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INVESTIGATION OF RELATIONSHIP BETWEEN rs1800796 VARIANTS OF INTERLEUKINE-6 GENE AND CORONARY ARTERY DISEASE

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ABSTRACT

The most important characteristic of coronary artery disease, which is one of the most prevalent and most important healthy problem today, is that it can lead to life-threatening myocardial infarction in advanced stages. It is more important to take protective preventions by knowing the risk factors that cause the disease rather than the treatment of this disease.

This study included determining the frequency of interleukin-6 (IL-6) gene 572 G / C polymorphism in individuals with coronary artery disease (CAD) and determining the role of that polymorphism in the development of CAD. In the current study, DNAs were isolated from the blood of a total of 185 individuals (103 coronary patients and 82 controls) by the salt method. Genotypes of IL-6 572 G / C polymorphism were detected by using molecular techniques (PCR, RFLP and electrophoresis) from these isolated DNAs. The results obtained were evaluated statistically. According to these results, the frequencies of 572 G / C genotype were 83% for GC, 17% for GC, 0% for CC in control subjects for CAD; whereas in patients, GG 72%, GC 28% and CC 0% were detected in the patients. No statistically considerable difference was determined between control and patient groups in terms of frequency of 572 G / C alleles and the GG genotype was significantly higher in the patient group. Based on the results of the currently study, we can say that there is no correlation between coronary artery disease and IL-6 572 G / C polymorphism frequency.

Keywords: Coronary artery disease, CAD, IL-6 polymorphism, rs1800796.

ÖZET

Günümüz hastalıklarından koroner arter hastalığı toplumda sık görülen önemli sağlık sorunlarından biri olarak karşımıza çıkmaktadır. Koroner arter hastalığının günümüzde bilinen en önemli özelliği, hastalığın ileri evrelerinde hayatı tehdit eden miyokard enfarktüsüne neden olabilmesidir. Bu hastalıkta risk faktörlerinin bir an önce belirlenerek koruyucu önlemlerin hayata geçirilmesi tedavisinden daha önemlidir. Yapılan bu çalışma koroner arter hastalığı (KAH) olan bireylerde interlökin-6 (IL-6) geni 572 G / C polimorfizm sıklığının belirlenmesi ve belirlenen bu polimorfizmin koroner arter hastalığının gelişimindeki rolünün ortaya çıkarılmasını içermektedir. Mevcut çalışmada, 103 koroner hastası ve 82 kontrol olmak üzere toplam 185 bireyin kanları toplandı ve bu kanlardan tuz yöntemiyle DNA'lar izole edildi. İzole edilen bu DNA'lardan moleküler teknikler (PCR, RFLP ve elektroforezde görüntüleme) kullanılarak IL-6 572 G / C polimorfizminin genotipleri saptandı. Elde edilen sonuçlar istatistiksel açıdan değerlendirildi. Bu sonuçlara göre, -572 G / C genotip sıklığı KAH için kontrol bireylerde GG % 83, GC % 17, CC % 0; hasta bireylerde ise GG % 72, GC %28, CC % 0 olarak saptandı. 572 G-C allel sıklıkları açısından gruplar arasında istatistiksel olarak önemli bir farklılığın olmadığı, GG genotipinin ise hasta grubunda önemli derecede yüksek olduğu belirlendi. Yaptığımız bu çalışmanın sonuçlarına dayanarak şunu söyleyebiliriz ki, koroner arter hastalığı ile IL-6 572 G / C polimorfizm sıklığı arasında bir ilişki yoktur.

Anahtar Kelimeler: Koroner arter hastalığı, KAH, IL-6 polimorfizm, rs1800796.

1. INTRODUCTION

Coronary artery disease (CAD) in the community is known as the main cause of mortality and morbidity, as well as a consequence of the development of atherosclerosis in the coronary arteries [1, 2]. CAD is a very complex genetic based disease that is affected by genetic influences and environmental factors [3]. Important risk factors for CAD can be listed as follows: Positive family history, lipid metabolism disorders, diabetes mellitus, hypertension, smoking and obesity [4, 5, 6, 7]. The most important characteristic of CAD, which is one of the most prevalent and most important

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healthy problem today, is that it can lead to life-threatening myocardial infarction in advanced stages. Inflammatory processes play a considerable role in the pathogenesis of atherosclerosis which is a multifactorial disease [8, 9, 10, 11]. According to reports, around 17.5 million people worldwide are estimated to have lost their lives with CAD every year. This occurred in the majority of cardiovascular events below 75 years of age [12]. Several studies emphasize the importance of inflammation both in the initiation and advancement of atherosclerosis [6, 13, 14, 15]. Therefore, in recent years, the contribution of inflammation in CAD has been more investigated [16].

