The Association of the BRAF V600E Mutation with Clinicopathologic Characteristics in Chinese Population with Conventional Papillary Thyroid Carcinoma

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Research

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Abstract

Objective:

The aim of the study is to evaluate the association of the BRAFV600E mutation with the clinicopathologic characteristics in Chinese population with papillary thyroid carcinoma (PTC).

Methods

A total of 943 PTC patients who underwent thyroidectomy from 2014 to 2016 at Henan Provincial People's Hospital were included in the present study. The *BRAF*^{V600E} mutation was examined in each resected specimen by quantitative Real-time PCR (qRT-PCR) technique.

Results

The PTC patients were subclassified into the overall, PTC>10mm and papillary thyroid microcarcinoma(PTMC) groups. The positive rate of *BRAF*^{V600E} mutation was 85.4% in Chinese patients with PTC. In both overall PTC and PTC> 10mm groups, the *BRAF*^{V600E} mutation was much more frequently detected in elderly patients and patients at T1 stage ($P< 0.05$). In addition, the positive rate of *BRAF*^{V600E} mutation was significantly higher in PTC patients without concomitant Hashimoto's thyroiditis in overall PTC and PTMC groups ($P< 0.05$). Furthermore, logistic regression analysis suggested that the risk of having a larger tumor diameter was increased by 6-fold when *BRAF*^{V600E} mutation in the PTMC group. No association between the *BRAF*^{V600E} mutation and other clinicopathologic factors was observed.

Conclusion

The *BRAF*^{V600E} mutation was significantly associated with patients age and T stage. Furthermore, the risk of having a larger tumor size was significantly increased when *BRAF*^{V600E} mutation in the PTMC group. which suggests that *BRAF*^{V600E} mutation might play an important role in the activation of early thyroid carcinogenesis, the effect might weaken in the progression of PTC.

Introduction

It is important to note that the global incidence of thyroid cancer has been rapidly increasing [1, 2], currently ranking ninth among all cancers. In addition, the global incidence rate of thyroid cancer in women is reported to be three times than that in men [2, 3]. Papillary thyroid carcinoma (PTC) is the main subtype of thyroid cancer, which accounts for 85%–90% with an early onset age [2, 3]. Although ultrasonography-guided fine-needle aspiration (US–FNA) biopsy is a standard technique for diagnosing thyroid malignancies measuring >1–1.5 cm, ~15%–25% of these malignancies are classified as indeterminate [4], and ~49% of PTCs measure ≤1 cm^2, which increases the difficulty in performing US–FNA biopsy. The World Health Organization defines tumors ≤1 cm in diameter as papillary thyroid microcarcinoma (PTMC) [5], which challenges the diagnosis of a US–FNA biopsy. The clinical significance of PTMC remains unclear, although previous reports have indicated that PTMC is related to distant metastasis, mortality, and recurrence [6]; therefore, early PTMC detection and a simultaneous estimation of its clinical significance are essential.

Several genetic biomarkers have been developed to assist in the pathological diagnosis of PTC. Because of its high prevalence and high specificity, *B-type Raf kinase* (*BRAF*)^{V600E} mutation was found to be the most important candidate biomarker for PTC diagnosis. The *BRAF*^{V600E} mutation abnormally activates the mitogen-activated protein kinase pathway and up-regulates cell proliferation and differentiation, eventually resulting in tumorigenesis [7-9]. The global prevalence of the *BRAF*^{V600E} mutation ranges from 33.2% to 69.7% [10-23] and is even higher (i.e., from 40.1% to 75.4%) in Chinese patients with PTC [24-30]. While some previous studies have indicated that the *BRAF*^{V600E} mutation might be associated with poor prognostic factors, such as extrathyroidal extension, lymph node metastasis, and advanced tumor stage [10-16, 25-29], other studies have not found any association between the mutation and these factors [17-22, 30]. The association between the *BRAF*^{V600E} mutation and specific clinicopathologic features of PTC remains controversial, and a research focus on the association of the mutation with PTMC has been rare.

In the present study, we aimed to analyze the status of the *BRAF*^{V600E} mutation in 943 patients with PTC and retrospectively examine its possible association with clinicopathologic risk factors.

