INTRODUCTION

Similar to other forms of differentiated thyroid cancer, follicular thyroid cancer most commonly presents as an asymptomatic mass that cannot be distinguished from a benign follicular neoplasm based on cytological, ultrasonography or clinical features alone. The diagnosis of follicular thyroid carcinoma (FTC) is made based on morphology, depending on the presence of capsular and/or vascular invasion in thyroidectomy specimens. Therefore, molecular markers that can help distinguish between FTCs and benign follicular neoplasms, and can also identify life-threatening FTCs, have been investigated.

The BRAF V600E mutation is the most common genetic alteration in thyroid tumorigenesis and has been observed in 29%-83% of papillary thyroid carcinomas (PTCs). RAS mutations are the next most common alterations. N-RAS codon 61 (n = 6 of 9, 66.7%) and H-RAS codon 61 (n = 3 of 9, 33.3%) were found in NHs. K-RAS codons 12-13, K-RAS codon 61, N-RAS codons 12-13 and H-RAS codons 12-13 were not found in NHs. N-RAS codon 61 (n = 7 of 21, 33.3%), K-RAS codons 12-13 (n = 6 of 21, 28.6%), H-RAS codon 61 (n = 4 of 21, 19.0%), K-RAS codon 61 (n = 3 of 21, 14.3%) and N-RAS codons 12-13 (n = 1 of 21, 4.7%) were found in FTCs, and N-RAS codon 61 (n = 10 of 22, 45.5%), K-RAS codons 12-13 (n = 5 of 22, 22.7%), H-RAS codon 61 (n = 5 of 22, 22.7%), K-RAS codon 61 (n = 1 of 22, 4.5%) and N-RAS codons 12-13 (n = 1 of 22, 4.5%) were observed in FTAs.}

KEYWORDS: follicular, human genes, RAS mutations, thyroid cancer
second most common genetic alteration in thyroid tumours. Recent studies have reported that 10%-20% of PTCs and 40%-50% of FTCs harbour RAS mutations.\[^{3,7}\] These mutations have been associated with poor prognoses and tumour dedifferentiation.\[^{8,9}\]

The RAS genes consist of three families: N-RAS, H-RAS and K-RAS. RAS point mutations mostly occur in codons 12, 13 and 61.\[^{10,11}\] However, the implications for diagnostic detection of RAS mutations by fine-needle aspiration (FNA) or surgical specimens are not clear because RAS mutations occur not only in thyroid cancers, but also in histologically benign nodules including follicular thyroid adenomas (FTAs) and nodular hyperplasia (NH).\[^{3,7}\] The frequency of RAS mutations in FTCs and FTAs is controversial, probably because a small number of cases were evaluated in previous studies, which also used different methodologies. Some reports have suggested that RAS mutations are more prevalent in FTCs than FTAs.\[^{13-15}\] However, our preliminary study found no significant difference in the prevalence of any RAS mutation subtype between FTCs and FTAs.\[^{16}\] After finishing that study, we wondered whether a RAS mutation would be helpful to distinguish NHs from FTCs and FTAs and eventually reduce unnecessary thyroid surgery. There is no reliable report describing a RAS analysis of NH to date.

Therefore, the aims of this study were (a) to compare the frequency of RAS mutations among follicular thyroid nodules, (b) to determine differences in RAS mutations between benign NH and follicular neoplasm and (c) to determine if RAS analysis can help reduce unnecessary surgery, if benign NH can be differentiated from follicular neoplasm by RAS analysis.

In the present study, we analysed the clinical significance and diagnostic utility of RAS mutations for differentiating NHs from follicular neoplasms.

## 2 | MATERIALS AND METHODS

### 2.1 | Materials

Our institutional review board approved the present retrospective study, and the requirement for informed consent was waived. We analysed surgically confirmed NH (n = 50), FTAs (n = 57) and FTCs (n = 39). The material was retrieved from the files of the Pathology Department, Soonchunhyang University Bucheon Hospital, from January 2002 to May 2015. We included 56 FTAs and 35 FTCs, all of which were evaluated in our previous study, and we additionally evaluated 50 NH, 1 FTA and 4 FTCs. Haematoxylin and eosin (H&E)-stained sections were evaluated histologically by a pathologist (JJ Kwak) to classify the tumours according to the 2004 World Health Organization histological classification of thyroid tumours. RAS mutations were investigated in all 146 samples.

