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ORIGINAL ARTICLE

The Relation of TSH Receptor Polymorphism to the Behavior of Papillary Thyroid Carcinoma in Egyptian Population

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ABSTRACT

Background: Thyroid cancer is the most common endocrine cancer, in which genetic mutations play a major role. We studied thyroid stimulating hormone (TSH) receptor gene polymorphism (rs179247 and rs12101255) in papillary thyroid carcinoma (PTC).

Methods: The study was conducted on fifty patients with documented PTC. Patients with thyroid nodules were selected from Alexandria University hospital outpatient clinics after excluding hyperthyroidism, autoimmune thyroid diseases, and non-suspicious nodules. Eligible patients were subjected to total thyroidectomy in the head and neck and endocrine surgery unit. DNA, extracted from formalin fixed paraffin embedded normal and malignant thyroid tissues, was analyzed by real time polymerase chain reaction using TaqMan® Genotyping Assay.

Results: No difference was found between normal and malignant tissues regarding TSH receptor polymorphism. No relations were found in both polymorphisms with serum TSH, malignant nodule size, multiplicity of the lesions, TIRADs staging, or Bethesda classification. Rs179247 genotype AA (vs. AG and GG: P=0.044*) was associated with extrathyroidal extension.

Conclusions: In conclusion TSH receptor polymorphism rs179247, and not rs12101255, may predict extrathyroidal extension in papillary thyroid cancer.

Keywords: TSHR polymorphism; TSHR rs12101255; TSHR rs179247; Papillary thyroid carcinoma; Extrathyroidal extension.

INTRODUCTION

One of the most famous cancers in endocrinology is thyroid cancer, and the most predominant type of thyroid carcinoma, reaching about 80% of all thyroid carcinomas, is papillary carcinoma (PTC). Due to the identification of subclinical cases, the incidence of thyroid carcinoma has grown thrice during the last thirty years [1]. Thyroid cancer identification has grown as a result of a number of improvements in healthcare practices, including greater access to the healthcare system, more frequent biopsy and surgery, increasing use of high-resolution ultrasound examination, and more extensive tissue analysis by pathologists [2].

The main molecule controlling proliferation, differentiated function of thyroid follicles is the TSH receptor (TSHR). The TSHR gene has ten exons and is found on chromosome 14q. Its molecular weight is 87 kDa, and it encodes the creation of 764-amino acid protein. Large amino-terminal ectodomain is encoded by the gene's first nine exons, whereas seven transmembrane segments with a carboxyl-terminal region are encoded by exon 10 [3].

Familial non-autoimmune autosomal dominant hyperthyroidism (FNAH) or sporadic congenital non-autoimmune hyperthyroidism (SNAH) are arised from constitutively activating germline mutations [4]. Both toxic multinodular goiters and about 84% of solitary toxic thyroid nodules have

been shown to have somatic activating mutations [5]. Patients with less common disorders such familial gestational thyrotoxicosis, caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin and hyperfunctioning thyroid carcinomas [5] have also been shown to contain mutations [6].

Rarely do well-differentiated thyroid tumors have mutations in TSHR gene and Gsα subunit. It is thought that while an activated cAMP pathway promotes proliferation, it is insufficient to cause normal thyrocytes to turn cancerous. Coexisting TSHR mutations and oncogenic mutations like RAS and RET/PTC are found in the majority of hyper-functioning malignant tumors, and the neoplasms' hyper-functioning characteristics are influenced by the TSHR and Gs mutations [3].

The most prevalent variation among people that determines their susceptibility to various diseases is single nucleotide polymorphisms. Results of association studies displayed TSHR is susceptibility locus specific to Graves disease (GD) and identified an exclusive susceptibility region on TSHR intron 1, where 5 GD-associated SNPs mapped. These SNPs are the most extensively researched variations in TSHR gene and include rs179247, rs2284720, rs12101255, rs12101261, rs2268458 [7]. The highest correlation with GD was found in TSHR SNPS rs179247 and rs12101255 in various populations from Asia, Europe, and South America [8, 9].

No previous studies were done with these SNPs and PTC. Therefore, we aimed at studying their association with PTC and their relationship with different clinical and pathological characteristics.

