

## Assessment of BRAF-V600E, KRAS, NRAS and EGFR mutations in papillary thyroid carcinoma and Hashimoto's thyroiditis

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### Abstract

**Objective:** The present study compared three study groups composed of patients with only papillary thyroid carcinoma (PTC), patients with only Hashimoto's thyroiditis (HT) and patients with PTC+HT in terms of BRAF-V600E, KRAS, NRAS and epidermal growth factor receptor (EGFR) mutations. Also, the association between clinicopathological prognostic indicators including tumor multifocality, extrathyroidal extension (ETE), lymph node (LN) metastasis and recurrence and BRAF-V600E mutations were investigated in the PTC and PTC+HT groups.

**Methods:** A total of 53 patients (two males and 51 females) who underwent a hemi/total thyroidectomy due to suspicion of malignancy or malignant lesion according to the thyroid cytopathology participated in the study. The study groups were composed of 19 patients with PTC, 18 with PTC+HT and 16 with HT according to the histopathological examination records. Histopathological sections from the paraffin blocks of the patients were in-

vestigated for BRAF-V600E, KRAS, NRAS and EGFR gene mutations using real-time polymerase chain reaction (PCR) assay.

**Results:** There was no significant difference between the groups in terms of BRAF-V600E, KRAS, NRAS and EGFR mutation rates. Also, presence of the BRAF-V600E mutation was not correlated with the prognostic indicators for the patients with PTC and PTC+HT.

**Conclusion:** In the present study, no significant association was found between PTC and HT, and the BRAF-V600E, KRAS, NRAS and EGFR mutations. Further studies with a larger number of patients may help to clarify the clinicopathological and diagnostic importance of the BRAF-V600E, KRAS, NRAS and EGFR mutations in thyroid diseases.

**Keywords:** Papillary Thyroid Carcinoma, Hashimoto Thyroiditis, BRAF Kinases, K-ras Oncogenes, Mutation.

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## Introduction

Papillary thyroid carcinoma (PTC) is the most common malignancy of the thyroid gland, accounting for more than 80% of all thyroid malignancies.<sup>[1-3]</sup> The survival rate is quite high despite its malignant nature, with 10-year survival rates being more than 90%. Hashimoto's thyroiditis (HT), known also as chronic lymphocytic thyroiditis, is a chronic autoimmune disease that causes hypothyroidism in iodine-sufficient areas.<sup>[4]</sup> Histopathologically, HT is characterized by variable degrees of lymphocytic infiltration, fibrosis, oncocytic changes, and to a certain extent by cellular atypia.<sup>[5]</sup> In 1955, Dailey et al.<sup>[6]</sup> reported a causal relationship between PTC and HT. Kim et al.<sup>[7]</sup> demonstrated that PTC occurred approximately three-times higher in the presence of HT. However, the prognostic role of HT coexistence in patients with PTC has remained controversial in the literature.<sup>[3]</sup>

The B-Raf proto-oncogene (BRAF), a member of the mitogen-activated protein kinase (MAPK) signaling pathway, is an intracellular serine/threonine-specific protein kinase that has a downstream effect on epidermal growth factor receptor (EGFR) signaling.<sup>[8]</sup> The BRAF-V600E gene mutation induces a substitution of valine with glutamate at codon 600 and converts BRAF into an activator of proliferation and differentiation of tumor cells through the MAPK pathway.<sup>[9]</sup> Various studies have claimed that the presence of a BRAF-V600E mutation is associated with poor prognostic indicators, including tumor multifocality, ETE, LN metastasis, recurrent disease and advanced TNM in PTC.<sup>[1,10]</sup> Rat sarcoma viral (RAS) oncogenes including KRAS, NRAS and HRAS have a significant effector role in several signaling cascades including MAPK that regulate gene expression. RAS oncogenes have a pivotal role in the regulation of cell growth and differentiation.<sup>[11]</sup> Among all RAS mutations, the NRAS codon 61 and KRAS codon 12 mutations are the most frequently encountered mutations in cancer.<sup>[12]</sup> RAS point mutations are common genetic alterations reported in thyroid lesions.<sup>[13,14]</sup> Epithelial growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that is expressed in various human tissues including neoplasms. Activated EGFR was reported to inhibit apoptotic mechanisms and induce cell proliferation through the MAPK signaling pathway.<sup>[15]</sup> EGFR overexpression has been found in many types of thyroid malignancies including PTC, follicular thyroid cancer and anaplastic thyroid carcinoma.<sup>[15-17]</sup> Specific activating mutations of EGFR are well-established for lung adenocarcinomas, however, the

clinicopathological significance of EGFR mutations has not yet been fully elucidated for thyroid carcinomas.

