Human-Centered AI in Medical Education: Between Hype, Hope, and Responsibility

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Abstract

Thyroid carcinoma, the most common endocrine malignancy, presents with diverse histological subtypes and distinct genetic alterations. Recent advances in molecular genetics have improved our understanding of the oncogenic drivers underlying thyroid carcinogenesis. This short communication highlights the key genetic alterations associated with different thyroid cancer subtypes, including papillary, follicular, medullary, anaplastic, and Hürthle cell carcinoma. We discuss their clinical implications in diagnosis, prognosis, and targeted therapy, with a special focus on mutations in BRAF, RAS, RET, TP53, and TERT. Additionally, inherited cancer syndromes such as Cowden syndrome and DICER1 syndrome are reviewed.

Keywords: *Genetic alteration, Targeted therapy, Thyroid cancer*

Introduction

Thyroid carcinoma is a heterogeneous disease arising from follicular or parafollicular thyroid cells. While most thyroid cancers are well-differentiated and have a favorable prognosis, certain subtypes are aggressive and associated with poor outcomes. Genetic mutations play a pivotal role in thyroid carcinogenesis, influencing tumor initiation, progression, and response to therapy. A deeper understanding of these molecular events not only aids in diagnosis but also opens avenues for targeted therapeutic strategies.

Main Text

Papillary Thyroid Carcinoma (PTC)

Papillary thyroid carcinoma (PTC) is the most prevalent subtype, accounting for approximately 80–85% of all thyroid cancers[1]. It is characterized by a relatively indolent clinical course but can metastasize to regional lymph nodes.

BRAF Mutations

The most common genetic alteration in PTC is the B-Raf proto-oncogene, serine/threonine kinase (BRAF)^V600E mutation, found in nearly 60% of cases. This mutation leads to constitutive activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway, promoting tumor cell proliferation and survival[2]. Clinically, BRAF^V600E is associated with more aggressive tumor behavior, including extrathyroidal invasion, lymph node metastasis, and higher recurrence rates[1].

RAS Mutations

Mutations in the Rat sarcoma viral oncogene homolog (RAS) gene family (NRAS, HRAS, KRAS), particularly NRAS codon 61, are more commonly seen in the follicular variant of PTC. These mutations activate both the MAPK and phosphoinositide 3-kinase (PI3K)-AKT pathways, contributing to tumorigenesis. RAS mutations are typically mutually exclusive with BRAF mutations[3].

RET/PTC Rearrangements

REarranged during Transfection (RET)/PTC rearrangements result from fusion between the RET tyrosine kinase domain and various partner genes such as Coiled-Coil Domain Containing 6 (CCDC6) and Nuclear Receptor Coactivator 4 (NCOA4). These rearrangements are predominantly found in radiation-associated PTC and younger patients. They cause constitutive activation of RET and downstream MAPK signaling[4].

Follicular Thyroid Carcinoma (FTC)

Follicular thyroid carcinoma (FTC) accounts for 10–15% of thyroid malignancies and is often associated with vascular invasion and distant metastasis.

RAS Mutations

Similar to PTC, NRAS and HRAS mutations promote activation of the MAPK and PI3K-AKT pathways in FTC[3]. The presence of RAS mutations is useful in differentiating FTC from benign follicular adenomas, as the latter typically lack these alterations.

PAX8-PPARG Fusion

A specific chromosomal translocation t(2;3)(q13;p25) results in the Paired Box 8 (PAX8)–Peroxisome Proliferator-Activated Receptor Gamma (PPARG) fusion gene, observed in 30–35% of FTCs. This fusion produces a chimeric protein that interferes with normal thyroid cell differentiation and promotes oncogenesis[5].

Medullary Thyroid Carcinoma (MTC)

MTC arises from parafollicular or C cells of the thyroid and comprises 3–5% of thyroid carcinomas. It may occur sporadically or as part of inherited syndromes.

RET Mutations

Activating mutations in the RET proto-oncogene are central to the pathogenesis of both sporadic and hereditary MTC. Inherited RET mutations cause multiple endocrine neoplasia type 2 (MEN2) syndromes, including MEN2A, MEN2B, and familial MTC. Mutations at codons 634 and 918 are linked to aggressive disease and early onset[6].

Anaplastic Thyroid Carcinoma (ATC)

Anaplastic thyroid carcinoma is a rare but highly aggressive form of thyroid cancer, often arising from dedifferentiation of pre-existing differentiated thyroid carcinoma.