Patients And Methods

Patients

All patients with PTC in the present study who underwent either total thyroidectomy or near-total thyroidectomy in Henan Provincial People's Hospital, China, between October 2014 and October 2016. In total, 943 patients were recruited for this study [men: 233, mean age(average ±standard deviation), 52.0±11.6 years; women: 710, mean age, 45.4±11.6 years]. All patients received surgical treatment without radioactive iodine^{131} therapy before the surgery. The patients were classified into three groups according to pathologic tumor diameter as follows: the overall PTC group, PTC >10 mm group and PTMC group.

Histopathologic examinations

Histopathlogic examinations of all patient tissue samples were performed by highly experienced pathologists blinded to *BRAF* status. Difficult cases were discussed and diagnosed by at least two pathologists. TNM stage was classified based on the 8th edition of the American Joint Committee on Cancer. The majority of patients with PTC (88.8%; 838/943) were diagnosed as having T1-stage tumors. Lymph node involvement was observed in 377 (54.1%; 459/848)

patents. Hashimoto's thyroiditis was confirmed based on the postoperative pathologic findings. The mean follow-up duration was 27 postoperative months (range= 11–44 months). At the time of follow-up, only two patients died (one patient of breast cancer and another of PTC recurrence).

Analyses of the *BRAF^{V600E}* mutation

Hematoxylin and eosin-stained slides were reviewed by experienced pathologists. The representative tumor areas were marked to guide microdissection. The tumor areas from 3–4 pieces of 5-μm-thick sections of paraffin-embedded tissues were dissected for DNA extraction. The process was performed using the Puregene Tissue Kit (Qiagen, Valencia, CA, USA), according to the manufacturer's instructions. The absorbance of the DNA samples was measured using a spectrophotometer, and only the A260/A280 values between 1.8 and 2.0 were accepted for the next step in the analysis. The extracted DNA was stored at −80°C until use. The status of the *BRAF^{V600E}* mutation in each sample was examined by qRT-PCR using the AmoyDx *BRAF^{V600E}* Mutation Detection Kit (Amoy Diagnostics, Xiamen, China), and the presence of the mutation was evaluated following the manufacturer's instructions. The sample was classified as mutation-positive when the cycle threshold (*Ct*) was <28 and as negative when *Ct* was ≥28.

Statistical analyses

All statistical analyses in present study were analyzed were conducted using SPSS v. 21 (IBM Corporation, Waltham, NY, USA). Discrete variables were presented as number and percentage. Chi-squared or Fisher's exact test was used for categorical variables when comparing frequencies between the groups. All numerical data are expressed as means ± standard deviations, and differences between the means were compared using Student *t*-test and an analysis of variance for continuous variables. All significant factors by univariate analyses were subjected to logistic regression analysis. A probability value of <0.05 was considered statistically significant.

Results

The frequency of the *BRAF^{V600E}* mutation in patients with PTC

Of the 943 patients with PTC, there were 570 (60.4%) PTMC patients and 373 (39.6%) patients with PTC >10 mm. The rate of the *BRAF^{V600E}* mutation in all patients with PTC was 85.4% (806/943) (Table 1). Although the incidence of the *BRAF^{V600E}* mutation in the PTMC group (86.8%; 495/570) was higher than that in the PTC >10 mm group (83.4%; 311/373), there was no significant difference between the two groups (*P* = 0.140; Table 1).

The association between the *BRAF^{V600E}* mutation and clinicopathologic characteristics is detailed in Table 1. The mean age of patients positive of *BRAF^{V600E}* mutation was (46.3±11.8) years, which was elder than patients negative of *BRAF^{V600E}* mutation, logistic regression analyses estimated that advanced age was an independent predictive factor for the *BRAF^{V600E}* mutation [*P*= 0.03; odds ration(OR)= 1.02; 95% confidence interval(CI)= 1.00–1.03] (Table 2). Furthermore, the *BRAF^{V600E}* mutation was more likely to be present in patients with T1-stage tumors [T1 vs. T2= 86.4% vs. 83.8%; *P*< 0.001; OR(95%CI) = 5.78(0.33–0.79); T1: vs. T3 = 86.4% vs. 60.0%; *P*= 0.005; OR(95%CI)= 4.40(1.55-12.45)]. Moreover, *BRAF^{V600E}* mutation was more frequent in patients without Hashimoto's thyroiditis [concomitant Hashimoto's thyroiditis vs. without concomitant Hashimoto's thyroiditis= 70.0% vs. 85.5%; *P* = 0.001; OR(95% CI)= 0.37(0.19–0.70)]. Although the *BRAF^{V600E}* mutation was statistically associated with tumor diameter (*P*= 0.04), logistic regression analysis found no significant difference. No significant differences were found between the status of *BRAF^{V600E}* mutation and the patient's sex, tumor multifocality, lymph node metastasis, or TNM stages.

