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ORIGINAL ARTICLE

Association between Genetic Polymorphisms in microRNA Machinery Genes and Risk of Papillary Thyroid Carcinoma

Abbas Mohammadpour-Gharehbagh[1] · Zahra Heidari[2] · Moein Eskandari[3] · Abtin Aryan[4] · Saeedeh Salimi[1,5]

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Abstract

Evidence suggests that the microRNAs are involved in tumorigenesis and progression of various types of malignant tumors. Therefore, the aim of current research was to examine association between genetic variants in the miRNA machinery genes and risk of papillary thyroid carcinoma(PTC) in Iranian population. Peripheral blood samples were collected from 120 PTC patients and 130 healthy subjects. Genotyping of polymorphisms in miRNA Machinery genes (*DICER1* rs3742330, *DROSHA* rs6877842 and *XPO5* rs11077) polymorphisms was performed using PCR-RFLP method. Chi square and independent sample *t* tests were applied for categorical and continuous variables, respectively. In this study, we found that frequency of *DICER1* rs3742330G allele was significantly higher in controls compared to PTC patients. In addition, the *DICER1* rs3742330 polymorphism was associated with lower risk of PTC in dominant (AG + GG vs. AA, OR = 0.5, 95%CI = 0.3–0.9, $P = 0.03$) model. No association was found between *DROSHA* rs6877842 and *XPO5* rs11077 polymorphisms and PTC neither in dominant nor in recessive and allelic models. The frequency of *DROSHA* rs6877842GC genotype was higher in PTC patients with smaller tumor size (<1). Therefore, this polymorphism could be a protective factor for tumor development in PTC patients (OR = 0.3, 95%CI = 0.1–1, $P = 0.\ 04$). The current study indicated that *DICER1* rs3742330 polymorphism was associated with lower risk of PTC. Furthermore, *DROSHA* rs6877842 polymorphism could be a protective factor for tumor development in PTC patients.

Keywords Papillary thyroid carcinoma · DICER1 · DROSHA · XPO5 · Polymorphism

Introduction

Thyroid cancer (TC) considers among the major cancers that can affect the endocrine system [1]. Over the past decade, the number of people with TC has increased in the United States [2]. It is interesting that increased TC diagnosis has been known to be associated with increased papillary thyroid cancer (PTC) that constitutes higher than 80% of all thyroid carcinomas. PTC, known as the well-differentiated TC, is described by particular nuclear features and originates from follicular epithelial cells [3].

There is a lot of evidence that PTC development is associated with several risk factors including age, sex, Hashimoto's thyroiditis, thyroid-stimulating hormone concentrations, solitary nodularity, and anti-thyroglobulin antibodies positivity [4, 5]. Moreover numerous reports showed that genetic factors may involve in development of PTC [6–9].

MicroRNAs are described as small noncoding RNA molecules, which suppress post-transcriptionally mRNA translation. It is believed that microRNAs are present in various process such as cell proliferation, differentiation, metabolism, development, and apoptosis [10]. Studies have reported that the microRNAs are involved in tumorigenesis and progression of various types of malignant tumors [11]. Evidences showed that in human carcinogenesis, specific onco-microRNAs have been up regulated, and, tumor suppressor miRNAs have been deleted genetically [12, 13], therefore it seems that the pathophysiology of cancers, including papillary

✉ Saeedeh Salimi
sasalimi@yahoo.com; salimis@zaums.ac.ir

1 Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

2 Department of Endocrinology, Zahedan University of Medical Sciences, Zahedan, Iran

3 Department of Laboratory Sciences, School of Paramedical Sciences, Zahedan University of Medical Sciences, Zahedan, Iran

4 Radiology department, Zahedan University of Medical Sciences, Zahedan, Iran

5 Cellular and Molecular Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

thyroid carcinoma, is influenced by improper biogenesis of miRNA [14]. The role of miRNAs on differentiation and function of thyroid follicular cells as well as thyroid tumorigenesis is described [15].

Biosynthesis of miRNAs occurs in several steps. At first step the miRNA gene is transcribed by RNA polymerase II into pri-miRNA in the nucleus. The nuclear RNase DROSHA, and DGCR8 protein, convert pri-miRNA into ~70 nt long precursor (with a hairpin structure), known as pre-miRNA. Ran GTPase (*RAN*) /exportin 5 (*XPO5*) complex exports pre-miRNA to the cytoplasm, and TAR RNA-binding protein (TRBP) and DICER cut pre-miRNA into miRNA duplexes (almost 20 bp) which finally is converted to miRNA [16]. In microRNA machinery genes, polymorphisms can resulted into atypical expression of miRNA and subsequently affect the target genes expression; therefore, they may be risk factors for abnormalities like tumors [17]. Hence, the aim of current research was to examine association between genetic variants in the miRNA Machinery genes (*DICER1* rs3742330, *DROSHA* rs6877842 and *XPO5* rs11077) and risk of PTC.

