Scientific Research Publishing

Journal of Cancer Therapy, 2022, 13, 417-424
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Association Study of Thyroid Papillary Carcinoma with Depression and BDNF Expression

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How to cite this paper: Lin, H.B., Wu, K.M., Zhang, X.G., Huang, X.J., Wu, C.C. and Cai, H.X. (2022) Association Study of Thyroid Papillary Carcinoma with Depression and BDNF Expression. *Journal of Cancer Therapy*, **13**, 417-424.
https://doi.org/10.4236/jct.2022.137036

Received: June 6, 2022
Accepted: July 12, 2022
Published: July 15, 2022

Abstract

Objective: To analyze the correlation between Val66Met gene of brain-derived neurotrophic factor (BDNF) and papillary thyroid carcinoma (PTC) complicated with depression. To evaluate the clinical value of papillary thyroid carcinoma. **Methods:** Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) were used to assess the correlation of BDNF in the blood of patients with depressive disorder of thyroid papillary carcinoma using polymerase chain reaction PCR. The relationship between BDNF gene polymorphism and the incidence of thyroid papillary carcinoma was analyzed, and the susceptibility factors of thyroid papillary carcinoma complicated with depression were explored. **Results:** Compared with normal control group, T3 and T4 of PTC in non-depressed group were decreased, while TSH and TPOAb were increased ($P < 0.05$). Compared with normal control group, T3, T4 and TPOAb were increased and TSH was decreased in PTC depression group ($P < 0.05$). PTC depression score was higher than that of healthy control group ($P < 0.05$), and PTC combined depression score was higher than that of normal control group ($P < 0.05$). The depression rate of PTC combined with depression was 86.7%, which was higher than that of other groups ($P < 0.05$). The distribution of RS6265 locus genotype of BDNF gene was significantly different between PTC with depression group and PTC without depression group ($P < 0.05$). **Conclusion:** There is a significant difference between PTC with depression and PTC without depression, which is related to SNP rs6265 of BDNF gene. AG and GG are both risk sites of PTC with depression, and GG type is more prone to PTC with depression.

Keywords

Papillary Thyroid Carcinoma, Depressive Disorder, Brain-Derived Neurotrophic Factor, Polymerase Chain Reaction

1. Introduction

At present, the incidence of thyroid cancer is increasing year by year globally. According to statistics in 2020, there are 586,000 cases of thyroid cancer worldwide, ranking 9th in incidence [1]. Differentiated thyroid cancer (DTC) accounts for more than 95% of all thyroid cancers [2]. Thyroid cancer is the most common endocrine malignancy and its incidence has been increasing rapidly in the past decade. Papillary thyroid carcinoma (PTC) is the main type of thyroid cancer, accounting for 80% - 85% of all thyroid malignant tumors [3]. PTC has shown a trend of high morbidity in recent years, and can be transferred through lymphatic metastasis, thus increasing the recurrence rate and tumor-specific mortality of original site tissues and distant local tissues [4] [5] [6]. Therefore, research on the molecular biological mechanism of PTC occurrence and development is helpful for the diagnosis, prevention and treatment of thyroid papillary carcinoma. It has been found that brain-derived neurotrophic factor (BDNF) can activate tyrosine kinase receptor B (TrkB) signaling pathway through binding, and participate in biological processes such as proliferation, differentiation, apoptosis, migration and invasion of tumor cells [7] [8]. Recently, it has been proposed that thyroid papillary carcinoma is the result of the main effector gene or other genetic, environmental factors, living habits, psychology and other factors. At present, there are few reports about the relationship between papillary thyroid carcinoma and BDNF gene. A literature search showed that no expert consensus has been reached on effective lifestyle, behavioral and psychological intervention programs or measures to delay the development of papillary thyroid carcinoma and the association between papillary thyroid carcinoma and BDNF gene [9]. We speculate whether there is a link between BDNF gene in patients with papillary thyroid carcinoma and depression. To this end, we used polymerase chain reaction (PCR) to detect BDNF gene polymorphism in patients diagnosed with thyroid papillary carcinoma with depressive disorder, patients without depressive disorder and normal controls. To analyze the relationship between BDNF gene polymorphism level and the incidence of thyroid papillary carcinoma, explore the susceptibility factors of patients with thyroid papillary carcinoma complicated with depressive disorder, provide basic data for the pathogenesis of thyroid papillary carcinoma and its prevention and treatment, and provide scientific basis for the association study of patients with thyroid papillary carcinoma with depressive disorder.