The present study was aimed to investigate the incidence of BRAF-V600E, KRAS, NRAS and EGFR gene mutations in patients with only PTC, with only HT and patients with PTC+HT. The relationship between the BRAF-V600E gene mutation and clinicopathological prognostic indicators including tumor multifocality, extrathyroidal extension (ETE), lymph node (LN) metastasis and recurrence was also investigated in PTC and PTC+HT groups.

## Materials and Methods

### *Patients and sample collection*

The present study was conducted with the approval of the lymphological ethics committee with document number 2018/0345#. The study was carried out with a total of 53 patients (two male, 51 female) aged 18-76 years (mean age±SD: 41.15±14.39 years), who underwent a hemi/total thyroidectomy between January 2014 and August 2018 due to suspicion of malignancy or malignant lesion according to the thyroid cytopathology. There were 19 patients with PTC, 18 with PTC+HT and 16 with HT according to the histopathological examination records. Histopathologic specimens of the patients were reevaluated to verify the diagnosis of PTC and HT by a senior pathologist who was experienced in thyroid, head and neck histopathologic examinations. The specimens were also examined for the following histopathological findings: tumor multifocality, lymphovascular invasion, perineural invasion, ETE and LN metastases. The diagnosis of HT was confirmed by antithyroid peroxidase antibodies (anti-TPO). Follow-up data regarding locoregional recurrences and/or distant metastases were recorded from patient files.

### *DNA extraction methods and analysis technique*

After the pathologist selected adequate tissue blocks for the isolation of DNA from lesion-representative, formalin-fixed and paraffin-embedded thyroid tissue samples of the surgical specimens, 10 µm thick slices were prepared using a microtome (Leica RM2255 rotatory microtome, Leica Microsystems, Bannockburn, IL) and referred to the Medical Genetics laboratory in Eppendorf tubes to elute DNA. Genomic DNA was extracted from the specimens using conventional xylene/ethanol treatment, overnight incubation with proteinase K, and subsequent DNA purification utilizing the Exgene™ Cell SV kit (GeneAll Biotechnology, Seoul, Korea).

**Analysis of BRAF-V600E, KRAS, NRAS and EGFR gene mutations**

Genomic DNA obtained from the lesion-representative tissue samples was utilized for polymerase chain reaction (PCR) amplification and direct sequencing to evaluate the presence of BRAF-V600E, KRAS, NRAS and EGFR gene mutations. Ten common mutation regions for codons 12, 13 and 61 of KRAS, nine common point mutation regions for codons 12, 13, 61 and 146 of NRAS, codon 600 of BRAF and 59 mutation regions for exons 18, 19, 20 and 21 of EGFR were in vitro amplified for mutation detection. Evaluation of KRAS and V600E BRAF status using real-time PCR assay was performed using the KRAS/BRAF Mutation Analysis Panel Kit for Real-Time PCR (EntroGen Inc., California, USA), whereas the NRAS Mutation Analysis Kit (EntroGen Inc., California, USA) and EGFR Mutation Analysis Kit for Real-Time PCR (EntroGen Inc., California, USA) were utilized to detect NRAS and EGFR mutations, respectively.

Detection of the amplification products was performed with the use of fluorescent hydrolysis probes. Probes tagged with the fluorescein amidite (FAM) fluorophore were complementary to the KRAS, NRAS, BRAF-V600E and EGFR genes. The internal control gene probe tagged with a VIC fluorophore allowed for a controlled analysis of the DNA template in the reaction. Reagent preparation with 50 ng of test genomic DNA per reaction with Light-Cycler 480 II (Roche Diagnostics, Mannheim, Germany) data analysis using the absolute quantification/second derivative maximum method was completed according to the manufacturer’s instructions. The assay can detect a 1% mutation occurrence in a background of wild-type DNA.

**Statistical Analysis**

IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) software was used for the statistical analysis of the

study data. Fisher-Freeman-Halton test, Fisher’s Exact Chi-square and Yates’s correction for continuity were used for the comparison of qualitative data. One-way analysis of variance (ANOVA) was used to compare the ages between groups. A p-value less than 0.05 was considered statistically significant.

**Results**

There was no significant difference in terms of mean age and gender distribution between the groups (Table 1). Distribution of the genetic mutations within the patient groups is shown in Table 2. BRAF-V600E, KRAS, NRAS and EGFR mutation rates were not significantly different among the groups. All but one female patient in the PTC group with BRAF-V600E and KRAS (Codon 12) mutations had a single gene mutation. There was no significant difference regarding the incidence of tumor multifocality, ETE, LN metastasis and recurrence between the patients with and without BRAF-V600E mutations within the PTC and PTC+HT groups (Table 3).

