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Expression of WD Repeat Domain 5 (WDR5) is Associated with Progression and Reduced Prognosis in Papillary Thyroid Carcinoma

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Background: The WD repeat domain 5 (WDR5) is an essential component of methyltransferase complexes. The expression of WDR5 has been reported in several types of malignancy. This study aimed to investigate the expression of the WDR5 gene and protein in a human papillary carcinoma cell line *in vitro*, including the use WDR5 gene silencing, and the expression of the WDR5 protein in papillary thyroid carcinoma tissue, and clinicopathological characteristics including overall survival (OS).


Material/Methods: The role of WDR5 in proliferation and migration of the human papillary thyroid carcinoma cell line, KTC-1, was investigated using the cell counting kit-8 (CCK-8) assay and transwell assay after silencing WDR5 expression. Expression levels of WDR5 in 84 patients with papillary thyroid carcinoma were detected using immunohistochemistry. The correlation between WDR5 expression and clinicopathological features was analyzed using the chi-squared test. The prognostic role of WDR5 was evaluated by univariate analysis with the log-rank test, and by multivariate analysis with the Cox regression model.

Results: WDR5 expression promoted the proliferation and migration of the KTC-1 cells. In tumor tissue from patients with papillary thyroid carcinoma, low expression and high expression levels of WDR5 were found in 72.6% and 27.4%, respectively. Increased expression of WDR5 was significantly associated with lymphatic invasion and reduced survival rates. WDR5 expression was an independent negative prognostic biomarker.

Conclusions: Expression of WDR5 promoted cell proliferation and migration *in vitro* and was associated with reduced prognosis in patients with papillary thyroid carcinoma.

MeSH Keywords: **Biological Markers • Cell Proliferation • Neoplasm Invasiveness • Prognosis • Thyroid Neoplasms**

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Background

Worldwide, the incidence of thyroid cancer has been increasing, and at a more rapid rate than can be explained solely by improved methods in diagnosis [1,2]. In the United States, between 1988 to 2005, there were 30,766 cases new cases of thyroid cancer, with the incidence in women shown to increase from 6.4 per 100,000 population in 1988 to 14.9 per 100,000 population in 2005, and the incidence in men increased from 2.5 per 100,000 population in 1988 to 5.1 per 100,000 population in 2005 [3].

Most patients with thyroid cancer have a favorable outcome due to modern comprehensive treatments that include surgery, the use of radioactive iodine (RAI) thyroid ablation, and thyroid stimulating hormone (TSH) suppression [3,4]. Thyroid cancer can be classified by histopathology into papillary thyroid carcinoma, follicular thyroid carcinoma, medullary carcinoma, Hürthle cell carcinoma, and anaplastic carcinoma [5]. Papillary thyroid carcinoma accounts for more than 85% of all types of thyroid cancer [6]. The overall 5-year survival for patients with early-stage papillary thyroid carcinoma is almost 100% [7]. However, a proportion of patients suffer from aggressive disease or recurrence, and the therapeutic options for patients with more aggressive tumors are limited.

WD repeat domain 5 (WDR5) is an essential component of H3K4 methyltransferase complex that regulates cell polarity, nuclear deformability and cell migration [8]. WDR5 is one of several histone H3 lysine 4 (H3K4) methyltransferase (H3K4MT) complexes, that also includes ASH2L, RbBP5, and mDPY-30 [9]. As a chromatin-regulatory scaffold protein, the overexpression of WDR5 has been demonstrated in several types of human malignancy, including neuroblastoma, breast cancer, bladder cancer, pancreatic and colorectal cancers [10,11]. However, the expression and role of the WDR5 gene in the progression and prognosis of thyroid cancer remain unknown.

Therefore, this study aimed to investigate the expression of the WDR5 gene and protein in a human papillary carcinoma cell line *in vitro*, including the use WDR5 gene silencing, and the expression of the WDR5 protein in papillary thyroid carcinoma tissue, and to investigate the association with clinicopathological characteristics including overall survival (OS).

