Original Article
Yonsei Med J 2018 Aug;59(6):746-753
https://doi.org/10.3349/ymj.2018.59.6.746
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

mRNA Expression of *SLC5A5* and *SLC2A* Family Genes in Papillary Thyroid Cancer: An Analysis of The Cancer Genome Atlas

Sunghwan Suh[1]*, Yun Hak Kim[2]*, Tae Sik Goh[3], Dae Cheon Jeong[4], Chi-Seung Lee[5], Jeon Yeob Jang[6], Wonjae Cha[7], Myoung-Eun Han[2], Seong-Jang Kim[8], In Joo Kim[9], and Kyoungjune Pak[9]

[1]Department of Internal Medicine, Dong-A University College of Medicine, Busan;
[2]Department of Anatomy, School of Medicine, Pusan National University, Yangsan;
Departments of [3]Orthopaedic Surgery and [9]Nuclear Medicine, and Biomedical Research Institute, Pusan National University Hospital, Busan;
[4]Department of Statistics, Korea University, Seoul;
[5]Biomedical Research Institute, Pusan National University Hospital and School of Medicine, Pusan National University, Busan;
[6]Department of Otorhinolaryngology-Head and Neck Surgery, Ajou University Hospital, Suwon;
[7]Department of Otorhinolaryngology-Head and Neck Surgery, Pusan National University Hospital, Busan;
[8]Department of Nuclear Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea.

Purpose: The present study investigated the dynamics and prognostic role of messenger RNA (mRNA) expression responsible for ^{18}F-fluorodeoxyglucose (FDG) uptake in FDG positron emission tomography (PET) and radioactive iodine (^{131}I) uptake in whole-body radioactive iodine scans (WBS) in papillary thyroid cancer (PTC) patients.

Materials and Methods: The primary and processed data were downloaded from the Genomic Data Commons Data Portal. Expression data for sodium/iodide symporter (solute carrier family 5 member 5, *SLC5A5*), hexokinase (*HK1–3*), glucose-6-phosphate dehydrogenase (*G6PD*), and glucose transporter (solute carrier family 2, *SLC2A1–4*) mRNA were collected.

Results: Expression of *SLC5A5* mRNA were negatively correlated with *SLC2A1* mRNA and positively correlated with *SLC2A4* mRNA. In PTC with BRAF mutations, expressions of *SLC2A1*, *SLC2A3*, *HK2*, and *HK3* mRNA were higher than those in PTC without BRAF mutations. Expression of *SLC5A5*, *SLC2A4*, *HK1*, and *G6PD* mRNA was lower in PTC without BRAF mutation. PTCs with higher expression of *SLC5A5* mRNA had more favorable disease-free survival, but no association with overall survival.

Conclusion: Expression of *SLC5A5* mRNA was negatively correlated with *SLC2A1* mRNA. This finding provides a molecular basis for the management of PTC with negative WBS using ^{18}F-FDG PET scans. In addition, higher expression of *SLC5A5* mRNA was associated with less PTC recurrence, but not with deaths.

Key Words: Thyroid cancer, *SLC5A5*, fluorodeoxyglucose, positron emission tomograph

Received: March 14, 2018 **Revised:** May 29, 2018 **Accepted:** June 15, 2018
Co-corresponding authors: Tae Sik Goh, MD, PhD, Department of Orthopaedic Surgery and Biomedical Research Institute, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea.
Tel: 82-51-240-7389, Fax: 82-51-240-7442, E-mail: taesikgoh@pusan.ac.kr and Kyoungjune Pak, MD, PhD, Department of Nuclear Medicine and Biomedical Research Institute, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea.
Tel: 82-51-240-7389, Fax: 82-51-240-7442, E-mail: ilikechopin@me.com

*Sunghwan Suh and Yun Hak Kim contributed equally to this work.
•The authors have no financial conflicts of interest.

INTRODUCTION

The incidence of thyroid cancer continues to increase worldwide, including Korea.[1,2] Papillary thyroid cancer (PTC) usually has a favorable prognosis with an excellent survival rate.[1,2] However, a minority of PTC patients develop locoregional recurrence, including cervical lymph node metastases, and some of them may eventually succumb to the cancer.[3] Treatment of PTC employs a three-tiered approach, including surgery, radioactive iodine ablation (RAI), and long-term exogenous hormone replacement.[3] Following surgery and RAI, neck ultrasonography and whole-body radioactive iodine scan (WBS) are usually employed to detect residual tumors or metastasis.[3]

Nowadays, positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) has become a standard modality for staging, restaging, and monitoring treatment responses in a variety of tumors.[4] However, routine use of PET scans as a work-up is not recommended in thyroid cancer. In PTC patients with high thyroglobulin levels and negative WBS, ^{18}F-FDG PET should be considered in order to detect suspected tumor recurrence or metastasis.[3]

In the field of oncology, messenger RNA (mRNA) has emerged as a major molecular player in cancer genes, because mRNA is a core part of protein synthesis.[5] In cancer, mutated DNA is transcribed into complementary mRNA, which is then translated into malfunctioning cancer protein. However, few studies have investigated the role of mRNA as a prognostic predictor.[5] Recently, The Cancer Genome Atlas (TCGA) Research Network Initiative provided a detailed description of the genomic landscape of 509 PTC cases, named the "Integrated Genomic Characterization of PTC."[6]

^{18}F-FDG, a glucose analog, is transported to tumor cells via glucose transporter (GLUT) proteins and then phosphorylated by hexokinase (HK).[7] ^{123}I or ^{131}I are radiopharmaceuticals that are applied in WBS and transported transcellularly to thyrocytes by the sodium/iodide symporter (NIS).[8] Therefore, we investigated mRNA expression of these genes, which are connected with FDG PET and WBS, to discern potential prognostic roles of mRNA using PTC data from TCGA.

