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Original Article

Association between microRNA polymorphisms and papillary thyroid cancer susceptibility

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Abstract: Objectives: Papillary thyroid cancer (PTC) is the most common subtype of thyroid cancer, which accounts for 80-90% of all thyroid cancer cases. Though the pathological mechanism hasn't been fully understood, it is reported that both environmental and genetic factor may contribute to the PTC susceptibility. MicroRNAs (miRNAs) are small non-coding RNA molecules which function as the suppressors to participate in a variety of biological processes. Accumulating evidence suggests that polymorphisms of miRNAs were associated with the tumorigenesis of various cancers, including PTC. In this article, we focus on the association between four common microRNA polymorphisms (miR-146a, miR-608, miR-933, and miR-149) and PTC risk in a Han Chinese population. Methods: In this case-control study, we recruited 1,398 participants in total, including 369 PTC patients, 278 patients with thyroid benign nodules (BN) and 751 normal controls. The miRNAs polymorphisms were genotyped and analyzed by using MALDI-TOF mass spectrometry. The odd ratios and their 95% confidence interval (95% CI) were calculated to evaluate the association between miRNAs polymorphisms and PTC risk. Furthermore, a meta-analysis based on previous studies was conducted to comprehensively assess the diagnostic performance of miR-146a in the PTC diagnosis. Results: The miR-146a polymorphisms were shown to be significantly correlated with elevated risk of PTC under the heterozygous, homozygous, dominant and allelic models by comparing the genotype distribution between PTC cases and healthy controls, as well as between PTC cases and BN cases. However, the result of meta-analysis showed no significant association between miR-146a polymorphisms and PTC risk. Conclusions: Our study indicated that the miR-146a polymorphism was significantly associated with PTC risk. In contrast, meta-analysis revealed no evidence of association between miR-146a variants and PTC risk. Further studies are required to elucidate the role of miR-146a in the etiology of PTC.

Keywords: Papillary thyroid cancer, thyroid benign nodules, microRNA, polymorphism

Introduction

Thyroid cancer is the most common type of endocrine malignancy in adults. The new thyroid cancer cases in 2012 were estimated to be more than 290000 worldwide, accounting for nearly 2.1% of all cancer cases diagnosed in 2012 [1]. In China, the incidence rate of thyroid cancer was about 1.770 per 100,000 Chinese [2]. There are four main histological subtypes of thyroid carcinoma, including papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC). Among these histological subtypes, papillary thyroid cancer accounts for over 80% of all thyroid cancer cases [3]. Females have a higher risk of developing thyroid cancer than males, with approximately 3:1 female-to-male ratio of thyroid cancer patients [4].

Epidemiological studies have reported that a variety of environmental factors and genetic abnormalities may contribute to the occurrence of thyroid cancer. Ionizing radiation is one of well-established causes of PTC. A pooled-analysis revealed a dose-risk relationship between radiation exposure during childhood and thyroid cancer [5]. Further evidence was found in the Chernobyl fall-out. A substantial increase in thyroid-cancer incidence was found in children who resided in the contaminated areas [6]. Iodine intake was also reported as a risk factor for thyroid cancer in several studies but definitive evidences were still in absence [7].

MicroRNAs, small noncoding RNA molecules (19-25 nucleotides long), participate in a variety of biological processes and function as the suppressors to regulate the stability and the

Table 1. Demographic and clinical characteristics of study population

Characteristics	Thyroid cancer (N = 369)	Benign nodule (N = 278)	Healthy individual (N = 751)	*P*-value
Age at enrollment (mean ± SD, yrs)	48.31 ± 11.91	46.77 ± 10.24	45.21 ± 11.22	0.983
Gender (%)				
Male	107 (29.0)	68 (24.5)	212 (28.2)	0.392
Female	262 (71.0)	210 (74.6)	539 (71.8)	
TSH level (mean ± SD, mIU)	2.03 ± 1.54	1.74 ± 1.25	0.97 ± 0.23	0.626
Family history of cancer (%)	29 (7.9)	18 (6.5)	38 (5.1)	0.175
Prior history of radiation (%)	11 (3.0)	3 (1.1)	8 (1.1)	0.041
Histological variants of PTC (%)				
Classic	233 (63.1)	-	-	
Follicular variant	61 (16.5)	-	-	
Tall cells	46 (12.5)	-	-	
Others	29 (7.9)	-	-	
Location (%)				
One lobe	263 (71.3)	-	-	
Both lobe	106 (28.7)	-	-	
Tumor size (%)				
Mean (cm)	1.32 ± 0.97	-	-	
≤ 10 mm	167 (45.3)	-	-	
> 10 mm	202 (54.7)	-	-	
Invasion (%)	63 (17.1)	-	-	
TNM stage (%)				
Stage I-II	255 (69.1)	-	-	
Stage III-IV	114 (30.9)	-	-	

