Interleukin-1B (-511) gene polymorphism is associated with acute coronary syndrome in the Turkish population

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ABSTRACT. ***Objectives:*** **acute coronary syndrome (ACS) is defined as an inflammatory disease associated with development of atherosclerosis and instability. IL-1 is a candidate inflammatory cytokine that is thought to trigger ACS. The purpose of this study was to determine the relationship between IL-1 gene family polymorphisms (IL-1RN, IL-1B in positions -511 and +3953) and ACS in the Turkish population.** ***Methods:*** **a total of 381 people participated in the study, with 117 control subjects and 264 ACS patients. Of the 264 ACS patients, 112 were diagnosed with stable angina pectoris (SAP) and 152 were diagnosed with unstable angina pectoris (USAP). The polymerase chain reaction (PCR) was used to determine the genotype of IL-1RN. The genotypes of IL-1B (-511 and +3953) were determined by PCR, followed by restriction enzyme digestion of the PCR products.** ***Results:*** **there were no significant differences in both IL-1RN, IL-1B (-511 and +3953) genotype distributions and IL-1RN allele frequencies between ACS patients and the control subjects. In addition, no association was observed in the allele frequency of IL-1B (-511 and +3953) between ACS patients and controls (p = 0.113 and p = 0.859, respectively), or between SAP patients and controls (p = 0.575 and p = 0.359, respectively). However, IL-1B allele 1 (C) (-511) polymorphism in USAP patients was found to be significantly different from that of control subjects (p = 0.041, OR: 2.01; 95% CI: 1.985-3.933). A significant difference was also observed between USAP and SAP patients for IL-1B (+3953) allele 1 (C) polymorphism; (p = 0.043, OR: 1.522; 95% CI: 1.012-2.88).** ***Conclusion:*** **these results show that IL-1RN gene polymorphism has no association with ACS. However, the allele 1 (C) of IL-1B (-511) may be a risk factor for susceptibility to USAP in the Turkish population.**

Keywords: interleukin-1B, interleukin-1 receptor antagonist, polymorphism, acute coronary syndrome

Acute coronary syndrome (ACS) is defined as a spectrum of clinical manifestations of acute coronary artery disease, extending from acute myocardial infarction through minimal myocardial injury to unstable angina. Coronary plaque rupture has been shown to be the real reason for sudden, acute coronary syndromes [1]. While the exact mechanism of plaque rupture remains unclear, it has been suggested that inflammatory responses play an important role in the onset, development, and evolution of atherosclerotic lesions [2] and vulnerable plaques destabilization [3]. One of the candidate inflammatory cytokines thought to play a role in the development of ACS is interleukin-1 (IL-1). Evidence for a role of IL-1 in ACS was observed when the IL-1 receptor antagonist gene (IL-1RN) was disrupted in mice [4], leading to enhancement of atherosclerotic plaque development. It has also been shown that the gene product of IL-1RN, the IL-1 receptor antagonist molecule (IL-1Ra), plays important roles in controling circulating levels of cholesterol and in foam cell progression [5]. Moreover, the severity of atherosclerosis was shown to be decreased in the absence of IL-1B in a mouse model of atherosclerosis (apoE-deficient mice), when these mice were also made deficient in IL-1B [6].

Interleukin-1 (IL-1) is a cytokine that is involved in immunity, sepsis, trauma, infection and inflammation [7]. The IL-1 family is made up of three members, two of which are agonists (IL-1α and IL-1B) and one is an antagonist (IL-1Ra). IL-1Ra inhibits IL-1-induced inflammation action by binding to the IL-1 receptor type I (IL-1RI) and blocking the binding of IL-1 [8]. Both the IL-1RN and the IL-1B (IL-1B) genes are mostly polymorphic. There is a variable number of 86-base pair tandem repeats (VNTR) contained within intron 2 of the IL-1RN gene [9-11]. Single nucleotide polymorphisms (SNPs) have been determined at promoter position -511 C/T [12] and in exon 5 at position +3953 C/T in the IL-1B gene [13]. The polymorphisms within these genes are suggested to influence IL-1 expression [14]. Moreover, polymorphisms resulting in IL-1 overproduction may increase susceptibility to autoimmune diseases such as atherosclerosis [14].

