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Mir 143 rs353293 G>A Polymorphism is Not Associated with the Risk of Thyroid Cancer in the Iranian Population: A Case-Control Study

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ABSTRACT

Background: Single nucleotide polymorphisms (SNPs) in the promoter region of miRNAs may disturb miRNAs processing, alter their expression, and ultimately affect an individual's susceptibility to cancer. We conducted a case-control study to evaluate the association of rs353293 G>A with the risk of thyroid cancer in the Iranian population.

Methods: 192 patients with thyroid cancer including (papillary, follicular, medullary, and undifferentiated) and 125 healthy subjects were enrolled in this case-control study. rs353293 G>A polymorphism in the promoter region of miR-143/145 were analyzed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) to find the association of this SNP with thyroid cancer. Logistic regression analyses were conducted to evaluate adjusted odds ratios (ORs) for the potential confounding factors (age and sex), and 95% confidence intervals (95% CIs) between patients with thyroid cancer and controls.

Results: We found no association between rs353293 G>A polymorphism and thyroid cancer.

Conclusion: This study suggests that the functional polymorphism in rs353293 is not associated with development of thyroid cancer. Future investigations with larger sample size should be performed to confirm our observations.

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Introduction

Thyroid cancer is considered as the most prevalent and widespread type of endocrine malignancy with rising trend in its incidence during the last decades.[1] It is divided into four histological subgroups including papillary thyroid cancer (PTC; conventional or follicular variant), follicular thyroid cancer (FTC; conventional or oncocytic type), medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC).[2] The first two originate from well-differentiated thyroid follicular cells, while the last two are poorly or non-differentiated carcinoma.[2] Among these, PTC, the fifth leading cancer in females, accounts for over 80% of the new cases.[3]

Although the exact etiology of PTC is not fully elucidated, numerous pedigree and genomic association studies have reported that genetic susceptibilities may contribute to PTC.[4] According to the failure in recognizing the single gene that is responsible for predisposing or contributing to PTC due to its low penetrance, the interaction of two or more genes, and also regulatory genes rather than protein-encoding genes, might be the possible mechanism leading to the occurrence and development of PTC.[5]

MicroRNAs (miRs) are small non-coding regulatory RNAs of approximately 20-25 nucleotides long that modulate the expression of protein-coding genes (mRNAs) by binding to specific target sequences in the 3` untranslated regions (3` UTR) of their transcripts.[6, 7] They regulate translational interference or degradation of mRNAs.[8] These elements are involved in many physiological and pathological processes such as cell

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apoptosis, differentiation, and proliferatio.[9]

Recent evidence determines that mutation in miRNA genes or single nucleotide polymorphisms (SNPs) may affect target-binding activity, expression, or process of mature miRNA, thus affecting their target gene expression.[10] As clusters of target genes may be controlled by a classic miRNA, functional SNPs in miRNA genes may impact on expression of numerous genes and subsequently maintain several signaling pathways which may impact on susceptibility to certain human diseases.[11]

Until now, more than 1000 miRNAs have been recognized in humans that many of them are differentially altered in almost all kinds of cancers.[12] miR-143 as a tumor suppressors is coordinately expressed in a variety of cell lines and cancer tissues and its dysregulation was observed in early stages of malignant transformation.[12] It is a negative regulator of target genes (BRAF, RAS) and signaling pathways (MEK, ERK) in thyroid cancers.[13] miR-143 gene is located on chromosome 5q33.[12] Previous studies have reported that genetic polymorphisms in the promoter region of miR-143 gene may be related to the susceptibility to colorectal cancer,[14] prostate cancer[15] and cervical squamous cell carcinoma.[16]

Several single nucleotide polymorphisms (SNPs) were indicated to be associated with the risk of PTC with different designs and in different populations.[17] However, no study has been investigated the possible association of SNPs in the promoter region of miR-143 with thyroid cancer. In this study, we hypothesized that a potentially functional rs353293 G>A in the promoter region of miR-143 may have contribution to or be associated with thyroid cancer. We conducted a case-control study to evaluate the association of rs353293 G>A with thyroid cancer in the Iranian population.

Materials and Methods

In the current study, 192 patients with thyroid cancer including (papillary, follicular, medullary, and undifferentiated) and 125 healthy subjects were enrolled. Cases were newly diagnosed histological proven subjects. Healthy subjects had no family history of malignancy and autoimmune disease. Clinical parameters including tumor type and tumor stage were extracted from medical records of the patients. Blood samples were obtained from subjects for genotyping after receiving an informed written consent from the participants. The research study was approved by the Ethics local committee of Shiraz University of Medical Sciences, Shiraz, Iran.

SNP Selection Criteria

Polymorphism in mir-143 gene single-nucleotide was selected since it is a common polymorphism with the minor allele frequency of more than 0.1. As we mentioned, literature indicates association of SNP in mir-143 gene with several types of cancers; however, its association with PTC has not been investigated.