TSH, thyroid stimulating hormone; TNM, tumor, node, metastasis.

expression of their target mRNA by binding to their 3'untranslated region (3'UTR) [8-10]. MiRNAs are coded by the genome and processed by RNAse III enzymes, then binds to the target mRNA with the corresponding antisense sequences [11, 12]. Single nucleotide polymorphism (SNP) located within microRNA sequence may change the properties of microRNAs and thereby affect the process of miRNA maturation or alter the ability to bind to the target mRNA [13].

Accumulating evidence suggests that microRNA polymorphisms are involved in the tumorigenesis of diverse malignancies [13-16]. It has been revealed that aberrant level of miRNAs was observed in PTC cases compared with healthy controls [17]. By regulating the gene expression, microRNAs can change the formation and function of the thyroid tissues. Moreover, some microRNAs might function as oncogenes or tumor suppressors in the development of neoplasm [9].

To our current knowledge, rs2910164 (miR-146a) is one of the most common miRNAs SNPs which has been reported to be concerned with PTC risk [18-20]. Besides, rs2292832 (miR-149) has also been widely studied in various cancers, including PTC [21]. Another SNP, miR-608 is shown to be a tumor suppressor which was significantly downregulated in several malignancies, yet the association between miR-101 and PTC has not been investigated [9, 22, 23].

In our study, we aim to investigate the association between miRNAs variants and PTC susceptibility. Besides, we also conducted a meta-analysis to summarize the overall effect of miR-146a SNP on the PTC risk.

Material and methods

Ethics statement

Our research is approved by Ethics Committee of the First Affiliated Hospital of Zhengzhou

University. Written informed consents were signed and provided by all the participants (or their guardians) recruited in this study.

Study population

In our case-control study, we enrolled a total of 1,398 participants from the First Affiliated Hospital of Zhengzhou University from May 2010 to June 2014. 369 PTC patients were recruited from the Department of Ultrasound and 278 people with thyroid benign nodules (BN) were selected from the Department of Ultrasound as positive controls 751 people without previous history of cancer in the general outpatients were enrolled as health controls in present study. Moreover, patients previously undergoing surgical or medical treatments for any thyroid diseases were excluded as well. Some clinical characteristics (age, gender, family history of cancer and prior history of radiation) and biochemical indicators, like thyroid stimulating hormone (TSH) level, were investigated afterwards, and the results are presented in **Table 1**. 3-5 ml venous blood was obtained from each participant to extract the miRNAs.

SNP selection

The data of SNPs on miRNAs in our study was acquired from the miRBase database (release 17.0) [24]. Tag-SNPs on miRNAs were retrieved with the minor allele frequency (MAF) threshold of 0.05 and the r^2 greater than 0.8 [25]. Based on the for mentioned criteria, our SNPs on miRNAs were identified, miR-146a (rs2910164), miR-608 (rs4919510), miR-933 (rs79402775) and miR-149 (rs2292832), as the studied SNPs in present study.

DNA extraction and genotyping

With the 3-5 ml venous blood samples collected from each participant, we used TRIzol solution (Invitrogen) to extract the RNAs according to the manufacturer's instructions, and the purity of the RNAs was testified with Agilent BioAnalyzer 2100 [18]. After purification, we placed the specimens on the MassARRAY iPLEX platform (Sequenom, San Diego, CA, USA), using an allele-specific matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry assay to genotype the SNPs [25]. MassARRAY Assay Design software was used to design primers for amplification and extension reactions.

Statistical analysis

The data was analyzed with SPSS 20.0 software. The student's t-test was conducted to compare the between-group difference in regards to the clinical characteristics. The four genetic models such as heterozygous, homozygous, dominant and allelic models were constructed to evaluate the PTC risk conferred by miRNAs polymorphisms. The distribution of genotype frequencies were analyzed by using chi-square test. The odds ratio and its corresponding 95% confidence intervals (95% CI) were calculated to assess the association between the miRNAs SNPs and PTC risk. A *P* value less than 0.05 were considered as statistically significant. Additionally, we also performed a meta-analysis based on the previous studies about the association between miR-146a polymorphisms and PTC susceptibility.

