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Association of FOXO1 Rs17592236 Polymorphism and Tumor Size in Papillary Thyroid Carcinoma

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Abstract

Background: A group of transcription factors involved in several cellular processes like cell growth, proliferation, cell cycle, differentiation and apoptosis which are critical to the cell biology of cancer is Forkhead Box O (FOXO) family. FOXOs are known as putative tumor suppressors. FOXO1 is a member of FOXO family which its abnormal expression or function has been indicated to promote cell proliferation and tumorigenesis. The probable effects of FOXO1 rs17592236 polymorphism on Papillary thyroid carcinoma (PTC) and its clinical findings were evaluated.

Methods: In total, 156 PTC patients and 158 healthy subjects were participated in the study. Genotyping of FOXO1 rs17592236 polymorphism was carried out using RFLP-PCR method.

Results: There was no association between the FOXO1 rs17592236 polymorphism and PTC in codominant, recessive, dominant, overdominant, and log-additive models. The frequency of rs17592236A allele was 13% in PTC and 17% in control group and were not statistically significant (p= 0.15). The analysis of the relationship between FOXO1 rs17592236 polymorphism and clinical specifications of papillary thyroid carcinoma demonstrated no significant relationship between rs17592236 polymorphism and PTC in different ages (< 40 and≥ 40), gender (male/female), extrathyroidal expansion, N stage, vascular invasion and capsular invasion in PTC patients. There was a relationship between FOX1 rs17592236 polymorphism and a larger tumor size (≥ 1 cm) only in log-additive model (OR= 2.96, 95% CI= 0.88-9.98; p= 0.04).

Conclusions: FOXO1 rs17592236 polymorphism was not associated with PTC; however, this variant was associated with a larger tumor size (≥ 1 cm) only in log-additive model.

Keywords: FOXO1, Papillary thyroid carcinoma, Polymorphism, Tumor size.

Introduction

Cancers are among leading causes of death worldwide. These diseases can affect any tissue or organ due to the unlimited and uncontrolled cell growth. This can be followed by migration and invasion of cancerous cells from their origin to other parts of the body (1, 2).

The incidence of thyroid cancer as the most common form of endocrine malignancy has increased dramatically during the past three decades. This cancer accounts for about 1.3% of all cancers and approximately 0.5% of death from cancer per year (3). Papillary thyroid carcinoma (PTC) has the highest prevalence as a thyroid cancer subtype that represents about 80% of all thyroid cancer patients (4). Evidence suggests that exposure of the head and neck, imbalanced iodine intake, exposure to chemical toxins and ionizing radiation, and family history are considered as probable risk factors for these cancers. Therefore, the

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genetic and environmental factors contribute to the susceptibility of thyroid cancer (4, 5).

One of the transcription factors is Forkhead Box O (FOXO) family, which can control target genes involved in cellular metabolism, cell growth, proliferation, differentiation, survival and apoptosis which are critical to the cell biology of cancer. Indeed, these proteins involve in DNA damage repair and scavenging of reactive oxygen species which are necessary for the initiation of tumorigenesis. The activation or repression of target genes of FOXO proteins can be done through the DNA binding FOX domain in nucleus. In addition, nucleoplasmic movement between nucleus and cytoplasm is controlled by the specific signal sequences (6).

Evidence showed that FOXOs are putative tumor suppressors and in adult mice simultaneous loss of Foxo1, Foxo3, and Foxo4 transcription factors could lead to increased hematopoietic lineage–specific tumors. However, the activation of FOXO results in the arrest of cell cycle and apoptosis or anoikis induction in multiple types of tumor cells (7).

FOXOs are known as important signaling proteins, located downstream of AKT. Phosphorylation of FOXOs with AKT or other kinases leads to their interaction with the 14-3-3 protein and subsequently results in their transfer from the nucleus to the cytoplasm and their inactivation. The cellular functions (proliferation and growth) are mediated by this regulatory pathway of FOXO which is initiated by the PI3K/AKT pathway. Therefore, the inhibition of FOXO by AKT/PKB pathway leads to inhibition of tumor suppression. A growing number of evidence suggests that the dysregulation of the FOXO protein's function is related to cancer progression and tumorigenesis(8, 9) There are four various FOXO proteins in mammals, namely FOXO1 (FKHR), FOXO4 (AFX), FOXO3 (FOXO3a or FKHRL1), and FOXO6. These proteins trigger different genes in several pathways including apoptosis, autophagy, cell cycle, signaling, DNA repair, metabolism, inflammation, and immune response (9).

FOXO1 has a wide range of functions in mammals. It can initiate tumor suppression and extend the mammalian lifespan similar to other FOXO proteins. This transcription factor is known as a key target in tumorgenesis prevention. Abnormal FOXO1 expression or function has been indicated to promote cell proliferation and tumorgenesis in prostate, breast, and endometrial cancer cells (6, 10).