### 2.2 | DNA isolation

Follicular thyroid carcinoma or FTA areas were marked using the H&E-stained sections as a guide. Each marked area was prepared from four to five sections (10 μm thick) using a microtome and transferred to an Eppendorf tube. Microdissected specimens from the paraffin-embedded blocks were subjected to treatment with a deparaffinization solution (Qiagen, Hilden, Germany) to remove the paraffin. DNA was isolated using a QIAamp DNA FFPE Tissue Kit (Qiagen) according to the manufacturer's protocol.

### 2.3 | Detection of K-, N- and H-RAS mutations by pyrosequencing

Primers were designed using PyroMark Assay Design software (ver. 2.0; Qiagen). Polymerase chain reaction (PCR) was performed using a PyroMark PCR Kit (Qiagen) after initial denaturation at 95°C for 15 minutes, followed by 45 cycles of a three-step PCR protocol that included 30 seconds of denaturation at 95°C, 30 seconds of annealing at 60°C and 30 seconds of elongation at 72°C. This was followed by a final 10-minute extension phase at 72°C.

Briefly, 5 μL genomic DNA was amplified using template-specific PCR primers (including one biotin-labelled primer) and template-specific PCR conditions. Next, the PCR products were immobilized on streptavidin Sepharose beads, and single-stranded DNA was prepared to allow subsequent annealing of the sequencing primer to the template DNA. Then, the primed single-stranded DNA was released from the streptavidin surface and transferred to a PyroMark Q24 system (Qiagen) for pyrosequencing.

### 2.4 | Statistical analysis

The sex and age of the patients who were analysed for RAS mutations were tabulated (Table 1). The three groups were compared using Student's t test (for patient age) or the chi-square test (for sex). To compare the frequency of RAS mutations among NHs, FTCs and FTAs, we used Fisher's exact test or Pearson's chi-square test, as appropriate. P-values ≤0.05 were considered significant. The statistical analysis was performed using MedCalc (ver. 12.7.4.0; MedCalc Software, Ostend, Belgium) and SPSS statistical software (ver. 21.0; IBM Corp, Armonk, NY, USA).

## 3 | RESULTS

### 3.1 | Patients

The age of the patients ranged from 12 to 82 years (mean, 43.5 years). The mean age of the patients with NH, FTC and FTA was 41.9, 49.3 and 40.9 years, respectively. The patients with FTA were significantly younger than the patients with FTC (P = 0.046). There were 134 female and 12 male patients in this study.

### 3.2 | RAS point mutations

We checked for the presence of N-RAS, H-RAS and K-RAS gene mutations in 50 NHs, 57 FTAs and 39 FTCs (Table 2). In all, 52 mutations in the 46 nodules of the 146 NHs and follicular neoplasms were detected: nine nodules of 50 NHs (18%), 18 nodules of 39 FTCs (46.2%)
and 19 nodules of 57 FTAs (33.3%). Six nodules showed two point mutations (three FTCs: K-RAS 12-13 and H-RAS 61 [n = 1], K-RAS 12-13 and N-RAS 61 [n = 1] and K-RAS 61 and H-RAS 61 [n = 1]; and three FTAs: K-RAS 12-13 and N-RAS 61 [n = 2], K-RAS 12-13 and H-RAS 61 [n = 1]).

N-RAS codon 61 (n = 6 of 9, 66.7%; Figure 1) and H-RAS codon 61 (n = 3 of 9, 33.3%) were found in NHs. K-RAS codons 12-13, K-RAS codon 61, N-RAS codons 12-13 and H-RAS codons 12-13 were not found in NHs.

