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ORIGINAL RESEARCH

Investigation of relationship between IL-6 gene variants and hypertension in Turkish population

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Abstract Hypertension (HT) is a common and life threating health problem worldwide leading to stroke, heart attack and renal failure. It is characterized by elevated blood pressure forced heart load. Human interleukin-6 (IL-6) and C- reactive protein (CRP) are known to be involved in inflammatory processes. IL-6 gene is a polymorphic gene which −174 G/C is a common and −572 G/C is a rare polymorphisms identified in promoter region. Publications on IL-6 gene polymorphisms raised the question whether this gene polymorphisms lead to susceptibility to HT or not. To investigate the effects of IL-6 gene −174 G/C (rs 1800795) and −572 G/C (rs1800796) polymorphisms on plasma IL-6 and CRP levels and their associations with hypertension disease in Turkish population we analyzed −174 G/C and −572 G/C polymorphisms and plasma IL-6 and CRP levels in 111 healthy controls and 108 hypertension patients from Adıyaman, Turkey. We determined the genotypes using polymerase chain reaction-restriction fragment length polymorphism and analyzed plasma levels of IL-6 by ELISA and CRP by automated standard biochemical methods. We have found no statistically significant differences between IL-6 gene −174 G/C and −572 G/C genotypes and allelic frequencies and IL-6 and CRP plasma levels and HT ($p > 0.05$). No CC genotype was found in control subjects for −572 G/C polymorphism. In conclusion, we found relation to −174 G/C and −572 G/C gene variants between neither IL-6 and CRP levels nor hypertension. The −572 G allele and GG genotype are predominant in Turkish population in Adıyaman, Turkey whereas the CC genotype is very rare.

Keywords Hypertension · IL-6 gene polymorphism · −174 G/C, −572 G/C gene variants · CRP

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Introduction

Hypertension (HT) is one of the most common chronic, complex genetic disease world-wide. Its occurrence is influenced by both genetic and environmental factors (Li et al. 2005; Kearneya et al.2004; Conen et al. 2009; Wang et al. 2011). It is characterized by high blood pressure forced heart load. It is known as an important risk factor for cardiovascular, renal disease and stroke but the underlying mechanisms of how high blood pressure cause to cardiovascular disease (CVD) are still uncertain. It leads to poor life quality and increases morbidity and mortality (Li et al. 2005, Chae et al. 2001; Nakajima et al. 1999; Johansson 1999). However molecular mechanisms of hypertension are not fully understood, the inflammation is known to be playing an essential role in pathogenesis of hypertension and cardiovascular diseases. Inflammation is an independent risk factor that may act on initiation and development of HT disease (Li et al. 2005; Bautista et al. 2005; Sesso et al. 2006). Recent studies show increased baseline plasma inflammatory marker levels such as IL-6 and C-reactive protein (CRP) in HT and CVD (Wang et al. 2011; Sesso et al. 2006; Humphries et al. 2001; Gao et al. 2011; Bermudez et al. 2002; Ridker et al. 2000).

Interleukin-6 is a cytokine that plays an essential role in cellular and humoral immune response and is related to inflammation, host defense, and tissue injury (Gao et al. 2011; Ridker et al.2000). It is one of the most important acute-phase response mediators and regulates CRP production in hepatocytes (Gao et al. 2011; Ridker et al. 2000; Jenny et al. 2002; Berg et al. 2009; Baumann and Gauldie 1994). It has been found that both IL-6 and CRP are associated with HT and coronary heart disease in the manner of endothelial dysfunction and impaired fibrinolysis (Humphries et al. 2001; Boos and Lip 2006). However plasma IL-6 levels are very low in healthy individuals they increased rapidly in infection, trauma or stress conditions (Jenny et al. 2002). Plasma IL-6 levels show great differences even among healthy individuals, related to both genetic and environmental factors (Gao et al. 2011; Jenny et al. 2002). These differences may be explained by IL-6 gene variations (Sesso et al. 2006; Gao et al. 2011; Fishman et al. 1998). The IL-6 gene is located at p21 of chromosome 7, contains a 1.3 kb coding sequence with five exons and encodes a 23.7 kd protein. It is a polymorphic gene which −634 C/G, −598 A/G, −597 G/A, −572 G/C, −174 G/C polymorphisms were identified in its promoter region (Wang et al. 2011; Nakajima et al. 1999; Sesso et al. 2006; Gao et al. 2011; Jenny et al. 2002; Baumann and Gauldie 1994; Wypasek et al. 2010; Tanaka et al. 2005; Sanders et al. 2009; Timasheva et al. 2008; Kitamura et al. 2002; Illig et al. 2004). Therefore most of the studies on IL-6 gene focus on promoter region polymorphism analyses. Three single nucleotide polymorphisms (SNPs) in the gene promoter region (−597 G/A; −572 C/G and −174 G/C) have been found to be related to increased gene expression and elevated plasma levels of IL-6 (Humphries et al. 2001; Gao et al. 2011; Rivera-Chavez et al. 2003; Tonet et al. 2008).