MATERIALS AND METHODS

Data acquisition and characteristics

The primary and processed data were downloaded from the Genomic Data Commons Data Portal (https://gdc-portal.nci.nih.gov/) in August 2016. All TCGA data were available without restrictions on publications or presentations according to TCGA publication guidelines. We downloaded data regarding somatic mutations, mRNA expression [normalized by RNAseq by the Expectation-Maximization (RSEM) method], and clinical information, which were last updated in May 2016. This process was performed using the 'cgdsr' package in R statistical software (The R Foundation for Statistical Computing, 2016). Of the 509 PTC cases, 118 patients in the PTC cohort were excluded. The reason for exclusion were 1) samples from metastatic tissues, 2) patients with not available or - infinite gene expression, and 3) patients with insufficient clinical information (age, sex, stage, BRAF mutation, and RAS mutation). mRNA expression data for NIS (solute carrier family 5 member 5, *SLC5A5*), hexokinase (*HK1–3*), glucose-6-phosphate dehydrogenase (*G6PD*), and glucose transporter (solute carrier family 2, *SLC2A1–4*) were collected.

Statistical analysis

Disease-free survival (DFS) and overall survival (OS) were analyzed with a logrank test after being divided into two groups with a median mRNA expression value and generation of Kaplan-Meier survival plots. After $\log_2$ transformation, Spearman rank correlation analysis was used to determine the association between mRNA expression patterns, and the Mann-Whitney U test was used to compare mRNA expression patterns in PTC patients with or without genetic mutations (BRAF and RAS). Thyroid differentiation score was calculated by averaging the $\log_2$ transformed fold change of 16 genes (deiodinase, iodothyronine, type I; deiodinase, iodothyronine, type II; dual oxidase 1; dual oxidase 2; forkhead box E1; GLIS family zinc finger 3; NK2 homeobox 1; paired box 8; *SLC26A4*; *SLC5A5*; *SLC5A8*; thyroglobulin; thyroid hormone receptor, alpha; thyroid hormone receptor, beta; thyroid peroxidase; and thyroid stimulating hormone receptor).[9] Statistical analyses were per-

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	n (%)
Age	
≥45	212 (54.2)
<45	179 (45.8)
Sex	
Male	111 (28.3)
Female	280 (71.6)
Histological type of PTC	
Classical	273 (69.8)
Follicular	85 (21.8)
Tall cell	29 (7.4)
Others	4 (1.0)
Extrathyroidal extension	
Yes	114 (29.2)
Minimal	102 (26.1)
Moderate	11 (2.8)
Very advanced	1 (0.2)
No	265 (67.8)
NA	12 (3.0)
Lymph node metastasis	
Yes	161 (41.2)
No	222 (56.8)
NA	8 (2.0)
Distant metastasis	
Yes	9 (2.3)
No	382 (97.7)
TNM (The American Joint Committee on Cancer 7th)	
I/II	266 (68.0)
III/IV	125 (32.0)
BRAF mutation	
Yes	234 (59.8)
No	157 (40.2)
RAS mutation	
Yes	52 (13.3)
No	339 (86.7)

PTC, papillary thyroid cancer; NA, not assessed.

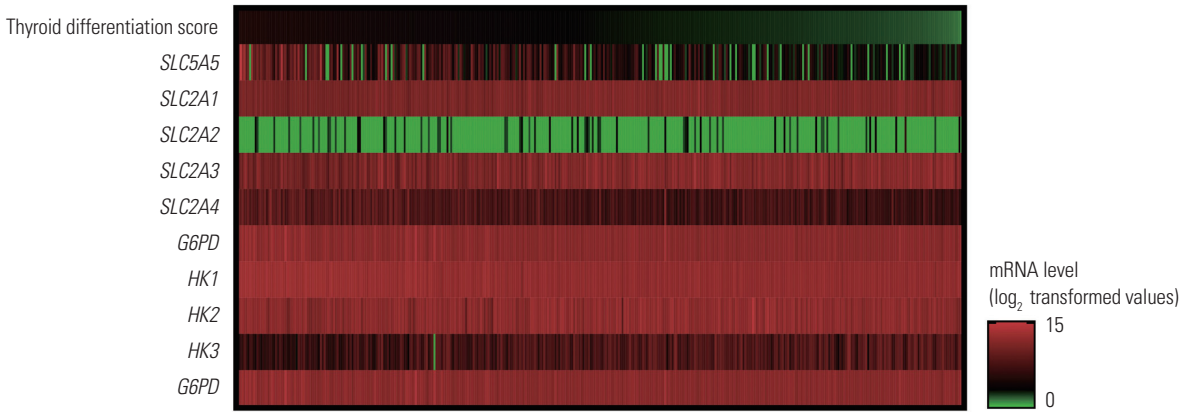

Fig. 1. Heatmap of mRNA expression according to thyroid differentiation score. Genes assessed were *SLC5A5*, *SLC2A1*, *SLC2A2*, *SLC2A3*, *SLC2A4*, *HK1*, *HK2*, *HK3*, and *G6PD*.