N-RAS codon 61 (n = 7 of 21, 33.3%), K-RAS codons 12-13 (n = 6 of 21, 28.6%; Figure 2), H-RAS codon 61 (n = 4 of 21, 19.0%), K-RAS codon 61 (n = 3 of 21, 14.3%) and N-RAS codons 12-13 (n = 1 of 21, 4.7%) were found in FTCs, and N-RAS codon 61 (n = 10 of 22, 45.5%), K-RAS codons 12-13 (n = 5 of 22, 22.7%; Figure 3), H-RAS codon 61 (n = 5 of 22, 22.7%), K-RAS codon 61 (n = 1 of 22, 4.5%) and N-RAS codons 12-13 (n = 1 of 22, 4.5%) were observed in FTAs.

Of the 52 mutations, 23 (44.2%) were in N-RAS codon 61 (observed in 6 NHs, 7 FTCs and 5 FTAs), 11 (21.2%) were in K-RAS codons 12-13 (observed in 6 FTCs and 5 FTAs), 12 (23.1%) were in H-RAS codon 61 (observed in 3 NHs, 4 FTCs and 5 FTAs), 4 (7.7%) were in K-RAS codon 61 (observed in 3 FTCs and 1 FTA), and the remaining two mutations (3.8%) were in N-RAS codons 12-13 (observed in 1 FTC and 1 FTA). We did not detect mutations in H-RAS codons 12-13.

A significant difference in the frequency of the K-RAS codon 12-13 mutation was observed between NHs and FTCs (P = 0.017), whereas no other RAS mutation subtypes were significantly different among the three groups.

### Table 1: Demographics of nodular hyperplasia, follicular carcinoma and follicular adenoma

| Variables | NH (n = 50) | FTC (n = 39) | FTA (n = 57) | Total (n = 146) | P-value<sup>a</sup> | Post hoc comparison<sup>b</sup> | NH vs FTA | NH vs FTC | FTA vs FTC |
|-----------|-------------|-------------|-------------|----------------|----------------|----------------|-------------|------------|------------|
| Age (y), mean ± SD | 41.9 ± 10.5 | 49.3 ± 18.2 | 40.9 ± 13.1 | 43.5 ± 14.3 | 0.022 | 1 | 0.083 | 0.046 |
| Sex, n (%) | | | | | | | | | |
| Male | 3 (6.0) | 1 (2.6) | 8 (14.0) | 12 (8.2) | 0.124 | | | |
| Female | 47 (94.0) | 38 (97.4) | 49 (86.0) | 134 (91.8) | | | | |
| Volume (mm³), mean ± SD | 6.0 ± 6.2 | 11.9 ± 11.0 | 9.8 ± 11.3 | 8.8 ± 9.9 | 0.007 | 0.1 | 0.032 | 1 |

FTA, follicular thyroid adenoma; FTC, follicular thyroid carcinoma; NH, nodular hyperplasia; SD, standard deviation.  
<sup>a</sup>P-values were calculated by one-way analysis of variance or Kruskal-Wallis test for continuous variables and chi-square test or Fisher’s exact test for categorical variables.  
<sup>b</sup>Post hoc comparison was conducted by Bonferroni’s correction. Bold values indicate significant differences at a significance level of .05.

### Table 2: Frequency of RAS mutation between nodular hyperplasia, follicular carcinoma and follicular adenoma

| Variables | NH (n = 50) | FTC (n = 39) | FTA (n = 57) | Total (n = 146) | P-value<sup>a</sup> | Post hoc comparison<sup>b</sup> | NH vs FTA | NH vs FTC | FTA vs FTC |
|-----------|-------------|-------------|-------------|----------------|----------------|----------------|-------------|------------|------------|
| RAS mutation (%) | | | | | | | | | |
| (−) | 41 (82.0) | 21 (53.8) | 38 (66.7) | 100 (68.5) | 0.017 | 0.342 | 0.025 | 0.875 |
| (+) | 9 (18.0) | 18 (46.2) | 19 (33.3) | 46 (31.5) | | | | |
| RAS mutation per site (%) | | | | | | | | | |
| K12/13 | 0 (0.0) | 6 (28.6) | 5 (22.7) | 11 (21.2) | 0.009 | 0.178 | 0.017 | 1 |
| K61 | 0 (0.0) | 3 (14.3) | 1 (4.5) | 4 (7.7) | 0.093 | | | |
| N12/13 | 0 (0.0) | 1 (4.7) | 1 (4.5) | 2 (3.8) | 0.731 | | | |
| N61 | 6 (66.7) | 7 (33.3) | 10 (45.5) | 23 (44.2) | 0.712 | | | |
| H12/13 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA | | | |
| H61 | 3 (33.3) | 4 (19.0) | 5 (22.7) | 12 (23.1) | 0.805 | | | |
| RAS mutation frequency in total | 9/300 (3.0) | 21/234 (9.0) | 22/342 (6.4) | 52/876 (5.94) | 0.013 | 0.197 | 0.016 | 0.984 |