2. Data and Methods

2.1. General Information

Eighty patients with thyroid papillary carcinoma admitted to the Department of Surgery of the Fourth People's Hospital of Haikou from October 2021 to April 2022 were enrolled in this study. 30 patients were divided into thyroid papillary carcinoma depression group (PTC+ depression). 50 patients with papillary thyroid carcinoma in the non-depressed group (PTC+ non-depressed group) and

30 healthy controls (Personnel who came to The Fourth People's Hospital of Haikou for physical examination during the same period). Psychology questionnaire for measuring: the mental health association of Hainan province with diagnosis certificate of psychiatrists and researchers try to be a one-on-one screening of psychiatry and neurology, eliminate past or current with nerve disease and conform to the diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV) criteria of axis I mental disorder patients with thyroid papillary carcinoma. Each tested person needs to know the detailed basic information of the individual, including age, sex, marriage, education level, monthly income, reimbursement method, occupation, disease type. Inclusion criteria: 1) papillary thyroid carcinoma was diagnosed by pathology and cytology; 2) all subjects were excluded from major organ diseases such as heart, brain, liver and kidney. There was no significant difference in age and gender among the three groups ($P > 0.05$). This study was approved by the Ethics Committee of the Fourth People's Hospital of Haikou, in accordance with the Helsinki Declaration, and all subjects signed informed consent.

2.2. Experimental Methods

2.2.1. Self-Rating Depression Scale (SDS) Scoring Method

SDS uses a 4-level score with 20 items, and its standard is: "1" means no or rarely; "2" sometimes. "3" indicates most of the time; "4" means most or all of the time. If it is a positive score, the rough score is 1, 2, 3 and 4. For reverse grading, it is rated 4, 3, 2 and L. Of these, sections 2, 5, 6, 1 L, 12, 14, 16, 17, 18 and 20 are entitled reverse scoring. Add up each score of 20 items to get rough score; multiply the rough score by 1.25 and round it to the whole number to get the standard score. According to the Results of Chinese norm, the standard score of depression is 53.62 for mild depression, 63 - 72 for moderate depression, and >72 for severe depression.

2.2.2. BDNF Genotype Identification

5 ml of morning fasting elbow venous blood was collected in a vacuum tube with 0.5 mol of anticoagulation, −20˚C Freezer storage. Genomic DNA extraction and identification: 2 ml blood was taken out, and genomic DNA was extracted from blood cells using the blood Genomic DNA extraction Kit (Beijing Tiagen Biochemical Technology Co., LTD.) according to the instructions. Quantitative and purity identification of genomic DNA and BDNF genotype identification were carried out. 2 ml blood was used for thyroid hormone and antibody detection

2.2.3. Detection of Serum

Thyroid hormone and antibodies, such as Thyroid peroxidase antibody (TPOAb) and Triiodothyronine (T3); Thyroxine (Tetraiodothyronine, T4); Transpulmonary thyrotropin Pressure TSH. Detection of T3, T4, TSH, TPOAb, kit, purchased from DMC Company in the United States by immunochemical fluorescence method. Measured:

Normal reference range of T3: 0.92 - 2.79 nmol/L.

T4 normal reference range: 58.10 - 161.30 nmol/L.
Normal reference range of TSH: 0.550 - 4.780 μIU/ml.
TPOAb normal range the reference range is <60 U/ml.

2.3. Statistical Analysis

Statistical software SPSS 21.0 (SPSS, Chicago, IL, USA) was used to process and analyze the data. Measurement data were expressed as mean ± standard deviation, and counting data were expressed as percentages. T test was used for comparison of measurement data and Chi-square test was used for analysis of counting data. Genotype distribution frequency was verified by Hardy-Weinberg equilibrium, survival rate was calculated by Life Table, survival curve was made by Kaplan-Meier method, and influencing factors of prognosis were evaluated by Logistic regression analysis. $P < 0.05$ on both sides was considered as significant difference in statistical results.

3. Test Results

3.1. General Information of Patients

The general information of patients was shown in Table 1. There were no significant differences in age, sex, years of education, marital status and income between the PTC+ depressed group and the PTC+ non-depressed group ($P > 0.05$).