Table 2. Correlation between mRNA Expression of *SLC5A5* and Other Genes Assessed in this Study

Protein	mRNA	Spearman r	95% CI	*p* value
Glucose transporter	*SLC2A1*	-0.219	-0.314 to -0.119	<0.001
	SLC2A2	-0.010	-0.112 to 0.092	0.844
	SLC2A3	-0.015	-0.117 to 0.087	0.768
	SLC2A4	0.148	0.047 to 0.247	0.003
Hexokinase	*HK1*	0.433	0.346 to 0.512	<0.001
	HK2	-0.227	-0.322 to -0.128	<0.001
	HK3	0.034	-0.069 to 0.135	0.506
Glucose 6 phosphatase	*G6PD*	0.036	-0.067 to 0.137	0.483

CI, confidence interval.

formed using GraphPad Prism 7 for Mac OS X (GraphPad Software Inc, San Diego, CA, USA).

RESULTS

Patient characteristics

A total of 391 PTC cases were included in this study (111 males and 280 females; age: 47.2±15.8 years). According to histological PTC types, 273 cases were included in the classical type, 85 in the follicular type, 29 in the tall cell variant, and four in others. Extrathyroidal extension was observed in 114 patients. Median follow-up duration was 30.1 months. Patient characteristics are summarized in Table 1.

Correlation of mRNA expression of *SLC5A5* with other assessed genes

mRNA expression patterns according to thyroid differentiation are described in a heatmap plot of 391 PTC patients (Fig. 1). Among the *SLC2* family genes, expression of *SLC5A5* mRNA was negatively correlated with that of *SLC2A1* (r=-0.2187, $p<0.0001$) and positively with that of *SLC2A4* (r=0.1483, $p=0.0033$). Among *HK* family genes, expression of *SLC5A5* mRNA was positively correlated with that of *HK1* (r=0.4326, $p<0.0001$) and negatively with that of *HK2* (r=-0.2268, $p<0.0001$) (Table 2, Fig. 2).

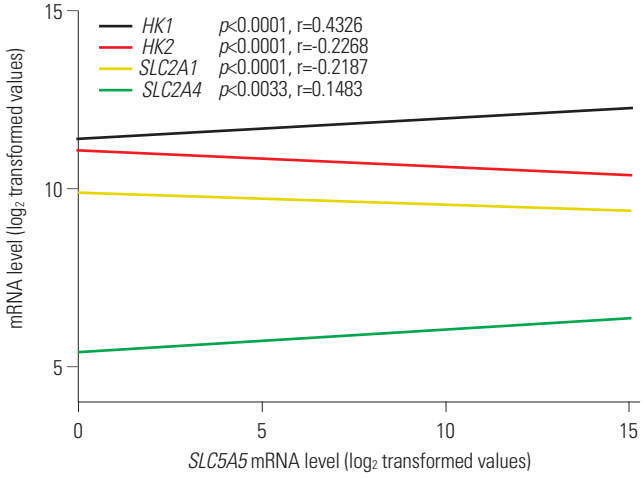

Fig. 2. Correlation of mRNA expression of *SLC5A5* with the other genes.

mRNA expression according to genetic mutation status

Most mRNA expression patterns were significantly associated with either BRAF or RAS mutation. In PTC patients with BRAF mutation, expression of *SLC2A1* ($p<0.0001$), *SLC2A3* ($p<0.0001$), *HK2* ($p=0.0018$), and *HK3* ($p<0.0001$) mRNA was significantly higher than in PTC patients without BRAF mutations. However, expression of *SLC5A5* ($p<0.0001$), *SLC2A4* ($p<0.0001$), *HK1* ($p<0.0001$), and *G6PD* ($p<0.0001$) mRNA was

https://doi.org/10.3349/ymj.2018.59.6.746

lower in PTC patients with BRAF mutations (Fig. 3). In PTC patients with RAS mutations, expression of *SLC2A4* (p<0.0001) and *HK1* (p<0.0001) mRNA was higher, and *SLC2A1* (p<0.0001), *SLC2A3* (p<0.0001), and *HK3* (p<0.0001) mRNA expression was lower than in PTC patients without RAS mutations (Table 3, Fig. 4).