METHODS

Patient characteristics and laboratory evaluation

The study was conducted on fifty patients with documented PTC in Alexandria main University Hospital, Alexandria, Egypt. Patients were recruited from both Endocrinology and Surgery clinics. The study protocol reviewed and approved by the Ethical Committee, Faculty of Medicine, University of Alexandria according to Declaration of Helsinki and its subsequent modifications (S/N. 0201171, on 15/11/2018), and informed written consent for patients' participation in clinical research was collected before inclusion in the study according to ethical guidelines. History taking, clinical examination, ultrasonographic examination, thyroid function tests (TSH, free T3 and free T4) and thyroid peroxidase antibodies (anti TPO) were performed for patients presenting with thyroid nodules. Patients with clinical and/or biochemical hyperthyroidism or hypothyroidism, with positive anti TPO, ultrasonographic evidence of autoimmune thyroid disease or with non-suspicious thyroid nodules were excluded. Songraphically suspicious nodules were subjected to fine needle aspiration according to American college of radiology thyroid imagingreporting and data system TI-RADS [10] and pathological examination according to Bethesda classification for reporting thyroid cytopathology [11]. Thyroidectomy was done for patients with suspicious or malignant nodules. Pathological examination of the final specimens was done in the pathology department. Patients with benign neoplasms or lymphocytic thyroiditis in their final pathology were excluded. Included patients signed an informed consent authorized by ethics committee in Alexandria faculty of medicine. Both malignant and normal thyroid tissues were used and compared for both rs179247 and rs12101255.

DNA isolation and genotyping of TSHR SNPs

Genomic DNA was purified from formalin fixed paraffin embedded (FFPE) malignant and normal thyroid tissues (1µl each) using QIAamp® DNA FFPE Tissue Kit (QIAGEN, USA). TSHR gene polymorphism rs12101255 and rs179247 were detected by AssaysC_2692853_10 and C_31754698_10, Applied biosystems-Life Technologies, USA respectively by 5' nuclease assay, using Rotor- gene Q real time PCR system (Qiagen, Germany).

Statistical analysis

Data was examined using IBM SPSS software package version 20.0 (IBM Corp., Armonk, NY). Qualitative data reported using numbers and percentages. Kolmogorov-Smirnov test used to confirm that the distribution was normal. Quantitative data described using range (minimum and maximum), mean, standard deviation, and median. Significance of the results assessed at the 5% level. The F-test (ANOVA), Hardy-Weinberg, student t-test, chi-squared test, Fisher's exact or Monte Carlo correction, and others were used.

RESULTS

TSHR polymorphism (rs179247)

No statistically significant difference found between malignant thyroid tissue and normal juxta nodular tissue. Genotype AG was found in 50%, AA in 40% and GG in 10% of the patients, equally in both tumor and normal tissues. There was no difference in the allele frequency between malignant and normal tissues (Table 1).

TSHR polymorphism (rs12101255)

No statistically significant difference found between malignant thyroid tissue and normal juxta nodular tissue. Genotype distribution CC and CT was 72% and 28% respectively in tumor tissues. Genotype distribution CC, CT and TT was 72%,

24% and 4% respectively in normal tissues. There was no difference in the allele frequency between malignant and normal tissues (Table 2).

Relation between rs179247 in malignant tissues with different clinicopathological parameters

No relationship observed between genotypes and TSH level, suspicious nodule size, TIRADS, Bethesda class, T stage, multiplicity of lesions, lymphovascular and perineural invasion. The AA genotype was associated with higher incidence of extrathyroidal extension (MCp=0.044*) (Table 3).

Relation between rs12101255 in malignant tissues with different clinicopathological parameters

No relationship observed between genotypes and TSH level, suspicious nodule size, TIRADS, Bethesda class, T stage, multiplicity of lesions, extrathyroidal extension, lymphovascular and perineural invasion (Table 4).

Table (1): Comparison of genotypic distribution between Tumor and normal tissue according to polymorphism rs179247 in patients with thyroid carcinoma

rs179247	Tumor (n = 50)		Normal (n = 50)		χ^2	p
	No.	%	No.	%		
AA	20	40.0	20	40.0	0.000	1.000
AG	25	50.0	25	50.0		
GG	5	10.0	5	10.0		
HWE	**0.484**		**0.484**			
Allele						
A	65	65.0	65	65.0	0.000	1.000
G	35	35.0	35	35.0		

χ^2: **Chi square test**, HWE: **Hardy-Weinberg**, p: p value for comparing between the studied groups