In humans, the FOXO protein is encoded by the FOXO1 gene mapped in chromosome 13q14.1 (11). There are several SNPs in FOXO1 gene which their association with several diseases have been indicated. There are still a few reports about the relationship between these variants and cancer; therefore, this study aimed to evaluate the effects of FOXO1 rs17592236 polymorphism and PTC as well as its clinical findings.

Materials and Methods

Study group

A case-control study was conducted on 156 PTC patients and 158 sex- age- and BMI-matched controls with no previous history of cancer or other disorders in the Southeast Iranian population. All cases and controls were selected between January 2017 and February 2019. The study protocol was approved by the ethical committee of Zahedan University of Medical Sciences and the participants signed a written informed consent.

DNA extraction

From 500 µl K2 EDTA-treated peripheral blood, the human genomic DNA was isolated through the salting out method and kept at -20 °C in nuclease-free distilled water.

Genotyping of FOXO1 polymorphisms

To genotype FOXO1 rs17592236 polymorphism, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was carried out. The fragment containing the rs17592236 polymorphism was amplified with the forward: 5′-TGGTTGGGCAGGAAAGTGA-3′ and reverse: 5′- CCACCTGGACTGAAACAAG -3′primers (12).

Amplification of PCR was performed in 18 µL, containing 9 µl of 2X master mix, 1 µL

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each primer (10 μM), 6 μL deionized water and 100 ng DNA template, which were added to a 200 μL PCR reaction tube. The cycling program was as follows: a starting denaturation at 95 °C for 5 min, and then 30 cycles of 30 sec at 95 °C, 30 sec at 54 °C, extension at72 °C for 30 sec, and final extension step of 72 °C for 5 min. Then, digestion of 332 bp PCR product was done with the Eco47I restriction enzymes. The digested products were detected by 2% agarose gel, with Safe stain. Eco47I cleavage site for G allele of the rs17592236 (G/A) polymorphism produced 220bp and 102bp fragments.

Statistical analysis

Statistical analysis was performed using SPSS version 23 (SPSS for Windows, SPSS Inc, Chicago, IL, USA). The clinical and demographic specifications were evaluated using Fisher exact test or independent Student's t test.

Differences between the genotypic and allelic distribution of the study groups and clinical features of PTC were calculated using SNPStats (http://bioinfo.iconcologia.net/snpstats/start.htm) in various genetic models by obtaining the odds ratio (OR) and their CI of 95% (95% CI).

Results

General and clinical specifications of the PTC and control subjects are shown in Table 1. The frequencies of FOXO1 rs17592236 GA and AA genotypes were higher in PTC patients, but the differences were not statistically significant (Table 2). In addition, the FOXO1 rs17592236 polymorphism was not related to PTC in codominant, recessive, dominant, overdominant, and log-additive models. The frequency of rs17592236A allele was 13% in PTC and 17% in control group which was not statistically significant (p= 0.15).

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

	PTC n= 156	**Control n= 158**	**p-value**
Age	36.1±12.1	33.8±10.4	0.80
Gender			
Male	29(18.6)	28(18)	0.77
Female	127(81.4)	106(82)	
Location			
Right Lobe	69(44.2)		
Left Lobe	70(44.9)		
Both Lobes	17(10.9)		
Tumor Size			
< 1cm	30 (19.2)		
≥ 1cm	111(71.2)		
Unknown	15(9.6)		
TNM stage			
I	88(56.4)		
II	18(11.5)		
III	16(10.3)		
IV	16(10.3)		
Unknown	18(11.5)		
N stage			
N0	91(58.3)		
N1	46 (29.5)		
Unknown	19(12.2)		
M stage			
M0	132(84.6)		
M1	5(3.8)		
Unknown	19(12.2)		

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Vascular invasion	
Positive	20(12.8)
Negative	118(75.6)
Unknown	18(11.5)
Capsular invasion	
Positive	22(14.1)
Negative	116(74.4)
Unknown	18(11.5)
Extrathyroidal expansion	
Positive	17(10.9)
Negative	120(76.9)
Unknown	19(12.2)

Table 2. Allelic and genotypic frequency of FOXO1 rs17592236 polymorphism in PTC patients and control group.

