

## RESEARCH ARTICLE

# A Cyclin D1 (CCND1) Gene Polymorphism Contributes to Susceptibility to Papillary Thyroid Cancer in the Turkish Population

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### Abstract

Cyclin D1 is an important positive regulator of the G1/S phase of the cell cycle. We investigated the association between the CCND1 G870A polymorphism and susceptibility to papillary thyroid cancer in Turkish people. This study covered 102 patients with papillary thyroid cancer and 174 healthy controls. CCND1 genotyping was determined by the PCR-RFLP method. We found that the A allele frequency was higher in the cases than in the controls ( $p=0.042$ ). On stratification analysis, papillary thyroid cancer risk was significantly elevated in individuals older than 45 years with the A allele (OR=1.91, 95% CI, 1.09-3.35,  $p=0.024$ ) and in females with the A allele (OR=1.73, 95% CI, 1.06-2.84,  $p=0.029$ ), compared to the G allele. According to the subject age, there was an increased papillary thyroid cancer risk for the individuals older than 45 years with the AA genotype (OR=2.28, 95% CI, 1.02-5.13,  $p=0.046$ ) compared to the AG+GG combined genotypes. In conclusion, it is suggested that the CCND1 G870A polymorphism may contribute to the susceptibility to papillary thyroid cancer, especially in those who were older subjects ( $45 \leq$  years old) and female, in the Turkish population.

**Keywords:** Papillary thyroid cancer - cyclin D1 gene - polymorphism - Turkish population

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### Introduction

Thyroid cancer is the most common malignancy of the endocrine system and contributes to more than 50% of all deaths from endocrine cancers (Du et al., 2013). Among thyroid cancers, papillary thyroid cancer (PTC) is the most, accounting for 80-90% of all the thyroid malignancies (Ranjbari et al., 2013; Wang et al., 2013). Environmental factors such as radiation exposure, smoking, diet (iodine deficiency), and hormonal factors contribute to PTC development, and genetic factors are also related to the susceptibility of developing PTC (Sturgis and Li, 2009; Du et al., 2013; Ozdemir et al., 2013). Genetic polymorphism existing in the human genome plays an important role in the development of cancers (Wang et al., 2013).

Disturbances in the control of cell cycle play an important role in cancer formation (Sherr, 1996). Cyclin D1 is a key regulatory protein in the cell cycle, playing a critical role in the transition from G1 to S phase of the cell cycle. Cyclin D1 regulates cell cycle progression by activating cyclin dependent kinase 4 (CDK4) and cyclin dependent kinase 6 (CDK6), which in turn phosphorylate the retinoblastoma (Rb) protein. The phosphorylation of Rb releases the transcriptional factor E2F, which then activates a number of downstream genes necessary for cell

cycle progression. This event lead to progression through G1/S transition (Cortessis et al., 2003; Huang et al., 2006a; Knudsen, 2006; Knudsen et al., 2006).

Cyclin D1 is encoded by the CCND1 gene located on chromosome 11q13. Betticher et al. (1995) identified G870A polymorphism in exon 4 of the CCND1 gene. This polymorphism doesn't cause to an amino acid change, but CCND1 mRNA is alternatively spliced to produce two transcripts. The CCND1 G870 allele splices transcript a, whereas the CCND1 870A allele mainly splices transcript b. The protein encoded by transcript b, cyclin D1b, however, lacks the degradation signal encoded by exon 5 and hence may have a longer half-life, resulting in deregulated cell proliferation. Increased expression of cyclin D1 may lead to premature cell passage through G1/S transition, which result in the propagation of unrepaired DNA damage, accumulation of genetic errors, and a selective growth advantage for the altered cells (Sawa et al., 1998; Zheng et al., 2001; Knudsen et al., 2006; Huang et al., 2006a; Akkiz et al., 2010; Zeybek et al., 2013).