Table (2): Comparison of genotypic distribution between Tumor and normal tissue according to polymorphism rs12101255 in patients with thyroid carcinoma

rs12101255	Tumor (n = 50)		Normal (n = 50)		χ^2	p
	No.	%	No.	%		
CC	36	72.0	36	72.0	1.797	^{MC}p= 0.537
CT	14	28.0	12	24.0		
TT	0	0.0	2	4.0		
HWE	**0.249**		**0.449**			
Allele						
C	86	86.0	84	84.0	0.157	0.692
T	14	14.0	16	16.0		

χ^2: **Chi square test**, MC: **Monte Carlo,** HWE: **Hardy-Weinberg**, p: p value for comparing between the studied groups

Table (3): Relation between rs179247 tumor with different parameters (n = 50)

rs179247 tumor								
	AA (n = 20)		AG (n = 25)		GG (n = 5)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Lymph-vascular invasion								
Not identified	10	50.0	17	68.0	2	40.0	χ^2= 2.271	^{MC}p= 0.315
Present	10	50.0	8	32.0	3	60.0		
Peri-neural invasion								
Not identified	17	85.0	24	96.0	4	80.0	χ^2= 2.627	^{MC}p= 0.275
Present	3	15.0	1	4.0	1	20.0		

rs179247 tumor								
	AA (n = 20)		AG (n = 25)		GG (n = 5)		Test of Sig.	p
Extra thyroidal extension								
Not identified	13	65.0	23	92.0	3	60.0	χ^2= 6.095*	^{MC}p= 0.044*
Present	7	35.0	2	8.0	2	40.0		
T stage								
T1	7	35.0	13	52.0	2	40.0	χ^2= 1.397	^{MC}p= 0.554
T2 – T3	13	65.0	12	48.0	3	60.0		
Multiple lesions								
No	15	75.0	14	56.0	3	60.0	χ^2= 1.874	^{MC}p= 0.394
Yes	5	25.0	11	44.0	2	40.0		
TSH								
Min. – Max.	0.50 – 3.34		0.64 – 3.60		0.52 – 2.50		F= 1.026	0.366
Mean ± SD.	1.73 ± 0.81		2.01 ± 0.85		1.55 ± 0.75			
Median	1.66		2.0		1.68			
Nodule size								
Min. – Max.	1.0 – 7.0		1.0 – 4.20		1.40 – 3.80		H= 1.851	0.396
Mean ± SD.	2.80 ± 1.52		2.26 ± 1.01		2.74 ± 1.01			
Median	2.65		1.90		3.0			
TIRADS								
3	3	15.0	3	12.0	0	0.0	χ^2= 0.861	^{MC}p= 1.000
4	7	35.0	8	32.0	2	40.0		
5	10	50.0	14	56.0	3	60.0		
Besthda								
IV	2	10.0	6	24.0	1	20.0	χ^2= 4.940	^{MC}p= 0.249
V	15	75.0	17	68.0	2	40.0		
VI	3	15.0	2	8.0	2	40.0		
Sex								
Male	3	15.0	5	20.0	3	60.0	χ^2= 4.181	^{MC}p= 0.098
Female	17	85.0	20	80.0	2	40.0		
Age (years)								
Min. – Max.	15.0 – 52.0		8.0 – 68.0		20.0 – 57.0		F= 2.332	0.108
Mean ± SD.	35.35 ± 11.48		43.52 ± 13.71		36.40 ± 15.90			
Median	35.50		42.0		31.0			
Pathology								
NIFTP	0	0.0	2	8.0	0	0.0	χ^2= 4.527	^{MC}p= 0.646
Invasive follicular variant PTC	6	30.0	4	16.0	2	40.0		
Papillary carcinoma	11	55.0	17	68.0	3	60.0		
Papillary microcarcinoma	3	15.0	2	8.0	0	0.0		

SD: **Standard deviation**, F: **F for ANOVA test**, H: H for **Kruskal Wallis test**, χ^2: **Chi square test**, MC: **Monte Carlo,** p: p value for comparing between different genes, *: Statistically significant at $p \leq 0.05$