**Discussion**

In the literature, the incidence of the BRAF-V600E point mutation has been reported to be between 27.3% and 90.2% of patients with PTC, whereas the frequency of BRAF-V600E mutations in HT was reported to be much lower.<sup>[1,3]</sup> Kim et al<sup>[3]</sup> found the frequency of BRAF-V600E to be 82.3% and 58.3% in PTC and HT, respectively. In the present study, BRAF-V600E mutations were present in 31.6% of the PTC group whereas it was 27.8% and 12.5% in the PTC+HT and HT groups, respectively.

RAS mutations may be detected in non-malignant thyroid lesions as well as in malignant tumors, particularly those associated with follicular histology.<sup>[5,13]</sup> KRAS and NRAS codon 61 mutations were demonstrated to be related to the follicular variant of PTC.<sup>[18]</sup> Therefore, RAS

**Table 1.** Age and gender distribution of the groups.

		PTC	PTC+HT	HT	p
Age Mean±SD		45.68±14.73	47.94±14.84	48.0±14.26	0.862
Gender n, %	Female	16 (84.2%)	18 (100%)	16 (100%)	0.100
	Male	3 (15.8%)	0 (0%)	0 (0%)	

HT: Hashimoto’s thyroiditis, n: Number of patients, PTC: Papillary thyroid carcinoma, PTC+HT: Papillary thyroid carcinoma+Hashimoto’s thyroiditis, SD: Standard deviation.

**Table 2.** Distribution of genetic mutations in patient groups.

		PTC	PTC+HT	HT	Total	p
		n (%)	n (%)	n (%)	n (%)	
BRAF	Positive	6 (31.6%)	5 (27.8%)	2 (12.5%)	13 (24.5%)	0.441
	Negative	13 (68.4%)	13 (72.2%)	14 (87.5%)	40 (75.5%)	
KRAS	Positive	2 (10.5%)	1 (5.6%)	2 (12.5%)	5 (9.4%)	0.854
	Negative	17 (89.5%)	17 (94.4%)	14 (87.5%)	48 (90.6%)	
NRAS	Positive	0 (0%)	0 (0%)	1 (6.3%)	1 (1.9%)	0.302
	Negative	19 (100%)	18 (100%)	15 (93.8%)	52 (98.1%)	
EGFR	Positive	1 (5.3%)	0 (0%)	1 (6.3%)	2 (3.8%)	0.752
	Negative	18 (94.7%)	18 (100%)	15 (93.8%)	51 (96.2%)	

HT: Hashimoto's thyroiditis, n: Number of patients, PTC: Papillary thyroid carcinoma, PTC+HT: Papillary thyroid carcinoma+Hashimoto's thyroiditis.

**Table 3.** Incidence of tumor multifocality, ETE, LN metastasis and recurrence for patients with and without BRAF-V600E in the PTC and PTC+HT groups.

	PTC	PTC+HT
	n (%)	n (%)
<b>Multifocal Tm</b>		
BRAF-V600E (+)	3/6 (50%)	2/5 (40%)
BRAF-V600E (-)	3/13 (23.1%)	2/13 (15.4%)
<b>ETE</b>		
BRAF-V600E (+)	1/6 (16.7%)	1/5 (20%)
BRAF-V600E (-)	1/13 (7.7%)	None
<b>LN metastasis</b>		
BRAF-V600E (+)	1/6 (16.7%)	None
BRAF-V600E (-)	1/13 (7.7%)	1/13 (7.7%)
<b>Recurrence</b>		
<b>Locoregional</b>		
BRAF-V600E (+)	1/6 (16.7%)	None
BRAF-V600E (-)	None	None
<b>Distant</b>		
	None	None

ETE: Extrathyroidal extension, HT: Hashimoto's thyroiditis, LN: Lymph node, n: number of patients, PTC: Papillary thyroid carcinoma, PTC+HT: Papillary thyroid carcinoma+Hashimoto's thyroiditis, Tm: Tumor

mutations, especially involving NRAS codon 61 in benign follicular lesions, may refer to precursor lesions for their malignant counterparts.<sup>[13]</sup> The incidence of RAS oncogene mutations was reported in a wide range in the literature: 0-85% for adenomas, 14-62% for follicular carcinomas, 0-50% for papillary cancer and 0-60% for anaplastic carcinomas.<sup>[19]</sup> In the present study, no NRAS mutation was detected within the PTC or PTC+HT groups whereas there was one patient (6.3%) having a NRAS mutation in the HT group. KRAS mutation rates were 10.5%, 12.5% and 5.6% of patients in the PTC, PTC+HT and HT groups, respectively. Different from the literature, there were three patients with RAS mutations composed of two KRAS and one NRAS mutation within the HT group.

