Genetic differences in follicular thyroid carcinoma between Asian and Western countries: a systematic review

Toru Odate[1], Naoki Oishi[1], Huy Gia Vuong[2], Kunio Mochizuki[1], Tetsuo Kondo[1]

[1]Department of Pathology, University of Yamanashi, Chuo, Yamanashi, Japan; [2]Department of Pathology, Oklahoma University Health Sciences Center, Oklahoma City, OK, USA

Contributions: (I) Conception and design: T Odate; (II) Administrative support: T Odate, N Oishi, K Mochizuki, T Kondo; (III) Provision of study materials or patients: T Odate, HG Vuong; (IV) Collection and assembly of data: T Odate, HG Vuong; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tetsuo Kondo, MD, PhD. Department of Pathology, University of Yamanashi, 1110 Shimokato, Chuo, Yamanashi 409-3898, Japan. Email: ktetsuo@yamanashi.ac.jp.

Abstract: Thyroid cancer is the most common endocrine malignancy, and follicular thyroid carcinoma (FTC) is the second most common thyroid cancer following papillary thyroid carcinoma (PTC). *RAS* mutation and *PAX8/PPARγ* rearrangement are the two representative genetic alterations in FTC, and there are studies from various countries on their regional frequencies. In this study, we systematically reviewed all available literature aiming to create a complete global map showing the frequencies of these common oncogenic drivers in FTC and to highlight the trends in Asian and Western countries. We performed a search in two electronic databases and identified 71 studies that fit our criteria from 1,329 studies found with our database search terms. There were 54 articles with 1,143 FTC patients and 39 articles with 764 FTC patients available for calculating the frequency of *RAS* mutation and *PAX8/PPARγ* rearrangement, respectively. *NRAS* mutation was the most frequent *RAS* mutation in all regions, followed by *HRAS* and *KRAS* mutation. The frequency of *RAS* mutation in Asian countries was higher than Western countries (34% *vs.* 27%, P=0.006) when the mutation detection method was not taken into account. In contrast, this difference in *RAS* mutation incidence between Asian and Western countries (28% *vs.* 25%, P=0.47) did not show up in our subgroup analysis incorporating only studies using direct sequencing method. The reported difference of *RAS* mutation frequency in the previous literature might not be due to the true prevalence of *RAS* mutation. They could be attributed to the difference in the detection method. As to *PAX8/PPARγ* rearrangement, Western countries overall had a much higher prevalence than Asian countries (23% *vs.* 4%, P<0.001), but some European countries had a low incidence, implying regional heterogeneity of *PAX8/PPARγ* rearrangement. A substantial lack of mutation data in FTC was found in several regions of the world such as Central Asia, Middle East, Africa, and Central and South America. Our results provide the most comprehensive global status of representative genetic alterations in FTC and highlight the similarities and differences between Asian and Western countries.

Keywords: Follicular thyroid carcinoma (FTC); PAX8/PPARγ; RAS; systematic review

Introduction

Thyroid cancer is the most common endocrine malignancy with 567,000 new cases and 41,000 deaths worldwide in 2018 (1). Thyroid cancer generally derives from follicular epithelial cells. Follicular thyroid carcinoma (FTC) is the second most common thyroid cancer originating from thyroid epithelial cells following papillary thyroid carcinoma (PTC) (2).

BRAF mutation is the most common genetic alteration in PTC, accounting for approximately 60% of the alterations (3). In contrast, *RAS* mutation is the most prevalent oncogenic drivers in FTC (4), although recent studies using next generation sequencing (NGS) revealed novel driver mutations other than *RAS* such as *DICER1*, *EIF1AX*, and *EZH1* (5). *RAS* mutation is also associated with poor prognosis in FTC. Several studies indicated that *RAS*-mutated FTCs were associated with poor overall survival and distant metastasis (6,7). The incidence of *RAS* mutation in FTC varies among studies ranging from 10.5% to 56.9%, which is higher than follicular adenoma (FA) from 8% to 48% (8,9). Some of this variation is due to the relatively small number of samples available for the studies and the use of different methodologies (9). Moreover, some researchers tried to explain the geographical difference in the incidence of *RAS* mutation in terms of iodine intake of the populations. The results remain controversial (10,11).