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DONORS AND METHODS

Subjects

A total of 264 ACS patients and 117 control subjects from the Turkish population were enrolled in this study. All individuals were of Turkish origin, nationality and all were resident in Turkey. One hundred and fifty two of the ACS patients were diagnosed with unstable angina pectoris (USAP), while 112 were diagnosed with stable angina pectoris (SAP). All of the ACS patients with USAP were scheduled for coronary angiography, experienced ischemic chest pain at rest lasting ≥ 20 minutes and demonstrated at least one of the following: new or presumably new ST-segment deviations on electrocardiogram (electrocardiographic evidence of ST-segment elevation or depression), enzyme abnormalities (creatine kinase-MB higher that the upper reference limit in ≥ 2 samples obtained with an interval of > 6 hours), and/or troponin T ≥ 0.02 ng/mL, and also non-Q-wave myocardial infarction (MI). Study exclusion criteria were acute Q-wave MI, neoplastic disease, renal failure, acute or chronic infectious or immunological conditions, cancer, cardiogenic shock, acute pulmonary edema, history of active liver disease, recent CABG, PTCA, surgery, or gastrointestinal bleeding. During the same period, 112 patients diagnosed with SAP were enrolled. These patients were scheduled for elective angioplasty. One hundred and seventeen control subjects were recruited from healthy individuals with no history of coronary artery disease, and from patients whose coronary angiography results showed less than 30% lumen diameter reduction.

Risk factor assessment

Information on age, gender, familial coronary artery disease (CAD), smoking habit and history of hypertension was obtained by a questionnaire. Weight and height of case and control subjects were measured and body mass index (BMI) was calculated. Triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL) and low density lipoprotein (LDL) levels were determined enzymatically, and were also measured enzymatically after dextrane sulfate magnesium precipitation as previously described [15]. The presence of *diabetes mellitus* (DM) was defined as a repeated fasting glucose level > glucose 126 mg/dL, or the use of anti-diabetic drugs or both. Artery blood plasma samples were collected just before the index procedure and stored at -80˚C until use. hs-CRP was measured by ELISA (DSL-10-42100UsCRP ELISA KIT, Diagnostic Systems Laboratories, Inc). Plasma fibrinogen concentrations were detected using a Dade Thrombin Reactive kit (Dade Bhering).

Genotyping

Blood samples were collected and kept in tubes with EDTA. Genomic DNA isolation was performed using GENTRA DNA isolation kits (Gentra Systems, D5500). The VNTR region contained within intron 2 of the IL-1RN gene, IL-1B (-511) and IL-1B (+3953) was amplified by PCR; genotyping of the IL-1RN gene was determined by PCR as previously described [16]. Genotyping of the IL-1B (-511) polymorphism was performed by PCR followed by restriction endonuclease digestion of the PCR products overnight with 5 U AvaI at 37°C [16]. Genotyping of the IL-1B (+3953) polymorphism was performed by PCR followed by restriction endonuclease digestion of the PCR products overnight with 5U TaqI at 65°C [16].

Statistical analysis

Mann-Whitney U and x^2 tests were used for comparison of two groups of individuals according to ACS risk factors. Allele and genotype frequencies among cases and controls were compared with Hardy-Weinberg predictions using x^2 analysis. Multivariate logistic regression was used to assess the independent association of the IL-1RN, IL-1B allele status with the presence of ACS and to adjust for confounding factors. The model was adjusted for age, gender, hypertension, and smoking habits. The results were expressed as odds ratio (OR) and 95% confidence interval (CI). Probability of values of $p < 0.05$ (2-sided) were considered statistically significant. SPSS 13.0 software program was used for all statistical analyses.

ETHICS APPROVAL

This research was approved by the ethics committee of Marmara University in Turkey. All human subjects' rights in this research are protected, and any necessary approval was secured from the ethics committee.

RESULTS

Baseline characteristics of the controls, ACS, SAP and USAP groups are given in *table 1*. There was a significant difference between the groups with respect to age, diabetes, gender, weight, BMI, hypertension and smoking habits. Both CRP ($p = 0.001$) and fibrinogen ($p = 0.022$) levels were significantly higher in ACS patients than healthy controls *(table 1)*. A significant difference was found between USAP patients and the control subjects for CRP ($p = 0.001$), diabetes ($p = 001$) and fibrinogen ($p = 0.007$) levels.