Survival analysis

PTC cases with higher expression of *SLC5A5* mRNA had a favorable prognosis regarding DFS (hazard ratio 0.3319, p=0.004); however, there was no association with OS (Fig. 5). In addition, *SLC2A2* and *SLC2A3* mRNA had unfavorable prognosis regarding OS. Among the *HK* family genes, higher ex-

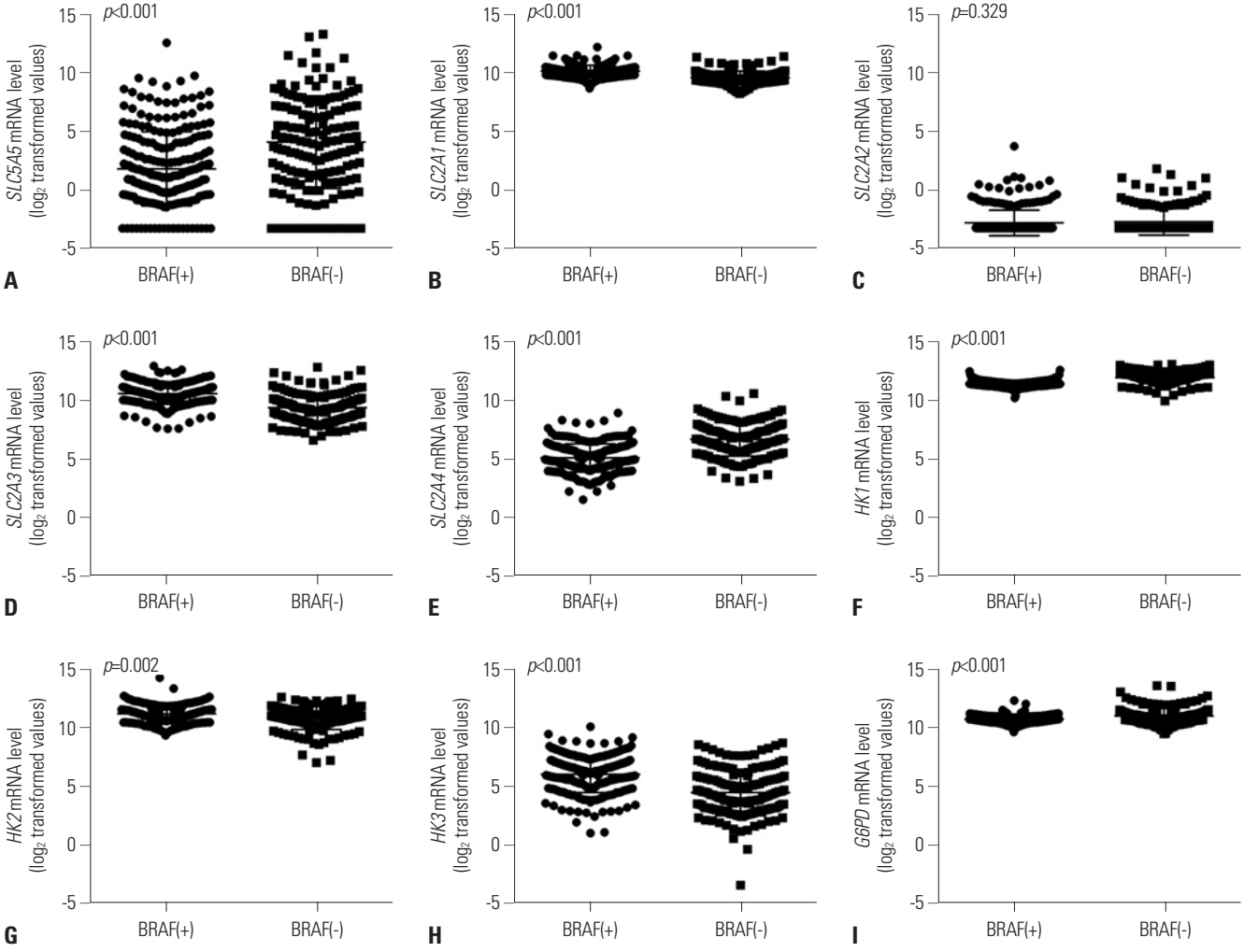

Fig. 3. mRNA expression dynamics according to BRAF mutation status. (A) *SLC5A5*, (B) *SLC2A1*, (C) *SLC2A2*, (D) *SLC2A3*, (E) *SLC2A4*, (F) *HK1*, (G) *HK2*, (H) *HK3*, and (I) *G6PD*.

Table 3. Median mRNA Expression according to BRAF or RAS Mutation Status

Protein	mRNA	BRAF			RAS		
		(+), n=234	(-), n=157	*p* value	(+), n=52	(-), n=339	*p* value
Sodium-iodide symporter	*SLC5A5*	1.19	4.03	<0.001	2.96	1.87	0.335
Glucose transporter	*SLC2A1*	10.02	9.45	<0.001	9.462	9.887	<0.001
	SLC2A2	-3.32	-3.32	0.329	-3.32	-3.32	0.432
	SLC2A3	10.50	9.21	<0.001	8.81	10.26	<0.001
	SLC2A4	4.80	6.55	<0.001	7.19	5.29	<0.001
Hexokinase	*HK1*	11.36	11.93	<0.001	11.91	11.47	<0.001
	HK2	11.14	10.92	0.002	11.05	11.03	0.898
	HK3	6.29	4.38	<0.001	3.76	5.87	<0.001
Glucose 6 phosphatase	*G6PD*	10.70	10.89	<0.001	10.82	10.75	0.244

The median of $\log_2$ transformation of mRNA expression is indicated.

pression of *HK1* mRNA was associated with a better prognosis concerning DFS (0.4055, p=0.013), although PTC patients with higher expression of *HK3* mRNA showed a worse prognosis in DFS (2.299, p=0.0227) (Table 4).