Some oncogenic genetic rearrangements also contribute to tumorigenesis in follicular thyroid neoplasms, and *PAX8/PPARγ* rearrangement is the most common in FTC and FA at about 30% and 10% occurrence (12). This gene rearrangement results in the production of the PAX8/PPARγ fusion protein which acts as an oncoprotein by inhibiting endogenous PPARγ activity, although the mechanisms of tumorigenesis induced by this fusion gene are not fully understood (13). Other chromosomal rearrangements including *DERL-COX6C* and *CREB3L2-PPARγ* make up only a subset of FTCs (14). Recent large cohort studies suggested that *PAX8/PPARγ* did not correlate with invasiveness or affect prognosis in FTC (15). Geographical differences in the incidence of *PAX8/PPARγ* rearrangement in FTC is better recognized than *RAS* mutation in FTC. Interestingly, *PAX8/PPARγ* rearrangement is considered to be much more common in Western countries than in Asia. This may be attributed to ethnic differences, iodine intake, or radiation exposure, but there is no definitive conclusion (16-18).

The genetic alterations in thyroid cancer have received attention as possible diagnostic or treatment targets (4). However, when adopting therapeutic or diagnostic strategies based on molecular information, there should be careful consideration of the various genetic backgrounds of different populations, especially in Asian and Western countries. Although there are studies on the frequency of *RAS* mutation and *PAX8/PPARγ* rearrangement in FTC from various regions, worldwide comprehensive information is still limited. Grasping world trends of genetic backgrounds in FTC is important for the sake of clinical practice. Therefore, we systematically reviewed the available literature on the subject with the goal of creating a global mutational map of FTC. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/gs-20-356).

Methods

Literature search

We searched the electronic databases of PubMed, Web of Science for relevant English papers from the inception in 1987 to September 2019 using the following search terms: (follicular OR follicular thyroid) AND (carcinoma OR cancer OR tumor) AND (RAS OR NRAS OR HRAS OR KRAS OR PAX8 OR PPARγ). Additionally, we performed a manual search by reviewing the citations within the included publications and reviews. Our study protocol generally followed the recommendation of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (19).

Selection criteria and abstract screening

We imported all search results from each electronic database into EndNote (Clarivate Analytics, PA, USA) and deleted duplicates. Two reviewers independently screened titles and abstracts of included studies (TO and HGV). We only included studies in the final analysis that contained information on the frequency of any of the *RAS* mutations or the *PAX8/PPARγ* fusion gene in FTC. We did not include the studies dealing with only borderline tumors introduced by recent WHO classification such as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), follicular tumor of uncertain malignant potential (FT-UMP), and well-differentiated tumor of uncertain malignant potential (WDT-UMP) (20). The exclusion criteria were (I) studies on thyroid tumors other than FTC
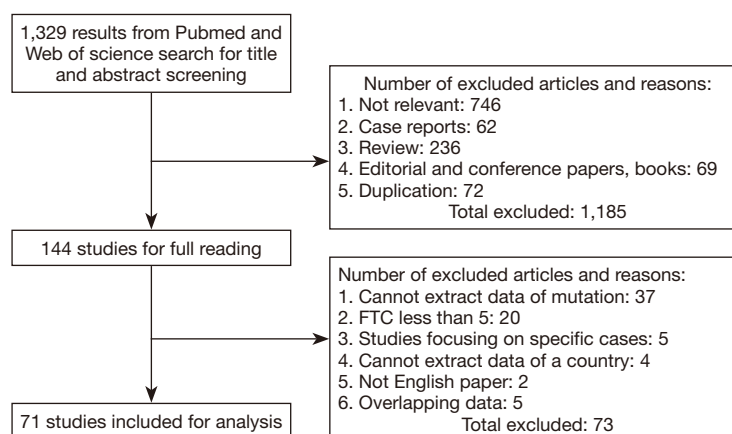
Figure 1 Study flowchart.

including Hurthle cell carcinoma which was previously considered an oncocytic variant of FTC; and (II) case reports, reviews, editorial papers, conference and meeting abstracts, or books. The 2 reviewers resolved any discrepancies between them through discussion and consensus.

Full-text screening

Subsequently, the reviewers read the full text of all potential articles and excluded many from our study. After completing the selection of articles, we extracted the data into a standardized extraction form. Any disagreements were solved, again, by discussion and consensus. The data extracted from the studies included information about the institutions, country, year of publication, admission period of the study, mutation detecting methods, type of samples, study design, age, gender, and frequency of genetic alterations. Extracted genetic alterations were exon 1 or exon 2 mutation of each *RAS* gene and *PAX8/PPARγ* rearrangement.

Data analysis

Statistical analyses were conducted using the GraphPad Prism 8 software (GraphPad software, San Diego California, USA). Categorical variables were compared using the Pearson chi-square test. A P value <0.05 was considered statistically significant.

