Original Article

Prognostic and clinical significance of HOXC9 and HOXD10 in papillary thyroid cancer

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Background: The homebox superfamily play an important role in tumorigenesis. HOXC9 and HOXD10 were reported playing critical roles in tumor progression in many malignant tumors. This study aimed to research the expression of HOXC9 and HOXD10 in papillary thyroid cancer, and to verify the prognostic and clinical significance of HOXC9 and HOXD10.

Methods: Immunohistochemistry was used to determine the expression of HOXC9 and HOXD10 in 98 pairs of papillary thyroid cancer and paracancer tissues. Clinicopathologic data were collected and analyzed to verify the prognostic and clinical significance of HOXC9 and HOXD10.

Results: The expression of HOXC9 and HOXD10 decreased in papillary thyroid cancer. The low expression of HOXC9 was associated with Hashimoto's thyroiditis and lymph node metastasis ($P<0.05$). The low expression of HOXD10 was associated with extrathyroidal extension and lymph node metastasis ($P<0.05$). The co-expression rates of HOXC9 and HOXD10 was 44.90%. The low expression of both HOXC9 and HOXD10 was associated with lymph node metastasis ($P<0.05$).

Conclusions: The expression of HOXC9 and HOXD10 was downregulated in papillary thyroid cancer. Low expression of HOXC9 and HOXD10 might be related to the malignancy of papillary thyroid cancer. HOXC9 and HOXD10 may be used as diagnostic and prognostic biomarkers in the future.

Keywords: Papillary thyroid cancer (PTC); HOXC9; HOXD10; clinical significance

Submitted Mar 01, 2021. Accepted for publication Mar 24, 2021.
doi: 10.21037/tcr-21-373
View this article at: https://dx.doi.org/10.21037/tcr-21-373

Introduction

Thyroid cancer is the most common endocrine tumor in humans. The incidence of thyroid cancer has increased recently because of the improving diagnostic approach. Papillary thyroid cancer (PTC) is a major type (80–85%) of thyroid cancer (1). The clinical biological behavior of PTC is relatively inert, and the 10-year survival rate can reach more than 90% after reasonable treatment. However, due to its anatomical location (adjacent to trachea, esophagus, laryngeal recurrent nerve, parathyroid and other important organs), a considerable number of patients with advanced or recurrent PTC cannot obtain good surgical effect, but also have to face serious postoperative complications and organ function loss (2). Although the prognosis of PTC is optimistic, the recurrence rate was relatively high after a 15-year follow-up. And a small group of PTC patients seem to have higher risk of metastasis and recurrence (3-5). Therefore, early diagnosis and screening of high-risk population has always been the key to the prevention and

treatment of PTC. The understanding of the pathogenesis of PTC is the basis to assist clinicians in population risk assessment and early diagnosis.

The homebox (HOX) superfamily play an important role in cell differentiation and morphogenesis. The dysregulation of HOX gene can affect various pathways and result in tumorigenesis and metastasis (6,7). Many HOX genes have been found to be expressed aberrantly, that influence the biological behavior and prognosis of many cancers (8-11). Our previous studies found HOXC9 and HOXD10 were aberrantly hypermethylated through Methyl-Seq and quantitative methylation-specific PCR (Q-MSP) in PTC (12,13). HOXC9 and HOXD10 were reported to play critical roles in tumor progression and to be associated with poor prognosis in many malignant tumors like colorectal cancer, gastric cancer, breast cancer and neuroblastoma (14-17). Their functions as tumor suppressors were primarily verified in vitro. However, the expression of HOXC9 and HOXD10 and their biological significance have not been identified in PTC. This study aims to investigate the expression and clinical significance of HOXC9 and HOXD10 in PTC. We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/tcr-21-373).

Methods

Clinical samples

Totally 98 PTC patients were enrolled in this study. The inclusion criteria were patients who received initially surgery by designated physicians at the Department of Head and Neck Surgery, Fudan University, Shanghai Cancer Center (Shanghai, China) from January 2015 to December 2017. All of the patients were pathologically confirmed as PTC. Patients who had undergone previous thyroidectomy or revision neck dissection were excluded. Tumors less than 3 mm were too small to get enough samples, were also excluded. Lobectomy and isthmectomy was performed in T1 and T2 tumor confined to unilateral lobes. Total thyroidectomy was performed in T3 and T4 tumor or some of the patients with high risk factors. These risk factors include multifocal cancer, lymph node metastasis, distant metastasis, family history, and early exposure to ionizing radiation. Total thyroidectomy is also feasible in some cases where postoperative radionuclide therapy is considered necessary. Central neck dissection was performed in cN1 and most of cN0 patients. Additional modified lateral lymph node dissection was performed in patients with clinically suspicious lateral lymph node metastasis (cN1b). The clinicopathological data of these patients enrolled are summarized in *Table 1*. The tumor-node-metastasis (TNM) stages were according to the American Joint Cancer Committee (AJCC) TNM grading system (8th ed. 2017). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Fudan University Shanghai Cancer Center (No.: 050432-4-1911D) and informed consent was taken from all the patients.

