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An Association Between GAS5 rs145204276, NEAT1 rs512715, and MEG3 rs4081134 Gene Polymorphisms and Papillary Thyroid Carcinoma

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Abstract

Background: This study explores the association between growth arrest-specific 5 (GAS5) rs145204276, nuclear paraspeckle assembly transcript 1 (NEAT1) rs512715, and Maternally Expressed 3 (MEG3) rs4081134 polymorphisms and their impact on susceptibility to papillary thyroid carcinoma (PTC), considering differential expression of long noncoding RNAs (lncRNAs) in PTC.

Methods: A case-control study involving 125 papillary thyroid carcinoma (PTC) patients and 125 controls was conducted. Genotyping of polymorphisms was performed using tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) and PCR-restriction fragment length polymorphism (PCR-RFLP) methods.

Results: No significant association was found between the two groups regarding genotypes and allelic frequencies of GAS-5 145204276 and MEG3 rs4081134 polymorphisms. Genetic models also showed the same results. Regarding NEAT1 rs512715, The PTC group had more GC genotypes and over-dominant models of NEAT1 rs512715 than controls, while controls showed a higher frequency of recessive models.

Conclusion: GAS5 rs145204276 and MEG3 rs4081134 polymorphisms showed no significant association with papillary thyroid carcinoma (PTC) risk. In contrast, NEAT1 rs512715 exhibited a significant impact on PTC development.

Keywords: Gene, Growth arrest-specific 5, Maternally expressed 3, Nuclear paraspeckle assembly transcript 1, Papillary thyroid carcinoma, Polymorphism.

Introduction

Thyroid cancer originates from follicular cells or parafollicular C cells. The malignancy of these cells can give rise to follicular-derived thyroid carcinoma and medullary thyroid carcinoma, respectively. Follicular-derived thyroid carcinoma involves papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), both are called well-differentiated thyroid carcinoma, and less common anaplastic and poorly differentiated thyroid carcinoma (1). Thyroid carcinomas derived from follicles account for most of the cancers in this category (2) but have a less invasive tendency and mainly metastasis to the regional lymph node than other follicular-derived thyroid carcinomas (3).

Only about 2% of all human genomic DNA is estimated to encode protein coding RNAs, and the remaining 98% encodes noncoding RNAs. The non-coding RNAs are subdivided based on their length into two major

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subgroups: small ncRNAs (20-200nt) and long ncRNAs (lncRNAs,>200) (4- 6). LncRNAs affect numerous cellular physiological and pathological processes mainly by controlling the significant steps of gene expression, and their aberrant function can cause different diseases like cancer. Accumulating studies have shown that lncRNAs can play oncogenic or tumour-suppressor roles through interaction with cellular hallmarks of cancer during proliferation, death, growth, angiogenesis, invasion, and metastasis (7). The different expression patterns of lncRNAs have been demonstrated by microarray analysis of PTC and its adjacent healthy tissue (312 upregulated and 363 downregulated lncRNAs) (8).

The GAS5 gene (Gene ID: 60674) is a tumour-suppressive lncRNA located in the 1q25 chromosome (9). Several cancers have shown that GAS5 is downregulated, and it's up-regulation causes higher apoptosis rates and lower colony-forming abilities in vitro (10-15). Multiple studies also suggested that worse pathological features of cancers are compatible with lower GAS5 gene expression levels (12, 15). The expression of GAS5 in PTC is decreased. The different mechanisms of action for GAS5 in PTC have been proposed. Yongcan et al. demonstrated that GAS5 downregulation could inhibit the anti-tumorigenic IFN/STAT1 signalling pathway (16). Zhang et al. suggested that GAS5 modulates Phosphatase and tensin homolog (PTEN) expression by acting as mia R-222-3p sponge and influencing the oncogenic phosphatidylinositol 3-kinase (PI3K/AKT) signalling pathway in PTC cells (17). A lncRNA called nuclear paraspeckle assembly transcript 1 (NEAT1) (Gene ID: 283131) is transcribed from the loci on chromosome 11q, encoding two transcriptional variants, one encoding NEAT1-1 and another encoding NEAT1-2 (18). It was recently proposed that NEAT1 involves in tumorigenesis. A genome-wide Analysis reported an increase in NEAT1 expression in PTC compared to the normal thyroid tissues, and a knockdown of NEAT1 expression could lead to apoptosis induction and inhibition of migration (19). Maternally expressed gene 3 (MEG3) (Gene ID: 55384) is a long non-coding RNA (lncRNA) on chromosome 14q32.3 (20). There is evidence that MEG3 expression is decreased in several types of cancer (21). In papillary thyroid carcinoma tissues with lymph-node metastasis, MEG3 was significantly downregulated compared to primary thyroid cancer tissues, and overexpression of MEG3 expression could block tumor migration and invasion (22).