Material and Methods

Patients

From 125 patients with a diagnosis of papillary thyroid carcinoma confirmed by histopathology who underwent radical surgical resection at Yidu Central Hospital from 2010 to 2012,

84 patients were included in this retrospective study. The study inclusion criteria were adequate tissue available for immunohistochemistry, the use of standard adjuvant therapy if required, and no other history of malignancy. The study protocol was reviewed and approved by the Ethics Committee of Yidu Central Hospital of Weifang. All surgical procedures and all tissue specimens were provided following informed patient consent. The tumor TNM stage in each case was determined according to the guidelines of the Seventh American Joint Committee on Cancer and Union for International Cancer Control (AJCC/UICC) staging system [12].

Cell culture and WDR5 gene silencing

The KTC-1 human papillary thyroid carcinoma cell line was purchased from the Cell Bank of Chinese Academy of Sciences (Shanghai, China), and cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) in 5% CO₂ at 37°C.

WDR5 gene silencing was investigated using small interfering RNA (siRNA) (Santa Cruz Biotechnology, Santa Cruz, CA, USA), with a scrambled RNA sequence used as a control. The transfection of siRNA was performed with Lipofectamine 2000 (ThermoFisher Scientific, Waltham, MA, USA), according to the manufacturer's instructions. At 48 hours after transfection, the effects of gene silencing on the expression of WDR5 was studied using Western blot.

Immunohistochemistry for WDR5

Formalin-fixed, paraffin-embedded papillary thyroid carcinoma tissues were deparaffinized and dehydrated with graded ethanol and xylene. Endogenous peroxidase was blocked with 3.0% H₂O₂. Citric acid buffer (pH, 6.0) was used for optimal antigen retrieval, and the tissue sections were incubated in 5% bovine serum albumin (BSA) to block nonspecific antibody binding. The primary mouse polyclonal antibody to human WDR5 (Catalog No. AF5810) (recommended concentration, 5–15 µg/mL) (R&D Systems, Minneapolis, MN, USA) was incubated on the tissue sections at 4°C overnight. The horseradish peroxidase (HRP)-conjugated secondary biotinylated antibody was incubated on the tissue section at room temperature for one hour. The brown chromogen, 3,3'-diaminobenzidine (DAB) was used for antigen visualization. The negative control included substitution with phosphate-buffered saline (PBS) for the primary antibody.

The results of immunohistochemistry were evaluated by two senior pathologists using a semi-qualitative scoring system, as previously described [13]. The immunohistochemistry scoring system had two components, the percentage of positively stained cells, and the staining intensity score. The percentage of positive cells were given the following scores: 0, <10% positive;