Recent studies have shown that inflammatory molecules such as tumor necrosis factor (TNF alpha) interleukin-1-beta (IL-1β), interleukin-6 (IL-6) play a critical role in plaque formation in atherosclerosis and in the process of CAD formation. Interleukin-6 (IL-6) is proinflammatory cytokine that plays a main role in immune, inflammatory, acute phase responses and atherosclerotic processes [9, 13, 14, 17]; and it, as a pleiotropic cytokine with a size of 23.7 kDa, is one of the major inflammatory cytokines and acts in regulating the inflammatory response of CAD [18, 19].

The interleukin-6 gene is located on the chromosome 7p21, while the IL-6 gene 572 G / C (rs1800796) is located on the region of promoter that affects the transcription of the IL-6 gene [4, 6]. Its serum levels and their relationship with CAD risk have been extensively researched [10, 14, 20, 21].

Due to these reasons, this study was planned to determine the frequency of IL-6 gene 572 G / C polymorphism and to explain its relationship with coronary artery disease.

2. MATERIAL AND METHODS

2.1. Study Population and Sample Collection

The present study was carried out with 82 healthy controls and 103 patients with coronary artery disease were received to Adıyaman 82nd Year State Hospital, Cardiology Department. Our study was carried out in accordance with the Declaration of Helsinki and was made with the approval of Adıyaman University Ethics Guidelines Committee and a written informed consent form was ensured from all the patients. The CAD study group consisted of 103 patients who underwent elective coronary angiography for assessment of cardiac symptoms, abnormalities in electrocardiograms (ECGs), or positive stress tests. Patients having a history of acute coronary syndrome in the last one month, valvular heart disease, congenital heart disease, chronic cardiac failure, hepatic dysfunction, cardiomyopathy, chronic kidney disease, respiratory illness, active infection and prior stroke were excluded from the present study. Selective coronary angiography was carried out for all patients under local anesthesia via the entire femoral artery by using the Judkins technique. Coronary tree segments were constructed based on the AHA proposed classification, which was modified for the Arterial Revascularization Therapy Study (ARTS) I and II. A lesion is defined as a significant value when visual assessment results in a 60% reduction in luminal diameter.

2.2. Genotyping Assays, Genomic DNA Extraction, PCR

Genomic DNAs were isolated from blood samples (8 mL) using salt method [22]. Isolated DNA samples were amplified in thermal cycler (BIORAD, T100) for IL-6 gene with below written primers subject to PCR conditions and PCR mixture (Table 1). The forward and backward primers used to amplify the IL-6 572 G / C region were 5'- GGAGACGCCTTGAAGTAACTGC- 3', and 5'- GAGTTTCCTCTGACTCCATCGCAG- 3', respectively. Thermal cycling program was set up for IL-6 as four steps (Table 2). After amplification, all PCR products were stored at 4°C till next procedure.
After amplified PCR products were checked by using agarose gel electrophoresis, a 164-bp fragment was cleaved with 1U *BsrB*I restriction endonuclease (NEB, R0102S) according to the manufacturer's instructions. All PCR products obtained from the digestion reaction were separated using 2% agarose

gel electrophoresis. The fragments were visualized with BioDoc Imaging System and then interpreted with Biometra Instrument Programme. Following cleavage with *BsrB*I restriction endonuclease, three different genotypes were determined including CC (163-bp), GC (163-101, and 62-bp) and GG (101 and 62-bp) (Figure 1).

Table 1. PCR components used in this study

Component	Volume
10x PCR Buffer ($NH_2(SO_4)$)	2.5µl
2 mM dNTP Mix	2.5µl
Primer For (10 µM)	0.5µl
Primer Rev (10 µM)	0.5µl
25 mM $MgCl_2$	1.5µl
Taq DNA Polimeraz (10 U/µl)	0.2µl
Genomic DNA (200 ng/µl)	1µl
Nuclease-free water	X µl
Total Volume	**25 µl**

Table 2. Thermal Cycler Protocol for PCR.