Results

Clinical characteristics of thyroid neoplasm cases and health controls

In our research, we enrolled 369 patients suffering from PTC and 751 normal outpatients without any symptoms of cancer and endocrine diseases. Meanwhile, 278 BN patients were selected as positive controls compared with PTC cases. Clinical characteristics of enrolled participants are presented in **Table 2**. The ages of the participants range from 30 to 60 years old, and the number of female patients is approximately twice more than that of males, which also confirm the previous finding that the incidence rate of PTC was more prevalent in women than men [26, 27]. To investigate the effect of environmental factors on the PTC susceptibility, we examined the previous history of radiation in the three study groups. There are 11 PTC patients (3.0% of all) reported to be previously exposed to the radiation, while only 1.1% participants respectively in the BN group as well as in the healthy controls have previous exposure to radiation. The exposure to radiation was one of risk factors for PTC based on our results ($P = 0.041$). Moreover, we also reviewed the family history of cancer in the participants. A slightly higher rate of family cancer history was observed in PTC cases, but there is no significant difference among the three study groups ($P > 0.05$). Thyroid stimulating hormone (TSH) level in vivo was also taken into account in this study. No significant difference in TSH

Table 2. Associations of selected SNPs in microRNA gene with PTC and benign thyroid nodule susceptibility

SNP	Genotype/Allele	PTC	BN	Control	PTC vs. Control		PTC vs. BN	
					OR (95% CIs)	*P*-value	OR (95% CIs)	*P*-value
miR-146a (rs2910164 G>C)	GG	186	157	414	Ref.		Ref.	
	GC	150	105	278	1.20 (0.92-1.56)	0.173	1.21 (0.87-1.67)	0.263
	CC	33	16	59	1.24 (0.78-1.97)	0.350	1.74 (0.92-3.28)	0.084
	GC+CC	183	121	337	1.21 (0.94-1.55)	0.137	1.28 (0.93-1.74)	0.126
	Minor allele (C)	216	137	396	1.16 (0.95-1.41)	0.147	1.27 (0.99-1.62)	0.064
miR-608 (rs4919510 G>C))	GG	136	102	279	Ref.		Ref.	
	GC	186	142	370	1.03 (0.79-1.35)	0.823	0.98 (0.70-1.38)	0.918
	CC	47	34	102	0.94 (0.63-1.41)	0.784	1.04 (0.62-1.73)	0.890
	GC/CC	233	176	472	1.03 (0.78-1.31)	0.924	1.01 (0.80-1.26)	0.950
	Minor allele (C)	280	210	574	0.99 (0.82-1.18)	0.900	0.99 (0.72-1.37)	0.965
miR-933 (rs79402775 G>A)	GG	275	201	562	Ref.		Ref.	
	GA	86	73	182	0.97 (0.72-1.29)	0.816	0.86 (0.60-1.24)	0.417
	AA	8	4	7	2.24 (0.84-6.51)	0.095	1.46 (0.43-4.92)	0.538
	GA/AA	94	77	189	1.02 (0.76-1.35)	0.911	0.89 (0.63-1.27)	0.525
	Minor allele (A)	102	81	196	1.07 (0.83-1.38)	0.613	0.94 (0.69-1.29)	0.703
miR-149 (rs2292832 T>C)	TT	131	122	321	Ref.		Ref.	
	TC	175	128	339	1.27 (0.96-1.66)	0.091	1.27 (0.91-1.78)	0.158
	CC	63	28	91	1.69 (1.16-2.48)	0.006	2.09 (1.26-3.49)	0.004
	TC/CC	238	156	430	1.36 (1.05-1.76)	0.020	1.42 (1.03-1.95)	0.031
	Minor allele (C)	301	184	521	1.29 (1.08-1.55)	0.005	1.39 (1.11-1.75)	0.005

PTC, papillary thyroid cancer; BN, benign nodule; OR, odds ratio; CI, confidence interval.