Clinicopathologic characteristics in the PTC >10mm group

Similar to that in all patients with PTC, multiple logistic regression analysis suggested that the *BRAF^{V600E}* mutation was more common in elderly patients in the PTC>10mm group[(46.3±11.7) vs. (41.0±13.1); *P*= 0.002, OR(95%CI)= 1.04(1.02–1.06)] (Table 2). Furthermore, the *BRAF^{V600E}* mutation was inclined to be positive in T1 stage cancer[T1 vs. T2= 85.4% vs. 83.8%; *P*< 0.001; OR(95%CI) = 5.91(2.23–15.67); T1 vs. T3= 85.4% vs. 60.0%; *P*=0.005; OR(95%CI)= 4.90(1.63-14.75)]. Although the *BRAF^{V600E}* mutation was statistically associated with a large tumor diameter and more lesions in the PTC >10mm group(*P*< 0.05)(Table 1), logistic regression analysis found no significant differences (Table 2). There were also no significant differences in the *BRAF^{V600E}* mutation status among other clinicopathologic characteristics in the PTC >10mm group.

Clinicopathologic characteristics in the PTMC group

In the PTMC group, *BRAF^{V600E}* mutation-positive patients had a larger tumor diameter than that *BRAF^{V600E}* mutation-negative patients [(6.3± 2.3) vs. (5.1± 2.4) mm, *P*< 0.001] (Table 1), logistic regression analysis suggested that the risk of having a larger tumor diameter was increased by 6-fold when *BRAF^{V600E}* mutation in the PTMC group (*P*= 0.001; OR= 6.26, 95% CI= 2.12–20.13) (Table 2). Similar to the PTC group patients, the positive rate of *BRAF^{V600E}* mutation in PTMC group patients without Hashimoto's thyroiditis was 87.9% (470/525), which was significantly higher than that in patients concomitant with Hashimoto's thyroiditis(71.4%, 25/35)[(*P*= 0.03, OR(95%CI)= 0.41(0.18–0.92)] (Table 1). No significant differences were found between the *BRAF^{V600E}* mutation status and age, tumor multifocality, lymph node metastasis, or TNM stages.

Discussion

The present study showed an 85.4% frequency rate of the *BRAF^{V600E}* mutation in conventional PTC, the proportion was slightly higher in the PTMC group. Previous studies have shown that the *BRAF^{V600E}* mutation is common in PTC patients, the overall prevalence varying from 40.1% to 76.52% in Chinese

patients with PTC [24-30] and from 33.2% to 70% in Western countries [11-23]. The possible reasons for the variation in positive mutation rates are PTC subtype, geographic region, ethnicity, and technical differences for *BRAF*^{V600E} examination.

The present study showed that the *BRAF*^{V600E} mutation was much more frequent in elderly patients in both the overall PTC group and PTC>10 mm group. Previous studies have also revealed an association between the *BRAF*^{V600E} mutation and elderly patients [23, 27, 28]. The youngest patients in our cohort were 15 years of age. The positive rate of the *BRAF*^{V600E} mutation was 60% (3/5) in patients <20 years of age, and it is interesting that this rate increased to more than 80% in those aged ≥20 years. The possible reason for this phenomenon is that the *BRAF*^{V600E} mutation might occur early in thyroid carcinogenesis, in addition, the effect might become more remarkable along with the development and progress of PTC. However, no such relationship was noted in the results of other studies [24, 25, 29].