Step	Cycle	Temp (°C)	Time
1	1 X	94 °C	7 min
		94 °C	30 sec
2	35 X	59 °C	40 sec
		72 °C	40 sec
3	1 X	72 °C	7 min
4		4 °C	∞

2.3. Statistical Analysis

Pearson Chi Square test, One Proportion Exact p value was used to compare the categorical variables (allele, genotype, etc.) between groups. On the other hand, we compared parameter values between two groups by means of two independent sample t test. SPSS software (IBM, SPSS Statistics 20) was used for the analyses. The p values < 0.05 were considered as statistically significant.

3. RESULTS

This study included determining the frequency of interleukin-6 (IL-6) gene 572 G / C polymorphism in individuals with coronary artery disease (CAD) and determining the role of that polymorphism in the development of coronary artery disease. In the current study, DNAs were isolated from the blood of a total of 185 individuals (103 coronary patients and 82 controls) by the salt method [22]. Genotypes of IL-6 572 G / C polymorphism were detected by using molecular techniques (PCR, RFLP and electrophoresis) from these isolated DNAs (Figure 1). The results obtained were evaluated statistically. It was determined that 68 individuals (83%) of 82 individuals had GG genotype and 14 of them (17%) had GC genotype in the control group of IL-6 gene 572 G / C polymorphism genotypes distribution. CC genotype was not found in any individual in the control group. A total of 103 individuals with CAD diagnosed were found to have GG genotypes in 74 (72%) and GC genotypes in 29 (28%). As in the control group, CC genotype was not found in patients with CAD. In the control group, the G allele frequency of the IL-6 572 G / C polymorphism was determined as 90% (136 alleles) and the C allele frequency was 10% (14 alleles); whereas in the CAD group, G allele frequency was determined as 84% (148 alleles) and C allele frequency as 16% (29 alleles) (Table 3). No statistically considerable difference was determined between control and the patient groups in

terms of frequencies of 572 G / C genotypes. In the patient group, the GG genotype was significantly higher than the control group.

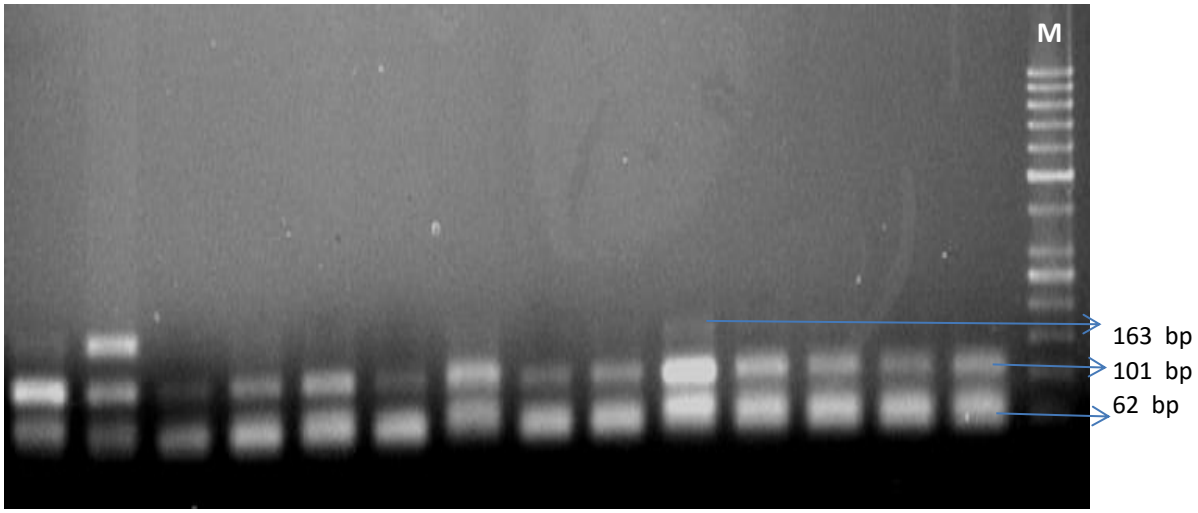

Figure 1. Agarose gel (2% (w/v) electrophoresis of IL-6 gene 572 G / C polymorphism. M indicates DNA ladder.