Results

We found 1,329 articles through title and abstract screening

and selected 144 of them for full-text reading. After reading these articles' full texts, we excluded 73 studies for the following reasons: (I) inability to extract frequency data of genetic alterations, (II) number of FTC samples in the study was less than 5 FTCs and inadequate for estimating frequency, (III) the study focused on specific FTCs such as radiation induced or FTCs with distant metastases, (IV) no information as to country of samples, (V) not an English language paper, and (VI) overlapping data between the studies. We used the remaining 71 studies that included data of at least one genetic alteration in our final analysis (*Figure 1*). The characteristics of all included studies are listed in *Table 1*.

RAS mutation frequency in FTC patients by geographic region

There were 54 articles with a combined 1,143 FTC patients available for calculating the frequency of *RAS* mutation. These included 19 studies from Asia (5,6,10,21-34,36,37), 21 studies from Europe (11,39-41,43,46-53,55-60,63,65), 12 studies from North America (11,67-77), 1 study from Oceania (83) and 1 study from the Middle East (38). We extracted the data on each *RAS* mutation, including *NRAS*, *HRAS* and *KRAS*, from these articles and then calculated the frequency of FTC patients who had a *RAS* mutation. *Table 2* and *Figure 2A* show the worldwide frequency of *RAS* mutation. *NRAS* mutation is the most frequent in all regions, followed by *HRAS* and *KRAS* mutation.

Most of the Asian countries had a greater than 30% prevalence of *RAS* mutation, while some European countries such as Germany (8%), Portugal (12%) and Turkey (0%)

Table 1 Characteristics of included studies

Ref. no	Author/year/country	Sample	Detection method		No. with a mutation/total no.				
			RAS	PAX8/PPARγ	NRAS	HRAS	KRAS	Any RAS	PAX8/PPARγ
(6)	Fukahori/2012/Japan	FFPE	DS, Others		23/58	5/58	5/58	33/58	
(10)	Vuong/2016/Japan and Vietnam	FFPE	DS		17/51, 4/23	0/51, 0/23	0/51, 0/23	17/51, 4/23	
(16)	Hibi/2004/Japan	FFPE, Frozen		RT-PCR, FISH					0/6
(17)	Mochizuki/2015/Japan	FFPE		RT-PCR					1/21
(21)	Bandoh/2018/Japan	FFPE	NGS		0/9		0/9	0/9	
(22)	Fukushima/2003/Japan	ND	DS		4/8	0/8	0/8	4/8	
(23)	Kaihara/1994/Japan	Frozen	DS, others		2/7			2/7	
(24)	Oishi/2016/Japan	FFPE	DS, others		9/35			9/35	
(25)	Oyama/1995/Japan	FFPE	DS		3/6		0/6	3/6	
(26)	Vuong/2017/Japan	FFPE	DS	RT-PCR	5/41	0/41	0/41	5/41	0/39
(5)	Yoo/2016/Korea	Frozen	NGS	NGS	6/27	6/27	3/27	15/27	1/27
(27)	Bae/2014/Korea	FFPE	PS		2/13			2/13	
(28)	Kim/2012/Korea	FFPE	DS	FISH	8/37	2/37	1/37	11/37	3/31
(29)	Jang/2016/Korea	FFPE	DS		5/10		5/10		
(30)	Jeong/2015/Korea	FFPE	PS		8/39	4/39	9/39	21/39	
(31)	Jung/2018/Korea	FFPE	DS		9/40	7/40	2/40	18/40	
(32)	Jung/2016/Korea	Frozen	NGS		4/13	1/13	0/13	5/13	
(33)	Song/2017/Korea	FFPE	DS	FISH	14/67	1/67	1/67	16/67	1/48
(34)	Duan/2019/China	FFPE	NGS	NGS	10/53	4/53	3/53	17/53	1/53
(35)	Chia/2010/Malaysia	FFPE		FISH					2/18
(36)	Liu/2004/Taiwan	Frozen	DS		1/8	1/8	1/8	3/8	
(37)	Khan/2013/India	Frozen	DS		0/8	0/8	0/8	0/8	
(38)	Schulten/2013/Saudi Arabia	FFPE, Frozen	DS		1/10	1/10	0/10	2/10	
(39)	Bouras/1998/France	Frozen	Others		1/6	0/6	0/6	1/6	
(40)	Bouras/1995/France	Frozen	Others			0/5		0/5	
(41)	Cristofaro/2006/France	Frozen	DS	RT-PCR	8/21			8/21	9/21
(42)	Lacroix/2005/France	Frozen		RT-PCR					4/23
(43)	Eszlinger/2017/Germany	FNA	PS	qPCR	1/12	0/12	0/12	1/12	0/12
(44)	Klemke/2012/Germany	FFPE		RT-PCR, FISH					2/21
(45)	Karger/2005/Germany	Frozen		qPCR					0/7
(46)	Basolo/2000/Italy	FFPE	Others		2/5			2/5	
(47)	Censi/2017/Italy	FNA	DS		3/29	1/29	0/29	4/29	
(48)	Eszlinger/2015/Italy	FNA	PS		7/21	3/21	0/21	10/21	
(49)	Guerra/2014/Italy	FNA	PS		5/21		3/21	8/21	
(50)	Manenti/1994/Italy	FFPE, Frozen	DS, others		2/21	3/21	0/21	5/21	
(51)	Poma/2018/Italy	FFPE	DS	RT-PCR	5/20	0/20	1/20	6/20	1/20
(52)	Proietti/2013/Italy	FFPE	DS	qPCR	10/29	1/29	1/29	12/29	1/29

