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The effect of CASP3 rs4647610 and rs4647602 polymorphisms on tumour size and cancer stage in papillary thyroid carcinoma

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most frequent form of thyroid cancer whose incidence has increased in recent years. Dysregulated apoptosis is known in the pathogenesis of various cancers. Caspase-3 is an important apoptotic component and its abnormal function may play a key role in cancer pathogenesis. We tested the hypothesis of a link between CASP3 single nucleotide polymorphisms rs4647610 and rs4647602 on PTC and its clinical outcomes.

Material and methods: A total of 134 PTC patients and 151 healthy controls were genotyped for CASP3 rs4647610 and rs4647602 single nucleotide polymorphisms (SNPs) using PCR-RFLP method.

Results: Allele and genotype frequencies of both SNPs were not different between cases and controls. The combined genotypes and haplotypes were not linked to PTC. However, the frequencies of *CASP3* rs4647610 GA and AA genotypes were higher in PTC patients with larger tumour size (≥1 cm), and the rs4647610 SNP was associated with increased tumour size in the dominant model (OR 3.4 [95% CI, 1.1–11], $P = 0.04$). The *CASP3* rs4647602CA and AA genotypes were higher in PTC patients with lower TNM stage (I–II) compared to higher stages (III–IV). No association was observed between CASP3 polymorphisms and other PTC outcomes.

Conclusion: Although CASP3 rs4647610 and rs4647602 SNPs are not associated with PTC, rs4647610 is linked to larger tumour size, and rs4647602 to lower stage of cancer.

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Introduction

Thyroid cancer is one of the most common endocrine neoplasms and its incidence has increased globally over recent years. Papillary thyroid carcinoma (PTC) is the most frequent form of thyroid cancer and accounts for approximately 80–85% of all thyroid carcinomas [1,2]. PTC is more common in women and Caucasians, and its incidence increases with age [3]. PTC develops through follicular epithelial cells and is characterized by its papillary appearance and typical nuclear features [4]. Radiation exposure, family history, female gender and age are among the most common risk factors. In addition, high iodine intake, Hashimoto's thyroiditis and obesity are regarded as other risk factors for this cancer [5]. Several epidemiological studies have shown the role of genetic factors as well as environmental factors in PTC susceptibility [5–7], and a 4- to 10-fold increased risk of this cancer is observed in individuals with first-degree relatives [8].

Apoptosis is the main controlled biological process in cell death. It is involved in cell growth and development, immunity, tumour suppression, maintenance of tissue homoeostasis, and removal of damaged and abnormal cells [9]. Dysregulation of apoptosis is well known in the pathogenesis of various diseases including cancers. In cancerous cells, it is a vital mechanism to avoid an increase in the proliferation of abnormal cells [10]. Caspases are a group of the cysteine-aspartic acid proteases which play key roles in apoptosis. Caspase-3, as one of the most studied apoptotic proteins, is a significant component in apoptosis. The inactive caspase-3 is directly digested by Caspase-8, –9 and –10 and acts as the main executor of apoptosis [11,12]. Numerous studies have demonstrated that the altered levels of caspase-3 in malignant tissues may be important candidate targets in chemotherapy [13–15].

The gene coding for caspase-3 (*CASP3*) is mapped to 4q35.1. There are several genetic variants in this gene, and their effect on various diseases has been elucidated. *CASP3* rs4647610 and rs4647602 are two single nucleotide polymorphisms (SNPs) and their association with several cancers has been reported [16,17]. A recent meta-analysis showed the impact of CASP3 polymorphisms on overall cancers [18]. We hypothesised an association between *CASP3* rs4647610 and rs4647602 SNPs and PTC and certain clinical features.

Materials and methods

A total of 134 patients with PTC and 151 healthy controls were enrolled between January and December 2017. PTC

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was diagnosed according to American Thyroid Association (ATA) guidelines by pathological examination of individuals who referred to the Outpatient Endocrinology Clinic of Zahedan (South-East of Iran). The controls were selected from the same clinic and had no history of disease or cancer. All participants with a history of thyroid diseases, neck irradiation or thyroid surgery, exposure to iodinated contrast media in the last 6 months and other cancers were excluded. Both groups were matched according to gender, age, race and body mass index (BMI). The Human Research Ethics Committee of Zahedan University approved the protocol of the study. All study participants provided a written informed consent.