3.2. Comparison of T3, T4, TSH and TPOAb Levels in Each Group

Compared with normal control group, T3 and T4 in PTC+ non-depressive group were decreased, while TSH and TPOAb were increased ($P < 0.05$). Compared with normal control group, T3, T4 and TPOAb in PTC+ depression group were increased, while TSH was decreased ($P < 0.05$) (see Table 2).

3.3. Comparison of BAI and BDI Scores among Different Groups

Pairwise comparison, PTC+ depression score was significantly different from healthy control group ($P < 0.05$). The PTC+ non-depressive score was higher than that of the healthy control group ($P < 0.05$), and the PTC+ depressive score was higher than that of the normal control group ($P < 0.05$) (see Table 3).

3.4. Comparison of Depression Positive Rate among Groups

The depression rate in PTC+ depression group was 86.7%, higher than that in other groups ($P < 0.05$), as shown in Table 4.

3.5. Genotype and Allele Frequency Distribution of BDNF Gene (rs6265 Locus) in PTC+ Depressed Group and PTC+ Non-Depressed Group

The distribution of rs6265 genotype was significantly different between the PTC+ depression group and the PTC+ non-depression group (Table 5). AG and

GG were both risk loci for PTC+ depression, and GG type was more prone to PTC+ depression.

Table 1. General data of patients [Mean ± SD or N (%)].

Characteristics	PTC + depression (n = 30)	PTC+ non-depressed (n = 50)	Healthy control (n = 30)	P value
Age (years)	45.15 ± 10.25	44.01 ± 9.74	45.88 ± 10.5	0.134
Gender				0.674
Female	13 (43.3)	24 (48)	12 (30)	
Male	17 (56.7)	26 (52)	18 (70)	
Education years				0.308
≤12 years	14 (43.3)	26 (52)	14 (43.3)	
>12 years	16 (56.7)	24 (48)	16 (56.7)	
Marriage status				0.797
Single	13 (43.3)	24 (48)	15 (50)	
Married	17 (56.7)	26 (52)	15 (50)	
Salary (yuan)				0.273
≤5000	12 (40)	22 (44)	13 (43.3)	
>5000	17 (60)	28 (56)	17 (56.7)	

Table 2. Comparison of thyroid function between different groups $\left(\overline{x} \pm s\right)$.

indicators	Healthy control (n = 30)	PTC+ depression (n = 30)	PTC+ non-depressed (n = 50)
T3	1.69 ± 0.19	1.75 ± 0.23*	0.47 ± 0.12 *
T4	92.53 ± 12.41	96.14 ± 15.34*	46.97 ± 14.16*
TSH	2.11 ± 0.39	2.03 ± 0.47*	17.24 ± 12.11*
TP0Ab	17.48 ± 5.24	373.44 ± 45.69*	396.50 ± 72.83*

Note: All indexes were compared with normal control group *P < 0.05, **P < 0.01.

Table 3. Comparison of depression scores between different groups.

	Healthy control (n = 30)	PTC+ non-depressed (n = 50)	PTC + depression (n = 30)	*t*	P
depression	2.02 ± 2.62	3.47 ± 2.78**	5.52 ± 3.86**##	15.358	<0.001

Note: PTC+ depression compared with normal control group, *P < 0.05, ** *P* < 0.01; Compared with PTC+ non-depressed group, #P < 0.05, ##P < 0.01.

Table 4. Comparison of positive rates of anxiety and depression among different groups (Cases (%)).

	Healthy control (n = 30)	PTC+ non-depressed (n = 50)	PTC + depression (n = 30)	X^2-*value*	P-*value*
depression	1 (3.3)	1 (2)	26 (86.7)	23.297	<0.001

Table 5. Comparison of genotype and allele frequency distribution of RS6265 locus of BDNF gene between PTC+ non-depressed group and PTC+ depressed group (N %).