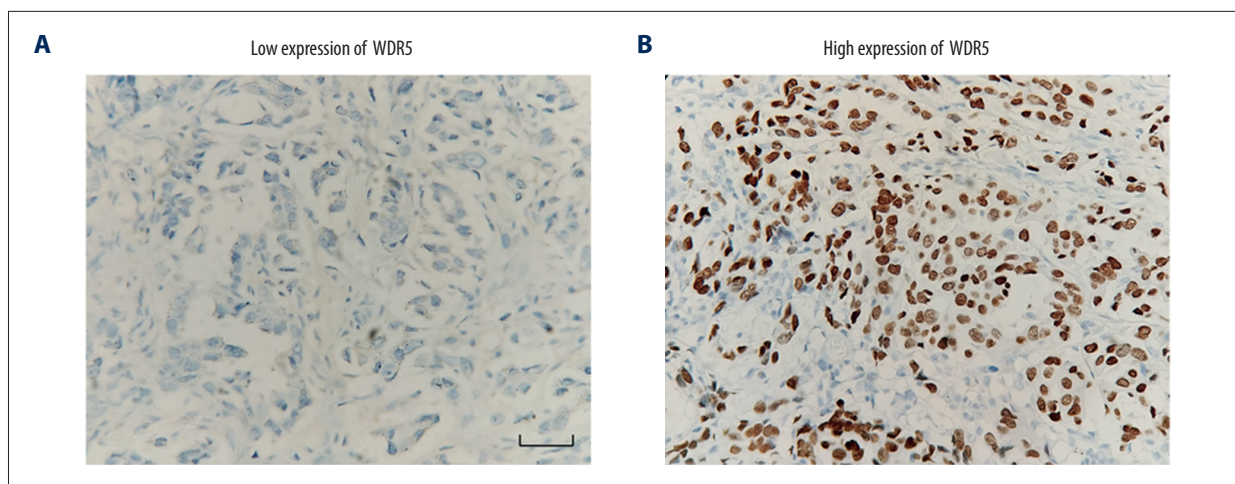


Figure 1. Photomicrographs of the immunohistochemistry show the expression of WDR5 in papillary thyroid carcinoma tissue. The patients with papillary thyroid carcinoma were classified into groups with low expression (A) and high expression (B) of WDR5 using immunohistochemistry. Representative images of low (A) expression and high (B) expression of WDR5 are shown. Scale bar: 50 μ m.

1, 10–30% positive; 2, 30–50% positive; and 3, >50% positive cells. The immunostaining was given the following scores: 0, negative staining; 1, weak staining; 2, moderate staining; and 3, strong staining. The final immunohistochemistry scores were equal to the sum of the two scores, for the percentage of positively immunostained cells and cell immunostaining intensity, and ranged from 0–9. The study cohort was classified into subgroups with different WDR5 expression according to the cut-off, which was established using the receiver operating characteristic (ROC) curve, as previously described [14].

Cell proliferation assay

Cell proliferation of the KTC-1 human papillary thyroid carcinoma cells was evaluated using the cell counting kit-8 (CCK-8) assay (Dojindo, Kumamoto, Japan) following silencing WDR5 expression, as previously reported [15,16]. Briefly, KTC-1 cells were transfected with scrambled short-interfering RNA (siRNA) and siWDR5. Then, 24 hours following the transfection, the KTC-1 cells were cultured in a 96-well plate at the density of 4×10^3 cells/well. After cell culture 1, 2, and 3 days, 10 μ l of CCK-8 reagent was added to each well and incubated for 3 hours. The optical density (OD) of each well was measured at 450 nm with a microplate reader. Data were obtained from experiments performed in triplicate. Cell proliferation was determined by calculating the proliferation ratio of the OD₄₅₀ between the control groups and the study groups.

Cell migration assay

Cell migration of the KTC-1 cells was evaluated with the Matrigel transwell assay using a pre-coated transwell chamber (BD Biosciences, San Jose, CA, USA) after silencing WDR5

gene expression, as previously described [13]. Briefly, KTC-1 cells were transfected with scrambled siRNA and siWDR5 to silence WDR5 gene expression. Then, 5×10^4 cells were seeded into the upper chamber with 20% FBS in the lower chamber as a chemoattractant. After 24 hours, the cells in the upper chamber were gently removed and the cells in the lower chamber were fixed and stained with 0.5% crystal violet. Cells were counted under a microscope in at least five random visual fields and data were obtained from three independent experiments.

Statistical analysis

Data were analyzed using SPSS software (Chicago, IL, USA). Correlation between WDR5 expression and patient clinical parameters was calculated using the chi-squared (χ^2) test. Univariate survival analysis was performed using the Kaplan-Meier method and the log-rank test. The Cox regression model was used to determine the role of WDR5 as an independent prognostic marker. Statistical differences in cell proliferation and migration were analyzed with Student's t-test. $P < 0.05$ was considered as statistically significant.

Results

Expression of WDR5 in papillary thyroid carcinoma

The expression of WDR5 in papillary thyroid carcinoma was evaluated with immunohistochemistry. A total of 84 patients were classified into subgroups with different WDR5 expression (Figure 1A, 1B). Low and high expression of WDR5 determined by immunohistochemistry was found in 72.6% and 27.4% of cases, respectively (Table 1). In most cases of papillary thyroid

Table 1. Clinicopathological and demographic data of the patients with papillary thyroid carcinoma.