Table (4): Relation between rs12101255 tumor with different parameters (n = 50)

rs12101255 tumor						
	CC (n = 36)		CT (n = 14)		Test of Sig.	p
	No.	%	No.	%		
Lymph-vascular invasion						
Not identified	19	52.8	10	71.4	χ^2= 1.439	0.230
Present	17	47.2	4	28.6		
Peri-neural invasion						
Not identified	32	88.9	13	92.9	χ^2= 0.176	^{FE}p= 1.000
Present	4	11.1	1	7.1		
Extra thyroidal extension						
Not identified	28	77.8	11	78.6	χ^2= 0.004	^{FE}p= 1.000
Present	8	22.2	3	21.4		
T stage						
T1	17	47.2	5	35.7	χ^2= 0.542	0.462
T2 – T3	19	52.8	9	64.3		
Multiple lesions						
No	23	63.9	9	64.3	χ^2= 0.001	0.979
Yes	13	36.1	5	35.7		
TSH						
Min. – Max.	0.50 – 3.60		0.74 – 2.70		t= 0.405	0.687
Mean ± SD.	1.89 ± 0.91		1.78 ± 0.57			
Median	1.87		1.80			
Nodule size						
Min. – Max.	1.0 – 7.0		1.0 – 4.0		U= 245.0	0.880
Mean ± SD.	2.59 ± 1.32		2.36 ± 1.05			
Median	2.58		2.10			
TIRADS						
3	4	11.1	2	14.3	χ^2= 0.460	^{FE}p= 0.827
4	13	36.1	4	28.6		
5	19	52.8	8	57.1		
Besthda						
IV	9	25.0	0	0.0	χ^2= 4.849	^{MC}p= 0.076
V	23	63.9	11	78.6		
VI	4	11.1	3	21.4		
Sex						
Male	7	19.4	4	28.6	χ^2= 0.489	^{FE}p= 0.476
Female	29	80.6	10	71.4		
Age (years)						
Min. – Max.	8.0 – 68.0		22.0 – 53.0		t= 0.997	0.325
Mean ± SD.	40.53 ± 14.64		37.0 ± 9.58			
Median	41.0		37.0			
Pathology						
NIFTP	2	5.6	0	0.0	χ^2= 1.785	^{MC}p= 0.683
Invasive follicular variant PTC	7	19.4	5	35.7		
Papillary carcinoma	23	63.9	8	57.1		
Papillary microcarcinoma	4	11.1	1	7.1		

SD: **Standard deviation**, t: **Student t-test**, U: **Mann Whitney test**, χ^2: **Chi square test,** FE**: Fisher Exact,** MC: **Monte Carlo**, p: p value for comparing between different genes

DISCUSSION

Our aim was to study the relation between these two SNPs (rs179247 and rs12101255) with differentiated thyroid cancer by comparing malignant to normal thyroid tissues in the same patients, and to look for any correlation with the tumor behavior.

These two SNPs were not previously studied in differentiated thyroid cancer. However, we have chosen to test them, considering several reports of their association with Graves' disease.

Association studies conducted provided compelling evidence and established TSHR as a GD-specific susceptibility locus and pointed to anexclusive susceptibility region located in TSHR intron 1, where at least five GD-associated SNPs were mapped: rs179247, rs2284720, rs12101255, rs12101261, and rs2268458SNPs representing the most widely studied variations in TSHR gene [7]. TSHR SNPS rs179247 and rs12101255 showed strongest association with GD in different populations from South America, Europe and Asia [8, 9].

Three large case-control studies conducted on Caucasian patients with GD in both Poland and UK showed that both rs179247 allele A and rs12101255 allele T exhibited strong association with GD but failed to show any association with any specific clinical characteristic [12].

Colobran et al. not only found that TSHR rs179247 AA genotype alleles conferred GD risk but also influenced the age of onset, which was younger for the AA versus GG genotype [13].

In another study conducted in china, Liu et al established that rs12101255 major allele T was significantly higher in GD cohorts, raised risk of GD. Besides, the TT genotype frequencies in GD were higher than the control group with a possibility of increasing the risk of GD. There were No significant differences observed in allele and genotype distribution of rs179247 between patients and control persons, but in ophthalmopathy patients with GD, major allele A was significantly higher compared to healthy subjects [14].

In Brazil, another study by Bufalo et al. stated that inheritance of the thyroid-stimulating hormone receptor AA genotype for rs179247 raised risk for GD by almost 3 times [15]. Contradicting that, in Iraq, another study showed that both genotypes AG and GG of rs179247 were higher in a significant way in GD cases compared to controls [16]. These findings were confirmed by several meta-analysis studies tightfitting the strong association of rs179247 and rs12101255 and GD [17, 18].