Materials and Methods

In this case-control study, a total of 120 PTC patients (mean age 33.5 ± 10.2 years) and 130 healthy subjects (mean age 35.9 ± 11.9 years) were recruited. This study was approved by the Ethics Committee of Zahedan University of Medical Science (IR. ZAUMS. REC.1395.208). Each participant signed informed written consent. The PTC was diagnosed based on fine needle aspiration cytology which admitted to endocrinology clinic. All subjects with previous neck irradiation, thyroid disease, thyroid surgery, other malignancies and systemic diseases were excluded from the study. Also the participants with endocrine and autoimmune diseases, diabetes mellitus, malignancies, hepatic and renal dysfunction and other systemic disease were excluded from control group.

Sample Preparation and Genotyping

After collecting peripheral blood samples in EDTA tubes, they were stored at −20 °C until DNA extraction. DynaBio kit (Takapoozist, Iran) was used, as outlined by the manufacturer to isolate genomic DNA. The primers were used for the detection of genotypes as previously described [18]. The PCR-RFLP method was applied for genotyping of *DICER1* rs3742330, *DROSHA* rs6877842 and *XPO5* rs11077 polymorphisms. The PCR assay was conducted in a final volume of 15 μL, consisting of 100 ng of DNA, 7 μL of Taq DNA Polymerase 2X Master Mix, 5 μl of ddH_2O, and 1 μL of each primer. PCR conditions were as follows: 5 min of denaturation at 95 °C, 30 cycles consisting of denaturation at 95 °C for 30 s; 30 s of annealing at 58 °C, 58 °C, and 68 °C (*DICER1* rs3742330, *DROSHA* rs6877842 and *XPO5* rs11077, respectively); 30 s of extension at 72 °C; and 5 min of extension at 72 °C. PCR products of *DICER1* rs3742330, *DROSHA* rs6877842 and *XPO5* rs11077 were digested with *Ban*I, *Sau96*I, and *Eco*RI restriction enzymes.

Statistical Analysis

For analyzing the data, SPSS version 23 was used. For continuous variables, independent sample *t* test was applied, while for categorical variables, Chi square test was used. To evaluate the relationship between PTC and genotypes, the odds ratio (OR) in the logistic regression analysis (95% CI) was measured. The Hardy-Weinberg equilibrium (HWE) was used to examine the genotypes distribution of variants. The P-values less than 0.05 were considered as significant.

Result

Table 1 indicates the demographic features of the two groups. Allele and genotype frequencies of polymorphisms in PTC patients and controls are presented in Table 2. Although the frequencies of the *DICER1* rs3742330AG and GG genotypes were lower in PTC patients than those in the controls, the differences were not statistically significant ($P = 0.07$ and $P = 0.1$). However, the *DICER1* rs3742330 polymorphism was associated with lower risk of PTC in dominant (AG + GG vs. AA, OR = 0.5, 95%CI = 0.3–0.9, $P = 0.03$) and allelic (G vs. A, OR = 0.6, 95%CI = 0.3–0.9, $P = 0.02$) models but not recessive model (GG vs. AA + AG, OR = 0.3, 95%CI = 0.06–1.5, $P = 0.14$).

The frequency of *DROSHA* rs6877842 GC genotype was lower in PTC patients than controls, however; the difference was not significant ($P = 0.06$). No association was found between *DROSHA* rs6877842 polymorphism and PTC neither in dominant (GC + CC vs. GG, OR = 0.6, 95%CI = 0.3–1.1, $P = 0.07$) nor in recessive (CC vs. GG + GC, OR = 1.1, 95%CI = 0.5–7.8, $P = 0.9$) and allelic (C vs G, OR = 0.6, 95%CI = 0.3–1.1, $P = 0.14$) models. No association was found between *XPO5* rs11077 polymorphism and PTC susceptibility in dominant, recessive and allelic models. Tables 3 and 4 present the relation between *DICER1* rs3742330 and *DROSHA* rs6877842 polymorphisms and the clinical/pathological and demographic characteristics of PTC patients. In PTC patients, there was no association between *DICER1* rs3742330 and *XPO5* rs11077 (data not shown) polymorphisms with gender, age, tumor size, N stage, TNM stage, vascular/capsular invasion, and extrathyroidal expansion. Also, no relation was observed between *DROSHA*