Table 1 (*continued*)

Table 1 (continued)

Ref. no	Author/year/country	Sample	Detection method		No. with a mutation/total no.				
			RAS	PAX8/PPARγ	NRAS	HRAS	KRAS	Any RAS	PAX8/PPARγ
(53)	Banito/2007/Portugal	FFPE, Frozen	DS	qPCR, FISH	2/25	1/25	0/25	3/25	7/17
(54)	Marques/2004/Portugal	Frozen			qPCR, FISH				6/24
(55)	Borowczyk/2019/Poland	FFPE	NGS		2/35	6/35	0/35	8/35	
(56)	Swierniak/2016/Poland	Frozen	NGS	NGS	0/20	0/20	2/20	2/20	0/20
(57)	Esapa/1999/UK	FFPE, Frozen	DS, others		4/9	0/9	0/9	4/9	
(58)	Lemoine/1989/UK	FFPE	Others		1/10	3/10	0/10	4/10	
(59)	Capella/1996/Spain	FFPE	Others		2/10	0/10	0/10	2/10	
(60)	Duman/2014/Turkey	FFPE	NGS				0/13	0/13	
(61)	Sahpaz/2015/Turkey	FFPE		qPCR					3/9
(62)	Pauzar/2012/Croatia	FFPE		RT-PCR					7/18
(63)	Eszlinger/2014/Denmark	FFPE, FNA	qPCR	qPCR	3/24	1/24	0/24	4/24	3/24
(64)	Ferraz/2012/Denmark	FFPE, FNA	qPCR						4/20
(11)	Shi/1991/Hungary and Canada	FFPE	Others		1/6, 0/10	2/6, 1/10	0/6, 0/10	3/6, 1/10	
(65)	Celestino/2012/Norway	FFPE, Frozen	DS	RT-PCR, FISH	2/7	1/7		3/7	0/7
(66)	Dwight/2003/Sweden	Frozen		RT-PCR, FISH					10/34
(15)	Boos/2013/Switzerland	FFPE		FISH					5/31
(67)	Apple/1998/USA	FFPE	Others				0/10	0/10	
(68)	Giordano/2014/USA	FFPE	Others					3/17	5/17
(69)	Karga/1991/USA	FFPE	Others		2/14	0/14	0/14	2/14	
(70)	Liu/2008/USA	FFPE	DS					13/64	
(71)	Mostoufi/2018/USA	FFPE	Others		0/6	1/6	1/6	2/6	0/6
(72)	Nikiforov/2011/USA	FNA	NGS					4/11	1/11
(73)	Nikiforov/2009/USA	FNA	DS	RT-PCR				2/6	1/6
(74)	Nikiforova/2003/USA	FFPE, Frozen	Others	RT-PCR, FISH	14/33	3/33	0/33	17/33	13/33
(75)	Nikiforova/2013/USA	FFPE, Frozen	NGS		9/18	0/18	1/18	10/18	
(76)	Nikita/2016/USA	FFPE	DS	RT-PCR	1/5	0/5	0/5	1/5	1/5
(77)	Yip/2015/USA	FNA	NGS	NGS				3/10	0/10
(78)	Aldred/2003/USA	ND		RT-PCR					2/19
(79)	Algeciras/2010/USA	FFPE		RT-PCR					13/21
(80)	Giordano/2006/USA	FFPE		RT-PCR					7/13
(81)	Kroll/2000/USA	ND		RT-PCR					5/8
(82)	Cerutti/2004/Brazil	FFPE		RT-PCR					4/13
(83)	Mond/2014/Australia	FFPE, Frozen	DS	RT-PCR	5/27	3/27	0/27	8/27	1/9
(84)	Cheung/2003/Australia	Frozen		RT-PCR					6/13

FFPE, formalin-fixed paraffin-embedded; FNA, fine needle aspiration; NGS, next generation sequencing; DS, direct sequencing; PS, pyrosequencing; RT-PCR, reverse transcription PCR; qPCR, quantitative PCR; FISH, fluorescence in situ hybridization.