level was found among the three study groups ($P > 0.05$). Apart from the biochemical indicators and clinical characteristics in all participants, we examined the conditions of PTC in patients including histological variants, tumor location, tumor size and tumor lymph node metastasis. In all of the histological variants, the classic type accounts for 63.1% of PTC cases (233 PTC patients). Follicular variant and tall cells types in all the PTC cases were 16.5% and 12.5%, respectively. The other types were 7.9% in all PTC cases. The majority of the malignancies are located on one lobe of thyroid (accounts for 71.3%), while the rest are located on the both lobes (28.7%) and the mean size of the tumor is 1.32 ± 0.97 cm. 17.1% of PTC cases showed the signs of invasion to the adjacent tissues. According to the TNM staging, 69.1% of PTC cases were diagnosed at the early stage (stage I-II).

Association between microRNA polymorphism and PTC susceptibility

We genotyped the blood sample of each participant and compare the difference in the genotype distribution between PTC cases and healthy controls, as well as between PTC cases and BN cases. The frequencies of genotype distribution and the odds ratios are shown in **Table 2**. No significant association between miR-146a polymorphisms and PTC risk was observed under the four established genetic models. Similarly, neither miR-608 nor miR-933 variants conferred PTC risk under the four genetic models. However, the miR-146a polymorphisms were shown to be significantly correlated with elevated risk of PTC under the heterozygous, homozygous, dominant and allelic models by comparing the genotype distribution between PTC cases and healthy controls, as well as between PTC cases and BN cases.

Meta-analysis of the correlation between microRNA polymorphism and PTC risk

To comprehensively evaluate the association between miR-146a polymorphisms and PTC risk, we conducted a meta-analysis to estimate the overall odds ratio by combining all the data extracted from eligible studies. After literature retrieval and screening, 18 relevant articles were initially identified and filtered. Finally, only 7 studies were included in our meta-analysis [18-20, 28]. The included studies were listed in

Table 3. Characteristics of four included studies that examined risk of PTC relation to miR-146a G>C polymorphism

First author	Year	Country	Ethnicity	Sample size		Source of control	Case			Control			Allelic model	
				Case	Control		GG	GC	CC	GG	GC	CC	OR (95% CIs)	*P*-value
Jazdzewski K	2008	Finland	Caucasian	206	274	Health controls	99	104	3	150	105	19	1.20 (0.89-1.61)	0.230
		Poland	Caucasian	201	475	Health controls	115	82	4	286	163	26	0.99 (0.75-1.30)	0.922
		USA	Caucasian	201	152	Health controls	91	101	9	90	52	10	1.36 (0.96-1.90)	0.080
Jones AM	2008	UK	Caucasian	781	6122	Health controls	436	271	41	3540	2179	339	1.00 (0.88-1.34)	0.989
Marino M	2012	Italian	Caucasian	307	206	Health controls	180	105	22	105	84	17	0.79 (0.60-1.06)	0.118
Wei WJ	2013	China	Asian	753	760	Health controls	294	323	136	277	345	138	0.95 (0.82-1.09)	0.450
Current study	2014	China	Asian	369	751	Health controls	186	150	33	414	278	59	1.16 (0.95-1.41)	0.147

Table 4. Meta-analysis results of the association between miR-146a polymorphism and PTC risk

Genetic models	No. of study (Cases/Controls)	OR [95% CI]	P_{OR}	Model	P_h
Overall	7 (2,818/8,740)				
G vs. C		1.01 [0.94-1.08]	0.862	Fixed	0.224
GG+GC vs. CC		1.08 [0.91-1.27]	0.374	Random	0.022
GG vs. CC+GC		0.91 [0.76-1.08]	0.084	Fixed	0.084
GG vs. CC		0.90 [0.75-1.08]	0.254	Fixed	0.159
GC vs. CC		1.17 [0.86-1.59]	0.308	Random	0.001
Caucasian	5 (1,696/7,229)				
G vs. C		1.00 [0.91-1.02]	0.984	Fixed	0.234
GG+GC vs. CC		1.11 [0.88-1.41]	0.835	Random	0.023
GG vs. CC+GC		0.77 [0.59-1.01]	0.052	Fixed	0.052
GG vs. CC		0.79 [0.60-1.04]	0.089	Fixed	0.089
GC vs. CC		1.03 [0.79-1.33]	0.828	Random	0.012
Asian	2 (1,122/1,511)				
G vs. C		1.02 [0.90-1.09]	0.803	Fixed	0.107
GG+GC vs. CC		1.03 [0.77-1.38]	0.379	Random	0.070
GG vs. CC+GC		1.03 [0.82-1.29]	0.789	Fixed	0.789
GG vs. CC		1.01 [0.79-1.29]	0.955	Fixed	0.955
GC vs. CC		1.52 [0.89-2.58]	0.125	Random	0.001

OR, odd ratio; CI, confidence interval; P_{OR}, *P* value of odd ratio; P_h, *P* value of heterogeneity.