DISCUSSION

In this study, expression of *SLC5A5* mRNA was negatively correlated with that of *SLC2A1* and *HK2* and was positively correlated with *SLC2A4* and *HK1*. During the natural evolution of

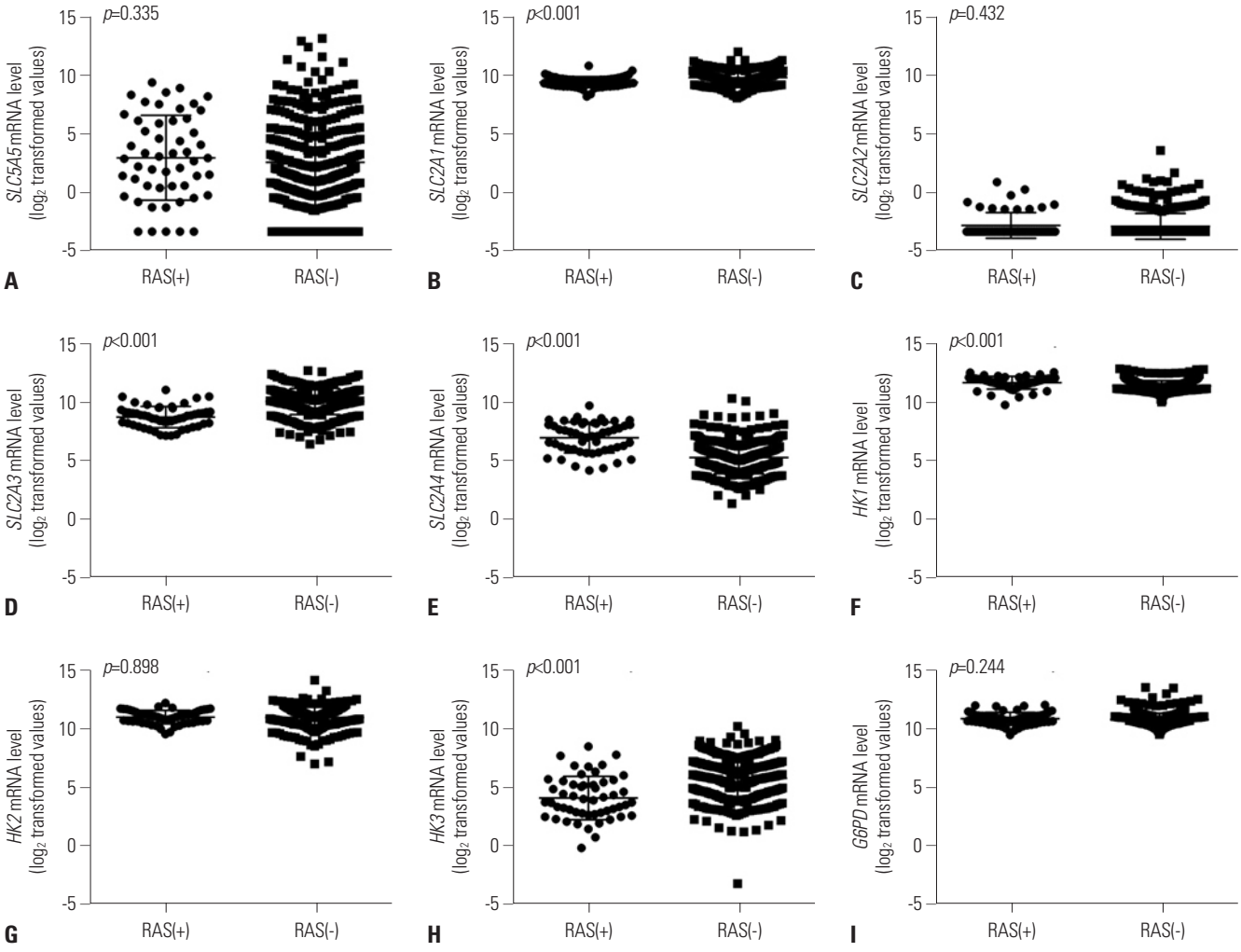

Fig. 4. mRNA expression patterns according to RAS mutation status. (A) *SLC5A5*, (B) *SLC2A1*, (C) *SLC2A2*, (D) *SLC2A3*, (E) *SLC2A4*, (F) *HK1*, (G) *HK2*, (H) *HK3*, and (I) *G6PD*.

