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Progress in the Study of Gene Mutations Associated with Papillary Thyroid Carcinoma

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Abstract

In recent years, there has been a global rise in cases of papillary thyroid carcinoma (PTC), the predominant form of thyroid cancer. Advances in molecular biology have intensified the focus on the genetic mutations associated with this malignancy. Researchers have conducted extensive investigations into these mutations to elucidate their roles in the initiation, progression, treatment, and prognosis of PTC. This review synthesizes studies on the genetic mutations implicated in PTC, examining specific mutated genes, mechanisms of mutation, correlations with clinicopathological features, and their influence on treatment outcomes and prognosis. The objective is to provide a theoretical framework for enhancing the diagnosis, treatment, and prognostic assessment of PTC in the future.

Keywords

Papillary Thyroid Carcinoma, Gene Mutation, Diagnosis, Treatment, Prognosis

1. Introduction

Thyroid carcinoma arises from the thyroid follicular or parafollicular epithelium and is one of the most prevalent endocrine malignancies. It is classified into several subtypes based on tumor origin and differentiation: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), oncocytic carcinoma (OCA), poorly differentiated thyroid carcinoma (PDTC), differentiated high-grade thyroid carcinoma (DHGTC), anaplastic thyroid carcinoma (ATC), and medullary thyroid carcinoma (MTC). Among these, PTC is the most common, accounting for approximately 80% - 85% of cases [1]. The rising incidence of PTC is often attributed to improvements in screening and diagnostic techniques [2]. With rapid advancements in molecular biology, research increasingly underscores the

significant role of gene mutations in PTC pathogenesis. This review aims to analyze the relevant studies on these genetic mutations to inform future strategies for diagnosis, treatment, and prognosis of PTC.

2. Overview of Genetic Mutations in Papillary Thyroid Cancer

The advent of molecular marker analysis has significantly enhanced our understanding of the pathogenesis of papillary thyroid carcinoma (PTC). Key gene mutations linked to PTC include the BRAF V600E mutation, TERT promoter mutation, and RAS gene mutation, with the BRAF V600E mutation being the most prevalent [3] [4]. The 2015 American Thyroid Association guidelines for the management of adult patients with thyroid nodules and differentiated thyroid cancer introduced risk stratification to tailor appropriate treatment options for PTC patients. Within the context of PTC, predictive molecular markers can be utilized for risk stratification, with a focus on their relevance to PTC recurrence and tumor-related mortality [5]. This review concentrates on the implications of BRAF V600E mutations, TERT promoter mutations, RAS mutations, and TP53 mutations.

2.1. BRAF V600E Mutation

BRAF is a cytoplasmic protein kinase integral to the MAPK signaling pathway, which is frequently activated in various malignancies [6]. Among the BRAF mutations, the T1799A point mutation is particularly noteworthy; it results in a lysine-to-glutamate substitution at position 600, termed the BRAF V600E mutation. This mutation is commonly found in papillary thyroid carcinoma (PTC), with reported frequencies ranging from 40% to 90% across different populations. The BRAF V600E mutation leads to heightened activation of BRAF kinase within the MAPK pathway [4], which in turn results in uncontrolled cell proliferation and tumorigenesis. Given its prevalence, this mutation has been the focus of extensive research in recent years. Sancisi *et al*. found no significant correlation between BRAF V600E mutations and distant metastasis or fatal outcomes in PTC [7]. In contrast, Lai *et al*. identified a clear association between the presence of BRAF V600E mutations and larger initial tumor size, increased rates of distant metastasis, and advanced stages of disease. Their findings suggest that tumors harboring the BRAF V600E mutation may exhibit greater aggressiveness and a higher propensity for dissemination to distant metastasis [8]. Ye *et al*. reported that in patients with a positive BRAF V600E mutation, independent risk factors for PTC recurrence included tumor size > 1 cm, extrathyroidal invasion (invasion of adjacent thyroid structures), and lateral regional lymph node metastasis [9]. Wei *et al*. conducted a literature review and identified several risk factors associated with BRAF V600E positivity in PTC patients, including age (≥ 45 years), male sex, multifocality, lymph node metastasis, vascular invasion, extrathyroidal invasion, and advanced stage [5]. Zhang *et al*. and Harahap *et al*. also found significant links between BRAF V600E positivity and extrathyroidal invasion, lymph node