Table 2 Frequency of *RAS* mutations and *PAX8/PPARγ* rearrangement in FTC patients by country

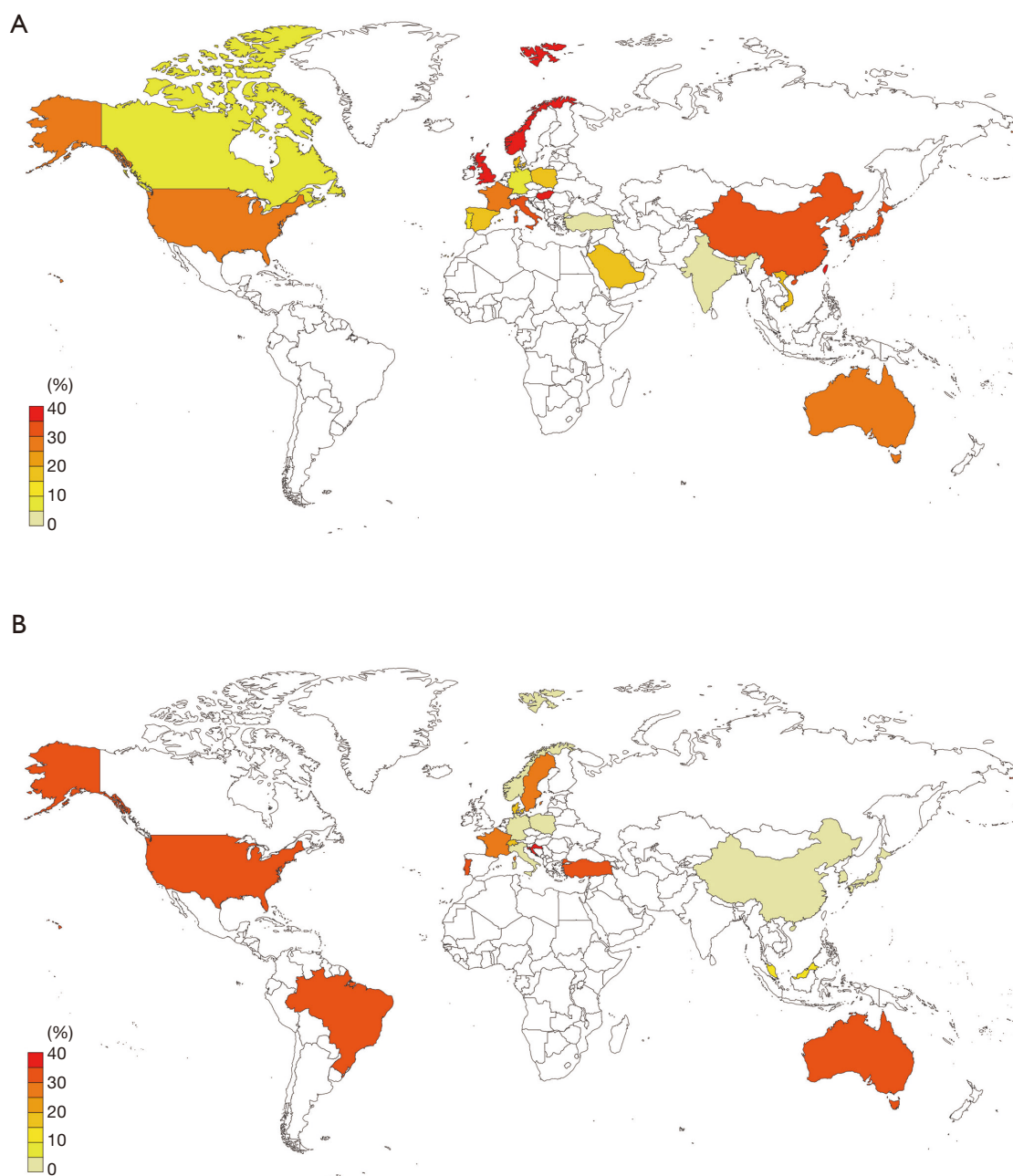| Country/region	No. studies	NRAS	HRAS	KRAS	Any RAS	PAX8/PPARγ
		No. with a mutation/total no. [%]				
Asia						
China	1 (34)	10/53 [19]	4/53 [8]	3/53 [3]	17/53 [32]	1/53 [2]
Japan	10 (6,10,16,17,21-26)	63/215 [29]	5/158 [3]	5/173 [3]	73/215 [34]	1/66 [2]
Korea	8 (5,27-33)	56/246 [23]	21/223 [9]	16/223 [7]	93/246 [38]	5/106 [5]
Malaysia	1 (35)					2/18 [11]
Taiwan	1 (36)	1/8 [13]	1/8 [13]	1/8 [13]	3/8 [38]	
Vietnam	1 (10)	4/23 [17]	0/23 [0]	0/23 [0]	4/23 [17]	
India	1 (37)	0/8 [0]	0/8 [0]	0/8 [0]	0/8 [0]	
Overall	23	134/553 [24]	31/473 [7]	25/488 [5]	190/553 [34]	9/243 [4]
Europe						
France	4 (39-42)	9/27 [33]	0/11 [0]	0/6 [0]	9/32 [28]	13/44 [30]
Germany	3 (43-45)	1/12 [8]	0/12 [0]	0/12 [0]	1/12 [8]	2/40 [5]
Italy	7 (46-52)	34/146 [23]	8/120 [5]	5/141 [4]	47/146 [32]	2/49 [4]
Portugal	2 (53,54)	2/25 [8]	1/25 [4]	0/25 [0]	3/25 [12]	13/41 [31]
Poland	2 (55,56)	2/55 [4]	6/55 [11]	2/55 [4]	10/55 [18]	0/20 [0]
UK	2 (57,58)	5/19 [26]	3/19 [16]	0/19 [0]	8/19 [42]	
Switzerland	1 (15)					5/31 [16]
Spain	1 (59)	2/10 [20]	0/10 [0]	0/10 [0]	2/10 [20]	
Turkey	2 (60,61)			0/13 [0]	0/13 [0]	3/9 [33]
Croatia	1 (62)					7/18 [39]
Denmark	2 (63,64)	3/24 [13]	1/24 [4]	0/24 [0]	4/24 [17]	7/44 [16]
Hungary	1 (11)	1/6 [17]	2/6 [33]	0/6 [0]	3/6 [50]	
Norway	1 (65)	2/7 [29]	1/7 [14]		3/7 [43]	0/7 [0]
Sweden	1 (66)					10/34 [29]
Overall	30	61/331 [18]	22/289 [8]	7/311 [2]	90/349 [26]	62/337 [18]
North America						
USA	15 (67-81)	26/76 [34]	4/76 [5]	2/86 [2]	57/194 [29]	48/149 [32]
Canada	1 (11)	0/10 [0]	1/10 [10]	0/10 [0]	1/10 [10]	
Overall	16	26/86 [30]	5/86 [6]	2/96 [2]	58/204 [28]	48/149 [32]
South America						
Brazil	1 (82)					4/13 [31]
Overall	1					4/13 [31]
Oceania						
Australia	2 (83,84)	5/27 [19]	3/27 [11]	0/27 [0]	8/27 [30]	7/22 [32]
Overall	2	5/27 [19]	3/27 [11]	0/27 [0]	8/27 [30]	7/22 [32]
Middle East						
Saudi Arabia	1 (38)	1/10 [10]	1/10 [10]	0/10 [0]	2/10 [20]	
Overall	1	1/10 [10]	1/10 [10]	0/10 [0]	2/10 [20]	