Although EGFR mutations have not been studied as extensively as BRAF mutations in thyroid malignancies, exon 19 and 21 deletions have been shown in PTC and undifferentiated thyroid carcinomas.<sup>[20,21]</sup> Masago et al.<sup>[21]</sup> demonstrated EGFR mutations in 30.4% of patients with PTC, of which three of them had a mutation in exon 19 whereas four of them had a mutation in exon 21. The detection of EGFR mutations has been suggested to be an indicator of biologically aggressive tumor behavior in thyroid malignancies.<sup>[15]</sup> In the present study, an EGFR mutation was detected in a patient (5.2%) who had a multifocal tumor (two foci 15 mm and 6 mm in size) in the PTC group,

while there was one patient (6.3%) in the HT group with an EGFR mutation. None of the patients in the PTC+HT group had an EGFR mutation.

There is an ongoing debate in the literature on whether the BRAF-V600 mutation represents a poor prognostic factor in PTC. Elisei et al. demonstrated that the risk of advanced TNM stage was approximately four times higher in PTC patients having the BRAF-V600 mutation and reported that presence of the BRAF-V600 mutation was an independent poor prognostic factor for PTC.<sup>[10]</sup> Ito et al.<sup>[22]</sup> found no relationship between the BRAF-V600E mutation and poor prognostic factors, including LN metastasis, ETE, distant metastasis and advanced disease in patients with PTC. In a meta-analysis reported by Liu et al.<sup>[1]</sup>, there were significant associations between the BRAF-V600E mutation and multifocality, ETE, LN metastasis, advanced disease and recurrence. In contrast, in a cohort of Turkish patients with PTC, Kurt et al.<sup>[23]</sup> investigated the relationship between the BRAF-V600E mutation and prognostic factors including thyroid capsule invasion, ETE, LN and/or distant metastasis, and reported no significant relationship between the BRAF-V600E mutation and the prognostic factors. However, the authors stated that the limited number of participants might mask a potentially significant relationship between the BRAF-V600E mutation and the prognostic factors. The coexistence of PTC and HT accompanied by BRAF-V600E positivity was reported to be less associated with ETE and LN metastasis since HT hampers PTC progression.<sup>[24]</sup> Kim et al.<sup>[3]</sup> reported that multifocal tumor, ETE and LN metastasis were present less in PTC patients with HT, however the authors reported that HT and the BRAF-V600E mutation had an independent effect on tumor progression rather than a mutual effect. In the present study, the ratio of multifocal tumor, ETE, LN metastasis and recurrence was 31.5%, 10.5%, 10.5% and 5.3% in the PTC group, respectively, whereas it was 22.2%, 5.6%, 5.6% and 0% in the PTC+HT group, respectively. Although the incidence of poor prognostic indicators was lower in the PTC+HT group than that in the PTC group, the difference was not significant. Also, multifocal tumor, ETE, LN metastasis and recurrence rates were not significantly different between patients with the BRAF-V600 mutation and patients without mutation within the groups. Though the presence of HT seemed to decrease the invasive potential of PTC according to the results of the present study, the difference was not significant between the PTC and PTC+HT groups in terms of prog-

nostic indicators. Similarly, there was no significant difference within the PTC and PTC+HT groups in terms of prognostic indicators between BRAF-V600 mutation-positive and negative patients. However, the absence of a significant difference can be attributed to the limited number of patients participating in the present study.

In this study, there was no significant difference between the groups regarding the number of patients with BRAF-V600, KRAS, NRAS and EGFR mutations. The incidence of gene mutations investigated in the present study was lower for patients with PTC than that reported in the literature. In the literature, it has been reported that HT can be clearly distinguished from PTC by the absence of any RAS mutation.<sup>[5,25]</sup> However, the RAS mutation was encountered in three patients within the HT group in our study and the RAS mutation rate was not significantly different in the HT group than the other groups. These contradictions between the present study and the literature findings regarding the incidence of BRAF-V600, KRAS, NRAS and EGFR mutations in PTC patients may be due to a number of facts, including different methodological techniques utilized for detecting mutations, number of patients participating in the study, environmental factors such as iodine deficiency or foodborne carcinogens and different ethnicities in the patient populations.

## Conclusion

No significant association was found between PTC and HT, and the BRAF-V600E, KRAS, NRAS and EGFR mutations in the present study. Although the presence of poor prognostic indicators was mostly more frequent in patients with the BRAF-V600E mutation within the PTC and PTC+HT groups, statistical analysis did not reveal any significance. Further studies with a larger number of patients may help to clarify the clinicopathological and diagnostic importance of BRAF-V600E, KRAS, NRAS and EGFR mutations in thyroid disease.

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**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

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