metastasis, and clinical stage [10] [11]. However, Wei *et al*. did not recognize tumor size (> 1 cm) or distant metastasis as risk factors for BRAF V600E mutation positivity in PTC patients [5]. Nechifor-Boila *et al*. reported that the presence of the BRAF V600E mutation, when combined with multiple risk factors (*e.g*., male sex, age ≥ 55 years, classic and high cellular variants, extrathyroidal invasion, multifocality, tumor size > 40 mm, and lymph node metastasis), offers a more nuanced prediction of adverse outcomes [12]. Similarly, Du *et al*. noted a significant correlation between BRAF V600E mutation positivity and an increased risk of lymph node metastasis in the central compartment of PTC patients [13]. Furthermore, studies by Janicki *et al*. and Cao *et al*. found that BRAF V600E mutation positivity in PTC patients with Hashimoto's thyroiditis was associated with multifocal lesions, although these patients exhibited a lower propensity for lymph node metastasis [14] [15]. The incidence of PTC in the context of Hashimoto's thyroiditis is lower than that of PTC in the general population, and it remains unclear whether Hashimoto's thyroiditis acts as a protective factor in BRAF V600E-positive PTC patients. Extensive clinical data is required to address this question. Moreover, another study examining the relationship between BRAF V600E mutation positivity and recurrence concluded that the BRAF V600E mutation alone does not serve as an independent predictive factor for PTC. Instead, a multivariate analysis incorporating additional risk factors (such as sex, age, and multifocality) should be utilized [5] [16] [17]. Although the association between BRAF V600E mutations and the invasive behavior of PTC remains a topic of debate, the American Thyroid Association (ATA) guidelines have incorporated the status of the BRAF V600E mutation since 2015 to enhance risk stratification for PTC patients, thereby providing valuable guidance for treatment planning [15].

2.2. TERT Promoter Mutation

Telomerase synthesizes repetitive DNA sequences to preserve telomere length, and research has shown that telomerase shortening is linked to cancer and aging. As telomerase becomes shorter, it can activate telomerase reverse transcriptase (TERT) and induce TERT promoter mutations [18]. TERT functions as the catalytic subunit of telomerase, and its promoter mutations can trigger telomerase activation, leading to tumor initiation [19]. Yang *et al*. observed a significantly higher frequency of TERT promoter mutations in older tumors, larger tumors, and invasive tissues, suggesting a potential correlation between these mutations, aging, and tumor development [20]. Additional studies indicate that TERT promoter mutations are present in 7% - 22% of patients with papillary thyroid carcinoma (PTC), with a prevalence rate of 11% among Chinese patients diagnosed with PTC [18]. Tanaka *et al*., Li *et al*., and Parvathareddy *et al*. confirmed a significant association between TERT promoter mutations and aggressive clinicopathological features of PTC [21]-[23]. Na *et al*. and Melo *et al*. reported a higher frequency of TERT promoter mutations in PTC patients with distant metastasis and recurrence, potentially linked to poorer prognoses and increased disease-specific

mortality [24] [25]. Furthermore, numerous studies indicate that the coexistence of BRAF V600E mutations and TERT promoter mutations is closely associated with aggressive clinicopathological features and poor prognosis in PTC, suggesting a possible synergistic effect between these mutations [21]. When both mutations are present, it typically indicates a poor prognosis for PTC patients and may be useful for clinical stratification [26]. Sako *et al*., Vuong *et al*., and Liu *et al*. found that the coexistence of BRAF V600E and TERT promoter mutations significantly enhances the aggressiveness of PTC [27]-[29]. The combined effect of these two oncogenes results in markedly higher specific mortality for PTC compared to individual mutations and conventional clinicopathological risk factors, such as extrathyroidal invasion. The American Thyroid Association (ATA) guidelines from 2015 acknowledged the potential prognostic value of TERT promoter mutations and BRAF V600E mutations, although these factors were not fully endorsed or routinely recommended [30]. The 2023 guidelines for the diagnosis and treatment of thyroid nodules and differentiated thyroid cancer suggested that the coexistence of BRAF V600E and TERT promoter mutations may influence recurrence risk stratification in PTC [31]. Nasirden *et al*. reported that PTC patients harboring both BRAF V600E and TERT promoter mutations exhibit a poor response to radioiodine therapy (RAI), indicating that these mutations could be predictive of resistance to RAI in late-stage PTC patients, including those with distant metastasis [32]. However, some studies contend that BRAF V600E and TERT promoter mutations are not significantly associated with PTC, and their coexistence does not necessarily correlate with increased aggressiveness or poor prognosis. Further clinical investigation is required to validate the relationship between these mutations and the development of PTC.