FTC, follicular thyroid carcinoma.

A

B

Figure 2 Global map of *RAS* mutation (A) and *PAX8/PPARγ* rearrangement (B) in FTC patients. Countries where the data are unavailable are shown in white. FTC, follicular thyroid carcinoma.

had much lower frequencies. In North America, *RAS* mutation was relatively high (28%). Although the frequency of *NRAS* and *HRAS* mutation was not different between Asian and European countries (24% *vs.* 21%, P=0.22 and 7% *vs.* 7%, P=0.71, respectively), Asian countries had a slightly higher *KRAS* mutation frequency than Western countries

(5% *vs.* 2%, P=0.016), and as a whole, the frequency of *RAS* mutation in Asian countries was statistically higher than Western countries (34% *vs.* 27%, P=0.006) (*Table 3*).

We thought that differences in the studies' detection methods might influence the reported *RAS* mutation frequencies. Therefore, we performed a subgroup analysis

Table 3 RAS mutation and *PAX8/PPARγ* rearrangement frequency in Western and Asian countries

Genetic alterations	No. with mutation/total no. [%]		P value
	Western countries	Asian countries	
NRAS	87/417 [21]	134/553 [24]	0.22
HRAS	27/375 [7]	31/473 [7]	0.71
KRAS	9/427 [2]	25/488 [5]	0.016*
Any RAS	148/553 [27]	190/553 [34]	0.006*
PAX8/PPARγ	110/486 [23]	9/243 [4]	<0.001*

Western countries include Europe and North American countries. *, P value <0.05.