SNP	PTC+ non-depressed (n = 50)	PTC+ depression (n = 30)	P	OR (95% CI)
rs6265				
AA	18 (36)	8 (26.7)	Ref. [5]	
AG	24 (48)	25 (83.3)	**0.0390**	1.818 (1.062 - 3.200)
GG	10 (20)	16 (53.3)	**0.000**	3.677 (1.959 - 6.881)
A	54 (24)	46 (86.7)	Ref. [6]	
G	48 (26)	55 (21.7)	**0.000**	1.983 (1.436 - 2.722)

SNP: Single Nucleotide Polymorphisms; OR: Odds Ratio; 95% CI: 95% confidence intervals; Ref: Reference.

4. Discussion

Thyroid cancer is the most common endocrine malignancy and its incidence has been increasing rapidly in the past decade. Papillary thyroid carcinoma (PTC) is the main type of thyroid cancer, accounting for 80% - 85% of all thyroid malignancies "1". In recent years, PTC has shown a high incidence and can be metastasized by lymphatic metastasis, thereby increasing the recurrence rate and tumor-specific mortality of original and distant local tissues. Therefore, research on the molecular biological mechanism of PTC occurrence and development is helpful for the diagnosis, prevention and treatment of thyroid papillary carcinoma. It has been found that brain-derived neurotrophic factor (BDNF) can activate the tyrosine kinas receptor B (TrkB) signaling pathway and participate in the biological processes of tumor cell proliferation, differentiation, apoptosis, migration and invasion by binding to the tyrosine kinas receptor B (TrkB). At the same time, many studies have found that miRNA is involved in biological processes such as cell growth, proliferation, differentiation and apoptosis, as well as the formation of many malignant tumors. More and more miRNAs are found in PTC, which will play an important role in PTC gene diagnosis and treatment. BDNF plays a broad and important role in the growth, development, differentiation, regeneration and functional maintenance of various types of neurons, and is essential for the regulation of hippocampal synaptic plasticity and memory. It was found that the fear memory of PATIENTS with PTSD was difficult to fade or the fear memory of patients with PTSD was repeated, suggesting that the maintenance disorder of fear memory fading might be the key to the occurrence and treatment of PTSD. The mechanism of fear memory extinction remains to be further studied.

The hippocampus is an important brain region for learning and memory, and the long-term enhancement effect (LTP) of neurons in the hippocampus is the neural basis of long-term memory. It was found that blocking the expression of BDNF in the hippocampus during the formation of long-term memory resulted in the deficiency of long-term memory consolidation, but did not affect the for-

mation of long-term memory, suggesting that the normal expression of BDNF plays a key role in the consolidation and long-term retention of memory. Injection of recombinant human BDNF into the hippocampus reverses long-term memory deficits caused by the protein synthesis inhibitor anisomycin, while injection of BDNF antisense nucleotide to block BDNF expression in the hippocampus of conditioned fear rats attenuated the fear response to conditioned stimuli. This indicates that BDNF is a key factor affecting the long-term maintenance of fear memory [10] [11]. R Vulturar *et al.* [12] reported the distribution of BDNF Val66Met allele in healthy Romanian volunteers (N = 1124). The frequency of Val allele was 80.74%, and that of Met allele was 19.26%.

5. Conclusion

The data from this study are extended in an effort to map the allele distribution of BDNF Val66Met in populations around the world, and emphasize that population stratification should be reported in future studies to control for phenotypic associations in samples of different populations. CHY Fu, MacGregor Legge *et al.* [13] focused on the contribution of brain-derived neurotrophic factor (BDNF) Val66Met polymorphism to major depressive disorder and attempted to determine whether the same neurological effects were observed in healthy individuals. There is a specific focus on the cortical thickness of the amygdala, the prefrontal region of the anterior cingulate cortex and the middle frontal and orbitofrontal cortices. Therefore, this study analyzed the role of BDNF in the pathological process of PTC and provided a new research basis for the diagnosis and treatment of clinical PTC. Therefore, this study explored the thyroid papillary carcinoma in gender, age, life style, especially whether the depression, and many other factors for the thyroid papillary carcinoma may affect factors, explored the thyroid papillary carcinoma disorder of depression in patients with risk factors, and analyzed the BDNF gene polymorphism level and incidence of thyroid papillary carcinoma, to provide basis for the early prevention and treatment of thyroid papillary carcinoma. The results showed that patients with AG type rs6265 in PTC with depression and those in PTC without depression were more susceptible to depression and anxiety.

Foundation Project

Hainan Health Commission Science and Technology Project (No. 21A200422)

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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