A number of studies have suggested that the CCND1 G870A polymorphism is associated with susceptibility to various cancers, including bladder cancer (Wang et al., 2002), breast cancer (Yu et al., 2008), colorectal

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cancer (Porter et al., 2002; Hong et al., 2005), esophageal adenocarcinoma (Casson et al., 2005), endometrial cancer (Kang et al., 2005), cervical cancer (Catarino et al., 2005), head and neck cancer (Zheng et al., 2005; Liu et al., 2011), hepatocellular carcinoma (Akkız et al., 2010), childhood acute lymphoblastic (Hou et al., 2005), lung cancer (Qiuling et al., 2003; Li et al., 2012), prostate cancer (Wang et al., 2003) and glioblastoma multiforma (Zeybek et al., 2013).

There have been no reports about the association of the CCND1 G870A polymorphism with PTC in literature. In this study, we investigated the CCND1 G870A allele and genotype frequencies in patients with PTC and healthy controls, and demonstrated the association between the CCND1 G870A polymorphism and risk of developing PTCs in Turkish population.

## Materials and Methods

### Subjects

A total of 102 patients with PTC and 174 healthy controls were qualified for this study. We performed a hospital-based case-control study. All samples were taken at the Department of General Surgery, Gaziantep University, between July 2012 and September 2014. The healthy, unrelated and cancer-free subjects, who visited hospital for a routine health checkup, were recruited for the study as controls. The samples were collected from PTC patients before any chemotherapeutic or radiation therapy treatment had been started. All the PTC patients and controls were citizens of the Turkish Republic. All samples were taken after informed consent, according to the declaration of Helsinki. Ethics committee approval required for the study was obtained from the Gaziantep University Medical Faculty Local Ethics Committee.

### DNA extraction

Blood samples obtained from the PTC patients and controls were collected into tubes containing EDTA. Genomic DNA was isolated from 10 ml blood samples in tubes with EDTA by the method of Miller et al. based on sodium dodecyl sulphate lysis, ammonium acetate extraction, and ethanol precipitation (Miller et al., 1988).

### Genotyping of CCND1 G870A polymorphism

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis was performed to determine the CCND1 G870A polymorphism. The 212 bp DNA fragment containing the G to A polymorphic site in the CCND1 was amplified using specific primers (Ella Biotech GmbH, Deutschland) as follows: 5'-AGTTCATTTCCAATCCGCC-3' and 5'-TTTCCGTGGCACTAGGTGTC-3'. The reaction mixture consisted of 0.2 µg of genomic DNA, 0.6 mmol/L of each primer, 0.2 µmol/L of each dNTP, 0.25 mmol/L MgCl<sub>2</sub>, 1X Taq buffer and 2.5 U of Taq DNA polymerase (MBI Fermentas, Lithuania) to a final volume of 50 µL. The reaction mixture was initially denatured at 94°C for 5 minutes, followed by 35 cycles of a denaturation step at 94°C for 1 minute, an annealing step at 60°C for 1 minute, and an extension step at 72°C for 1 minute. The PCR

programme was completed by a final extension step at 72°C for 7 minutes. The PCR products were digested with 5 U MspI enzyme (MBI Fermentas, Lithuania) at 37°C for overnight and electrophoresed on 4% agarose gel. The allele types were determined as follows: two fragments of 175 and 37 bp for AA genotype, three fragments of 141, 37 and 34 bp for GG genotype, and four fragments of 175, 141, 37 and 34 bp for AG genotype (Sobti et al., 2006) (Figure 1).

### Statistical analyses

All statistical analyses were carried out using SPSS version 14.01 for Windows (SPSS Inc., Chicago, IL). Hardy-Weinberg equilibrium analyses were performed to compare observed and expected genotype frequencies using a  $\chi^2$  test (df=1). Pearson's  $\chi^2$  test was used to determine whether there was any significant difference in allele and genotype frequencies between patients and controls. Differences in the distributions of demographic characteristics between the cases and controls were evaluated using the Student's t-test (for continuous variables) and  $\chi^2$  test (for categorical variables). The associations between the CCND1 G870A genotypes and the risk of PTC were estimated by computing the ORs and their 95% CIs from logistic regression analyses with adjustment for age, sex, smoking status and alcohol use. Statistical modeling was performed on the relative risk of the AA genotype or the GA genotype against the GG genotype independently. Additionally, the relative risk of the AA genotype against the GA + GG genotype or the AA + GA genotype against the GG genotype were calculated using logistic regression model. Probability levels less than 0.05 were used as a criterion of significance.