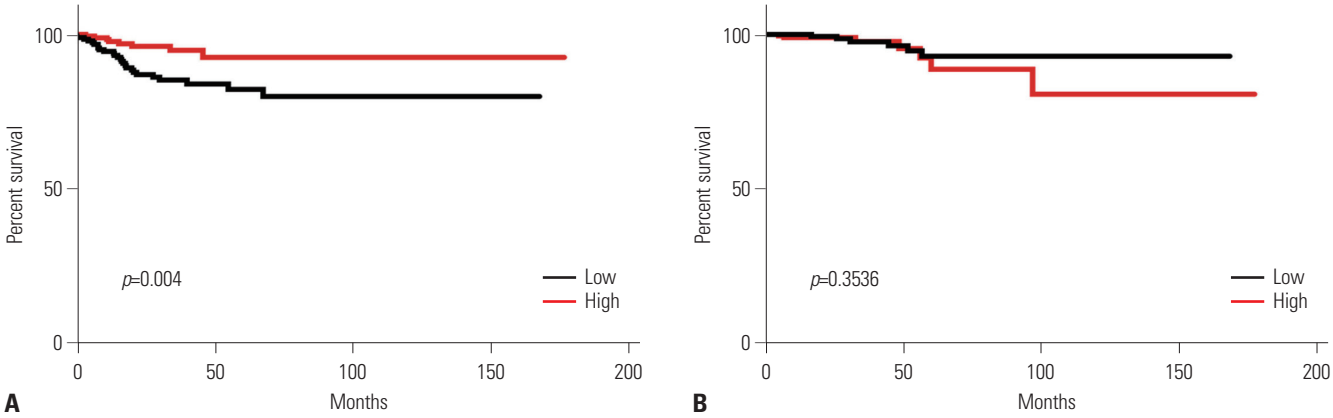

Fig. 5. Survival curves in the context of *SLC5A5* mRNA abundance. (A) Disease-free survival and (B) overall survival.

https://doi.org/10.3349/ymj.2018.59.6.746

Table 4. Survival Analysis according to mRNA Expression

Protein	mRNA	Disease-free survival			Overall survival		
		Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Sodium-iodide symporter	*SLC5A5*	0.332	0.169–0.650	0.004	1.660	0.550–5.007	0.354
Glucose transporter	*SLC2A1*	1.499	0.765–2.938	0.247	2.402	0.798–7.228	0.166
	SLC2A2	1.612	0.823–3.157	0.171	4.351	1.456–13	0.035
	SLC2A3	1.294	0.660–2.536	0.457	3.432	1.123–10.490	0.082
	SLC2A4	0.513	0.262–1.004	0.063	0.593	0.198–1.780	0.377
Hexokinase	*HK1*	0.406	0.207–0.794	0.013	1.339	0.450–3.983	0.596
	HK2	1.406	0.718–2.753	0.326	0.820	0.276–2.432	0.720
	HK3	2.299	1.174–4.504	0.023	1.806	0.605–5.392	0.317
Glucose 6 phosphatase	*G6PD*	0.809	0.413–1.585	0.538	1.099	0.367–3.287	0.864

CI, confidence interval.

differentiated thyroid cancer (DTC), either before diagnosis or over the course of treatment and follow-up, there is some loss of the ability to take up iodine owing to diminished *SLC5A5* expression. A defective iodide-trapping mechanism due to reduced *SLC5A5* expression appears to be an early and consistent feature of the oncogenic transformation of thyroid cells, and is associated with neoplastic transformation.[10] This phenomenon is often seen as DTC progresses to the later stages of cancer development, and explains why advanced, high-risk DTC patients have a poorer response to RAI than early-stage DTC patients.[11]

Among the 14 *SLC2A* subtypes, *SLC2A1* has been most widely investigated in various cancer types, including thyroid cancer, wherein some studies have found increased *SLC2A1* expression.[12,13] Furthermore, adverse effects of *SLC2A* overexpression on survival outcomes in PTC patients have been implied for associations between *SLC2A1* overexpression and tumor aggressiveness or dedifferentiation.[14,15] The expression of *SLC5A5* and *SLC2A1* mRNA is related to the accumulation of radioactive iodine (^{123}I or ^{131}I) and ^{18}F-FDG in thyroid cancer cells,[16] and the expression of these genes provides a molecular basis for the image modalities of gamma cameras and PET with these radiopharmaceuticals. High glucose uptake measured by FDG PET is associated with low *SLC5A5* expression, which indicates dedifferentiation in thyroid cancer.[17] This finding is a known phenomenon called "flip-flop" in FDG PET and WBS, which explains the mechanism of how FDG PET detects recurrent or metastatic cancer in patients, but WBS fails to detect tumors,[18] consistent with guidelines from the American Thyroid Association.[3] As a whole, our findings suggest that *SLC2A1* and *HK2* expression may be related to BRAF mutation and ^{18}F-FDG uptake of PTC, which leads to cancer aggressiveness or dedifferentiation. Further studies are needed to clarify the relationship among ^{18}F-FDG uptake, the expression of variable glucose transporters, *HK2*, and BRAF mutations.