None of the observed genotype frequencies deviated from the Hardy-Weinberg equilibrium. The genotype distribution and allele frequency of IL-1RN VNTR are shown in *table 2*. Three of the six alleles of the IL-1RN gene were observed in patients and the control subjects. Among these three alleles, no significant difference was observed between ACS patients and controls ($p = 0.348$), SAP patients and controls ($p = 0.577$) or USAP patients and controls ($p = 0.327$). For IL-1RN allele frequencies, no association was detected between the control group and patients: ACS ($p = 0.154$), SAP ($p = 0.400$), USAP ($p = 0.120$) *(table 2)*. Genotype distribution and allele frequency for IL-1B (-511) in ACS, SAP, USAP and the control groups are shown in *table 3A*. No difference was observed in the genotype distribution of IL-1B (-511) between ACS patients and the controls ($p = 0.292$), SAP patients and controls ($p = 0.837$) or USAP patients and the control ($p = 0.129$). In addition, no significant difference was observed in frequency of the IL-1B (-511) allele between ACS patients and controls ($p = 0.113$), SAP patients and

Table 1
Baseline characteristics of the control, ACS, SAP, USAP groups in a Turkish population

	Controls (n = 117)	ACS (n = 264)	SAP (n = 112)	USAP (n = 152)
Age (years ± SD)	52.4 ± 10.9	58.3 ± 11.3*	58.9 ± 10.6*	57.8 ± 11.9
Gender				
- Male (%)	48.7	73.1*	68.8*	76.3*
- Female (%)	51.3	26.9	31.3	23.7
Height (cm)	167.3 ± 8.4	167.2 ± 6.7	167.2 ± 6	168 ± 7.2
Weight (kg)	69.7 ± 8.7	77.6 ± 10*	77.7 ± 9.2*	77.5 ± 10.6*
BMI (kg/m^2)	25.6 ± 4.5	28.1 ± 3.1*	27.2 ± 3.2*	29.1 ± 3.1*
Familial CAD (%)	33.3	40.5	38.4	42.1
Hypertension (%)	44.4	59.8*	65.2*	55.3*
DM (%)	8.9	24.2**	23.2**	25**
Smoking				
Never (%)	66.7	29.9	36.6	25
Former (%)	18.8	23.9	25	23
Current (%)	14.5	46.2*	38.4*	52*
Triglyceride (mg/dL)	132.7 ± 37.6	135.6 ± 45.6	134.4 ± 42.4	136.6 ± 48.3
HDL (mg/dL)	42.4 ± 8.4	40.3 ± 9	40.5 ± 10	40.4 ± 8.1
LDL (mg/dL)	120.7 ± 33.5	128.3 ± 36.9	127.8 ± 31.2	125.8 ± 32.6
TC (mg/dL)	192.8 ± 40.6	204.4 ± 33.1	198.6 ± 38.2	195.3 ± 39.6
Triglyceride /HDL ratio	3.3 ± 1.3	3.5 ± 1.3	3.4 ± 1.3	3.5 ± 1.3
LDL/HDL ratio	3 ± 0.9	3.2 ± 1.1	3.1 ± 1.1	3.3 ± 1.1
TC/HDL ratio	4.8 ± 1.4	5 ± 1.3	4.9 ± 1.1	5.1 ± 1.2
CRP (mg/L)	0.8 ± 0.5	1.3 ± 0.7*	0.9 ± 0.6	1.4 ± 0.7*
Fibrinogen (mg/dL)	297.7 ± 59.9	316 ± 56.8*	309.9 ± 63.7	320.5 ± 50.9*

* $p < 0.05$ is taken to be statistically significant, ** $p < 0.001$ is taken to be statistically significant.
BMI: body mass index; CAD: coronary artery disease; DM: *diabetes mellitus*; HDL: high density lipoprotein; LDL: low density lipoprotein; TC: total cholesterol; CRP: C-reactive protein.