Table 3. Genotype and allele distribution of IL-6 gene 572 G / C polymorphism of control and coronary artery disease.

	n	**IL-6 -572 GENOTYPES**				**ALLELES**		
		GG (n) (%)	GC (n) (%)	CC (n) (%)	**Statistics**	G (n) (%)	C (n) (%)	**Statistics**
Control	82	68 (83)	14 (17)	0	*P‡=0.000*	136 (90)	14 (10)	*P‡=0.000*
Total Patients	103	74 (72)	29 (28)	0	*P‡=0.000*	148 (84)	29 (16)	*P‡=0.000*
Statistics			*P†=0.076*				*P†=0.077*	

†: Pearson Chi-Square Test, ‡: One Proportion Exact p Value

Table 4. Comparison of baseline characteristics of patients and the controls.

Group	**Control (n=82)** mean ± SD	**Patients (n=103)** mean ± SD	**Statistics**
Age	55.6173 ±1.1912	60.0588±1.2141	*P=0.16*
Gender (female/male)	26/56	39/64	*P=0.389*

Mean: average, SD: standard deviation

4. DISCUSSION

In the current study, we investigated the association between IL-6 572 G / C polymorphism and coronary artery disease risk. This healthy problem is a highly complex genetic and multi-factorial disease that affected by genetic influences and environmental factors. Karaman et al. reported that SNPs in candidate genes are susceptible to these multifactorial diseases [3]. Many reports with Asians showed us that a positive association detected between the 572 G / C polymorphism with CAD risk [27, 28, 33], while no such association in studies with Caucasian populations [21, 23, 24, 25].

A number of studies have been reported in the literature on the potential relationship between interleukin-6 (IL-6) gene polymorphisms and CAD. In the present study, when we analyze the control and all patient groups for IL-6 572 G / C allele frequency and genotype distribution (Table 3); 572 GG genotype frequency was 83% and GC genotype frequency was 17% in controls; and 572 GG genotype frequencies were found to be 72% and GC genotype frequencies to be 28% in all patients. 572 G allele frequency was 90% in patients and 84% in patients, while 572 C allele frequency was 10% in controls and 16% in patients.

According to SPSS analysis results, there was no statistically considerable difference between control and patients in terms of genotype and allele frequency. Humphries and colleagues have reported that the UK population does not correlate with coronary heart disease and IL-6 572 G / C polymorphism [24]. Another study reported that MI and IL-6 572 G / C polymorphisms are not related [25].

Contrary to our conclusions; Fragoso and colleagues showed that IL-6 572 G / C polymorphism in their Mexican population may be related to the risk of developing acute coronary syndrome [26]. Another study reported that IL-6 572 G / C polymorphism in the Chinese population is involved in the pathogenesis and progression of coronary heart disease [27]. Wei has even reported that the G allele is an important genetic marker [28]. In a meta-analysis study performed in 2013, the relationship between IL-6 572 G / C polymorphism and CAD risk was detected only in Asian populations. It has not been associated with this polymorphism in Caucasian populations [10]. In a study conducted by Jang et al. in 2008, 572 G / C polymorphism in Korean CAD patients was found to be significantly associated with inflammatory variables [13, 29]. Celik et al. showed that in a study conducted in 2015, there was a significant relationship between the IL-6 572 G / C gene polymorphism (in the presence of C allele) and adolescents having a parental history of premature CAD [1]. A Meta-analysis study reported that in the Asian population, the IL-6 C- 572 G gene polymorphism was indicated to be correlated with CAD susceptibility and the carriers of -572 G allele might be predisposed to CAD risk [30]. However, Li et al. reported that IL-6 572 G / C polymorphism significantly increased CAD risk [4, 31].

On the other hand; researchers reported that the C allele of 572 G / C polymorphism may be important to reduce the risk of CAD in Chinese [4, 6].

Wang and colleagues conducted a study in 2015 with 402 subjects with CAD and 402 control subjects. As a result of this study, it was reported that IL-6 -174G > C polymorphism and CAD sensitivity were significantly correlated, whereas there was no relation between IL-6 572 C / G and this disease [5, 32]. Jabir et al. reported that this polymorphism was not associated with Saudi CAD population [13]. Another study associated with this subject that the 572 G > C rs1800796 polymorphism were not associated with CAD risk in Chinese population [14].

Based on the results of our current study, we can conclude that there is no relationship between IL-6-572 G / C polymorphism frequency and CAD.

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