LncRNA gene polymorphisms might influence lncRNA function by altering RNA secondary structure, RNA stability and RNA-binding ability and increasing lncRNA roles in the pathogenesis of diseases (23). Therefore, we studied GAS5 rs145204276, NEAT1 rs512715, and MEG3 rs4081134 to determine the effects of these polymorphisms on PTC susceptibility.

Materials and Methods

Subjects

The procedures that involved participants were conducted by institutional, national, and international ethical standards, as well as with the Helsinki Declaration of 1964, its amendments, or comparable ethical standards.

We conducted a case-control study on 125 patients with PTC and 125 age- and gender-matched controls at Ali Ibn Abitaleb Hospital of Zahedan, Iran; PTC patients were diagnosed based on histologically confirmed evidence of PTC at the needle aspiration cytology. Patients with a history of malignancy and prior chemotherapy and radiotherapy, other thyroid diseases, and thyroid surgery were excluded from the study. The control group was selected from healthy people who came for routine health checkups without known thyroid disease and any history of malignancy and chronic diseases. The study participants provided written informed consent. The ethics committee of Zahedan University of Medical Sciences approved the study protocol (Ethical code: IR.ZAUMS.REC.1401.033).

Genotyping

Blood samples of cases and controls were preserved in K2 EDTA-containing tubes, and genomic DNA was extracted from 500 μL of

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blood using the salting-out method and stored at -20 °C until use. GAS5 rs145204276 polymorphism was genotyped using the amplification refractory mutation system-polymerase chain (ARMS-PCR) method s described previously (24). The following primers used for NEAT1 and MEG3 polymorphism: MEG3 rs4081134 (forward primer: 5'-TTTCTTGTAGCTGCCTCCTCC-3', and reverse primer: 5'-CGTCTGTTGGCTGTGAGTGAATGA-3'), and NEAT1 rs512715 (forward primer: 5'-TCTCTAGGTTTGGCGCTAAACTC -3', and reverse primer: 5'-GTAACTTTCAGCTGGATGGC -3'). As a final volume of 25 µl, PCR reactions were performed with 2.5 ng genomic DNA, 25 pmol of each primer, 0.1 mmol dNTP, 1.5 mM MgCl2, and 1 unit of Taq DNA polymerase. The protocol of PCR reactions was as follows: initial denaturation at 95°C for 5 minutes, then 30 cycles of 95 °C denaturation for 30 seconds, annealing temperature for 30 seconds, 72 °C extension for 30 seconds, and 72 °C final extension for 3 minutes was performed. NdeI and AluI restriction enzymes (Thermo Scientific, USA) digest PCR products for MEG3 and NEATI polymorphisms, respectively. A 2.5% agarose gel containing a safe stain separated the digested and PCR products.

Statistical analysis

The SPSS version 23.0 was used for statistical analysis, and a P-value less than 0.05 was considered statistically significant. The categorical and continuous variables were analyzed by using the $\chi 2$ and independent sample t-test. Regression logistic analysis also assessed polymorphism on PTC risk.

Results

Clinical and demographic data of PTC and control groups

Table 1 shows an overview of the clinical and demographic characteristics of the PTC and control groups. There were no significant differences between the groups regarding age and gender (P=0.133 and P= 0.781, respectively). Clinic pathological features I, including tumour size, TNM stage, capsular invasion, and vascular invasion, were obtained and recorded by endocrinologists.

Table 1. Demographic and clinical characteristics of PTC patients and controls (*: P- value < 0.05).