controls (p = 0.575) or SAP and USAP patients (p = 0.155). However, a significant difference was seen for allele 1 (C) of IL-1B (-511) between USAP patients and the controls (p = 0.041).
The genotype distribution and allele frequency for IL-1B (+3953) in ACS, SAP, USAP and the control groups are shown in *table 3B*. When the genotype distribution of IL-1B (+3953) was compared between groups, no significant difference was observed between ACS patients and the controls (p = 0.965), SAP patients and the controls (p = 0.630) or USAP patients and the controls (p = 0.569). In addition, no significant difference was observed in the frequency of the IL-1B (+3953) allele between ACS patients and the controls (p = 0.859), SAP patients and controls (p = 0.359) or USAP patients and the controls (p = 0.291). However, allele 1 (C) of the IL-1B (+3953) was found to be significantly different between USAP and SAP patients (p = 0.043).
According to multiple logistic regression analysis, there was no significant correlation between IL-1 gene family genotypes and acute coronary disease when adjusted for age, gender, hypertension and smoking habits *(table 4)*. However, analysis of IL-1B -511 homozygous mutants compared to homozygous wild-type showed an association between IL-1B -511 gene polymorphisms and USAP (OR: 2.451; 95% C.I.: 1.049-5.75) *(table 5)*.

Table 2
Genotype distribution and allele frequency of the IL-1RN VNTR polymorphism in a Turkish population

	Genotypes			
IL-1RN	**Control**	**ACS**	**SAP**	**USAP**
1/1	59 (50.4)	149 (56.4)	60 (53.6)	89 (58.6)
1/2	45 (38.5)	96 (36.4)	44 (39.3)	52 (34.2)
2/2	13 (11.1)	19 (7.2)	8 (7.1)	11 (7.2)
P *versus* control		0.348	0.577	0.327
P *versus* USAP			0.730	
	Alleles			
IL-1RN	**Control**	**ACS**	**SAP**	**USAP**
IL-1RN 1	0.696	0.746	0.733	0.756
IL-1RN 2	0.304	0.254	0.267	0.244
P *versus* control		0.154	0.400	0.120
P *versus* USAP			0.524	

Genotypes are expressed as number of patients (proportion as a % within brackets), p values are from Fisher's exact test.

Table 3
Genotype distribution and allele frequency of the IL-1B (**A**) (-511) and (**B**) (+3953) SNP polymorphisms in ACS, SAP, USAP and the control groups in a Turkish population

A		**Genotypes**		**Alleles**	
IL-1B (-511)	**C/C**	**C/T**	**T/T**	**C allele**	**T allele**
Control	28 (23.9)	58 (49.6)	31 (26.5)	0.488	0.512
ACS	81 (30.7)	128 (48.5)	55 (20.8)	0.549	0.451
SAP	29 (25.9)	57 (50.9)	26 (23.2)	0.514	0.486
USAP	52 (34.2)	71 (46.7)	29 (19.1)	0.576[a]	0.424[a]
B		**Genotypes**		**Alleles**	
IL-1B (+3953)	**C/C**	**C/T**	**T/T**	**C allele**	**T allele**
Control	69 (59)	41 (35)	7 (6)	0.764	0.236
ACS	157 (59.5)	93 (35.2)	14 (5.3)	0.771	0.229
SAP	59 (52.7)	45 (40.2)	8 (7.1)	0.728	0.272
USAP	98 (64.5)	48 (31.6)	6 (3.9)	0.803[b]	0.197[b]

Genotypes are expressed as number of patients (proportion as a % within brackets), p values are from Fisher's exact test. USAP[a] *versus* controls, $x^2 = 4.163$, 1 df ; p = 0.041, USAP[b] *versus* SAP, $x^2 = 4.102$, 1 df ; p = 0.043.

DISCUSSION

The pathophysiology of unstable coronary artery disease involves inflammatory mediators in the development of an atherosclerotic plaque and in thrombus formation by platelet aggregation [1]. A number of epidemiological studies have shown that various inflammatory agents such as adhesion molecules, chemokines, growth factors and cytokines have been are associated with ACS and are even implicated as markers for ACS [17]. It has been shown that both C-reactive protein (CRP) [18] and fibrinogen plasma levels are high in patients with acute coronary syndrome (ACS) when compared to control subjects [19]. In our study, a statistically significant difference was found between ACS patients and controls for CRP (p = 0.001) and fibrinogen levels (p = 0.022). Moreover, both CRP (p = 0.001) and fibrinogen levels (p = 0.007) were significantly elevated in USAP patients compared to control subjects.