Table 1 Demographic and clinical characteristics of papillary thyroid carcinoma patients and controls

	PTC $n = 120$	Control $n = 130$	P value
Age	33.5 ± 10.2	35.9 ± 11.9	0.1
Gender			
Male	22(18.3)	24(18.5)	
Female	98(81.7)	106(81.5)	1
Location			
Right Lobe	52(43.3)		
Left Lobe	56(46.7)		
Both Lobes	12(10)		
Tumor Size			
<1 cm	22(18.3)		
≥1 cm	86(71.7)		
Unknown	12(10)		
TNM stage			
I	69(57.5)		
II	13(10.8)		
III	13(10.8)		
IV	9(7.5)		
Unknown	16(13.4)		
N stage			
N0	69(57.5)		
N1	34(28.3)		
Unknown	17(14.2)		
M stage			
M0	99(82.5)		
M1	4(3.3)		
Unknown	17(14.2)		
Vascular invasion			
Positive	15(12.5)		
Negative	90(75)		
Unknown	15(12.5)		
Capsular invasion			
Positive	16(13.3)		
Negative	89(74.2)		
Unknown	15(12.5)		
Extrathyroidal expansion			
Positive	12(10)		
Negative	91(75.8)		
Unknown	17(14.2)		

rs6877842 and gender, age, N stage, TNM stage, extrathyroidal expansion, and vascular/capsular invasion. Nevertheless, *DROSHA* rs6877842GC genotype had a higher frequency in PTC patients who had smaller tumor size. Therefore, this polymorphism could be a protective factor for tumor development in PTC patients (OR = 0.3, 95%CI = 0.1–1, $P = 0.04$).

Discussion

Previous studies have reported that the expressions of target genes have been influenced by dysregulation of miRNAs in TC that consequently affected the imperative cellular process including proliferation, metastasis, invasion, and apoptosis [19–21]. The miRNA- mediated gene regulation is affected by genetic variants in 3′-UTR of the miRNA target genes, which can in turn increase the risk of cancer [22].

The DICER enzyme, involved in miRNA precursor cleavage, has been shown to contribute to oncogenic processes in different cancers [12]. Recently a rare genetic disorder, DICER1 syndrome, are known which could lead to the development of benign or malignant tumors. This complication is initiated from a mutation in *DICER1* gene and its association with pleuropulmonary blastomas, multinodular goiter and thyroid cancer has been reported. Although one copy of the mutations is adequate for tumor development, some patients with a mutation in this gene do not show abnormal growths. It is probable that a second mutation in *DICER1* gene which is affected the catalytic activity of the enzyme could be initiate the tumorigenesis [23]. Previous studies have shown that there is a correlation between reduced expression of *DICER1* gene and clinical aggressiveness or poor prognosis of several tumors like lung and ovary [24, 25]. Besides, it has been reported that the expression of *DICER1* mRNA is decreased in thyroid cancer; thus, impairment of miRNA processing including DICER probably contributes to the development of thyroid cancer [26]. The *DICER1* gene has been shown to contain SNP rs3742330. This SNP is situated in the 3′-UTR region. It is postulated that gene expression and stability are influenced by this region [27].

In this study we observed higher frequency of G allele in controls compared to PTC patients which was significantly different. In addition, the *DICER1* rs3742330 polymorphism was associated with lower risk of PTC in dominant (AG + GG vs. AA, OR = 0.5, 95%CI = 0.3–0.9, $P = 0.03$) model.

Several studies have investigated the role of *DICER1* polymorphisms in cancers. Kim et al found no direct association between *DICER1* rs3742330 and rs13078 polymorphisms and Hepatocellular carcinoma (HCC) risk while they illustrated that *DICER1* rs3742330 was related to the survival of patients with HCC [27]. Wojcikiewicz et al reported an association between *DICER1* rs3742330 polymorphism and risk of laryngeal cancer in Polish Population ($p = 0.0004$) [28]. Recently song et al reported a significant association between rs3742330 polymorphism and Gastric cancer susceptibility. Furthermore, the result from Stratified analysis confirmed that the G allele of rs3742330 was associated with a later stage of gastric cancer [17].