	PTC (N= 156)	**Control (N= 158)**	**p-value**	**OR (95% CI)**
GG, n (%)	120(77)	112(71)		1
GA, n (%)	32(21)	38(24)		
AA, n (%)	4(3)	8(5)		
Codominant			0.34	0.79(0.46-1.34)
				0.47(0.14-1.59)
Dominant (AG+AA vs. GG)			0.22	0.73(0.44-1.21)
Recessive (AA vs. GG+AG)			0.24	0.49(0.48-1.67)
Overdominant (GG+AA vs GA)			0.45	0.81(0.48-1.39)
Log-additive (AA vs GA vs GG)			0.16	0.74(0.49-1.13)
Allele				
G, n (%)	272(87)	262 (83)		1
A, n (%)	40(13)	54(17)	0.15	0.71(0.46-1.11)

The analysis of the relationship between FOXO1 rs17592236 polymorphism and clinical specifications of papillary thyroid carcinoma (Table 3) indicated no significant relationship between rs17592236 polymorphism and PTC in different ages (< 40 and≥ 40) and gender (male/female). In addition, there was no relationship between this variant and extrathyroidal expansion, N stage, vascular invasion, and capsular invasion in PTC patients. The frequencies of rs17592236 GA+AA genotypes (dominant model) were higher in PTC patients with tumor size greater than≥ 1 cm but the difference was relatively non-significant (OR= 3.04, 95% CI= 0.85-10.78; p= 0.056). However, rs17592236 polymorphism was related to a larger tumor size (≥1 cm) only in log-additive model (OR= 2.96, 95% CI= 0.88-9.98; p= 0.04). The frequencies of FOXO1 rs17592236 GA and AA genotypes were higher in PTC patients with higher tumor stages (III+IV), but the differences were non-significant in all models.

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Table 3. Association of FOXO1 rs17592236 polymorphism with clinical characteristics of papillary thyroid carcinoma.

Characteristics	p-value OR (95% CI)								
	GG	GA	AA	Codominant1	Codominant2	Dominant	Recessive	Overdominant	Log-additive
Age, years									
< 40	78(76.5)	22(21.6)	2(2)						
≥ 40	42(77.8)	10(18.5)	2(3.7)	***0.75*** 0.84(0.37-1.95)	1.86(0.25-13.66)	***0.85*** 0.93(0.42-2.04)	***0.52*** 1.92(0.26-14.04)	***0.65*** 0.83 (0.36-1.90)	***0.96*** 1.02 (0.52-1.99)
Gender									
Female	98(77.2)	26(20.5)	3(2.4)						
Male	22(75.9)	6(20.7)	1(3.4)	***0.95*** 1.03 (0.38-2.80)	1.48 (0.15-14.96)	***0.88*** 1.08 (0.42-2.77)	***0.75*** 1.48 (0.15-14.72)	***0.98*** 1.01 (0.37-2.75)	***0.82*** 1.10 (0.49-2.45)
Tumor size									
< 1 cm	27(90)	3(10)	0(0)						
≥ 1 cm	83(74.8)	25(22.5)	3(2.7)	***0.12*** 2.71 (0.76-9.69)	-	***0.056*** 3.04 (0.85-10.78)	***0.23*** -	***0.1*** 2.62 (0.73-9.35)	***0.04*** 2.96 (0.88-9.98)
N stage									
N0	69(75.8)	20(22)	2(2.2)						
N1	38(82.6)	7(15.2)	1(2.2)	***0.63*** 0.64 (0.25-1.64)	***0.91*** (0.08-10.34)	***0.36*** 0.66 (0.27-1.63)	***0.99*** 0.99 (0.09-11.20)	***0.34*** 0.64 (0.25-1.64)	***0.42*** 0.73 (0.33-1.60)
TNM stage									
I-II	86(8.11)	18(17)	2(1.9)						
III-IV	21(65.6)	10(31.3)	1(3.1)	***0.2*** 2.28 (0.92-5.64)	2.05(0.18-23.67)	***0.075*** 2.25 (0.94-5.41)	***0.69*** 1.68 (0.15-19.13)	***0.09*** 2.22 (0.90-5.48)	***0.096*** 1.92 (0.90-4.10)
Extrathyroidal expansion									
Negative	98(81.7)	19(15.8)	3(2.5)						
Positive	13(76.5)	3(17.6)	1(5.9)	***0.76*** 1.19 (0.31-4.58)	2.51 (0.24-25.98)	***0.62*** 1.37 (0.41-4.61)	***0.48*** 2.44(0.24-24.87)	***0.85*** 1.14 (0.30-4.35)	***0.51*** 1.39 (0.54-3.59)
Vascular invasion									
Negative	96(81.4)	19(16.1)	3(2.5)						
Positive	16(80)	3(15)	1(5)	***0.85*** 0.95 (0.25-3.57)	2.00 (0.20-20.44)	***0.89*** 1.09 (0.33-3.58)	***0.57*** 2.02(0.20-20.42)	0.9 0.92 (0.25-3.45)	0.75 1.17 (0.46-3.00)
Capsular invasion									
Negative	95(81.9)	19(16.4)	2(1.7)						
Positive	18(81.8)	3(13.6)	1(4.5)	***0.73*** 1.20 (0.32-4.48)	0.38 (0.03-4.40)	***0.99*** 0.99 (0.31-3.24)	***0.45*** 0.37 (0.03-4.25)	***0.74*** 1.24(0.33-4.61)	***0.79*** 0.87 (0.33-2.29)

Discussion

The present study showed no association between FOXO1 rs17592236 polymorphism and PTC in all genetic models. But this variant had a relationship with a larger tumor size (≥ 1 cm) only in log-additive model.