The DNA was extracted from blood samples from all participants using a DNA extraction kit (DynaBio, Takapoozist, Iran). Genotyping of *CASP3* rs4647610 and rs4647602 polymorphisms was done by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method as previously described [16,19,20].

Fisher's exact test and independent sample *t*-test were performed for analysis of categorical and continuous variables, respectively, using SPSS Version 19.0. The effects of polymorphisms on PTC were examined by measuring the odds ratio (OR) with 95% confidence intervals (CIs) according to logistic regression analysis (95% CI). The analysis of Hardy–Weinberg equilibrium (HWE) was performed using the $\chi 2$ test. $P < 0.05$ was considered statistically significant.

Results

Table 1 presents the clinical characteristics of PTC patients. The mean age [SD] was 34.6 [11.9] in PTC and 35.3 [11.3] in the control group ($P = 0.7$). The frequency of alleles and genotypes of CASP3 rs4647610 and rs4647602 polymorphisms was not different between the PTC patients and control group. Moreover, these polymorphisms did not affect the PTC susceptibility in the dominant and recessive models (Table 2). The analysis of combination effects of CASP3 rs4647602 and rs4647610 polymorphisms showed no significant differences (data not shown). Haplotype evaluation of both polymorphisms revealed that the frequency of G-C haplotype was more frequent in PTC and control groups, and the haplotype frequencies were similar between two groups (data not shown).

The results of demographic, clinical, and pathological features between the three genotypes of rs4647610 polymorphism are presented in Table 3. The frequencies of GG, GA and AA genotypes were not different between PTC patients <40 and ≥40 years as well as females and males. Moreover, this variant was not accompanied by N stage, extrathyroidal expansion, and vascular and capsular invasion in PTC patients. However, the GA and AA genotypes were more frequent in PTC patients with higher tumour size (≥1 cm) compared to tumour size <1 (34 vs. 15.4% and 4.3 vs. 0%, respectively); therefore, rs4647610 polymorphism was associated with a 3.4-fold risk of higher tumour size in the dominant model.

There was no association between rs4647602 genotypes and age, sex, tumour size, N stage, extrathyroidal expansion, and vascular and capsular invasion risk in PTC patients (Table 4). However the frequencies of rs4647602 CA and AA genotypes were higher in PTC patients with lower TNM stages (I–II) compared to higher stages (III–IV); therefore these genotypes were associated with decreased risk of stages III and IV and might play a protective role in the development stage. Moreover, these polymorphisms led to lower risk of stage III/IV in the dominant model.

Table 1. Clinical characteristics of papillary thyroid carcinoma patients.

Location	
Right lobe	59(44)
Left lobe	61(45.5)
Both lobes	14(10.5)
Tumour size	
<1 cm	26(19.4)
≥1 cm	94(70.2)
Unknown	14(10.4)
TNM stage	
I	78(58.2)
II	15(11.2)
III	13(9.7)
IV	10(7.5)
Unknown	18(13.4)
N stage	
N0	79(59)
N1	36(26.9)
Unknown	19(14.1)
M stage	
M0	109(81.3)
M1	6(4.5)
Unknown	19(14.2)
Vascular invasion	
Positive	18 (13.4)
Negative	99 (73.9)
Unknown	17(12.7)
Capsular invasion	
Positive	19(14.2)
Negative	97(72.4)
Unknown	18(13.45)
Extrathyroidal expansion	
Positive	15(11.2)
Negative	99(73.9)
Unknown	20(14.9)

Data N (%)

Discussion

Apoptosis is a conserved system of regulated cell death involved in the removal of redundant and damaged cells without any effect on integrity and structure of adjacent tissues. Two pathways lead to the activation of caspase-3, the final effector product responsible for the mechanics of cell death [12,21,22]. Apoptotic defects permit transformed

Table 2. Allelic and genotypic frequency of *CAS3* rs4647610 and rs4647602 SNPs in PTC and control groups.