One of the candidate inflammatory agents is IL-1, which stimulates the synthesis of acute phase proteins (APP) such as interleukin-6 (IL-6), fibrinogen and CRP, and is a central mediator of inflammation [4]. The IL-1 family genes, IL-1A, IL-1B, IL-1RN are clustered and mapped to chromosome 2q [20], and are known to be largely polymorphic [9-13]. An association between IL-1 gene family polymorphisms and various autoimmune diseases has been reported among different populations [21].

The IL-1RN allele 2 has been associated with several disease states and populations. An association between the IL-1RN allele 2 and carotid atherosclerosis [22], as well as CAD in patients with type 2 diabetes [23] has been shown. A protective effect of IL-1RN allele 2 has been described for restenosis after percutaneous transluminal coronary angioplasty [24]. Moreover, an association between the IL-1RN allele 2 and myocardial infarction (MI) at a young age in an Italian population has been reported [25]; however, no significant difference was found between IL-1RN allele 2 and myocardial infarction in other Caucasian populations [26]. Although, an association between single-vessel disease (SVD) and the IL-1RN allele 2 was observed in a Caucasian population from Sheffield, UK, no association was observed for single vessel CAD

Table 4
Multiple logistic regression analysis assessing the independent association of IL-1 gene polymorphisms and the presence of ACS

All subjects			
IL-1RN genotypes compared	**OR**	**95% CI**	**p**
2/2 and 1/2 *versus* 1/1	1.220	0.724-2.056	0.4
2/2 *versus* 1/1	0.448	0.172-1.168	0.1
2/2 *versus* 1/2 and 1/1	0.463	0.183-1.172	0.1
All subjects			
IL-1B -511 genotypes compared	**OR**	**95% CI**	**p**
T/T and C/T *versus* C/C	1.420	0.782-2.578	0.2
T/T *versus* C/C	1.838	0.881-3.837	0.1
T/T *versus* C/T and C/C	0.631	0.344-1.157	0.1
All subjects			
IL-1B +3953 genotypes compared	**OR**	**95% CI**	**p**
T/T and C/T *versus* C/C	0.974	0.574-1.651	0.9
T/T *versus* C/C	0.958	0.299-3.072	0.9
T/T *versus* C/T and C/C	0.945	0.312-2.865	0.9

OR: odd ratio; CI: confidence interval. All models matched for age, gender, hypertension, smoking habits and adjusted for randomized treatment assignment.

Table 5
Multiple logistic regression analysis assessing the independent association of IL-1 gene polymorphisms and the presence of USAP

All subjects			
IL1 RN genotypes compared	**OR**	**95% CI**	**p**
2/2 and 1/2 *versus* 1/1	0.133	0.211-1.78	0.346
2/2 *versus* 1/1	0.585	0.216-1.585	0.292
2/2 *versus* 1/2 and 1/1	0.492	0.187-1,294	0.151
All subjects			
IL1B -511 genotypes compared	**OR**	**95% CI**	**p**
T/T and C/T *versus* C/C	1.898	0.889-4.051	0.6
T/T *versus* C/C	2.451	1.049-5.75	0.04
T/T *versus* C/T and C/C	1.218	0.640-2.319	0.1
All subjects			
IL1B +3953 genotypes compared	**OR**	**95% CI**	**p**
T/T and C/T *versus* C/C	0.134	0.076-2.236	0.6
T/T *versus* C/C	0.615	0.183-2.071	0.5
T/T *versus* C/T and C/C	0.803	0.288-2.826	0.7

OR: odd ratio; CI: confidence interval. All models matched for age, gender, hypertension, smoking habits and adjusted for randomized treatment assignment.

or multiple-vessel disease (MVD) [27] in a London, UK Caucasian population. In addition, no association was found between the IL-1RN allele 2 and CAD [27], which is consistent with our results as we observe no significant difference between IL-1RN genotypes and ACS ($p = 0.348$). While the IL-1RN 1/1 genotype was seen more frequently in the USAP group (58.6%) than in the healthy control group (50.4%), this difference did not reach statistical significant ($p = 0.327$). Furthermore, no association was found between IL-1RN alleles and ACS ($p = 0.154$), SAP ($p = 0.400$) or USAP ($p = 0.120$).