2.3. RAS Gene Mutation

RAS proteins, located on the cytoplasmic surface of the cell membrane, function as switch proteins that regulate growth factor receptor signaling [33]. They transmit extracellular signals that promote cell proliferation, differentiation, and survival [34]. The RAS gene family comprises several oncogenes, with KRAS, HRAS, and NRAS being the most prevalent. Mutations in these genes activate RAS proteins, leading to enhanced cell proliferation and inhibited apoptosis. Approximately 30% of human cancers exhibit activation within the RAS-RAF-MEK-ERK pathway [34] [35]. Similar to BRAF mutations, RAS gene mutations can independently drive papillary thyroid carcinoma (PTC) via the MAPK kinase pathway [36]. Studies indicate that RAS mutations are among the most common genetic alterations in thyroid cancer, occurring in about 11.5% to 20% of cases, with a higher prevalence observed in Asian populations [37] [38]. Jung *et al*. reported a significant increase in RAS mutations after 2000, potentially linked to environmental factors, including exposure to certain chemicals or variations in iodine intake [39]. The relationship between RAS gene mutations and the aggressiveness of thyroid cancer remains contentious. A study by Hara *et al*. involving 91 PTC

patients with a mean follow-up period of 14 years (ranging from 1 to 40 years) found that 33% of PTC cases harbored RAS mutations [40]. However, only 10.5% of patients who survived beyond 35 years had RAS mutations, indicating a complex interplay between RAS mutations and aggressive thyroid cancer behavior. Despite the small sample size and ambiguous conclusions, Yip *et al*. conducted a retrospective study of 1510 thyroid cancer patients undergoing their first thyroidectomy and genetic testing [41]. Yip concluded that patients with BRAF V600E mutations or RET/PTC fusions (mutations that cause abnormal activation of the RET receptor tyrosine kinase, leading to tumor growth and spread) exhibited more aggressive disease compared to those with RAS mutations. Specifically, RAS mutation patients displayed less aggressive histological characteristics, a lower rate of extrathyroidal extension, and earlier stage disease. Additionally, Marotta *et al*. found that patients with only RAS mutations did not experience more frequent tumor recurrence or higher mortality, suggesting that RAS mutations alone may not be associated with the invasive behavior of PTC [42]. Riccio *et al*. also indicated that while RAS gene mutations are linked to an increased risk of malignancy, they are less correlated with PTC invasiveness compared to BRAF V600E mutations [43]. Therefore, more clinical studies are needed to determine whether RAS mutations are an independent risk factor for PTC. Research has also shown that RAS gene mutations are prevalent in follicular papillary thyroid carcinoma, a histological subtype that shares characteristics with follicular thyroid tumors rather than typical papillary carcinoma [44] [45]. This finding suggests that follicular papillary thyroid carcinoma may be biologically intermediate between follicular thyroid carcinoma (FTC) and typical papillary carcinoma [44]. Due to FTC's distinct pathogenesis, growth characteristics, molecular pathology, and more frequent hematogenous metastasis, it tends to be more invasive than PTC. Fukahori *et al*. demonstrated that RAS mutations in FTC are associated with poorer overall patient survival [46]. Further research is needed to confirm whether RAS mutations are an independent risk factor for FTC.