Table 3. The overall results of meta-analysis were shown in **Table 4**. Our result reported no significant association between miR-146a polymorphisms and PTC risk under the heterozygous, homozygous, dominant, recessive and allelic models. The subgroup analysis based on the ethnicity also revealed no significant association.

Discussion

In our research, we mainly focus on the association between microRNA polymorphism and PTC risk among Han Chinese.

By retrieving the miRBase database (release 17.0) [24], we selected four polymorphisms (miR-146a (G>C), miR-608 (G>C), miR-933 (G>A) and miR-149 (T>C)) as our studied SNPs. Meanwhile, we recruited 1398 participants from Department of Ultrasound the First Affiliated Hospital of Zhengzhou University, including 369 PTC patients in case group, 278 BN patients as positive controls and 751 healthy controls. Clinical characteristics of all participants were examined such as family history of cancer, prior history of radiation and TSH level in vivo, to study the effect of environmental factors on the PTC morbidity. Besides, we investigated some tumor-related characteristics in the PTC cases, containing histological variants, tumor location and size, invasion and TNM stage. Among all the environmental factors considered in present study, exposure to

radiation is the only one risk factors shown to significantly increase the PTC risk, which is also consistent with the previous researches [29-31]. The average TSH level and the family cancer history in PTC cases are relatively higher than other two groups, but no significant difference is observed among groups. Over half of the PTC cases were diagnosed as the classic types, and the tumors were located in one of thyroid lobe in nearly 70% PTC cases. Approximately 17% of PTC cases have the signs of tumor invasion to adjacent tissues. Nearly 70% PTC patients were diagnosed at the early stages. By comparing the genotype frequencies between groups, we found that the miR-146a polymorphisms were significantly associated with increased PTC risk and other studied miRNAs polymorphisms showed no association with the PTC susceptibility. It is reported that microRNAs function as post-transcriptional suppressors in gene expression and take part in various physiological processes, including cell proliferation, differentiation and metabolism [8, 20]. Besides, as shown in a number of studies, the aberrant expression of microRNAs is found in various human cancers [32, 33], such as breast cancer, hepatocellular carcinoma and thyroid cancer [21, 25, 34-36]. Therefore, it's hypothesized that the abnormal expression of microRNAs may lead to the aberrant proliferation of the tissue cells, which could probably progress into neoplasm. The underlying mechanism is still unclear, but some assumptions of the etiological mechanism have been suggested by some researchers. For example, the candidate targets of the microRNAs related to PTC could be p27kip1 (a cell cycle progression inhibitor) and KIT (a receptor tyrosine kinase that plays important roles in cell growth and differentiation) [32, 37, 38]. The microRNAs might initiate the carcinoma by dysregulating the expression of the target gene and the synthesis of the kinase.

Due to the limited sample size, we performed a meta-analysis with seven studies included in order to comprehensively evaluate the correlation between miR-146a variants and PTC risk. No significant association between miR-146a variants and PTC risk was found in this meta-analysis, which was inconsistent with our result. Several reasons might explain such inconsistency between the meta-analysis and our study. First, there were limited case-control studies focused on the association between miRNAs polymorphisms and PTC risk. Besides, a relatively high heterogeneity was found among the studies. In addition, the majority of the researchers only recruited participants without thyroid related diseases as healthy controls, such as Jazdzewski et al. [18], Jones et al. [28] and Marino et al. [19]. However, few studies took BN patients into consideration as positive controls, and there is only one article found [20].

In conclusion, our results indicated that miR-146a polymorphism was significantly associated with the susceptibility of PTC. However, the meta-analysis based on previous studies showed no significant association between miR-146a variants and PTC risk. The further studies may concentrate on the mechanism between miR-146a and PTC to identify whether the miR-146a polymorphism is a risk factor or not.

Disclosure of conflict of interest

None.

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