## Results

There were 102 PTC cases and 174 healthy controls included in this study. The cases and controls were adequately matched by sex, age groups ( $\leq 45$  years old and  $>45$  years old), smoking status and alcohol use. The mean ages of case and control groups were  $46.18 \pm 12.80$  (mean  $\pm$  SD) and  $41.92 \pm 17.83$ , respectively.

The distributions of the CCND1 genotypes were in Hardy-Weinberg equilibrium in the PTC patients ( $n=102$ ,  $\chi^2(1)=2.146$ ,  $p=0.143$ ) and the controls ( $n=174$ ,  $\chi^2(1)=0.547$ ,  $p=0.459$ ). Distributions of the CCND1 genotype and allele frequency between cases and controls were analyzed using Pearson's  $\chi^2$  test and shown in Table 1. The A allele frequency was higher in cases (0.637) than that in controls (0.549), and this difference was statistically significant ( $p=0.042$ ). The frequencies of the

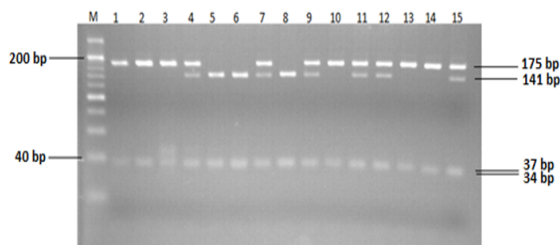
**Table 1. Distributions of the CCND1 Genotype and Allele Frequency Between Cases and Controls**

		Controls n (%)	Cases n (%)	p-value
Genotypes	AA	50 (29)	38 (37)	0.085
	AG	91 (52)	54 (53)	
	GG	33 (19)	10 (10)	
Alleles	A	191 (55)	130 (64)	0.042
	G	157 (45)	74 (36)	

**Table 2. Stratification Analysis of CCND1 Allele and Genotype Frequency in PTC**

		Controls	Cases	OR (95% CI)	p-value
		No. (%)	No. (%)		
<b>Sex<sup>a</sup></b>					
Female	A	95 (59)	100 (69)	1.73 (1.06-2.84)	0.029
	G	65 (41)	44 (31)	1 (Reference)	
	AA	28 (35)	30 (42)	1.63 (0.78-3.41)	0.194
	GG+AG	52 (65)	42 (58)	1 (Reference)	
Male	A	96 (51)	30 (50)	0.96 (0.53-1.72)	0.879
	G	92 (49)	30 (50)	1 (Reference)	
	AA	22 (23)	8 (27)	1.14 (0.43-3.00)	0.789
	GG+AG	72 (77)	22 (73)	1 (Reference)	
<b>Age<sup>b</sup>(years)</b>					
≤45	A	114 (56)	62 (60)	1.05 (0.63-1.75)	0.844
	G	90 (44)	42 (40)	1 (Reference)	
	AA	32 (31)	16 (31)	0.80 (0.35-1.84)	0.598
	GG+AG	70 (69)	36 (69)	1 (Reference)	
>45	A	77 (53)	68 (68)	1.91 (1.09-3.35)	0.024
	G	67 (47)	32 (32)	1 (Reference)	
	AA	18 (25)	22 (44)	2.28 (1.02-5.13)	0.046
	GG+AG	54 (75)	28 (56)	1 (Reference)	
<b>Alcohol use<sup>c</sup></b>					
Never	A	159 (54)	122 (64)	1.33 (0.90-1.96)	0.160
	G	137 (46)	70 (36)	1 (Reference)	
	AA	38 (26)	36 (38)	1.51 (0.83-2.75)	0.181
	GG+AG	110 (74)	60 (63)	1 (Reference)	
Ever	A	32 (62)	8 (67)	1.32 (0.35-5.04)	0.690
	G	20 (38)	4 (33)	1 (Reference)	
	AA	12 (46)	2 (33)	0.57 (0.09-3.77)	0.555
	GG+AG	14 (54)	4 (67)	1 (Reference)	
<b>Smoking status<sup>d</sup></b>					
Never	A	91 (49)	86 (65)	1.89 (1.17-3.04)	0.010
	G	95 (51)	46 (35)	1 (Reference)	
Ever	A	100 (62)	44 (61)	0.75 (0.40-1.41)	0.380
	G	62 (38)	28 (39)	1 (Reference)	