2.4. TP 53 Mutation

Oncoprotein 53 (TP53) is a critical tumor suppressor involved in cell cycle regulation, DNA repair, and apoptosis. The TP53 gene is widely distributed and is susceptible to mutations that may contribute to the development and progression of thyroid cancer [47]. TP53 also regulates miRNA expression, particularly that of the miR-34 family, which plays a key role in tumor suppression by inhibiting genes that promote cell proliferation. As a classic tumor suppressor gene, TP53 is associated with various malignancies, including thyroid cancer [48]. TP53 mutations are found in approximately 3.5% of individuals diagnosed with papillary thyroid carcinoma (PTC) [49]. Some researchers suggest that polymorphisms in TP53 may serve as risk factors for thyroid cancer. Among these, the Arg72Pro polymorphism (Rs1042522) in exon 72, where proline (CCC) replaces arginine (CGC), is the most extensively studied variant. Research indicates that the codon

72 polymorphism (Arg72Pro) is linked to cancer susceptibility [47] [50] [51]. Heidari *et al*. reported that the G allele polymorphism of Rs1042522 in TP53 correlates with smaller tumor size, a reduced risk of PTC, and a lower incidence of vascular invasion [47]. A study involving 140 cancer patients and 200 controls without cancer found that the TP53 Pro72 polymorphism is strongly associated with thyroid cancer. Specifically, the variant allele (GC + CC) is linked to increased susceptibility to thyroid cancer, particularly among younger individuals, non-smokers, females, and patients with elevated TSH levels. The frequency of the Pro allele mutation is heightened in these groups and is associated with greater thyroid aggressiveness, although further research is needed to validate these findings. Rogounovitch *et al*. also found, in the adult radiation-associated papillary thyroid carcinoma (PTC) group, that the prevalence of the homozygous Arg genotype decreased [52]. Additionally, other allele combinations of TP53 may elevate the risk of radiation-associated PTC during late childhood, adolescence, or in women. Yu *et al*. proposed that TP53 mutations, which serve as markers for tumor differentiation, could also function as prognostic indicators for PTC [53]. In patients exhibiting well-differentiated PTC, TP53 mutations occur less frequently but are more common in aggressive cases. Radu *et al*. and Asa *et al*. reported similar findings, noting that TP53 mutations are prevalent in poorly differentiated thyroid tumors [54] [55]. Jin *et al*.'s study also revealed a significantly higher incidence of TP53 mutations in invasive PTC pathology subtypes compared to other subtypes [56].

In the context of papillary thyroid carcinoma (PTC), four key gene mutations—BRAF V600E, TERT promoter, RAS gene, and TP53—play distinct roles in the initiation, progression, and prognosis of the disease. However, these mutations may not occur in isolation; they may also exhibit interconnections and interactions. Unfortunately, there is currently a scarcity of research exploring the potential associations between these mutations. To enhance our understanding of the occurrence and development of PTC, it is essential to conduct more clinical and basic research to elucidate the interrelationships and mechanisms underlying these mutations.

3. The Relationship between Gene Mutations and the Clinicopathological Characteristics of Papillary Thyroid Carcinoma

Gene mutations associated with papillary thyroid carcinoma (PTC) occur at multiple loci, with BRAF V600E, TERT, RAS, and TP53 representing notable hotspots. Mutations in these genes can lead to malignant biological behaviors, including tumor cell proliferation, invasion, metastasis, and pathological dedifferentiation. The BRAF V600E mutation is the most frequently observed in PTC. Wen *et al*. demonstrated a correlation between the BRAF V600E mutation and characteristics such as tumor size, irregular shape, unclear boundaries, and morphological changes in papillary thyroid carcinoma [57]. Several studies have

confirmed the significant association between BRAF V600E mutations and aggressive pathological features of PTC [58]. Máximo *et al*. found that TERT mutations are prevalent and suggest a possible link between clinicopathological characteristics of PTC and TERT mutations [59]. Melo *et al*. reported an increased likelihood of distant metastasis in PTC with TERT mutations, noting a higher incidence of bone and brain metastases compared to lung metastases [60]. However, some studies contest this perspective, arguing that when BRAF V600E and TERT mutations coexist, PTC presents a high clinical risk of recurrence and invasiveness [61] [62]. RAS gene mutations are predominantly found in follicular variant PTC (FVPTC) and follicular thyroid carcinoma (FTC), and they are associated with indolent growth, follicular morphology, intact encapsulation, and a low incidence of lymph node metastasis. Semsar-Kazerooni *et al*. observed that tumors with RAS gene mutations often fall into lower Bethesda categories (a classification system for thyroid cytology) [63]. Tumors with RAS mutations are typically managed through monitoring, with surgical resection considered only in cases of significant growth. Conversely, other reports suggest that RAS gene mutations may adversely affect the prognosis of PTC, shorten life expectancy, induce dedifferentiation of well-differentiated thyroid cancer (WDTC), and potentially influence the occurrence of distant metastasis and tumor recurrence [61]. TP53 mutations are rare in well-differentiated PTC but more common in poorly differentiated PTC and anaplastic thyroid carcinoma (ATC). It has been shown that TP53 mutations in PTC with concurrent BRAF mutations may facilitate progression to ATC [64].