DNA Extraction and Genotyping

DNA was extracted from peripheral blood leukocytes using salting out method according to Miller' instructions.[18] Polymerase chain reaction restriction–fragment length polymorphism (PCR–RFLP) was performed to identify rs353293 C/T polymorphisms. The primer sequences whereas follow:

Forward primer 5′- CCACTCCTCCTCTCTTCC -3′,

Reverse primer 5′- CACACACAAATAACACTGATACTA -3′.

PCR conditions were 94°C for 5 min followed by 35 cycles of 95°C for 30 seconds, 55°C for 30 seconds, and 72°C for 60 seconds, finished with a 5-minute extension at 72°C. PCR amplified fragments were digested using Hphl fast digest restriction enzyme (Fermentas).

Mean and standard deviations and frequencies of the basic characteristics were calculated. SNP distribution was tested by Chi-square test to meet the Hardy–Weinberg equilibrium. Difference in the distribution frequencies of age, sex and genotypes between cases and controls were analyzed by Student t-test or $\chi 2$. Logistic regression analysis was conducted to evaluate adjusted odds ratios (ORs) for the potential confounding factors (age and sex), and 95% confidence intervals (95% CIs) between patients with thyroid cancer and control group. The homozygote and allelic state for the rs353293 C/T were set as a reference. The data were analyzed by SPSS software package (version 22; SPSS Inc., Chicago, IL, USA). $P< 0.05$ was considered to be significant.

Results

The Clinical and pathological characteristics of the patients with thyroid cancer are presented in Table 1. The sex distribution for patients was 45 (23.4%) male and 147 (76.6%) female, and for controls was 46 (36.8%) male and 79 (63.2%) female. The mean age in patients and controls was 42.97±14.52 and 40.31±15.48, respectively. 164 out of 192 patients had PTC; 63.5% of the patients were in stage I of thyroid cancer. There was no significant difference between cases and controls in terms of age (P=0.06), but a significant difference was observed in sex distribution between case and control groups (P=0.001).

Genotype Frequency

Table 2 shows genotypes and allele frequencies of rs353293 G> gene polymorphisms in patients with thyroid cancer. Genotype frequency in both patients and controls were in accordance with Hardy–Weinberg equilibrium (P value for patients=0.09, *P* value for controls=0.26). The genotype frequencies for patients was: 56.2% GG, 34.4% AG, 9.4% AA, and for controls was: 58.4% GG, 33.6% AG, 8% AA. The allele frequency for patients was 73.4% G and 26.6% A, and for controls was 75.2% G and 24.8% A. No significant difference was found for allele frequency between cases and controls (P=0.64).

Association of Mir 143 with Clinical Features in Patients with Thyroid Cancer

The association between mir-143 rs353293 G>A polymorphisms and thyroid cancer was investigated using logistic regression analysis (Table 3). We conducted the analysis in three inheritance models adjusted for age and sex. In the co-dominant model GG genotype was set as

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Table 1: Clinic and pathological characteristics of the patients with thyroid cancer

Variables	Patients (n=192)	Controls (n=125)
Age	42.97±14.52	40.31±15.48
Sex		
Male	45 (23.4%)	46 (36.8%)
Female	147 (76.6%)	79 (63.2%)
Tumor type		
Papillary	164 (85.4%)	
Follicular	11 (5.7%)	
Medullary	12 (6.2%)	
Undifferentiated	5 (2.7%)	
Papillary tumor subtype		
Classic	152 (92.6%)	
Follicular variant	10 (6.1%)	
Columnar	2 (1.3%)	
Tumor stage		
I	122 (63.5%)	
II	40 (20.8%)	
III	18 (9.3%)	
IV	10 (5.2%)	
Missing	2 (1.2%)	

Table 2: Genotype and allele frequencies of rs353293 G/A gene polymorphisms in patients with thyroid cancer in comparison with controls

SNP	Genotype/allele	Patients with thyroid cancer (n=192)	Controls (n=125)	Odds ratio (95% CI)	P value
rs353293 G/A	GG	108	73	0.011 (0.008-0.013)	0.009
	AG	66	42	0.26 (0.22-0.33)	0.021
	AA	18	10	0.18 (0.17-0.19)	0.131
	G	282	188	1.1 (0.7-1.6)	0.64
	A	102	62		

Table 3: Association of mir-143 rs353293 G/A polymorphisms with thyroid cancer

rs353293 G/A	Total patients with thyroid cancer (n=192)		Patients with papillary thyroid cancer (n=164)	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Co-dominant				
GG	1			
AG	1.1 (0.6-1.7)	0.8	1.1 (0.6-1.7)	0.8
AA	1.2 (0.5-2.7)	0.6	1.2 (0.5-2.8)	0.6
Dominant				
GG	1		1	
AG+AA	1.1 (0.7-1.7)	0.7	0.9 (0.6-1.4)	0.7
Recessive				
AA	1			
GG+AG	0.8 (0.4-1.8)	0.6	0.8 (0.4-1.8)	0.6