XPO5 belongs to the importin-β family of nucleocytoplasmic transport factors. Through a GTP-

Table 2 Allelic and genotypic frequency of *DICER1*, *DROSHA* and *XPO5* polymorphisms in PTC patients and control group

	PTC (N = 120)	Control (N = 130)	P value	OR (95% CI)
DICER1 rs3742330				
AA, n(%)	91(75.8)	82(63.1)		1
AG, n(%)	27(22.5)	41(31.5)	0. 07	0.6(0.3–1.1)
GG, n(%)	2(1.7)	7(5.4)	0.1	0.3(0.05–1.3)
Dominant (AG + GG vs. AA)			0.03	0.5(0.3–0.9)
Recessive (GG vs. AA + AG)			0.14	0.3(0.06–1.5)
Allele				
A, n(%)	209(87)	205(79)		1
G, n(%)	31(13)	55(21)	0.02	0.6(0.3–0.9)
DROSHA rs6877842				
GG, n(%)	103(85.8)	100(77)		1
GC, n(%)	15(12.5)	28(21.5)	0.06	0.5(0.3–1)
CC, n(%)	2(1.7)	2(1.5)	0.97	1(0.1–7)
Dominant (GC + CC vs. GG)			0.07	0.6(0.3–1.1)
Recessive (CC vs. GG + GC)			0.9	1.1(0.5–7.8)
Allele				
G, n(%)	221(92)	228(88)		1
C, n(%)	19(8)	32(12)	0.14	0.6(0.3–1.1)
XPO5 rs11077				
AA, n(%)	45(37.5)	58(44.6)		
AC, n(%)	44(36.7)	50 (38.5)	0.7	0.9(0.5–1.4)
CC, n(%)	31(25.8)	22(16.9)	0.08	1.8(0.9–3.6)
Dominant (AC + CC vs. AA)			0.09	1.3(1–1.8)
Recessive (CC vs. AA + AC)			0.09	1.7(0.9–3.2)
Allele				
A, n(%)	134(56)	166(64)		
C, n(%)	106(44)	94(36)	0.08	1.4(1–2)

dependent process, XPO5 exports the pre-miRNAs from nucleus to cytoplasm. Afterwards, pre-miRNAs become more mature and turn into functional miRNAs in cell [29]. Because, the transporter XPO5 contribute in the miRNA synthesis pathway, the miRNA expression may be affected by the structural variations in *XPO5* gene that may resulted into the development of tumor [30].

Previous studies have demonstrated an association between rs11077 of *XPO5* gene with the risk of esophageal cancer, and laryngeal cancer [28, 31]. In this study we found no significant association between *XPO5* polymorphism and PTC as well as in dominant, recessive models, and demographic and clinical/pathological features in PTC. Wen et al reported that *XPO5* rs11077 polymorphism was associated with onset of TC. Furthermore, lower *XPO5* expression level was detected in patients with G allele [32].

DROSHA, as a major nuclease, belongs to the RNaseIII super family and catalyzes the initial stages of miRNA processing through the conversion of pri-miRNA into pre-miRNA [33]. In this study, no association was observed between *DROSHA* rs6877842 polymorphism and PTC neither in dominant nor in recessive and allelic models. However; the frequency of *DROSHA* rs6877842GC genotype was higher in PTC patients who had smaller tumor size (<1). Therefore, this polymorphism could be a protective factor for tumor development in PTC patients (OR = 0.3, 95%CI = 0.1–1, $P = 0.04$). Several studies have investigated the effect of *DROSHA* polymorphisms on cancer risk. Kim et al have found no significant association between *DROSHA* rs6877842 C > G and rs10719T > C polymorphisms and HCC risk in a Korean population [27]. In another study, Wojcikiewicz et al also observed no association between *DROSHA* rs6877842 and risk of laryngeal cancer [28]. The higher risk of bladder cancer in association with rs10719T > C in 3′- UTR of *DROSHA* was reported in Yuan et al study [34]. In another study conducted among Korean population, *DROSHA* rs874332 was associated with overall survival in breast cancer [35].