IL-1B plays an important a role in the pathogenesis of atherosclerosis. Polymorphisms in the IL-1B gene can affect the severity of and susceptibility to different diseases. One of the important SNPs located at the promoter region of the IL-1B gene is -511 C/T. It has been reported that individuals who have the IL-1B (-511) allele 2 have higher levels of IL-1RA [28]. In addition, LPS-induced IL-1B production has been shown to be increased 2-3 fold by T at -511 position [29]. IL-1B, IL-1RA and IL-6 regulate CRP production used to predict cardiovascular disease in healthy people and patients with CHD, and the increased CRP level is strongly predictive of a high risk of cardiovascular morbidity and mortality. It has been reported that males carrying IL-1B -511 T/T and -31C/C showed a higher body mass index and lean body patients with end stage renal disease and. but no association was seen with CRP level [30]. In addition, patients with hypertensive CHD carrying CRP +1059 and IL-1B -511 C/T or T/T showed reduced CRP levels compared to those carrying IL-1B-511 C/C [31]. Japanese researchers have described a relationship between IL-1B -511 polymorphism and atherogenesis in the subclavian and intracranial arteries [32]. The relationship between IL-1B (-511) and the severity of coronary heart disease has been studied in a Chinese population [33], but no significant difference was found between IL-1B (-511) polymorphism and either myocardial infarction or CAD [26, 27, 34]. In our study, no significant difference between IL-1B (-511) genotypes and ACS ($p = 0.292$) was observed. Although the frequency of the C/C genotype of IL-1B (-511) was high in USAP groups (34.2%) compared to the controls (23.9%), it did not reach statistical significance ($p = 0.129$). Furthermore, no significant difference was observed either between IL-1B (-511) genotypes and SAP ($p = 0.837$) or between ACS and IL-1B (-511) alleles ($p = 0.113$). However, an association was found between IL-1B (-511) allele 1 (C) and USAP ($x^2 = 4.163$, 1 df; $p = 0.041$). This result demonstrates that IL-1B (-511) C allele carriers had a significantly increased risk (approximately two-fold) of USAP than T allele carriers in the Turkish population (OR: 2.01; 95% CI: 1.985-3.933) *(table 3A)*.

Another IL-1B polymorphism is located at position +3953 in exon 5, and is thought to influence IL-1 expression. While studies have found an association between IL-1B (+3953) and increased plasma levels of IL-1B [13, 35], others have found no effect or a reduction in IL-1 levels [36, 37]. It has been reported that the patients with CHD carrying the T/T genotype of IL-1B +3953 showed two-fold higher CRP levels as compared to patients carrying the T/T genotype [38]. In addition, it was shown that people carrying the heterozygote IL-1B C/T genotype showed higher level of CRP [39]. Also, lower serum hsCRP levels were detected in the carriers of the +3954T allele [30]. Furthermore, no association was found between CAD and IL-1B gene polymorphism (+3953), or between either CAD and IL-1B +3953 allele frequency or CAD and the genotype distribution of IL-1B +3953 [24, 26, 34]. In this study, we also observed no significant difference between ACS and the control groups either in genotype distribution ($p = 0.965$) or in the frequency ($p = 0.859$) of the IL-1B (+3953) allele. However, we did observe a significant difference between USAP and SAP patients as regards the allele 1 (C) of IL-1B (+3953) ($x^2 = 4.102$, 1 df; $p = 0.043$). Thus, IL-1B (+3953) allele 1 (C) carriers were more likely to develop USAP than T allele carriers (OR: 1.522; 95% CI: 1.012-2.88) *(table 3B)*.

It has been reported that carrying the IL-1RN allele 2 is significantly associated with coronary atherosclerosis in patients with type 2 diabetes [23]. However, other researchers did not find an independent effect of IL-1 gene polymorphisms on CAD [26, 34]. To assess an independent association of IL-1 gene family polymorphisms with ACS, we performed a multiple logistic regression model

adjusted for age, gender, hypertension and smoking habits *(table 4)*. Although did not find an additional effect of IL-1 gene polymorphisms on ACS, we did find a significant effect on the development of USAP. In our analysis of IL-1B (-511) homozygous mutant (C/C) compared to homozygous wild-type (T/T), an association between the IL-1B (-511) gene polymorphisms and USAP was found (OR: 2.451; 95% CI: 1.049-5.75).

In conclusion, neither the IL-1RN genotype nor the IL-1RN allele was shown to have an association with ACS, but the presence of the IL-1B (-511) C allele appears to be a significant risk factor for USAP in the Turkish population. This is the first report showing an association between USAP and IL-1B (-511) gene polymorphisms.

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