Immunohistochemistry (IHC)

IHC was performed according to a standard protocol. Briefly, paraffin-embedded samples were cut into 4-μm sections and placed on polylysine-coated slides. Paraffin sections were baked overnight at 60 ℃, deparaffinized in xylene, rehydrated through graded ethanol, quenched for endogenous peroxidase activity in 0.3% hydrogen peroxide at 37 ℃ for 15 min, and processed for antigen retrieval by high pressure cooking in citrate antigen retrieval solution for 10 min. Sections were incubated at 37 ℃ for 1.5 h with mouse monoclonal antibodies against HOXC9 (1:200; Abcam, Cambridge, MA, USA) and HOXD10 (1:1,000; Abcam, Cambridge, MA, USA) in a moist chamber. Immunostaining was performed using the DAB substrate kit (ab64238, Abcam, Cambridge, MA, USA), which resulted in a brown-colored precipitate at the antigen site. Then, the sections were counterstained with hematoxylin and mounted in a non-aqueous mounting medium. All the repetitions included a no primary antibody control.

The staining intensity was scored as 0 (low, –), 1 (weak, +), 2 (medium, ++) or 3 (strong, +++). The extent of staining was scored as (0, <5%; 1, 5–25%; 2, 26–50%; and 3, >50%) according to the percentages of the positive staining areas in 5 random high-power fields. Scores for staining intensity and staining extent were then multiplied to obtain the final immunoreactivity score for each case. Tumors with a final immunoreactivity score of <3 were considered to be low (–), and those with a final immunoreactivity score of ≥3 were considered to be high (+) (18).

Statistical analysis

Statistical analyses were performed using Student's *t*-test, paired *t*-test, and Chi-square test. The odds ratios (ORs) for the relationships between each variable and the expression

Table 1 Clinical characteristic of all patients

Characteristic	Value
Patients number	98
Age	43.12±12.997
<55 years	74 (75.5)
≥55 years	24 (24.5)
Gender	
Male	25 (25.5)
Female	73 (74.5)
Invasion	
Yes	19 (19.4)
No	79 (80.6)
Size	1.455±0.9836
>1 cm	43 (43.9)
≤1 cm	55 (56.1)
Multifocal	
Yes	26 (26.5)
No	72 (73.5)
Bilateral	
Yes	16 (16.3)
No	82 (83.7)
Hashimoto's thyroiditis	
Yes	12 (12.2)
No	86 (87.8)
Lymph node metastasis	
Yes	54 (55.1)
No	44 (44.9)
TNM stage	
I	86 (87.8)
II	11 (11.2)
III	1 (1.0)
IV	0 (0.0)

Data are presented as n (%) or mean ± standard deviation.

of HOXC9 and HOXD10 were calculated by univariate logistic regression analysis. All confidence intervals (CIs) were stated at the 95% confidence level. A P value of <0.05 was considered to be statistically significant. SPSS 19.0 was used for data analysis (SPSS, Inc., Chicago, IL, USA).

Table 2 The expression of HOXC9 and HOXD10 in PTC tissues and adjacent tissues

Low expression	HOXC9, n (%)	HOXD10, n (%)
PTC tissues	40 (40.8)	33 (33.7)
Adjacent tissues	24 (24.5)	16 (16.3)
χ^2	7.864	5.939
P value	<0.05	<0.05

PTC, papillary thyroid cancer.

Results

The expression of HOXC9 and HOXD10 decreased in PTC

The expression of HOXC9 and HOXD10 decreased in PTC than in paracancer tissues. The low expression rates of HOXC9 and HOXD10 in PTC tissues were 40.8% and 33.7%, respectively, which were significantly higher than that of paracancer tissues (24.5% and 16.3%), with statistically significant differences (*Table 2*, *Figure 1*).