Factor	Number	Percentage
Gender		
Female	52	61.9%
Male	32	38.1%
Age		
<45 yrs	29	34.5%
≥45 yrs	55	65.5%
Tumor size (cm)		
≤2	32	38.1%
>2	52	61.9%
Tumor number		
Single	70	83.3%
Multiple	14	16.7%
Differentiation (grade)		
Good	39	46.4%
Moderate	30	35.7%
Poor	15	17.9%
Site		
Left	32	38.1%
Right	36	42.9%
Left+right	16	19.0%
T-stage		
I	33	39.3%
II	36	42.9%
III+IV	5	6.0%
N stage		
N0	49	58.3%
N1	35	41.7%
TNM stage		
I	48	57.1%
II	14	16.7%
III+IV	22	26.2%
WDR5 expression		
Low	61	72.6%
High	23	27.4%

Table 2. Correlations between WDR5 gene expression and clinicopathological factors in patients with papillary thyroid carcinoma.

Factors	WDR5 expression		P-value*
	Low	High	
Gender			
Female	38	14	0.905
Male	23	9	
Age			
<45 yrs	20	9	0.614
≥45 yrs	41	14	
Tumor size (cm)			
≤2	24	8	0.804
>2	37	15	
Tumor number			
Single	51	19	0.913
Multiple	10	4	
Differentiation (grade)			
Good	30	9	0.637
Moderate	20	10	
Poor	11	4	
Site			
Left	26	6	0.637
Right	24	12	
Left+right	11	5	
T-stage			
I	23	10	0.360
II	26	10	
III+IV	2	3	
N stage			
N0	36	13	0.007
N1	15	20	
TNM stage			
I	38	10	0.383
II	8	6	
III+IV	15	7	

* Calculated with the chi-squared test.

Table 3. Prognostic significance of WDR5 in parathyroid carcinoma evaluated with univariate and multivariate analysis.

Factor	5-year OS	P-value*	HR	95% CI	P-value#
Gender					
Female	91.0	0.409			
Male	93.1				
Age					
<45 yrs	88.3	0.475			
≥45 yrs	89.7				
Tumor size (cm)					
≤2	94.4	0.777			
>2	91.2				
Tumor number					
Single	93.3	0.477			
Multiple	88.9				
Differentiation					
Good	93.6	0.162	1		
Moderate+poor	91.4		2.29	0.33–15.9	0.402
Site					
Left	92.8	0.889			
Right	87.6				
Left+right	88.9				
T stage					
I	86.5	0.124	1		
II–IV	85.5		2.70	0.48–15.1	0.258
N stage					
N0	88.9	0.017	1		
N1	84.0		7.98	0.99–64.0	0.049
TNM stage					
I	93.0	0.161			
II	100				
III+IV	85.3				
WDR5					
Low	100.0	0.001	1		
High	76.2		6.89	1.70–27.9	0.007

* Calculated with the log-rank test. # Calculated with the Cox regression model. OS – overall survival; CI – confidence interval; HR – hazard ratio.