Most mRNA expression patterns in this study were significantly associated with PTC genetic mutations. Findings from a previous PTC TCGA showed that BRAF and RAS-like classes of PTC are significantly distinct in regards to differentiation state, and BRAF-like tumors exhibit a gene expression profile associated with a less differentiated state.[9] Morari, et al.[19] found that 230 DTC patients with a BRAF mutation had reduced *SLC5A5* mRNA abundance. In this study, expressions of *SLC2A1*, *SLC2A3*, *HK2*, and *HK3* mRNA were higher in PTC patients with BRAF mutations, which might reflect excessive glucose influx required for cancer cell proliferation facilitated by *SLC2A*,[20] a well-known prognostic marker of DTC.[21] This study is the first to show an association between mRNA and genetic mutation-prognosis. Our data suggest that mRNA expression helps to characterize a patient's risk and to identify individuals with a poor response to therapy. A larger number of patients with long-term follow-up may also confirm the clinical use of mRNA expression, reinforcing the predictive value of clinicopathological outcomes/markers, such as age and tumor size, as well as molecular markers, such as BRAF mutations.

We demonstrated that the expression of *SLC5*, *SLC2*, and *HK* genes (associated with survival) was associated with BRAF and RAS mutations, a well-known, adverse prognostic factor in PTC.[21] The BRAF gene encodes a serine/threonine kinase that belongs to the RAS-RAF-MEK-ERK-MAP kinase pathway, whose biological role is to mediate cellular responses to growth factors.[1,2] Furthermore, we demonstrated that expression of *SLC5A5*, *HK1*, and *HK3* mRNA was associated with PTC recurrence. Extranodal extension is also associated with poor prognosis in thyroid cancer.[22] Our study is the first to show an association between mRNA expression and genetic mutation in cancer prognosis. Our data suggests that mRNA expression may help to determine patient risk and individuals with a poor response to therapy. Ward, et al.[23] identified that patients with PTC who experienced early recurrence or metastasis show low expression levels of *SLC5A5* mRNA in primary tumors. As expected, *SLC2A2* and *SLC2A3* mRNA, which are known to be associated with BRAF and RAS mutations, had unfavorable prognosis regarding OS. As lower mRNA expression of *SLC5A5* reflects a poorer response to radioactive iodine therapy, it is reasonable that this population of patients have favorable prognosis in DFS. However, mRNA expression

of *SLC5A5* did not affect OS, as PTC is perceived to have a high survival rate, with a minority of patients showing recurrence or metastasis.[24] A larger number of patients with long-term follow-up may also confirm the clinical use of mRNA expression, reinforcing the predictive value of well-recognized clinical and pathological predictors of outcome.

Despite a vast amount of genetic and epigenetic information, the absence of solid prospective studies on thyroid cancer and information on the relationships among clinical, pathological, and genetic factors makes it difficult to discern the prognostic role played by genetic mutations.[5] The molecular characterization of thyroid cancer has begun to influence its diagnosis and treatment landscape. Gene expression analysis might also be clinically useful in the near future. In this study, we found evidence for the genetic basis of ^{18}F-FDG PET in PTC patients with negative WBS with RAI and the prognostic value of *SLC5A5* in PTC. Additionally, there is a demand for new drugs for PTC refractory to standard treatment with RAI, as the impact of tyrosine kinase inhibitors on survival is not satisfactory and their side effects are often fatal.[1,2] In addition to prognosis, the aforementioned mutations and respective molecular pathways, as well as genetic and epigenetic alterations recently identified by TCGA,[9] may serve as likely targets and areas of focus for personalized therapy. Furthermore, drugs inhibiting *SLC2A*-family genes might have great therapeutic potential by inducing starvation of tumor cells.[25] In addition, *SLC5A5* expression can be augmented by upregulation of both transcriptional and post-translational pathways. Some isoform-specific signal transduction pathways may play critical roles in tissue-specific *SLC5A5* regulation. Delineation of such signaling pathways may lead to methods that will further enhance functional *SLC5A5* expression in DTC, thus expanding the application of RAI to RAI-refractory PTC.[26] We could not analyze the other important genes related to iodine metabolism due to lack of data. In addition, we could only analyze expressions of mRNAs, not those of proteins. Further studies are needed to investigate the expression levels of proteins between *SLC2A* family and *SLC5A5*.

In conclusion, expression of *SLC5A5* mRNA was negatively correlated with *SLC2A1*. This finding provides a molecular basis for the management of PTC patients with negative WBS using ^{18}F-FDG PET scans. In addition, higher *SLC5A5* mRNA expression was associated with less frequent recurrence or metastasis, but not with deaths. Moreover, PTC patients with BRAF mutations had reduced *SLC5A5* mRNA expression and higher expression of *HK2* and *HK3* mRNA, which might reflect a less-differentiated state of PTC.

ACKNOWLEDGEMENTS

This work was supported by a Dong-A University research fund grant and the Basic Science Research Program through the National Research Foundation of Korea (2017R1D1A1B03029352/2017R1D1A1B03033235). The funding source had no role in the collection of the data or in the decision to submit the manuscript for publication.