\*Abbreviations: CI, confidence interval; OR, odds ratio; <sup>a</sup>Adjusted for age and smoking status; <sup>b</sup>Adjusted for sex and smoking status; <sup>c</sup>Adjusted for age; <sup>d</sup>Adjusted for age and sex



**Figure 1. RFLP Analysis of the CCND1 Genotypes.** M:20-bp DNA marker. Cases 1,2,3,10,13,14: AA genotype; cases 4,7,9,11,12,15: AG genotype; cases 5,6,8: GG genotype

AA, AG, and GG genotypes were 37, 53, and 10% in the cases, respectively, and 29, 52, and 19% in the controls respectively, but the difference was not statistically significant (p=0.085).

To evaluate the risk of PTC according to the CCND1 G870A allele and genotype, logistic regression analysis was conducted with adjustment for age, sex, smoking status and alcohol use. Using the G allele as the reference allele, the subjects carrying the A allele had 2.36-fold increase in the risk of PTC (95%CI, 1.54-3.61), but p-value was not significant (p=0.151). Compared to individuals with the GG genotype, individuals with the AA and AG genotype exhibited increased PTC risk with adjusted ORs of 2.04 (95%CI, 0.85-4.85) and 1.66 (95%CI, 0.74-3.75), respectively but this was statistically insignificant (p=0.109 and 0.220, respectively).

Table 2 shows the CCND1 allele frequencies in PTC cases and controls stratified by sex, age (≤45 years old and >45 years old), smoking status and alcohol use. When we used the G allele as a reference allele, we found that the PTC risk was statistically significant in older than 45 years individuals with the A allele (OR=1.91, 95%CI, 1.09-3.35, p=0.024). Additionally, females with the A allele had approximately 2-fold increased risk for development of PTC (95%CI, 1.06-2.84, p=0.029) compared to the G allele. According to distribution of alleles, there was not association between smoking and alcohol use and PTC risk (p>0.05).

The stratification of the analysis according to the subjects' age (≤45 years old and >45 years old) lead to the observation that there was a statistically significant 2.28-fold increase of PTC risk for the older than 45 years carrying the AA genotype (95%CI, 1.02-5.13, p=0.046) compared with the AG+GG combined genotypes (Table 2).

## Discussion

The loss of regulatory control of cell cycle, leading to uncontrolled cell proliferation, is a hallmark of cancer. Cyclins, the regulatory subunits of cyclin dependent kinases (CDKs), control the passage of proliferating cells through key checkpoints in the cell cycle (Sherr and Roberts, 1995; Hall and Peters, 1996). Cyclin D1 is one of the proteins that play an important role in the transition from the G1 phase to the S phase of the cell cycle. Cyclin D1 overexpression has been described in many human cancers (Knudsen et al., 2006). In the first study that implicated cyclin D1 in human tumors, CCND1 was linked in parathyroid adenomas to the parathyroid hormone gene (Motokura et al., 1991). Cyclin D1 expression has been reported to occur in some papillary thyroid carcinoma (Temim et al., 2006). The CCND1 gene has a single base polymorphism (G870A) in exon 4 splice site. The G870A polymorphism at the exon 4 splice site has been shown to increase the frequency of alternative splicing. The protein encoded by alternate transcript lacks the carboxy-terminal region encoded by exon 5. As a result, the carboxy-terminal end of the alternate transcript lacks sequences important for protein turnover and thus may have a longer half-life (Betticher et al., 1995).