TP53 Mutations

Tumor protein p53 (TP53), a tumor suppressor gene, is mutated in approximately 70% of ATC cases. This mutation results in loss of cell cycle control, increased genomic instability, and resistance to apoptosis[7].

TERT Promoter Mutations

Mutations in the promoter region of the Telomerase reverse transcriptase (TERT) gene (notably C228T and C250T) are frequently observed in ATC and aggressive PTC subtypes. These mutations enhance telomerase expression, contributing to cellular immortality and tumor progression[8].

Hürthle Cell Carcinoma (HCC)

Hürthle cell carcinoma, a rare and distinct variant, is characterized by oncocytic cells rich in mitochondria. It exhibits more aggressive behavior compared to conventional FTC.

Mitochondrial and Nuclear Mutations

HCCs often harbor mutations in mitochondrial DNA affecting genes involved in oxidative phosphorylation. They also display chromosomal instability and widespread loss of heterozygosity, suggesting a distinct genetic pathway from other follicular neoplasms[9].

Genetic Syndromes Associated with Thyroid Cancer

Cowden Syndrome

Cowden syndrome is an autosomal dominant disorder caused by germline mutations in the Phosphatase and Tensin Homolog (PTEN) tumor suppressor gene, leading to activation of the PI3K-AKT pathway. It is associated with increased risk of follicular thyroid carcinoma and multinodular goiter, requiring regular surveillance[10].

DICER1 Syndrome

DICER1 syndrome is a rare hereditary cancer predisposition syndrome caused by germline mutations in the DICER1 gene, which encodes an RNase III endoribonuclease critical for microRNA processing and gene regulation. Patients with DICER1 mutations have an increased risk of multinodular goiter and differentiated thyroid carcinoma, especially in pediatric populations[12]. Tumors in these patients often demonstrate unique molecular characteristics and a less aggressive clinical course.

Familial Non-Medullary Thyroid Cancer (FNMTC)

FNMTC accounts for 5–10% of non-medullary thyroid cancers. Susceptibility loci identified include Forkhead Box E1 (FOXE1), SLIT-ROBO Rho GTPase Activating Protein 1 (SRGAP1), and Hyaluronan Binding Protein 2 (HABP2), though the precise genetic basis is not fully elucidated[11].

Clinical Implications

Understanding the genetic basis of thyroid carcinoma has revolutionized clinical management. Molecular testing

is now integrated into diagnostic protocols, especially in indeterminate cytology. For instance, detection of BRAF^V600E supports PTC diagnosis and indicates potential resistance to radioiodine therapy. Conversely, RET mutations in MTC guide decisions about prophylactic thyroidectomy and familial screening. Targeted therapies, such as tyrosine kinase inhibitors (TKIs) against RET and BRAF, have shown promise in advanced thyroid cancers, marking a shift toward personalized oncology.

Conclusion

Genetic alterations are central to the pathogenesis, classification, and clinical behavior of thyroid carcinoma. Molecular profiling enhances diagnostic accuracy and facilitates tailored therapeutic interventions. As genomic technologies become more accessible, future research should focus on novel genetic drivers, resistance mechanisms, and combinatorial treatment strategies to improve patient outcomes.

Table 1. Genetic Alterations in Thyroid Carcinoma Subtypes

Thyroid Cancer Subtype	Key Genetic Alterations	Molecular Pathways Affected	Clinical Implications
Papillary Thyroid Carcinoma	BRAF^V600E, NRAS, HRAS, KRAS mutations, RET/PTC rearrangements	MAPK, PI3K-AKT	Aggressiveness (BRAF), radioiodine resistance, younger age (RET/PTC)
Follicular Thyroid Carcinoma	NRAS, HRAS mutations, PAX8-PPARG fusion	MAPK, PI3K-AKT	Differentiation from adenoma, metastatic potential
Medullary Thyroid Carcinoma	RET proto-oncogene mutations (codons 634, 918)	RET tyrosine kinase signaling	Early onset, familial syndromes, targeted TKIs
Anaplastic Thyroid Carcinoma	TP53 mutations, TERT promoter mutations	Loss of tumor suppressor, telomerase activation	Aggressive behavior, poor prognosis
Hürthle Cell Carcinoma	Mitochondrial DNA mutations, chromosomal instability	Oxidative phosphorylation, genomic instability	Distinct molecular pathogenesis, aggressive course
Genetic Syndromes	PTEN (Cowden), DICER1 (DICER1 syndrome), FOXE1, SRGAP1, HABP2 (FNMTC)	Tumor suppressors, miRNA processing, unknown	Increased hereditary risk, surveillance required

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