Differential expression of different types of mutations in malignant and nonmalignant tissues of the same patients has been described, so we were aiming to find similar difference in our study. As an example, differential expression of TSHR gain of function mutation has been reported in malignant thyroid tissues but not in normal tissues [19].

Cetani et al. analyzed TSHR gene mutations in 22 patients undergone total thyroidectomy for differentiated thyroid cancer. 15 patients manifested with solitary cold nodule in otherwise normal thyroid gland and 7 cases had cold nodule within a non-toxic nodular goiter. At the time of diagnosis, all cases were clinically euthyroid. Extraction of DNA was done from fresh frozen, or paraffin embedded malignant thyroid tissue and was compared to the normal juxtanodular tissue. None of DTC tissues contained their studied TSHR gene somatic mutations in portions coded by exon 9 and 10, and there was no difference between the normal and the malignant tissues. Two follicular cancers had heterozygous base substitution at codon 727 (Asp to Glu). Same pattern was detected in normal DNA specimens obtained from these cases, pointing that this substitution was not a somatic mutation but a neutral polymorphism [20].

In another study to determine role of TSH and TSH receptor on hepatocellular carcinoma (HCC), paired cancerous and non-cancerous HCC tissues were examined with TSHR expression assays. Overexpression of TSH as well as presence TSHR mutations were found in cancerous HCC tissues [21].

In a study examined the TSHR gene promoter hypermethylation in thyroid cancer in the backdrop of BRAF gene mutational status, 60 patients with untreated thyroid cancer were involved. The resected tumor tissue and adjacent normal tissue were used for the study. The results showed strong association between TSHR gene methylation and BRAF V600E mutation in thyroid cancer, depicting a positive connection between TSHR pathway and MAP Kinase pathway [22].

No previous studies were conducted on these two polymorphisms in thyroid cancer patients. Though no difference was found in both polymorphisms between both the malignant and nonmalignant thyroid tissue. Despite that six of our patients had different genotypes in malignant and nonmalignant tissues. Two patients had different genotypes in rs179247 and four patients in rs12101255. In rs12101255 none of our patients had the genotype TT, and in rs179247 genotype GG was the least expressed denoting a possible protective effect.

There was no association between the studied polymorphism and the clinical features of our patients including TSH, nodule size, Bethesda class, TIRADS, tumor staging, multiplicity of the nodules, lymphovascular and perineural invasion. However,

a positive correlation has been found between rs179247 and the occurrence of extrathyroidal extension. When compared to other genotypes, rs179247 AA was associated with more extrathyroidal extension. This finding has not been found in rs12101255.

In a prior study, 300 patients of PTC and 252 controls were genotyped for two tagSNPs (rs6464149 and rs7810757) in BRAF and six tagSNPs (rs17630128, rs2075179, rs7144481, rs2371462, rs2268477, and rs2288496) in TSHR in order to assess the potential functional tagging single nucleotide polymorphisms (tagSNPs) in BRAF and TSHR. The BRAF and TSHR genotype frequencies did not show difference between PTC cases and control persons, indicating that neither polymorphism contributes to PTC susceptibility. The study's sole noteworthy discovery was a TSHR tagSNP, rs2288496, which may have an impact on the frequency of lymph node metastases (LNM). PTC patients carrying the TSHR rs2288496 TC and CC variants were associated with higher TSH level and lower T4 and Anti-TG levels and were prone to developing LNM, but no relation was observed between these genotypes and tumor stage, number of cancer lesions, extrathyroidal extension and concomitant benign thyroid disease [23]. The study's sole noteworthy finding was a TSHR tagSNP, rs2288496, which may have an impact on the frequency of lymph node metastases (LNM). Although there was no correlation found between these genotypes and tumor stage, number of cancer lesions, extrathyroidal extension, or concurrent benign thyroid disease, PTC patients with the TSHR rs2288496 TC and CC variants had higher TSH levels, lower T4 and Anti-TG levels, and a higher risk of developing LNM [23].

Conclusion

From the results presented in the current study we can conclude that TSH receptor polymorphism rs179247, and not rs12101255, can be utilized as a predictive marker of extrathyroidal extension in papillary thyroid cancer in Egyptian population.

Recommendations

To strengthen and validate the findings of the current study, further analysis of TSH receptor mutations in a larger sample of papillary thyroid carcinoma patients among Egyptians and other ethnicities is recommended.

Conflict of interest

The authors declared that they have no conflicts of interest with respect to authorship and/or publication of this article.

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