Table 4: Association of mir-143 rs353293 G/A polymorphisms with thyroid cancer stages

rs353293 G/A	Patients with thyroid cancer (n=192)	
	Odds ratio (95% CI)	P value
Co-dominant		
GG	1	
GA	1.9 (0.7-5)	0.2
AA	0.4 (0.04-4.1)	0.4
Dominant		
GG	1	1
GA+AA	1.5 (0.6-3.9)	0.4
Recessive		
GG+GA	1	1
AA	3.2 (0.3-31)	0.3

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reference and compared with CAG, and AA genotypes. There were no significant differences between GG vs AG (adjusted OR=1.1, 95% CI=0.6-1.7, P=0.8), and GG vs AA (adjusted OR=1.2, 95% CI=0.5-2.7, P=0.6), and thyroid cancer in co-dominant model. In the dominant model, we compared GA/AA genotype to the reference genotype (GG) and no significant difference was detected (adjusted OR=1.1, 95% CI=0.7-1.7, P=0.7). In the recessive model, GG/GA genotypes were compared to the AA genotype, and no significant difference was observed (adjusted OR=0.8, 95% CI=0.4-1.8, P=0.6).

We also investigated the association between mir-143 rs353293 G>A polymorphisms and PTC in three genetic models. No association between rs353293 G>A polymorphisms and occurrence of PTC was detected in tested models. Obviously, there was no association between mir-143 rs353293 G>A polymorphism and stages of thyroid cancer stages (Table 4). We combined patients with stages 1 and 2 in one group, and stages 3 and 4 in another group. Logistic regression analysis in three models was performed to evaluate the association of mir-143 rs353293 G>A polymorphism with these groups. No association was found in terms of stage to the mir-125 rs353293 G/A polymorphism.

Discussion

To the best of our knowledge, this is the first study designed to assess the association of mir-143 rs353293 G>A polymorphisms in patients with thyroid cancer in an Iranian population. No significant difference was observed in both allelic and genotype frequencies between patients with thyroid cancer and control group. Furthermore, mir-143 rs353293 G>A polymorphisms were not associated with thyroid cancer. Similarly, mir-143 rs353293 G>A polymorphisms showed no effect on clinical stage of thyroid cancer.

Recently, it has been reported that genetic variants in the flanking region of miRNA may have contribution to the individual's susceptibility to cancers.[19] SNP rs999885 in the promoter region of miR-106b-25 cluster associate with an increased risk of hepatocellular carcinoma.[19] Also, Jahanbani et al. found that miR-143-3p was downregulated in patients with PTC.[20] In another study, Zhang and colleagues reported that miR-143 expression was decreased in patients with thyroid cancer and B-cell malignancies.[21] Yang et al. revealed that overexpression of miR-143 inhibited cell viability, proliferation, migration, invasion, and the reduction of apoptosis in FTC-133 thyroid carcinoma cell line.[22] Based on this background, we hypothesized that polymorphism in the flanking region of miR-143/145 may be associated with thyroid cancer.

miR-143/145 is clustered on the same chromosomal locus 5q33, which is a well-known fragile site in human genome. miR cluster 143/145 is considered as an anti-oncomir, and is highly downregulated in various carcinomas including cervical cancer, colorectal, breast, prostate, and bladder cancer.[23-27] It is well-documented that miR-143/145 is involved in multiple cellular pathways underlying carcinogenesis. For instance, miR-143/145 can promote cell apoptosis and differentiation, and suppress cell proliferation, invasion and migration.[28] Chu et al. reported that rs4705342TC/CC genotypes were associated with a significantly decreased risk of prostate cancer.[15] Liang et al. reported that rs4705343TC genotype was associated with an increased risk of cervical squamous cell carcinoma.[16]

The exact mechanism of miR-143/145 in tumorigenesis is not clear. Chenet al. identified that miR-143 suppressed colorectal cancer cell growth partly by inhibiting KRAS translation.[29] ERK5 is another target of miR-143, which promotes cell growth in response to receptor tyrosine kinases.[30] Tang et al. reported that rs4705342 in the promoter region of miR-143 was significantly associated with the susceptibility to prostate cancer.[31] In the present study, we failed to find any association between mir-143 rs353293 G>A polymorphism in patients with thyroid cancer. In addition, there was no association between mir-143 rs353293 G>A polymorphisms and thyroid cancer stages. These findings indicated that polymorphism in rs353293 may have different effects on different cancer types.

Our study had some limitations that should be discussed. Firstly, relatively small sample size may result in insufficient power to detect any association between the rs353293 and thyroid cancer. Future investigations with larger sample size should be performed to confirm our observations. On the other hand, all the participants were Iranian; therefore, replication large-scale studies are warranted to confirm this result in diverse ethnicities. In summary, this study suggested that the functional rs353293 polymorphism was not associated with thyroid cancer.

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Ethical Approval

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study."

Conflict of Interest: None declared.

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