Furthermore, in the present study, the *BRAF*^{V600E} mutation was more likely to be present in patients with a T1-stage tumor than in those with a T2- or T3-stage tumor in both overall and PTC >10 mm groups. This phenomenon also indicates that PTC patients having the *BRAF*^{V600E} mutation might be susceptible to an early T stage, and that the mutation might play an important role in the early stages of PTC, but it might also slow PTC progression; however, no significant difference was found among TNM stages, perhaps because all patients enrolled in the present study were in the early stages of the cancer (0 and 1). Previous studies have also found no relationship between the *BRAF*^{V600E} mutation and TNM stage [27-30].

Moreover, our data showed that the risk of having a large tumor was increased about 6-fold when *BRAF*^{V600E} mutation in the PTMC group, however, no influence was found in the PTC>10 mm group. This occurrence also indicated that the *BRAF*^{V600E} mutation might be an initiating factor in PTC; however, the probable effect decreased along withing. The reported studies have found no association between the mutation and tumor in PTMC [19, 29].

In addition, our results showed that the *BRAF*^{V600E} mutation was more frequent in PTC patients without concomitant Hashimoto's thyroiditis in both overall PTC and PTMC groups. The meta-analysis also suggested that patients negative for the *BRAF*^{V600E} mutation were significantly more likely to have Hashimoto's thyroiditis [22]. Other previous studies found no association between *BRAF*^{V600E} mutation and PTC concomitant Hashimoto's thyroiditis [17-22]. The possible reason of such a discrepancy might be the result of the study population that was different between our study and the above-mentioned study.

There was no relationship between the *BRAF*^{V600E} mutation and both lymph node metastasis and tumor stage in patients with PTC in the present study. Similar phenomena were also reported in previous studies [17-22, 30]; however, several studies have reported that the high-risk clinicopathologic parameters, such as lymph node metastasis and tumor stage, were associated with the *BRAF*^{V600E} mutation [10-16, 25-29]. The inconsistent results might be because of the following factors: geography or ethnicity, sample size, tumor subtypes, or the method used to test the *BRAF*^{V600E} mutation. In addition, 88.5% of patients with PTC (838/947) enrolled in the present study were at early stages of the disease, limiting the effect of the *BRAF*^{V600E} mutation on progressive clinical characteristics.

The results of our study found no association between the *BRAF*^{V600E} mutation and disease-free survival. Similar results were found in studies on both Korean and Japanese populations [10, 13, 20]; however, the *BRAF*^{V600E} mutation was reported as an independent prognostic factor in patients with PTC [19, 24]. Numerous reports have indicated that the *BRAF*^{V600E} mutation is associated with disease-free survival even in patients in the early stages of the disease [25-28]. The discrepancy among the results of the published studies might be associated with sample size, geographic and ethnic differences, duration of follow-up, and treatment regimen. Most patients with PTC are diagnosed at early stages of the disease and have a low mortality rate. Majority of the patients enrolled in the present study were at T1 or T2 stage at the time of diagnosis. The intensive initial treatment might be a potential reason for finding no association between the *BRAF*^{V600E} mutation and the disease because patients received all scheduled treatments [13, 30].

Strengths of the present study. Firstly, we analyzed the relationship between *BRAF*^{V600E} mutation and clinicopathological features in both PTMC and PTC> 10mm groups and found that there were different features in each group. Secondly, subjects enrolled in the present study were only conventional PTC to exclude heterogeneity and variations in tumor subtypes. Limitation of our study. Majority of patients enrolled in the present study were at T1or T2 stage when diagnosis and the limited time of follow-up were constrict the effect of clarifying the relationship of *BRAF*^{V600E} mutation and prognosis.

Conclusions

This study found that an 85.4% frequency in the *BRAF*^{V600E} mutation in patients with PTC. The *BRAF*^{V600E} mutation was associated with elderly patients and early tumor T stages in both overall PTC group and PTC >10 mm groupF, *BRAF*^{V600E} mutation was also related to the large tumor diameter in the PTMC group patients. which suggests that *BRAF*^{V600E} mutation might play an important role in the activation of early thyroid carcinogenesis, the effect might weaken in the progression of PTC.