PTC with a rapidly increasing incidence is still the most prevalent form of thyroid malignancy. Although the etiology of PTC is not well understood, there are some environmental and genetic factors contributing to its pathogenesis (4, 5). Evidence revealed that genetic alterations involve in the progression of PTC. Indeed, various studies investigated the association between other genetic variants and PTC including miRNA let7a-2 and pri-mir-34b/c, and MDM2 polymorphisms (13, 14).

FoxO1 as a member of Forkhead Box O (FOXO) family is expressed in mammalian. This transcription factor triggers target genes and activates or represses them through the DNA binding FOX domain as monomers or heterodimers (10). Evidence showed that over expression of FoxOs suppresses *in vitro* tumor growth and *in vivo* tumor size in breast cancer and indicate that FoxOs are tumor suppressors and therapeutic targets (10, 15).

Tn their study, Yun-Cheol et al indicated that lysine methylation of FOXO1 leads to lower stability of this protein and the expression of FoxO1 is decreased in human colon cancer (16). The role of FOXO1 as the target of miRNAs in tumorogenesis process, such as miR-27a and miR-96(17, 18). has been investigated in various studies.

In addition, FOXO1 gene is found in the commonly deleted region in prostate cancer and its expression is decreased in prostate cancer (19). Down-regulation of FOXO1 mRNA in Ewings sarcoma cells is observed because its gene is target of EWS-FLI1 fusion repressor (20).

In their study, Takahiro Kojima et al demonstrated the relation between reduced FOXO1 expression and metastasis as well as poor survival outcome in renal cell carcinoma

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cells. They also showed Knockdown of FOXO1, inhibition of apoptosis after doxorubicin treatment in cell renal cell carcinoma cells (21).

Although the role of FoxO transcription factors is established in cell cycle arrest, apoptosis, differentiation, DNA repair and subsequently tumorogenesis, there have been a few reports regarding the effects of FOXO variations and cancer susceptibility (22, 23).

Chao et al's study showed no association between FOXO1rs17592236, FOXO3 rs4946936 and FOXO4 rs4503258 polymorphisms in the miRNA target site in the 3' untranslated regions and Hepatocellular Carcinoma (HCC). However, they showed the relationship between rs17592236 CT/TT genotype and decreased risk of HCC development using multivariate logistic regression analysis (22). In their study, Haijiao et al indicated that miR-629-binding site in the 3'-UTR of FOXO3 gene could be affected by a functional polymorphism and there was a reduced risk of pancreatic carcinoma progression (23).

In Yang et al's study, FOXO3 rs17069665 was associated with higher ALL risk and rs9400241 was related to lower ALL risk (24). Wang et al. found the association between FOXO3a rs4946936 polymorphism and increased risk of childhood acute lymphoblastic leukemia (ALL) (25). Campa et al showed no association between FOXO3 rs3800231, rs9400239 and rs479744 variants and prostate cancer (26).

Regarding the role of FOXO1 in glycogenolysis and gluconeogenesis through insulin signaling, several studies investigated the association between FOXO1 polymorphisms and diabetes as well as diabetic nephropathy. Zhao et al showed the relationship between FOXO1rs17446614 and increased risk of type2 diabetic nephropathy (27). Li et al showed no association between seven FOXO1 polymorphisms and type 2 diabetes (28).

This study included a few novelties, such as the analysis of *FOXO1* polymorphisms and PTC and assessment of the effects of these variants on clinical or pathological features of PTC. However, our study had some limitations, such as small sample size or inadequate sample size in some subgroups which might affect the accuracy of the present results. If we had a larger sample size, the differences could be significant in some analysis. In addition, future works can examine the effect of FOXO1 polymorphisms on its expression and target genes expression in cancerous tissues. Therefore, similar studies with a larger sample size in different functional assays and ethnic groups are recommended to support the findings.

In conclusion, we found no relationship between FOXO1 rs17592236 polymorphism and PTC in all genetic models. But this variant was related to a larger tumor size ($\geq$ 1 cm) only in log-additive model in PTC patients.

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