	PTC n=125	Control n=125	*P*-value
Age, years (mean±SD)	36.3±12.4	34.1±10.6	0.133
Gender, number (%)			
Male	22 (17.6%)	23 (18.4%)	0.781
Female	103 (82.4%)	102 (81.6%)	
Tumor Size			
<1cm	30 (24)		
≥1cm	95 (76)		
Diagnosis age			
<40 years	49 (39.2)		
>40 years	76(60.8)		
N stage			
N0	81 (64.8)		
N1	44 (35.2)		
M stage			
M0	95 (76)		
M1	30 (24)		
Vascular invasion			
Positive	26 (20.8)		
Negative	99 (79.2)		
Capsular invasion			
Positive	24 (19.2)		
Negative	99 (79.2)		
Unknown	2 (1.6)		

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The genotypic and allelic distribution of GAS-5 145204276, MEG3 rs4081134, and NEAT1 rs512715 polymorphisms in PTC and control groups.

The genotypic and allelic frequencies of PTC and control subjects are shown in Table 2. No significant association was found between the two groups based on genotype and allelic frequencies of the GAS-5 145204276 polymorphism. Genetic models also showed the same results. Also, the same results were found regarding MEG3 rs 4081134 polymorphism and PTC risk. However, as shown in Table 2, the GC genotype of NEAT1 rs512715 in the PTC group was significantly more frequent than that in controls and may act as a risk factor for PTC development (OR=1.98; 95% CI=1.09-3.61; P = 0.024). The overdominant model also showed the same finding. However, our results suggested the recessive model as a protective factor for PTC development risk (OR=0.44; 95% CI=0.23-0.83; P = 0.013).

Table 2. The genotypic and allelic distribution of GAS5 rs145204276, NEAT1 rs512715, and MEG3 rs4081134 polymorphisms in PTC and control groups. Insertion/Insertion (Ins/Ins), Deletion/Insertion (Del/Ins), Deletion/Deletion (Del/Del), *: P- value < 0.05.

	PTC (N=125)	Control (N=125)	P-value	OR (95% CI)
GAS-5 145204276				
Ins/Ins, n (%)	90 (72)	87 (69.6)		
Del/Ins, n (%)	27 (21.6)	25 (20)		1
Del/Del, n (%)	8 (6.4)	13 (10.4)		
Codominant1 (Ins/Ins vs Del/Ins)			0. 891	1.04 (0.56-1.9)
Codominant2 (Ins/Ins vs Del/Del)			0.273	0.59 (0.23-1.5)
Dominant (Ins/Ins vs Del/Ins+ Del/Del)			0.667	0.89 (0.51-1.5)
Recessive (Ins/Ins+ Del/Ins vs Del/Del)			0.259	0.58 (0.23-1.47)
Overdominant (Ins/Ins+ Del/Del vs Del/Ins)			0.755	1.1 (0.59-2)
Allele				
Ins, n (%)	207 (82.8)	199 (79.6)		1
Del, n (%)	43 (17.2)	51 (20.42)	0.423	0.81 (0.51-1.27)
MEG3 rs4081134				
GG, n (%)	71(56.8)	74 (59.2)		
GA, n (%)	37 (29.6)	36 (28.8)		1
AA, n (%)	17 (13.6)	15 (12)		
Codominant 1 (GG vs GA)			0.811	1.07 (0.6-1.88)
Codominant 2 (GG vs AA)			0.553	1.2 (0.58- 2.7)
Dominant (GG vs GA+AA)			0.645	1.12 (0.68-1.86)
Recessive (GG+GA vs AA)			0.581	1.2 (0.58-2.6)
Overdominant (GG+AA vs GA)			0.922	1.02 (0.59-1.7)
Allele				
G	179 (71.6)	184 (73.6)		
A	71 (29.4)	66 (26.4)	0.688	1.1 (0.74- 1.6)
NEAT1 rs512715				
GG, n (%)	62 (49.6)	67 (53.6)		
GC, n (%)	46 (36.8)	25 (20)		1
CC, n (%)	17 (13.6)	33 (26.4)		
Codominant 1 (GG vs GC)			0.024*	1.98 (1.09-3.61)
Codominant 2 (GG vs CC)			0.091	0.55 (0.28-1.1)
Dominant (GG vs GC+CC)			0.527	1.17 (0.71-1.9)
Recessive (GG+GC vs CC)			0.013*	0.44 (0.23- 0.83)
Overdominant (GG+CC vs GC)			0.004*	2.23 (1.3-4.1)
Allele				
G	170 (68)	159 (63.6)		
C	80 (32)	91 (36.4)	0.345	0.82 (0.56-1.2)

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Discussion

We found no association between GAS5 rs145204276 and MEG3 rs4081134 polymorphisms and PTC development risk. However, our results demonstrated that the NEAT1 rs512715 significantly affected PTC development.