Abbreviations

PTC: Papillary thyroid carcinoma; US–FNA: Ultrasonography-guided fine-needle aspiration; PTMC: Papillary thyroid microcarcinoma; *BRAF: B-type Raf kinase*

Declarations

Authors' Contributions SLZ and LFK conceived of the study, participated in the design of the study and drafted the manuscript. YPG, LZ and YWZ participated in pathological finding analysis. TD and ZGX carried out *BRAF*^{V600E} mutation examination. CD and WCS performed the statistical analysis and clinical data collection. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was reviewed and approved by the Declaration of Helsinki and the Institute Research Ethics Committee of Henan Provincial People's Hospital. Written informed consent was obtained from all patients included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Association between the *BRAF*^{V600E} mutation and clinicopathologic characteristics of 943 patients with PTC.

Clinico pathologic characteristics	Overall PTC (n= 943)						PTC > 10 mm (n= 373)						PTMC (n= 570)		
	Total	Positive(n=806)		Negative(n= 137)		*P*	Total	Positive (n=311)		Negative (n=62)		*P*	Total	Positive (n=495)	
	N	n	(%)	n	(%)			N	(%)	n	(%)		N	n	(%)
Sex															
Male	233	199	(85.4)	34	(14.6)	0.974	107	86	(80.4)	21	(19.6)	0.323	126	113	(89
Female	710	607	(85.5)	103	(14.5)		266	225	(84.6)	41	(15.4)		444	382	(86
Age (years) *	943	(46.3 ± 11.8)		(44.0 ± 11.85)		**0.03**	373	(46.3 ± 11.7)		(41.0 ± 13.1)		**0.001**	570	(46.2 ± 10	
Tumor diameter (mm) *	943	(1.13 ± 0.88)		(1.31 ± 1.22)		**0.04**	373	(1.94 ± 0.92)		(2.29 ± 1.21)		**0.04**	570	(0.63 ± 0.2	
Lesion number*	943	(1.37 ± 0.69)		(1.26 ± 0.60)		0.09	373	(1.45 ± 0.78)		(1.24 ± 0.56)		**0.01**	570	(1.32 ± 0.6	
Hashimoto's thyroiditis															
Yes	50	35	(70)	15	(30)	**0.001**	15	10	(66.7)	5	(33.3)	0.07	35	25	(71
No	893	771	(85.5)	122	(14.5)		358	301	(84.1)	57	(15.9)		525	470	(87
Lymph node metastasis															
Yes	510	443	(86.9)	67	(13.1)	0.396	275	229	(83.3)	46	(16.7)	0.121	231	211	(91
No	433	384	(88.7)	49	(11.3)		98	88	(89.8)	10	(10.2)		339	299	(88
T staging															
T1	838	724	(86.4)	114	(13.6)	**0.001**	268	229	(85.4)	39	(14.6)	**0.005**	570	495	(86
T2	80	67	(83.8)	13	(16.3)		80	67	(83.8)	13	(16.3)		——	——	——
T3	25	15	(60.0)	10	(40.0)		25	15	(60.0)	10	(40.0)		——	——	——
Tumor staging															
0	856	728	(85.0)	128	(15.0)	0.245	320	262	(81.9)	58	(18.1)	0.055	536	466	(86
I	87	78	(89.7)	9	(10.3)		53	49	(92.5)	4	(7.5)		34	29	(85

Abbreviations: PTMC, papillary thyroid microcarcinoma; PTC, papillary thyroid carcinoma; LNM, lymph node metastasis.

*Numbers are presented as mean ± standard deviation.

Table 2. Multivariate analysis of the association of the *BRAF*^{V600E} mutation with clinicopathologic characteristics in papillary thyroid carcinoma patients.

	Overall		PTC > 10 mm		PTMC	
	P	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)
Age (years)	**0.03**	**1.02 (1.00–1.03)**	**0.002**	**1.04 (1.02–1.06)**	0.805	––
Tumor diameter (mm)	0.417	––	0.756	––	**0.001**	**6.53 (2.12–20.13)**
Hashimoto's thyroiditis	**0.001**	**0.35 (0.18–0.67)**	0.07	––	**0.03**	**0.41(0.18–0.92)**
T stage						
T1						
T2	**<0.001**	**5.78 (2.43–13.80)**	**<0.001**	**5.91 (2.23–15.67)**	––	––
T3	**0.005**	**4.40 (1.55–12.45)**	**0.005**	**4.90 (1.63–14.75)**	––	––

Notes: OR (95% CI) = Odds ratio (95% confidence interval).