FTA, follicular thyroid adenoma; FTC, follicular thyroid carcinoma; NA, not available; NH, nodular hyperplasia.  
<sup>a</sup>P-values were calculated by one-way analysis of variance or Kruskal-Wallis test for continuous variables and chi-square test or Fisher’s exact test for categorical variables.  
<sup>b</sup>Post hoc comparison was conducted by Bonferroni’s correction. Bold values indicate significant differences at a significance level of .05.
DISCUSSION

The presence of RAS mutations suggests the possibility of a broad spectrum of tumours, from benign follicular adenoma to FTC, follicular variants (FVs) of PTC, anaplastic carcinoma and poorly differentiated thyroid carcinoma.\(^8,17-20\)

\(H\)-RAS, \(N\)-RAS or \(K\)-RAS participation in the RAS-RAF-MAPK pathway is essential for controlling the proliferation, differentiation and survival of eukaryotic cells.\(^21\) The \(H\)-RAS, \(N\)-RAS and \(K\)-RAS oncogenic mutations found frequently in human tumours disrupt the normal outcome of those signalling pathways, thus leading to tumour development.\(^21\)

Somatic mutations in codons 12-13 and 61 of one of the three RAS genes have been found in 18%-52% of FTCs\(^13,15,22-25\) and 24%-53% of FTAs.\(^13-15,22,23\) The reported incidence of RAS mutations in both FTCs and FTAs probably varies because the number of cases is typically small. Our previous study targeting the Korean population with a relatively large number of surgically proved cases (35 FTCs and 56 FTAs) showed a similar RAS mutation frequency between FTCs (45.7%) and FTAs (33.9%).\(^16\) According to our previous study, the incidence rate of RAS mutations was not so helpful to differentiate FTCs from FTAs.\(^16\)

Several reports have suggested that RAS mutations are most frequently detected on codon 61 of \(N\)-RAS in FTCs.\(^3,8,12,13,26-28\) On the other hand, other studies have shown that mutations in \(N\)-RAS codon 61 predominate in various kinds of follicular thyroid lesion relative to other RAS mutations.\(^26,29,30\) We found no significant differences in RAS mutation frequency between FTCs and FTAs for any RAS mutation subtype. Nikiforova et al\(^3\) suggested that RAS-initiated FTCs develop through a benign follicular adenoma stage because both typically express Hector Battifora mesothelial-1 and galectin-C. Thus, activating RAS alone appears insufficient to detect malignant growth, but may be a predisposing factor for the acquisition of additional genetic or epigenetic alterations that lead to a fully transformed phenotype.\(^3\)

The present study may be the first to include a relatively large number of cases (n = 50) and analyse subtypes of RAS mutation in NHs. In the present study, \(N\)-RAS codon 61 was the most frequent not only in FTCs and FTAs but also in NHs. The frequency was not different among the three groups. \(K\)-RAS codons 12-13 were the second most commonly involved site in FTCs and FTAs, whereas no mutation was detected in NH. A significant difference was observed in the frequency of the \(K\)-RAS codon 12-13 mutation between NHs
and FTCs \( (P = 0.02) \), although the frequency of the K-RAS codon 12-13 mutation was not different between NHs and FTAs or FTCs and FTAs.

Because we included only surgically proven NHs or follicular neoplasms, we could not evaluate the long-term prognosis or RAS (+) benign nodules. We do not know whether NHs presenting with a RAS mutation have a different prognosis compared to NHs without a RAS mutation. However, one study \(^{31} \) showed that benign thyroid nodules harbouring RAS mutations had a larger mean volume \( (P = 0.017) \) and RAS mutation-positive nodules displayed a mean 27.6\% yearly volume increase, during RAS mutation-negative nodules remained unchanged after a 25-month follow-up.