Several lncRNAs have differential gene expression in PTC, contributing to its progression and development. It was reported by Xiao et al. that focally amplified long non-coding RNA in epithelial cancer (FALEC) expression, as a long noncoding RNA, in PTC tissue was higher than that in normal one. Furthermore, the inhibition of its expression inhibited tumor cell proliferation, invasion, and metastasis (25). Wang et al. indicated that lncRNA BRAF-activated non-protein-coding RNA (BANCR) was involved in PTC pathogenesis. They also observed increased proto-oncogene B-Raf (BRAF) expression in PTC tissue, which could be activated by epithelial-mesenchymal transition (EMT) in the tumor cell (26).

GAS5 has been shown to affect the cell cycle in malignant tumors, inhibiting their proliferation and acting as a tumor suppressor. The expression of GAS5 is significantly reduced in tissues and cells of PTC patients, and the upregulation of GAS5 expression leads to tumor growth inhibition. Recently, GAS5 has been proposed as the novel target for PTC treatment (27). A study by Guo et al. demonstrated that thyroid cancer tissues exhibit a lower expression of GAS5 than benign tumor tissues, associated with tumor lymph node metastasis, multiple cancer foci, and tumor node metastasis (TNM) staging. They also found a low survival rate related to the low expression of GAS5 (28). The GAS5 rs145204276 gene polymorphism is one of the well-studied polymorphisms of this gene. Studies have shown that rs145204276 is related to tumorigenesis and can change GAS5 gene expression (29). The evidence demonstrates the impact of GAS5145204276 Polymorphism on several kinds of the cancers, such as renal cell Carcinoma (29), gastric cancer (30), hepatocellular carcinoma (31), and breast Cancer (24).

Studies show decreased MEG3 expression in stomach, bladder, prostate, and lung cancers. Wang et al. demonstrated the downregulation of the MEG3 expression in PTC tissue. Furthermore, they showed a suppressor action of MEG3 overexpression on cell invasion and migration in TPC-1 and HTH83 thyroid cancer cell lines (22). Liu et al. concluded that MEG3 enhanced ^{131}I sensitivity in TC cells through miR-182, suggesting that MEG3 may act as a biomarker and therapeutic target for TC patients resistant to ^{131}I (32). To the best of our knowledge, this is the first study about the PTC risk and MEG3 rs4081134 polymorphism. However, we found no significant association between MEG3 rs4081134 polymorphism and PTC. Studies have been conducted on the relationship between this polymorphism and cancers such as Lung Cancer, neuroblastoma, and Leukemia (33-35).

Studies report that lncRNA NEAT1 could promote thyroid carcinoma progression. The suppression of miR-129-5p by lncRNA NEAT1 could inhibit PTC progression (36). Moreover, Sun et al. found an increase in NEAT1_2 expression in PTC, positively correlated with TNM stage and tumor size. They also demonstrated that When NEAT1_2 was knocked down, PTC cells underwent apoptosis and growth inhibition (37). For the first time, we showed a significant association between NEAT1 rs512715 polymorphism and PTC development risk. The recessive model is proposed as a protective factor for PTC development. In contrast, the overdominant model and GC genotype are regarded as risk factors. There is some evidence about the impact of the NEAT1 rs512715 polymorphism on several cancers. For example, a study by Wang et al. found no increase or decrease in lung cancer risk due to this polymorphism (38). According to Fang et al., allele "C" of rs512715 in NEAT1 was associated with the increased risk of cervical cancer in allelic, dominant, codominant, Overdominant, and log-additive models (39).

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In conclusion, we found no association between GAS5 rs145204276 and MEG3 rs4081134 polymorphisms and PTC development risk. However, our results demonstrated that NEAT1 rs512715 significantly affected PTC development.

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Conflict of interest
We declare that we do not have any conflicts of interest.

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