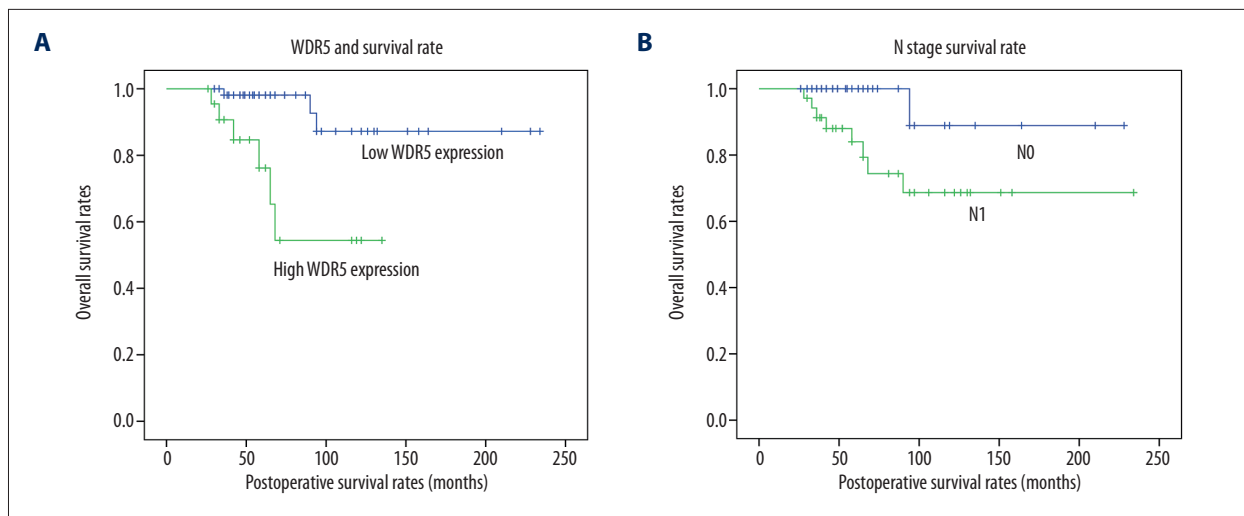


Figure 2. The correlation between WDR5 expression, N stage, and overall survival (OS) rates. The overall survival (OS) rates of patients with papillary thyroid carcinoma were stratified by WDR5 expression (A) and N stage (B), and were analyzed using with Kaplan-Meier method. Patients with high expression of WDR5 and positive N stage had poorer prognosis, or reduced OS.

carcinoma, the cellular expression of WDR5 was mainly in the cell nucleus, which was consistent with its function as a component of the H3K4 methyltransferase complex.

WDR5 was associated with lymphatic invasion in patient tissue samples of papillary thyroid carcinoma

The clinical significance of WDR5 was first evaluated by analyzing its correlation with clinicopathological factors including gender, age, tumor size, tumor number, differentiation, tumor site, T stage, N stage and TNM stage. WDR5 expression was significantly associated with lymphatic invasion ($P=0.007$) (Table 2). Patients with high WDR5 expression had a significantly increased risk of lymphatic invasion, indicating that WDR5 may be involved in the invasion and metastasis of papillary thyroid carcinoma.

The prognostic role of WDR5 in papillary thyroid carcinoma

The prognostic role of WDR5 was evaluated with univariate and multivariate analysis, respectively (Table 3). All clinicopathological factors were included in the univariate analysis, initially to estimate their correlation with overall survival (OS) rates. WDR5 expression was associated with significantly reduced prognosis in patients with papillary thyroid carcinoma ($P=0.001$). The 5-year OS rates for patients with low and high WDR5 expression were 100% and 76.2%, respectively. High expression of WDR5 significantly predicted reduced prognosis in patients with papillary thyroid carcinoma (Figure 2A). The presence of lymphatic invasion was also a prognostic factor in papillary thyroid carcinoma ($P=0.017$). The 5-year OS rates

of patients with N0 stage and N1 stage tumors were 88.9% and 84.0%, respectively (Figure 2B).

The clinicopathological risk with a P -value <0.20 were selected into the Cox regression model for multivariate analysis, including for WDR5 expression, lymphatic invasion, T stage, and tumor differentiation (grade). In multivariate analysis, WDR5 expression was identified as an independent risk factor in papillary thyroid carcinoma ($HR=6.89$; $P=0.007$). Also, positive lymphatic invasion was an independent prognostic factor for patients with papillary thyroid carcinoma ($HR=7.98$; $P=0.049$). These results indicated that WDR5 expression was predictive for prognosis in papillary thyroid carcinoma, and indicated that detection of WDR5 using immunohistochemistry might help to stratify patients with papillary thyroid carcinoma at high-risk and might guide individual patient treatment.