4. Impact of Genetic Mutations on Thyroid Cancer Treatment and Prognosis

Currently, the treatment for papillary thyroid cancer (PTC) primarily involves surgery, radioactive iodine therapy, and lifelong hormone replacement therapy (HRT). However, gene mutations can significantly impact the treatment approach and prognosis of PTC. For cases of radioactive iodine-refractory PTC, treatment plans should be tailored to specific gene mutations. Sorafenib has received approval from the U.S. Food and Drug Administration (FDA) for treating radioiodine-refractory differentiated thyroid cancer [65]. The genotype of metastatic tissue should be considered in future trials, particularly when utilizing specific inhibitors such as vemurafenib for BRAF V600E-mutated tumors [60]. For patients with radioiodine-refractory PTC who lack identifiable molecular targets, anti-angiogenic multi-kinase inhibitors (MKIs) are recommended as first-line therapy, with lenvatinib being an example approved by both the European Medicines Agency (EMA) and the FDA [66]. Selpercatinib and pralsetinib, both RET receptor tyrosine kinase inhibitors, effectively target RET fusion proteins in papillary thyroid carcinoma (PTC). Entrectinib and larotrectinib have shown efficacy in patients with TRK fusion proteins, while dabrafenib combined with trametinib is utilized for anaplastic thyroid cancer (ATC) with BRAF V600E mutations [61]. Dabrafenib, a selective BRAF inhibitor, enhances iodide uptake in radioiodine-

refractory PTC patients harboring the BRAF V600E mutation. One advantage of single kinase inhibitors is their shorter treatment duration, which can mitigate adverse drug reactions and the development of resistance [67]. Additionally, studies indicate that multi-target drugs may be more effective for PTC, particularly for invasive types, than single-pathway inhibitors [68]. Kinase inhibitors that target the MAPK or PI3K pathways have shown promise in redifferentiation therapy, providing insights for future combinations of multi-target agents with radioactive iodine (RAI) in the management of radioiodine-refractory differentiated thyroid cancer [69]. Mohamed Aashiq *et al*. are conducting Phase I clinical trials to evaluate the efficacy of dabrafenib and lapatinib in treating BRAF V600E mutation-positive patients with radioactive iodine-refractory differentiated thyroid cancer. Furthermore, a current Phase II clinical trial is assessing the effectiveness of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) in patients with RAS and BRAF V600E mutations who also have radioactive iodine-refractory differentiated thyroid cancer [68]. These studies aim to evaluate the efficacy of these treatments independently. Early identification of molecular markers for thyroid cancer could enhance the prediction of RAI effectiveness and the sensitivity of metastatic lesions to treatment, thereby facilitating the selection of optimal therapeutic strategies [70]. The development of novel targeted therapeutic agents through the identification of thyroid cancer molecular markers could also aid in the early detection of recurrence or metastasis, ultimately benefiting patients.

5. Conclusion and Outlook

In recent years, advancements in molecular biology technologies have propelled genetic research to the forefront of thyroid cancer studies. Progress in genetic testing for thyroid cancer has the potential to enhance early screening, enabling timely interventions and treatments during the disease's initial stages. With the increasing integration of basic research and clinical applications, the exploration and implementation of novel therapeutic approaches, as well as the innovation of early screening and diagnostic techniques, are poised to improve the standard of diagnosis and treatment for thyroid cancer. This progress will lead to better treatment outcomes and higher survival rates for patients. As large-scale genome sequencing becomes more widespread, additional genes associated with papillary thyroid cancer are likely to be discovered, along with insights into their pathogenic mechanisms. This advancement will stimulate the development of new targeted agents and therapeutic strategies, potentially enhancing cure rates and long-term survival for patients with papillary thyroid carcinoma. Concurrently, genetic testing—while considering the economic burden on patients—is set to become increasingly vital in the diagnosis and treatment of papillary thyroid cancer, providing more accurate and personalized medical care.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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