Table 4 Subgroup comparison of *RAS* mutation frequency between Western and Asian countries

Genetic alterations	No. with mutation/total no. [%]		P value
	Western countries	Asian countries	
NRAS	31/136 [23]	76/328 [23]	0.93
HRAS	4/115 [3]	11/283 [4]	0.84
KRAS	2/108 [2]	10/293 [3]	0.41
Any RAS	52/206 [25]	92/328 [28]	0.47

Western countries include Europe and North American countries.

incorporating studies using the direct sequencing method which is a gold standard for mutation detection and is the most prevalent method in our collection of studies. We found 21 studies with 534 FTC patients and divided them into Asian and Western countries. In the subgroup analysis, there was no statistical difference in *RAS* mutation frequency between Asian and Western countries (28% *vs.* 25%, P=0.47) (*Table 4*).

PAX8/PPARγ rearrangement in FTC patients by geographic region

There were 39 articles with 764 FTC patients available for calculating the frequency of *PAX8/PPARγ* rearrangement. These included 8 studies from Asia (5,16,17,26,28,33-35), 17 studies from Europe (15,41-45,51-54,56,61-66), 11 studies from North America (68,71-74,76-81), 1 study from South America (82), and 2 studies from Oceania (83,84). *Table 2* and *Figure 2B* show the frequencies of *PAX8/PPARγ* rearrangement. In Asian countries, the frequency of *PAX8/PPARγ* rearrangement is low, ranging from 2% to 11%. In North America, (all studies were from USA) the frequency was high (32%). On the other hand, European countries

had a variety of frequencies among countries. Germany, Italy, Poland and Norway had relatively low frequencies, less than 5%, but France, Portugal and Croatia had greater than 30% frequency. As a whole, Western countries had a higher prevalence of *PAX8/PPARγ* rearrangement than Asian countries (23% *vs.* 4%, P<0.001) (*Table 3*).

Discussion

In our systematic review, we studied the geographical distribution of two representative genetic alterations in FTC and highlighted the similarities and differences between Asian and Western countries. Our study included all available published articles creating a comprehensive worldwide review focusing on the frequency of genetic alterations in FTC. Our results showed that *RAS* mutation in Asia is significantly more prevalent than in Western countries, although the difference disappeared in our subgroup analysis that only incorporating studies using direct sequencing method. We also showed that the incidence of *PAX8/PPARγ* rearrangement in the West was much higher than that found in Asia.

Our literature review showed that the reported

frequencies of *RAS* mutation and *PAX8/PPARγ* rearrangement in FTC vary widely, with *RAS* mutation ranging from 0 to 57% and *PAX8/PPARγ* rearrangement ranging from 0 to 62%. There are several hypotheses as to why there is such variation, and the method of detecting these mutations might especially influence the data collected on mutational frequency in these studies (9). Vasko *et al.* reported that direct sequencing detected RAS mutation less frequently than other methods because direct sequencing is unable to detect small numbers of mutated alleles in samples (85).

Our study includes various kinds of detection methods for *RAS* mutation including direct sequencing, real-time quantitative PCR, allele specific PCR, allele-specific oligonucleotide hybridization (ASO), next generation sequencing (NGS), pyrosequencing, PCR-restriction fragment length polymorphism (RFLP), PCR-primer introduced restriction with enrichment for mutant alleles (PIREMA), multiplex PCR and liquid bead array assay. In our first analysis of the data, we did not consider the methodological differences between studies, and we found that differences in *RAS* mutation frequency was consistent with a previous report (8). However, our subsequent subgroup analysis that was limited to studies using the direct sequencing method resulted in no statistical difference in *RAS* mutation incidence between Asian and Western countries. This result implies that the difference between Asian and Western countries in *RAS* mutation frequency does not exist or is lower than previously thought. Western countries tend to use more varied types of methodology for detecting mutations than do Asian countries. Direct sequencing was the method used in 52% (10/19) of the studies from Asian countries but only 34% (9/26) of the studies from Western countries (*Table 1*). Detection methodology other than direct sequencing might decrease the apparent mutation frequency of *RAS* mutation in Western countries. In contrast to *RAS* mutation, the detection method of *PAX8/PPARγ* rearrangement is generally limited; almost all the studies used either reverse-transcription PCR (RT-PCR) or fluorescence *in situ* hybridization (FISH). Dwight *et al.* (66) reported slightly higher detection rates with FISH while Klemke *et al.* (44) reported that RT-PCR could detect *PAX8/PPARγ* rearrangement better than FISH. There was not a large difference between RT-PCR and FISH for detecting *PAX8/PPARγ* rearrangement, although there were several discrepant results. Even though studies from Asian countries adopted both the FISH and RT-PCR methods,

the incidence of *PAX8/PPARγ* rearrangement is consistently low, ranging from 0 to 10%. Therefore, it seems that factors other than detection methodology must account for the difference between Asian and Western countries in the incidence of *PAX8/PPARγ* rearrangement in FTC.