The current study had some limitation, including small sample size. Also, in some subgroups, the limited number of samples resulted in the insufficient power of analysis. Therefore, future researches with a larger

Table 3 Association of *DICER1* rs3742330 polymorphism with clinical characteristics of papillary thyroid carcinoma

Characteristics	*DICER1* rs3742330			P value		OR (95% CI)	
	AA	AG	GG	AG vs AA	GG vs AA	Dominant	Recessive
Age, years							
<40	58(74.3)	18(23.1)	2(2.6)				
≥40	33 (78.6)	9(21.4)	0(0)	0.8 0.9(0.4–2.2)	–	0.6 0.8(0.3–1.9)	–
Gender							
Female	75(76.5)	21(21.4)	2(2.1)				
Male	16(72.7)	6(27.3)	0(0)	0.6 1.3(0.5–3.9)	–	0.7 1.2(0.4–3.5)	–
Tumor size, cm							
<1	16(72.7)	5(22.8)	1(4.5)				
≥1	66(76.7)	19(22.1)	1(1.2)	0.9 0.9(0.3–2.8)	0.3 0.2(0.01–4)	0.7 0.8(0.3–2.3)	0.3 0.2(0.02–4)
N stage							
N0	54(78.3)	13(18.8)	2 (2.9)				
N1	24(70.6)	10(29.4)	0(0)	0.3 1.7(0.7–4.5)	–	0.4 1.5(0.6–4.8)	–
TNM stage							
I-II	63(76.8)	17(20.7)	2(2.5)				
III-IV	17(77.3)	5(22.7)	0(0)	0.9 1.1(0.4–3.4)	–	1 1(0.3–3)	–
Extrathyroidal expansion							
Negative	68(74.7)	21(23.1)	2(2.2)				
Positive	10(83.3)	2(16.7)	0(0)	0.6 0.7(0.1–2)	–	0.5 0.6(0.1–2.9)	–
Vascular invasion							
Negative	67(74.4)	21 (23.4)	2(2.2)				
Positive	12(80)	3(20)	0(0)	0.7 0.8(0.2–3.1)	–	0.7 0.7(0.2–2.8)	–
Capsular invasion							
Negative	66 (74.2)	21(23.6)	2(2.2)				
Positive	13(81.2)	3(18.8)	0(0)	0.6 0.7(0.2–2.8)	–	06 0.7(0.2–2.5)	–

sample size are required to approve or refute the present results. In conclusion, the current study indicated that *DICER1* rs3742330 polymorphism was related to a lower risk of PTC. Furthermore, DROSHA rs6877842 polymorphism could be a protective factor for tumor development in PTC patients.

Table 4 Association of *DROSHA rs6877842* polymorphism with clinical characteristics of papillary thyroid carcinoma

Characteristics	*DROSHA rs6877842*			P value		OR (95% CI)	
	GG	GC	CC	GC vs GG	CC vs GG	Dominant	Recessive
Age, years							
<40	66(84.6)	10(12.8)	2(2.6)				
≥40	37 (88.1)	5(11.9)	0(0)	0.9 0.9(0.3–2.8)	–	0.6 0.7(0.2–2.3)	–
Gender							
Female	85(86.7)	11(11.2)	2(2.1)				
Male	18(81.8)	4(18.2)	0(0)	0.4 1.7(0.5–6)	–	0.6 1.5(0.4–5)	–
Tumor size, cm							
<1	15(68.2)	6(27.3)	1(4.5)				
≥1	76(88.3)	9(10.5)	1(1.2)	0.04 0.3(0.1–1)	0.3 0.2(0.01–3.3)	0.03 0.3(0.1–0.9)	0.3 0.3(0.02–4)
N stage							
N0	62(89.9)	7(10.1)	0(0)				
N1	27 (79.5)	6(17.6)	1(2.9)	0.3 2(0.6-6.4)	–	0.2 2.3(0.7-7.2)	–
TNM stage							
I-II	72(87.8)	9(11)	1(1.2)				
III-IV	19(86.4)	2(9.1)	1(4.5)	0.8 0.8(0.2–4.2)	0.4 3.8(0.2–63)	0.9 1.1(0.3–4.6)	0.4 3.8(0.2–64)
Extrathyroidal expansion							
Negative	78(85.7)	11(12.1)	2(2.2)				
Positive	11(91.7)	1(8.3)	0(0)	0.7 0.7(0.1–5.5)	–	0.6 0.6(0.1–4.5)	–
Vascular invasion							
Negative	76(84.5)	12 (13.3)	2(2.2)				
Positive	13(86.7)	2(13.3)	0(0)	0.8 0.8(0.2–4.1)	–	1 1(0.2–4.9)	–
Capsular invasion							
Negative	75 (84.3)	12(13.5)	2(2.2)				
Positive	14(87.5)	2(12.5)	0(0)	0.9 0.9(0.2–4.4)	–	0.7 0.8(0.2–3.7)	–

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration.

Informed Consent Informed consents were obtained from the study participants. The study protocol was confirmed by the Ethics Committee of the Zahedan University of Medical Sciences.

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