WDR5 promoted the progression of papillary thyroid carcinoma cells

The expression of WDR5 in the papillary thyroid carcinoma cell line KTC-1 was silenced with small-interfering RNA (siRNA) transfection (Figure 3A). Two independent siRNAs were used in case of off-target effect, with a scrambled siRNA sequence as the negative control. The proliferation of KTC-1 cells was detected with cell counting kit-8 (CCK-8) assay after successful silencing of WDR5 expression. WDR5 gene silencing significantly reduced the proliferation of KTC-1 cells (Figure 3B), indicating that WDR5 was required in papillary thyroid carcinoma cell proliferation. Using the chi-squared test, WDR5 expression was shown to be significantly associated with lymphatic invasion in tissue sections. Therefore, cell migration of KTC-1 cells was assessed with the transwell assay, which

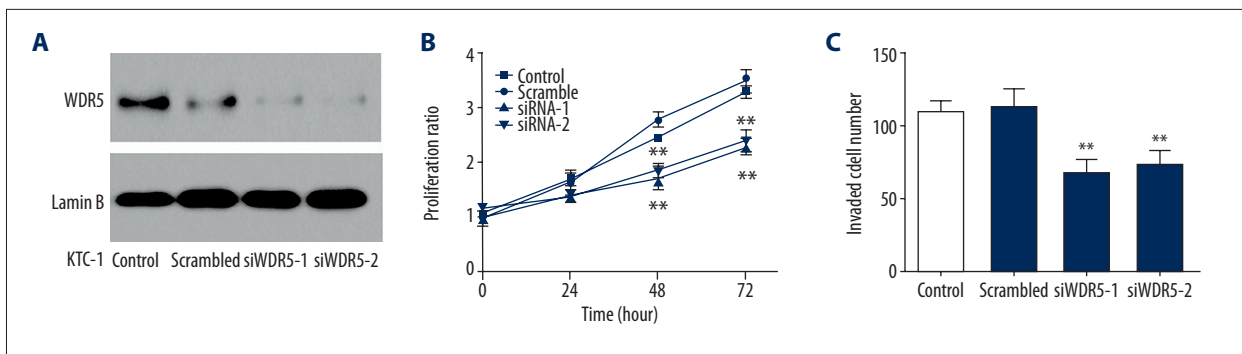


Figure 3. WDR5 expression was required for cell proliferation and migration of KTC-1 papillary thyroid carcinoma cells *in vitro*, as shown by the use of small interfering RNA (siRNA). **(A)** Expression of WDR5 in KTC-1 human papillary thyroid carcinoma cells was silenced with two independent small interfering RNAs (siRNAs) of WDR5. **(B)** Silencing of WDR5 significantly reduced the proliferation of KTC-1 human papillary thyroid carcinoma cells. **(C)** Silencing of WDR5 significantly reduced cell migration of KTC-1 human papillary thyroid carcinoma cells.

showed that silencing the WDR5 with siRNAs significantly reduced migration of KTC-1 cells (Figure 3C). These findings supported that WDR5 also had a role in cell migration of papillary thyroid carcinoma cells *in vitro*, which may reflect the invasive properties of the malignant cells *in vivo*.

Discussion

Worldwide, the incidence, morbidity, and mortality from thyroid cancer is increasing more rapidly compared with many other types of malignancy [17]. Technological innovations such as second-generation gene sequencing can help to identify gene alterations in thyroid cancer. Also, new biomarkers and drug targets have been identified, including vandetanib and cabozantinib that have been approved for the treatment of medullary thyroid cancer, while sorafenib and lenvatinib are now used in the treatment of radioactive iodine-refractory differentiated thyroid cancer in both the USA and Europe [18]. Several phase 2 and phase 3 randomized clinical trials are currently ongoing to develop targeted drug therapy of thyroid cancer. However, the most well-recognized biomarkers in thyroid cancer do not include those for papillary thyroid carcinoma. For example, PAX-8–PPAR was identified as a candidate target in follicular thyroid carcinoma [19], and RET is an established biomarker in medullary thyroid cancer [20]. Targeted therapy for papillary thyroid carcinoma has attracted less research attention compared with other types of thyroid cancer, and the therapeutic options for patients with advanced-stage papillary thyroid carcinoma remain limited.