There is a discussion as to the relationship between iodine intake and thyroid cancer. Iodine intake is considered a factor in the occurrence of thyroid cancers and also the manner of tumorigenesis itself. The association between a high BRAF mutation ratio in PTC and a high iodine intake has been investigated and involves some controversy: Guan *et al.* (86) reported that a high iodine intake increased the *BRAF* mutation in PTC in the Chinese population, whereas other studies showed no association between iodine intake and *BRAF* mutation in PTC (10,87). In FTC, the association between *RAS* mutation and iodine intake is also disputed. Some authors concluded that there was no association between the amount of iodine ingested and *RAS* mutation in FTC (10,88) while others reported a tendency for higher rates of RAS mutation with low iodine intake (11). At present, to the best of our knowledge, there are no reports that examined the association between *PAX8/PPARγ* rearrangement and iodine intake. The studies reporting on the frequency of *PAX8/PPARγ* in Asia are mainly from Japan and Korea where the iodine intake is high. Therefore, it is possible that the high incidence of *PAX8/PPARγ* rearrangement in this region is due to the large amount of iodine ingested. However, iodine intake alone cannot explain the wide range of frequencies among Western countries where most populations have average iodine intakes (89). Iodine intake does not appear to be a definitive factor for the incidence of *PAX8/PPARγ* rearrangement.

It is well documented that radiation exposure can induce thyroid cancer. The main risk factors for the development of thyroid cancer are the radiation dose and the age at exposure (90). Radiation exposure is also known to affect the mechanism of carcinogenesis of thyroid cancer by causing a specific type of genetic rearrangement (91). Specific fusion genes are associated with a particular histologic type of PTC. The solid variant of PTC often harbors *RET/PTC3* rearrangements while *RET/PTC1* rearrangements are associated with the classical type of PTC (92). The occurrence of *PAX8/PPARγ* rearrangement is also reported in radiation-induced PTCs (93). However, information on the association between genetic alterations in FTC and radiation exposure are limited mainly due to the low incidence of radiation-induced FTCs. Nikiforova *et al.* reported that radiation-induced FTC had higher rates

of *PAX8/PPARγ* rearrangement (3/3, 100%), although the non-radiation-induced counterparts also had a high incidence of the rearrangement (5/12, 42%) (18). Radiation exposure might increase the frequency of *PAX8/PPARγ* rearrangement in FTC, but the incidence of non-radiation-induced FTC in the USA is still high compared to Asian countries. We believe that radiation exposure does not explain the difference in *PAX8/PPARγ* rearrangement frequency in FTC between Asia and the West. Further studies from a novel point of view would be needed to explain this regional difference.

There are several limitations in our study. First, most of the studies we included are retrospective, which might cause some selection bias. Second, heterogeneity in sample preparation (FFPE *vs.* frozen tissue) might affect the included studies' results. In addition, we could not completely exclude the influence that detection methods might have had in finding the genetic mutations, although we performed a subgroup analysis to account for this. The mutation detection rates of the direct sequencing method might be affected by the institution and the technology available during the era the samples were tested. To overcome this limitation, we would need a large prospective study using consistent detection and sample preparation methods. Apart from the technical point of view, we must consider the influence of observer variation in the diagnosis. Follicular thyroid lesions with the fibrous capsule which include adenomatous goiter, follicular variant of PTC, FA, and FTC, often raise difficulties and discrepancy in diagnosis. Hirokawa *et al.* showed the difference in diagnostic criteria of these lesions between Japanese and American pathologists (94). Franc *et al.* reported the low diagnostic reproducibility of minimally invasive FTC (95). Generally, *PAX8/PPARγ* rearrangement and *RAS* mutation frequency in FTC is higher than FA (36% *vs.* 11% and 40% *vs.* 26%, respectively) (9,12). Therefore, potential histological heterogeneity of previously reported FTC cases might influence our result. Finally, we must note that prevalence of genetic events might depend on the actual prevalence of the cancer in the population. Currently, information is limited about the underlying factors that can cause FTC or induce the specific genetic alterations. A certain unknown factor in the region may contribute to the tumorigenesis of FTC and thereby increase the frequency of FTC with a specific genetic alteration. Uncovering all the factors that contribute to tumorigenesis in FTC would provide a better understanding of FTC patients' genetic background around the world.

In conclusion, our study highlights differences and similarities in the genetic backgrounds of Asian and Western countries to create a global map of *RAS* mutation and *PAX8/PPARγ* rearrangement. We further shed light on the lack of substantial data of genetic alteration in FTC within certain regions. Understanding the genetic information surrounding ethnical differences should improve the practice of clinical medicine in the future.

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Footnote

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