Relationship between clinicopathological features and the expression of HOXC9 and HOXD10 in PTC

The relationship between the clinicopathological features and the expression of HOXC9 and HOXD10 was analyzed to evaluate their prognostic value as a biomarker of PTC (*Tables 3*,*4*). The low expression of HOXC9 was associated with Hashimoto's thyroiditis and lymph node metastasis (P<0.05). The low expression of HOXD10 was associated with extrathyroidal extension and lymph node metastasis (P<0.05).

Correlation between HOXC9 and HOXD10 in PTC

The co-expression rates of HOXC9 and HOXD10 was 44.90%. Spearman analysis showed that the two were significantly correlated (P<0.05, *Table 5*). The low expression of both HOXC9 and HOXD10 was associated with lymph node metastasis (P<0.05, *Table 6*).

Discussion

The incidence of thyroid cancer, particularly PTC, has markedly increased over the past years around the

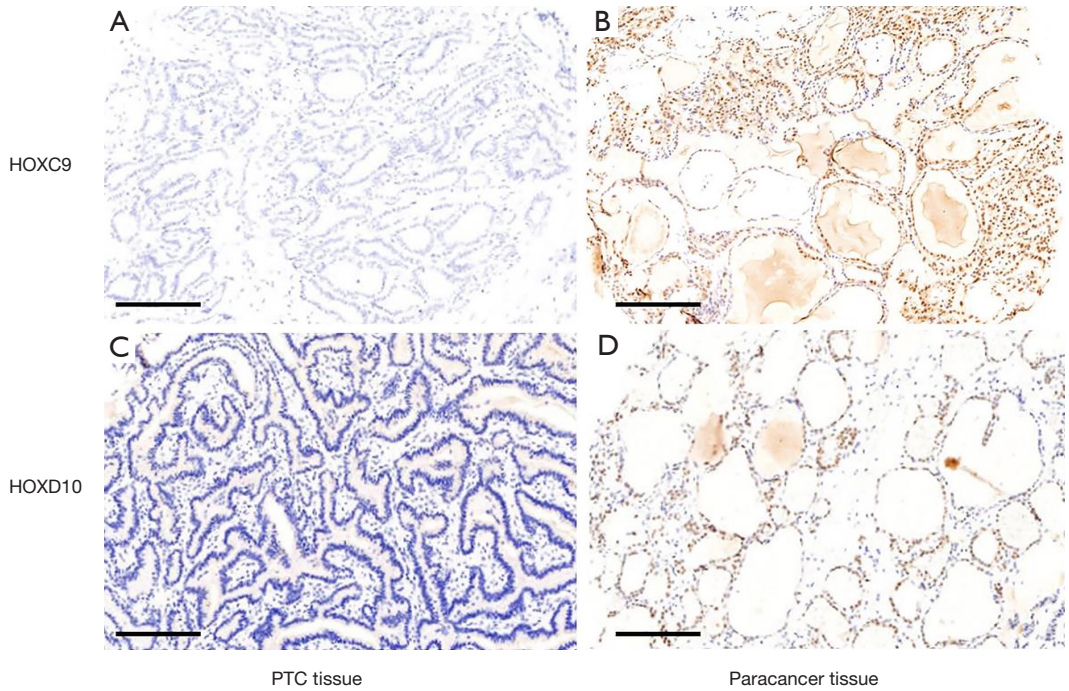

Figure 1 Immunohistochemical detection of HOXC9 and HOXD10 in PTC and paracancer tissues. The immunostaining of HOXC9 and HOXD10 by using the antibodies against HOXC9 (1:200; Abcam, Cambridge, MA, USA) and HOXD10 (1:1,000; Abcam, Cambridge, MA, USA). The brown region indicates the immunoreactivity of HOXC9 and HOXD10 protein in the tissues. Scale bar: 200 μm. (A) Low expression of HOXC9 in PTC; (B) normal expression of HOXC9 in paracancer tissues; (C) low expression of HOXD10 in PTC; (D) normal expression of HOXD10 in paracancer tissues.

world (1). At the same time, the number of the patients with refractory PTC has also increased. Early diagnosis and screening of high-risk population has always been the key to the prevention and treatment of PTC. The understanding of the pathogenesis of PTC is the basis to assist clinicians in population risk assessment and early diagnosis. Appropriate biomarkers could be used to help evaluate the risk of PTC. Our previous studies had made up a genome-wide DNA methylomics database of PTC by MethylCap-Seq to find candidate biomarkers. HOXC9 and HOXD10 were found to be aberrant hypermethylated in PTC (12,13). Methylation of CpG island in promoter region can reduce gene expression. Methylation of tumor suppressor can reduce its expression and lead to tumorigenesis. However, the expression of HOXC9 and HOXD10 and their clinicopathologic relationship in PTC were still unclear.