	PTC (n = 134)	control (n = 151)	OR (95% CI)	P value
rs4647610				
GG, n(%)	93(69.4)	106(70.2)	Reference	
GA, n(%)	37 (27.6)	39(25.8)	1.1(0.6–1.8)	0.77
AA, n(%)	4(3)	6(4)	0.8(0.2–2.8)	0.68
Dominant (AA+GA vs. GG)			1(0.6–1.7)	0.88
Recessive (AA vs. GA+GG)			0.7 (0.2–2.7)	0.65
Allele				
G, n(%)	223(83.2)	251(83.1)	Reference	
A, n(%)	45(16.8)	51(16.9)	1(0.6–1.5)	1.00
rs4647602				
CC, n(%)	89(66.4)	101(66.9)	Reference	
CA, n(%)	39(29.1)	46(30.5)	1(0.6–1.6)	0.85
AA, n(%)	6(4.5)	4(2.6)	1.7(0.5–6.2)	0.43
Dominant (AA+CA vs. CC)			1(0.6–1.7)	0.97
Recessive (AA vs. CA+CC)			0.9(0.6–1.7)	0.72
Allele				
C, n(%)	217(81)	248(82.1)	Reference	
A, n(%)	51 (19)	54(17.9)	1.1(0.7–1.6)	0.75

Data N (%)

cells escape destruction and so carcinogenesis, but are also linked to deregulated cell proliferation, differentiation and angiogenesis [23]. Therefore, the components of the apoptosis pathways are suitable candidates for investigation in cancer pathogenesis as well as treatment [24,25]. The altered levels of caspase-3 in cancerous tissues have been reported in several studies and are linked to clinical outcomes [26–28], leading to investigations of the possible effect of therapeutic agents on caspase-3 expression [29–31].

CASP3 is a polymorphic gene, and several polymorphisms are detected in exonic, intronic, promoter and 3′-UTR regions of this gene. We evaluated the probable effects of *CASP3* rs4647610 and rs4647602 SNPs on PTC and the demographic and clinical outcomes. Our findings showed no relationship between rs4647610 and rs4647602 SNPs and PTC. The synergic effects of two polymorphisms as well as haplotypes were not associated with PTC risk. However, CASP3 rs4647610 GA and AA genotypes were higher in PTC patients with larger tumour size (≥1 cm), and this polymorphism was associated with increased tumour size in the dominant model. The effects of CASP3 rs4647610 polymorphism were not age- and sex-dependent, and were not linked to N stage, TNM stage, extrathyroidal expansion, and vascular and capsular invasion risk. In addition, rs4647602CA and AA genotypes might play a protective role in PTC progression in higher stages (III–IV). No association was observed between rs4647602 and age, sex, N stage, extrathyroidal expansion, and vascular and capsular invasion risk.

Our data joins several others investigating these SNPs. Mittal et al. showed a higher frequency of rs4647603GG genotype and G allele carriers in bladder and prostate cancer patients [32,33] whilst Zhang et al. described rs4647602 AC and CC genotypes as risk factors for oesophageal squamous cell carcinoma which were more significant in individuals with age ≤57 years as well as in males. However, rs1049216 had no impact on this cancer [20], and a role for rs4647602 AC and CC genotypes on lung cancer was demonstrated by Lin et al., indicating that rs4647602 A allele has higher transcriptional activity [34]. A study conducted by Chen et al. showed that rs4647601 but not

Table 3. Association of *CAS3* rs4647610 genotypes with clinical characteristics of papillary thyroid