Although no nodules displayed clinical features suspicious of malignant conversion during follow-up in that study, the authors suggested that more careful follow-up and timely surgical management are needed for thyroid nodules presenting with RAS mutations and benign cytology. A prospective study with a large number of cases and a much longer follow-up would be necessary to assess the prognosis of benign nodules harbouring a RAS mutation.

Several limitations of this study should be mentioned. First, there were significant differences in the volumes of NHs and FTAs and in the mean ages of the patients with FTAs and FTCs. However, this was inevitable because we included all surgically confirmed NHs, FTAs and FTCs during the study period. However, we presumed that this demographic difference was not important when investigating the incidence of RAS mutations.

Second, we did not evaluate whether the FNA results were concordant with the surgical specimen results. Because this study investigated the incidence of RAS mutations in NH, FTAs and FTCs, surgical specimens provided more accurate information. Although several studies have demonstrated that pyrosequencing can easily detect point mutations in RAS on FNA results, further study using FNA results is needed.

## 5 CONCLUSIONS

The frequencies of RAS mutations among our Korean population were 18\% in NHs, 46.2\% in FTC and 33.3\% in FTAs. N-RAS codon 61 was the most frequent mutation in NHs, FTCs and FTAs, and the frequency was not significantly different among the three groups. K-RAS codons 12-13 were the second most commonly involved site in FTCs and FTAs, whereas no mutation was detected at this site in NHs. A significant difference was observed in the frequency of K-RAS codon 12-13 mutation between NHs and FTCs \( (P = 0.017) \).

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## CONFLICT OF INTEREST

Nothing to declare.

## AUTHOR CONTRIBUTION

Sun Hye Jeong and Hyun Sook Hong conceived the presented idea. Sun Hye Jeong, Hyun Sook Hong, Jeong Ja Kwak, Eun Hye Lee and Ji Ye Lee carried out the experiment and analysed the data. Sun Hye Jeong and Hyun Sook Hong wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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## REFERENCES

1. Grebe SK, Hay ID. Follicular thyroid cancer. *Endocrinol Metab Clin North Am*. 1995;24:761-801.
2. Lin JD, Chao TC. Follicular thyroid carcinoma: from diagnosis to treatment. *Endocr J*. 2006;53:441-448.
3. Nikiforova MN, Lynch RA, Biddinger PW, et al. RAS point mutations and PAX8-PPAR gamma rearrangement in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. *J Clin Endocrinol Metab*. 2003;88:2318-2326.
4. Cho U, Oh WJ, Bae JS, et al. Clinicopathological features of rare BRAF mutations in Korean thyroid cancer patients. *J Korean Med Sci*. 2014;29:1054-1060.
5. Fukushima T, Suzuki S, Mashiko M, et al. BRAF mutations in papillary carcinomas of the thyroid. *Oncogene*. 2003;22:6455-6457.
6. Kim TY, Kim WB, Song JY, et al. The BRAF mutation is not associated with poor prognostic factors in Korean patients with conventional papillary thyroid microcarcinoma. *Clin Endocrinol (Oxf)*. 2005;63:588-593.
7. Nikiforov YE. Thyroid carcinoma: molecular pathways and therapeutic targets. *Mod Pathol*. 2008;21(Suppl 2):S37-S43.
8. Garcia-Rostan G, Zhao H, Camp RL, et al. RAS mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. *J Clin Oncol*. 2003;21:3226-3235.
9. Volante M, Rapa I, Gandhi M, et al. RAS mutations are the predominant molecular alteration in poorly differentiated thyroid carcinomas and bear prognostic impact. *J Clin Endocrinol Metab*. 2009;94:4735-4741.
10. Lee SR, Jung CK, Kim TE, et al. Molecular genotyping of follicular variant of papillary thyroid carcinoma correlates with diagnostic category of fine-needle aspiration cytology: values of RAS mutation testing. *Thyroid*. 2013;23:1416-1422.
11. Bos JL. Ras oncogenes in human cancer: a review. *Cancer Res*. 1989;49:4682-4689.
12. Vasko V, Ferrand M, Di Cristofaro J, Carayon P, Henry JF, de Micco C. Specific pattern of RAS oncogene mutations in follicular thyroid tumors. *J Clin Endocrinol Metab*. 2003;88:2745-2752.
13. Esapa CT, Johnson SJ, Kendall-Taylor P, Lennard TW, Harris PE. Prevalence of RAS mutations in thyroid neoplasia. *Clin Endocrinol (Oxf)*. 1999;50:529-535.
14. Namba H, Rubin SA, Fagin JA. Point mutations of ras oncogenes are an early event in thyroid tumorigenesis. *Mol Endocrinol*. 1990;4:1474-1479.
15. Suarez HG, du Villard JA, Severino M, et al. Presence of mutations in all three ras genes in human thyroid tumors. Oncogene. 1990;5:565-570.

