreover, targeted therapies based on molecular alterations offer hope for patients with advanced, metastatic or treatment-refractory thyroid cancers. Despite these advances, challenges remain, including tumor heterogeneity, development of resistance and the need for combination treatment strategies. The dynamic nature of cancer genomics necessitates continuous research to uncover novel mutations, biomarkers and therapeutic targets. In clinical practice, multidisciplinary teams incorporating molecular pathologists, endocrinologists and oncologists are essential to translate genetic findings into effective patient care. Personalized treatment plans based on molecular profiles not only improve clinical outcomes but also reduce treatment-related morbidity. Moving forward, broader access to molecular diagnostics and the integration of liquid biopsies may further refine patient selection and real-time disease monitoring. In conclusion, understanding and targeting genetic alterations in thyroid cancer is central to modern oncology, promising improved survival and quality of life for patients [5].

Conclusion

In conclusion, the characterization of BRAF, RAS and RET/PTC mutations has significantly advanced our understanding and management of thyroid cancer. These genetic alterations serve as crucial diagnostic markers and therapeutic targets, enabling more personalized and effective care. Molecular testing is now a key component of the diagnostic workup for thyroid nodules, especially those with indeterminate cytology. Furthermore, the emergence of targeted therapies against BRAF and RET mutations marks a major leap forward in treating advanced thyroid cancers that are resistant to conventional therapies. Although challenges such as resistance and tumor heterogeneity persist, ongoing research continues to enhance our molecular toolkit. As

persist, ongoing research continues to enhance our molecular toolkit. As precision medicine evolves, integrating genetic profiling into routine thyroid cancer management will likely become standard practice. This approach promises not only better prognostic assessment but also the potential to tailor treatment to individual tumor biology. Ultimately, by focusing on the genetic underpinnings of thyroid cancer, we move closer to achieving optimal outcomes for all patients affected by this disease.

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Conflict of Interest

None.

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