The HOX family plays an important role in cell differentiation and morphogenesis. The dysregulation of HOX gene may play roles in tumorigenesis. Many HOX genes (like *HoxA5*, *HoxB13* and *HoxC6*) have been found to be aberrantly expressed through promoter methylation in cancers including lung cancer, breast cancer, gastric cancer and colon cancer (8,9,19). Previous studies verified the decreased expression of HOXD10 in some tumors and considered HOXD10 as a candidate tumor suppressor. In vitro, re-expression of HOXD10 resulted in significant inhibition of cell survival, induction of cell apoptosis, and impairment of cell migration and invasion (16). The expression of HOXD10 is reduced/lost frequently in hepatocellular carcinoma, and it was associated with vessel cancerous embolus, tumor cell differentiation, and even 3-year survival rate (20). Decreased expression of HOXD10 promotes a proliferative and aggressive phenotype in prostate cancer (21). On the other side, several previous studies demonstrated that HOXC9 acts as an oncogene. One study in colorectal cancer showed that higher expression of HOXC9 was associated with advanced tumor stage, risk of distant metastasis, tendency for venous invasion, and even overall survival (14). The similar results were reported in gastric cancer and breast cancer (22,23).

In this study, we investigate the expression of HOXC9 and HOXD10 in PTC by IHC. The expression of

Table 3 The relationship between HOXC9 expression and clinicopathological features of PTC

Clinicopathological feature	HOXC9 expression		P value
	High	Low	
Patients number	58 (59.2)	40 (40.8)	
Age			0.333
<55 years	47 (63.5)	27 (36.5)	
≥55 years	18 (75.0)	6 (25.0)	
Gender			0.352
Male	17 (68.0)	8 (32.0)	
Female	41 (56.2)	32 (43.8)	
Extrathyroidal extension			0.798
Yes	12 (63.2)	7 (36.8)	
No	46 (58.2)	33 (41.8)	
Size			0.097
>1 cm	21 (48.8)	22 (51.2)	
≤1 cm	37 (67.3)	18 (32.7)	
Multifocal			0.642
Yes	14 (53.8)	12 (46.2)	
No	44 (61.1)	28 (38.9)	
Bilateral			0.789
Yes	9 (56.3)	7 (43.8)	
No	49 (59.8)	33 (40.2)	
Hashimoto's thyroiditis			0.012*
Yes	3 (25.0)	9 (75.0)	
No	55 (64.0)	31 (36.0)	
Lymph node metastasis			0.022*
Yes	26 (48.1)	28 (51.9)	
No	32 (72.7)	12 (27.3)	
TNM stage			0.338
I	57 (66.3)	29 (33.7)	
II	8 (72.7)	3 (27.3)	
III	0 (0)	1 (100.0)	

Data are presented as n (%). *, statistically significant (P<0.05). PTC, papillary thyroid cancer.

HOXC9 and HOXD10 was decreased in PTC than that in paracancer tissues. Further analysis showed the low expression of HOXC9 was associated with Hashimoto's thyroiditis and lymph node metastasis (P<0.05). The low expression of HOXD10 was associated with extrathyroidal extension and lymph node metastasis (P<0.05). The co-expression rates of HOXC9 and HOXD10 was 44.90% (P<0.05). Both of HOXC9 and HOXD10 were associated with lymph node metastasis. The results suggested that both of them may play a role in the tumor biological behavior of

Table 4 The relationship between HOXD10 expression and clinicopathological features of PTC

Clinicopathological feature	HOXD10 expression		P value
	High	Low	
Patients number	65 (66.3)	33 (33.7)	
Age			0.813
<55 years	43 (58.1)	31 (41.9)	
≥55 years	15 (62.5)	9 (37.5)	
Gender			0.809
Male	16 (64.0)	9 (36.0)	
Female	49 (67.1)	24 (32.9)	
Extrathyroidal extension			0.017*
Yes	8 (42.1)	11 (57.9)	
No	57 (72.2)	22 (27.8)	
Size			0.139
>1 cm	25 (58.1)	18 (41.9)	
≤1 cm	40 (72.7)	15 (27.3)	
Multifocal			0.630
Yes	16 (61.5)	10 (38.5)	
No	49 (68.1)	23 (31.9)	
Bilateral			0.776
Yes	10 (62.5)	6 (37.5)	
No	55 (67.1)	27 (32.9)	
Hashimoto's thyroiditis			1.000
Yes	8 (66.7)	4 (33.3)	
No	57 (66.3)	29 (33.7)	
Lymph node metastasis			0.018*
Yes	30 (55.6)	24 (44.4)	
No	35 (79.5)	9 (20.5)	
TNM stage			0.674
I	51 (59.3)	35 (40.7)	
II	6 (54.5)	5 (45.5)	
III	1 (100.0)	0 (0)	

Data are presented as n (%). *, statistically significant (P<0.05). PTC, papillary thyroid cancer.