16. Jeong SH, Hong HS, Kwak JJ, Lee EH. Analysis of RAS mutation and PAX8/PPARgamma rearrangements in follicular-derived thyroid neoplasms in a Korean population: frequency and ultrasound findings. J Endocrinol Invest. 2015;38:849-857.

17. Jang EK, Song DE, Sim SY, et al. NRAS codon 61 mutation is associated with distant metastasis in patients with follicular thyroid carcinoma. Thyroid. 2014;24:1275-1281.

18. Gupta N, Dasyam AK, Carty SE, et al. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular-pattern cancers. J Clin Endocrinol Metab. 2013;98:E914-E922.

19. Howell GM, Hodak SP, Yip L. RAS mutations in thyroid cancer. Oncologist. 2013;18:926-932.

20. An JH, Song KH, Kim SK, et al. RAS mutations in indeterminate thyroid nodules are predictive of the follicular variant of papillary thyroid carcinoma. Clin Endocrinol (Oxf). 2015;82:760-766.

21. Fernández-Medarde A, Santos E. Ras in cancer and developmental diseases. Genes Cancer. 2011;2:344-358.

22. Lemoine NR, Mayall ES, Wyllie FS, et al. High frequency of ras oncogene activation in all stages of human thyroid tumorigenesis. Oncogene. 1989;4:159-164.

23. Motoi N, Sakamoto A, Yamochi T, Horiuchi H, Motoi T, Machinami R. Role of ras mutation in the progression of thyroid carcinoma of follicular epithelial origin. Pathol Res Pract. 2000;196:1-7.

24. Lemoine NR, Mayall ES, Wyllie FS, et al. Activated ras oncogenes in human thyroid cancers. Cancer Res. 1988;48:4459-4463.

25. Basolo F, Pisaturo F, Pollina LE, et al. N-ras mutation in poorly differentiated thyroid carcinomas: correlation with bone metastases and inverse correlation to thyroglobulin expression. Thyroid. 2000;10:19-23.

26. Fukahori M, Yoshida A, Hayashi H, et al. The associations between RAS mutations and clinical characteristics in follicular thyroid tumors: new insights from a single center and a large patient cohort. Thyroid. 2012;22:683-689.

27. Liu RT, Hou CY, You HL, et al. Selective occurrence of ras mutations in benign and malignant thyroid follicular neoplasms in Taiwan. Thyroid. 2004;14:616-621.

28. Yoshimoto K, Iwahana H, Fukuda A, et al. ras mutations in endocrine tumors: mutation detection by polymerase chain reaction-single strand conformation polymorphism. Jpn J Cancer Res. 1992;83:1057-1062.

29. Nikiforov YE. Molecular diagnostics of thyroid tumors. Arch Pathol Lab Med. 2011;135:569-577.

30. Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. Cancer Res. 2012;72:2457-2467.

31. Puzziello A, Guerra A, Murino A, et al. Benign thyroid nodules with RAS mutation grow faster. Clin Endocrinol (Oxf). 2016;84:736-740.

32. Park SJ, Sun JY, Hong K, et al. Application of BRAF, NRAS, KRAS mutations as markers for the detection of papillary thyroid cancer from FNAB specimens by pyrosequencing analysis. Clin Chem Lab Med. 2013;51:1673-1680.

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