Characteristics	GG (n, %)	GA (n, %)	AA (n, %)	GA vs GG P: OR (95% CI)	AA vs GG P: OR (95% CI)	Dominant P: OR (95% CI)	Recessive P: OR (95% CI)
Age, years							
<40	63(72.4)	21(24.1)	3(3.4)				
≥40	30(63.8)	16(34)	1(2.1)	0.2: 1.6(0.7-3.5)	0.8: 0.7(0.1-7)	0.3: 1.5(0.7-3.2)	0.7: 0.6(0.1-6)
Sex							
Female	77 (70.6)	29(26.6)	3(2.8)				
Male	16(64)	8(32)	1(4)	0.6: 1.3(0.5-3.4)	0.7: 1.6(0.2-16)	0.5: 1.4(0.5-3.4)	0.7: 1.5(0.2-15)
Tumor size, cm							
<1	22(84.6)	4(15.4)	0(0)				
≥1	58(61.7)	32(34)	4(4.3)	0.06: 3(1-10)	-	0.04: 3.4(1.1-11)	-
N stage							
N0	55(69.6)	21(26.6)	3(3.8)				
N1	22(61.1)	13(36.1)	1(2.8)	0.3: 1.6(0.7-3.6)	0.9: 0.8(0.1-8.5)	0.5: 1.3(0.6-3)	0.8: 0.7(0.1-7.2)
TNM stage							
I-II	60(64.5)	30(32.3)	3(3.2)				
III-IV	16(69.6)	6(26.1)	1(4.3)	0.6: 0.8(0.3-2.1)	0.9: 1.3(0.1-13)	0.7: 0.8(0.3-2.1)	0.8: 1.4(0.1-14)
Extrathyroidal expansion							
Negative	69(69.7)	27(27.3)	3(3)				
Positive	9(60)	5(33.3)	1(6.7)	0.6: 1.4(0.4-4.6)	0.4: 2.6 (0.2-27)	0.5: 1.5(0.5-4.7)	0.5: 2.3(0.2-24)
Vascular invasion							
Negative	69(69.7)	27(27.3)	3(3)				
Positive	11(61.1)	6(33.3)	1(5.6)	0.6: 1.4(0.5-4)	0.5: 2.1(0.2-22)	0.5: 1.5(0.5-4)	0.6: 1.9(0.2-19)
Capsular invasion							
Negative	66(68)	28 (28.9)	3(3.1)				
Positive	11(57.9)	7(36.8)	1(5.3)	0.5: 1.5(0.5-4.3)	0.6: 2(0.2-21)	0.4: 1.6(0.6-4.2)	0.6: 1.7(0.2-18)

OR = odds ratio; CI = confidence interval.

Table 4. Association of *CAS3* rs4647602 genotypes with clinical characteristics of papillary thyroid carcinoma.

Characteristics	CC	CA	AA	CA vs CC P: OR (95% CI)	AA vs CC P: OR (95% CI)	Dominant P: OR (95% CI)	Recessive P: OR (95% CI)
Age, years							
<40	57(65.5)	26(29.9)	4(4.6)				
≥40	32(68.1)	13(27.7)	2(4.3)	0.8: 0.9(0.4-2)	0.9: 0.9(0.2-5)	0.8: 0.9(0.4-1.9)	0.9: 0.9(0.2-5.2)
Sex							
Female	71 (65.1)	33(30.3)	5(4.6)				
Male	18(72)	6(24)	1(4)	0.5: 0.7(0.3-2)	0.8: 0.8(0.1-7.2)	0.5: 0.7(0.3-1.9)	0.9: 0.9(0.1-7.8)
Tumor size, cm							
<1	17(65.4)	8(30.8)	1(3.8)				
≥1	62(66)	27(28.7)	5(5.3)	0.9: 0.9(0.4-2.4)	0.8: 1.4(0.2-13)	1 1(0.4-2.4)	0.8: 1.4(0.2-13)
N stage							
N0	53(67.1)	22(27.8)	4(5.1)				
N1	23(66.7)	12(33.3)	1(2.8)	0.8: 1.1(0.5-2.6)	0.6: 0.6(0.1-5.2)	1 1(0.4-2.3)	0.6: 0.5(0.1-5)
TNM stage							
I-II	56(60.2)	32(34.4)	5(5.4)				
III-IV	20(87)	3(13)	0(0)	0.04: 0.3(0.1-1)	-	0.02: 0.2(0.1-0.8)	-
Extrathyroidal expansion							
Negative	66(66.7)	29(29.3)	4(4)				
Positive	13(86.7)	1(6.7)	1(6.7)	0.1: 0.2(0.02-1.4)	0.8: 1.3(0.1-12)	0.1: 0.3(0.1-1.4)	0.7: 1.7(0.2-16)
Vascular invasion							
Negative	65(65.7)	30(30.3)	4(4)				
Positive	13(72.2)	4(22.2)	1(5.6)	0.5: 0.7(0.2-2.2)	0.9: 1.3(0.1-12)	0.6: 0.7(0.2-2.2)	0.8: 1.4(0.2-13)
Capsular invasion							
Negative	65(67)	28 (28.9)	4(4.1)				
Positive	14(73.7)	4(21.1)	1(5.3)	0.5: 0.7(0.2-2.2)	0.9: 1.2(0.1-11)	0.6: 0.7(0.2-2.2)	0.8: 1.3(0.1-12)