PTC and they may have a synergistic effect. The combined application of the two biomarkers may improve the clinical value.

Our previous studies had showed the function of HOXD10 as a tumor suppressor in PTC (12). In this study, HOXD10 was showed to be low expressed in PTC. And the low expression of HOXD10 was associated with extrathyroidal extension and lymph node metastasis. The results were consistent with the previous studies in other malignant tumors. Nevertheless, the result in HOXC9 was

Table 5 the correlation between HOXC9 and HOXD10 expression in PTC tissues

HOXD10	HOXC9		P value
	High	Low	
High	44	21	0.016*
Low	14	19	

*, statistically significant (P<0.05). PTC, papillary thyroid cancer.

Table 6 The relationship between clinicopathological features and the low expression of both HOXC9 and HOXD10 in PTC

Clinicopathological feature	Low expression of both		P value
	No	Yes	
Patient number	79 (80.6)	19 (19.4)	
Age			1.000
<55 years	59 (79.7)	15 (20.3)	
≥55 years	20 (83.3)	4 (16.7)	
Gender			0.773
Male	21 (84.0)	4 (16.0)	
Female	58 (79.5)	15 (20.5)	
Extrathyroidal extension			0.517
Yes	14 (73.7)	5 (26.3)	
No	65 (82.3)	14 (17.7)	
Size			0.203
>1 cm	32 (74.4)	11 (25.6)	
≤1 cm	47 (85.5)	8 (14.5)	
Multifocal			0.574
Yes	20 (76.9)	6 (23.1)	
No	59 (81.9)	13 (18.1)	
Bilateral			0.506
Yes	12 (75.0)	4 (25.0)	
No	67 (81.7)	15 (18.3)	
Hashimoto's thyroiditis			0.240
Yes	8 (66.7)	4 (33.3)	
No	71 (82.6)	15 (17.4)	
Lymph node metastasis			0.023*
Yes	39 (72.2)	15 (27.8)	
No	40 (90.9)	4 (9.1)	
TNM stage			0.879
I	69 (80.2)	17 (19.8)	
II	9 (81.8)	2 (18.2)	
III	1 (100.0)	0 (0)	

Data are presented as n (%). *, statistically significant (P<0.05). PTC, papillary thyroid cancer.

different in PTC from other cancers. HOXC9 was usually showed as an oncogene in other cancers, like gastric cancer and breast cancer. But in this study, HOXC9 was showed as a tumor suppressor in PTC. Cause the low expression of HOXC9 was associated with lymph node metastasis. Chronic inflammation caused by Hashimoto's thyroiditis was speculated a predisposing factor of PTC. The low expression of HOXC9 may be one of the influencing factors between PTC and Hashimoto's thyroiditis. However, no related research in PTC has been reported before. This study is just a retrospective study and only the protein expression of paraffin specimens has been detected. Further studies at higher molecular level and prospective studies are yet needed.

In summary, this study firstly researched the expression and clinicopathologic relationship of HOXC9 and HOXD10 in PTC. The expression of HOXC9 and HOXD10 decreased in PTC. And the low expression of HOXC9 and HOXD10 was associated with some clinicopathologic features. The result showed that both of them may play a role in the tumor biological behavior of PTC. And the combined application of them may improve their clinical value as biomarkers.

Acknowledgments

The authors are grateful to Qing-Hai Ji for kindly providing the administrative supports.
Funding: This work was supported by the Science and Technology Project of Shanghai Science and Technology Committee (grant no. 12ZR1406800).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-373

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tcr-21-373

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-21-373). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Fudan University Shanghai Cancer Center (No.: 050432-4-1911D) and informed consent was taken from all the patients.

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Cite this article as: Cao YM, Wen D, Qu N, Zhu YX. Prognostic and clinical significance of HOXC9 and HOXD10 in papillary thyroid cancer. Transl Cancer Res 2021;10(7):3317-3325. doi: 10.21037/tcr-21-373