ORCID

Sunghwan Suh https://orcid.org/0000-0001-6865-966X
Yun Hak Kim https://orcid.org/0000-0002-9796-8266
Tae Sik Goh https://orcid.org/0000-0003-1861-5647
Kyoungjune Pak https://orcid.org/0000-0001-5051-1894

REFERENCES

1. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet 2016;388:2783-95.
2. Ahn HS, Welch HG. South Korea's thyroid-cancer "Epidemic"--turning the tide. N Engl J Med 2015;373:2389-90.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1-133.
4. Pak K, Cheon GJ, Nam HY, Kim SJ, Kang KW, Chung JK, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis in head and neck cancer: a systematic review and meta-analysis. J Nucl Med 2014;55:884-90.
5. Tavares C, Melo M, Cameselle-Teijeiro JM, Soares P, Sobrinho-Simões M. ENDOCRINE TUMOURS: Genetic predictors of thyroid cancer outcome. Eur J Endocrinol 2016;174:R117-26.
6. Chai YJ, Yi JW, Oh SW, Kim YA, Yi KH, Kim JH, et al. Upregulation of SLC2 (GLUT) family genes is related to poor survival outcomes in papillary thyroid carcinoma: analysis of data from The Cancer Genome Atlas. Surgery 2017;161:188-94.
7. Smith TA. FDG uptake, tumour characteristics and response to therapy: a review. Nucl Med Commun 1998;19:97-105.
8. Filetti S, Bidart JM, Arturi F, Caillou B, Russo D, Schlumberger M. Sodium/iodide symporter: a key transport system in thyroid cancer cell metabolism. Eur J Endocrinol 1999;141:443-57.
9. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014;159:676-90.
10. Ros P, Rossi DL, Acebrón A, Santisteban P. Thyroid-specific gene expression in the multi-step process of thyroid carcinogenesis. Biochimie 1999;81:389-96.
11. Winter J, Winter M, Krohn T, Heinzel A, Behrendt FF, Tuttle RM, et al. Patients with high-risk differentiated thyroid cancer have a lower I-131 ablation success rate than low-risk ones in spite of a high ablation activity. Clin Endocrinol (Oxf) 2016;85:926-31.
12. Ravazoula P, Batistatou A, Aletra C, Ladopoulos J, Kourounis G, Tzigounis B. Immunohistochemical expression of glucose transporter Glut1 and cyclin D1 in breast carcinomas with negative lymph nodes. Eur J Gynaecol Oncol 2003;24:544-6.
13. Haber RS, Weiser KR, Pritsker A, Reder I, Burstein DE. GLUT1 glucose transporter expression in benign and malignant thyroid nodules. Thyroid 1997;7:363-7.
14. Jóźwiak P, Krześlak A, Pomorski L, Lipińska A. Expression of hypoxia-related glucose transporters GLUT1 and GLUT3 in benign, malignant and non-neoplastic thyroid lesions. Mol Med Rep 2012;6:601-6.
15. Kim S, Chung JK, Min HS, Kang JH, Park DJ, Jeong JM, et al. Ex-

https://doi.org/10.3349/ymj.2018.59.6.746

pression patterns of glucose transporter-1 gene and thyroid specific genes in human papillary thyroid carcinoma. Nucl Med Mol Imaging 2014;48:91-7.
16. Chung JK. Sodium iodide symporter: its role in nuclear medicine. J Nucl Med 2002;43:1188-200.
17. Moon SH, Oh YL, Choi JY, Baek CH, Son YI, Jeong HS, et al. Comparison of 18F-fluorodeoxyglucose uptake with the expressions of glucose transporter type 1 and Na+/I- symporter in patients with untreated papillary thyroid carcinoma. Endocr Res 2013;38:77-84.
18. Chung JK, So Y, Lee JS, Choi CW, Lim SM, Lee DS, et al. Value of FDG PET in papillary thyroid carcinoma with negative 131I whole-body scan. J Nucl Med 1999;40:986-92.
19. Morari EC, Marcello MA, Guilhen AC, Cunha LL, Latuff P, Soares FA, et al. Use of sodium iodide symporter expression in differentiated thyroid carcinomas. Clin Endocrinol (Oxf) 2011;75:247-54.
20. Yamamoto T, Seino Y, Fukumoto H, Koh G, Yano H, Inagaki N, et al. Over-expression of facilitative glucose transporter genes in human cancer. Biochem Biophys Res Commun 1990;170:223-30.
21. Pak K, Suh S, Kim SJ, Kim IJ. Prognostic value of genetic mutations in thyroid cancer: a meta-analysis. Thyroid 2015;25:63-70.
22. Suh S, Pak K, Seok JW, Kim IJ. Prognostic value of extranodal extension in thyroid cancer: a meta-analysis. Yonsei Med J 2016;57:1324-8.
23. Ward LS, Santarosa PL, Granja F, da Assumpção LV, Savoldi M, Goldman GH. Low expression of sodium iodide symporter identifies aggressive thyroid tumors. Cancer Lett 2003;200:85-91.
24. Schlumberger MJ. Papillary and follicular thyroid carcinoma. N Engl J Med 1998;338:297-306.
25. Ulanovskaya OA, Cui J, Kron SJ, Kozmin SA. A pairwise chemical genetic screen identifies new inhibitors of glucose transport. Chem Biol 2011;18:222-30.
26. Kogai T, Brent GA. The sodium iodide symporter (NIS): regulation and approaches to targeting for cancer therapeutics. Pharmacol Ther 2012;135:355-70.