OR = odds ratio; CI = confidence interval.

rs4647602 and rs4647603 led to squamous cell carcinoma of the head and neck, especially in younger individuals and males [35]. The study of López-Trigo et al. found no relationship between *CASP3* rs1049216, rs2705897, and rs4647603 polymorphisms and prostate cancer; however, in overweight patients and smokers, the *CASP3*-rs1049216 G allele increased the risk of prostate cancer. Indeed, the rs4647603T allele was associated with prostate cancer in obese patients [36]. Guo et al. revealed that CASP3-rs1049216 TT genotype was associated with cervical cancer risk and cancer progression [37]. In the study of Deng et al., rs6948, rs1049216 and rs12108497 polymorphisms were not related to hepatocellular carcinoma, but rs12108497 was involved in cancer pathogenesis in smokers [38]. Hosgood et al.'s findings showed that rs1049216CC genotype might lead to decreased multiple myeloma risk; however, no relation between rs6948 and multiple myeloma was observed [39]. A meta-analysis conducted by Yan et al. on 3142 cancer patients and 3670 controls showed that *CASP3* rs2705897CC genotype was associated with increased risk of cancer, but rs1049216 C allele and C carrier led to decreased cancer risk whereas rs4647603 G allele and G carriers were associated with higher cancer susceptibility [40]. In a recent meta-analysis performed by Hashemi et al. on the association between *CASP3* polymorphisms and cancer, rs4647603 polymorphism was associated with a higher risk of cancer in the over-dominant model. They also showed the protective role of rs4647602 and rs2705897 polymorphisms in cancer in several models. Moreover, *CASP3* rs1049216 and rs6948 polymorphisms had no impact on cancer risk [18].

Regarding the in silico analysis performed by Teimoori et al., *CASP-3* rs4647602 and rs4647610 mutant alleles may create enhancer and silencer motifs for this gene. Moreover, they showed that although these polymorphisms might affect the splicing of *CASP-3* mRNA, these differences could not generate new cryptic splice acceptor or donor sites; therefore, these variants might not strongly affect the mRNA splicing [19]. The discrepancy in the effect of *CASP-3* SNPs on various cancers could be due to difference in cancer type, ethnicity, and possible interaction of genetic and environmental factors. Our study has some limitations which may affect the results. Firstly, the small sample size of the study may have affected the results. This limitation in subgroup analyses was more important as it led to non-significant P-values with different frequencies. In addition, lack of functional evaluation in cancerous tissue compared to intact adjacent tissues could be considered as another limitation.

Our study represents an advance in biomedical science as it points to the value of determining certain SNPs in caspase genes in the diagnosis and management of papillary thyroid carcinoma.

Summary table

What is known about this subject:

- Dysregulated apoptosis is known in pathogenesis of various cancers.
- Caspase-3 is an important apoptotic component and its abnormal function may play a key role in cancer pathogenesis.
- Altered levels of caspase-3 in cancerous tissues have been reported in several studies.

What this paper adds:

- The frequencies of CASP3 rs4647610 GA and AA genotypes were higher in PTC patients with larger tumor size (≥1cm), and rs4647610 polymorphism was associated with increased tumor size in the dominant model.
- The CASP3 rs4647602CA and AA genotypes were higher in PTC patients with lower TNM stages (I–II), and rs4647602 might play a protective role in PTC progression in higher stages (III–IV).

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Disclosure statement

The authors have no conflicts of interest to declare.

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