In this study was investigated association between the CCND1 G870A polymorphism and PTC risk in Turkish population. Using the G allele as the reference allele, individuals carrying the A allele had a 2.36-fold increase in the risk for PTC. In addition to this, compared with the GG genotype, AA and AG genotypes increased risk but not significantly associated with the risk of PTC. Several previous studies have reported no associations between the CCND1 G870A polymorphism and risk for various human solid tumors, including bladder (Cortessis et al., 2003), breast and colorectal cancers (Griew et al., 2003), esophageal adenocarcinoma (Liu et al., 2010) and oral squamous cell carcinoma (Gomes et al., 2008). In contrast with these studies, some authors observed that AA genotype was a risk factor for urinary bladder (Wang et al., 2002), colorectal (Jiang et al., 2006), endometrial (Kang

et al., 2005), prostate (Wang et al., 2003), hepatocellular (Akkız et al., 2010), esophageal (Casson et al., 2005), and head-neck (Zheng et al., 2001) cancers in different ethnic origins. These controversial results suggest that the effect of genotype on tumor behavior may exhibit some degree of tissue specificity (Mattihias et al., 1998). It is possible that these conflicting results in part reflect the many different mechanisms through which deregulated expression of CCND1 can occur in cancer (Catarino et al., 2005). Several factors, such as cancer type, geographic or ethnic differences, environmental and other factors, may play a significant role in different results.

Various studies showed that the CCND1 G870A polymorphism effect on cancer changed according to sex. Shi et al. (2003) indicated that the CCND1 AA genotype was associated with a significantly increased risk for lung cancer and the effects were more evident in males. Huang et al. (2006b) reported that the increased risk for colorectal cancer was found in males with the AA or AG genotype in Taiwan population. Additionally, in Non-Hispanic White population, high risk for squamous cell carcinoma of the head and neck was detected in female carrying the AA genotype (Zheng et al., 2001). In stratified analysis, we observed that the increased risk was in female with the A allele. Thyroid cancers are 2-3 fold more common in females than males (Brown et al., 2011). In our study, female ratio was 71% among patients with PTC. It seems that the CCND1 G870A polymorphism may not be a susceptibility marker for PTC of men in Turkish population, but a larger population studies are needed to confirm this finding.

PTC is more common in older age (Schlumberger, 1998; Pacini et al., 2006). In addition to this, the prognosis of PTC is better for younger patients than for patients who are older than 45 years (Zhang et al., 2013). In the present study, PTC risk was found to be significantly higher in individuals over the age of 45 carrying the AA genotype. Contrary to our results, previous studies reported that the increased risk was in younger subjects who carrying the AA or the AA+AG genotypes for different cancer types, including oral premalignant lesion (Huang et al., 2006a), lung cancer (Qiuling et al., 2003) and squamous cell carcinoma of the head and neck (Zheng et al., 2001).

In conclusion, this is the first study to demonstrate the association between the CCND1 G870A polymorphism and risk of papillary thyroid cancer. Our results suggest that the CCND1 G870A polymorphism may contribute to the susceptibility to papillary thyroid cancer, especially in those who were older subjects (>45 years old) and female, in Turkish population. This study has some limitations. First, it was a hospital-based case-control study, and subjects were selected at a single institution (Gaziantep University, Research Hospital) and thus may have been unrepresentative of papillary thyroid cancer patients in the general population. Second, the statistical power of our study was limited because of the relatively small number of cases enrolled. Third, we also limited our study to Turkish population. Therefore, larger prospective studies are needed to elucidate the precise role of the CCND1 G870A polymorphism in papillary thyroid cancer.

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