The incidence of papillary thyroid carcinoma is relatively high in China, but studies of predictive or prognostic biomarkers remain limited, in part due to the lack of available tumor tissue for immunohistochemistry. In the present study, tissue samples were obtained from 84 patients with papillary thyroid

carcinoma, which was not a large cohort. The WD repeat domain 5 (WDR5) is an essential component of methyltransferase complexes. In this study, there was a significant association between the expression of WDR5 and prognosis in papillary thyroid carcinoma, and this was the first study to report this finding. The results of the present study support the need for future prospective controlled studies to investigate the clinical significance of WDR5 expression and its role as a potential prognostic marker. Further studies are also required to investigate the underlying mechanism of the oncogenic role of WDR5.

Histone methylation is an important post-translational modification involved in several cellular processes, including chromatin formation, translational regulation, and repair of DNA damage [21]. As an essential component of H3K4 methyltransferase complexes, the oncogenic role of WDR5 has been shown in several types of malignancy, including gastric cancer, prostate cancer, and neuroblastoma [10,22,23]. WDR5 has been regarded as a potential epigenetic drug target for the treatment of mixed-lineage leukemia [24]. The findings of the present study were the first to demonstrate that WDR5 was associated with lymphatic invasion in papillary thyroid carcinoma and that WDR5 was a marker of prognosis in patients with papillary thyroid carcinoma. This result has clinical significance because there are now several small molecule inhibitors of WDR5 used in both *in vitro* and *in vivo* studies, including OICR-9429 [25]. There are also more specific emerging inhibitors of WDR5 with a higher IC_{50} that have been recently developed [26]. The available targeted drugs for patients with advanced-stage papillary thyroid carcinoma remain limited. The findings from the present study showed that WDR5 may be a potential drug target for advanced papillary thyroid carcinoma.

The findings of the present study showed that WDR5 promoted cell proliferation and migration of papillary thyroid carcinoma cells *in vitro*. As a component of H3K4 methyltransferase

complexes, it is likely that WDR5 was required for cell proliferation of papillary thyroid carcinoma cells, but the association between WDR5 and tumor invasion requires support with further studies. Several previous studies have attempted to identify the underlying mechanisms involved in the role of WDR5 in cancer progression. It was recently reported that the recognition of target genes by MYC were dependent on its interaction with WDR5 [27]. The MYC oncogenes encode a family of related transcription factors involved in the progression of several types of malignancy [28]. The findings from these previous studies might explain why silencing WDR5 gene expression significantly reduced cell migration of papillary thyroid carcinoma cells *in vitro* in the present study. Also, WDR5 has previously been shown to bind with TWIST1, and WDR5 was required for TWIST1-induced upregulation of HOXA9 and aggressive cell phenotypes associated with tumor invasion [23]. Also, recent studies have shown that WDR5 modulated cell motility and cell morphology by affecting nuclear morphology [29]. The methods used in these previous studies remain to be applied to investigate papillary thyroid carcinoma. It is hoped that the findings from the present study might focus attention on the role of WDR5 in papillary thyroid carcinoma and lead to further future studies to determine the mechanisms underlying its role in oncogenesis.

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Conclusions

The findings of this study showed that the expression of WDR5 was an independent prognostic biomarker in patients with papillary thyroid carcinoma. An *in vitro* studied supported that WDR5 expression was associated with the proliferation and migration of papillary thyroid carcinoma cells. The findings from this study support the need for further studies to investigate the mechanisms involved in the expression of WDR5 and its potential clinical role as a prognostic biomarker in patients with papillary thyroid carcinoma.

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Conflict of interest

None.

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