In light of the foregoing; the aim of our this study was to investigate the effects of IL-6 gene −174 G/C (rs 1800795), −572 G/C (rs1800796) polymorphisms on plasma IL-6 and CRP levels and their associations with hypertension disease.

Materials and methods

Study population

This study enrolled 108 healthy control subjects and 111 patients with essential hypertension who were admitted to the Cardiology Department of Adıyaman 82th Year State Hospital between February 2010 and January 2011. The study complies with the Declaration of Helsinki and the approval from the Ethic Committee of the Adıyaman University and written informed consent from each individual have been obtained.

Patients who have valve stenosis greater than mild degree or regurgitation, aortic coarctation, previous cardiac surgery, chronic kidney disease, hepatic dysfunction, respiratory illness, acute infection, chronic inflammatory disease or complex congenital heart disease were excluded from the study.

The blood pressure was measured three times after 5-min rest in the sitting position on both upper limbs with the use of automatic manometer (Omron M4 Plus, Omron Healthcare Europe, Hoofddorp, Holland). The mean value of the second and the third measurements were calculated. The measurements taken on the dominant limb were used. The blood pressure values above 140 mmHg for systolic blood

pressure (SBP) and above 90 mmHg for diastolic blood pressure (DBP) are considered as hypertension (Chobanian et al. 2003).

Blood assays

EDTA blood samples were centrifuged immediately and two plasma samples were separated for each subject. One of these samples was stored at −20 °C until IL-6 analyses was performed and the second sample was used immediately for analyzing CRP, lipids including total cholesterol, low-density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride levels (Commercial kit-Roche Diagnostics, Mannheim, Germany, auto analyzer-Roche/Hitachi Cobas c Systems, Basel, Switzerland). The plasma samples were tested for IL-6 levels using an ELISA kit (DIAsource IL-6 EASIA, ELISA reader -Epoc)

Genotype determination

Genomic DNA was extracted from EDTA blood samples by standard salting out method (Miller et al. 1988). Genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique.

IL6 gene −174 G/C and −572 G/C polymorphisms at promoter region were analyzed according to Karahan et al. (2005) and Humpries et al. (2001) with minor modifications as follows.

For −174 G/C, a 431-bp region was amplified by PCR using IL-6 Pro-F 5′CAGAAGAACTCAGATG ACTG3′ and IL-6 Pro-R 5′GTGGGGCTGATTGGA AACC3′ primer pair (Karahan et al. 2005). For −572 G/C polymorphism a 163-bp region was amplified by PCR using forward primer F:5′-GGAGACGCCTT GAAGTAACTGC-3′, and reverse primer R: 5′-GAG TTTCCTCTGAC TCCATCGCAG-3′ (Humpries et al. 2001). PCR conditions were provided as 50 ng genomic DNA, 1XPCR buffer, 1.5 mM $MgCl_2$, 100 mol dNTP mixture, 50 pmol of each primer and 0.5 U Taq polymerase in a total volume of 25 l. Cycling conditions were performed as 1 min at 95 °C pre denaturation step, 35 cycles of 1 min at 94 °C denaturation, 1 min at 59 °C (and 55 °C for −572 G/C) annealing and 1 min at 72 °C extension steps following by 5 min at 72 °C single cycle final extension step using thermal cycler (Applied Biosystems Veriti).

RFLP analysis

Interleukin-6 −174 G/C PCR products (431-bp) were digested with 5 Units of *Nla*III (Fermentas, St. Leon-Rot, Germany) restriction endonuclease at 37 °C overnight. Digested restriction fragments were electrophoresed on 1 % (wt/vol) agarose gel and bands were visualized under UV after ethidium bromide staining (Vilber Lourmat Marne La Vallee, France). Three different genotypes were determined including G/G with 229, 173, 29 bp and G/C with 229, 173, 122, 51, 29 bp and C/C with 229, 122, 51, 29 bp fragments.

For the IL6 −572 G/C PCR products (163 bp) the same procedure as above was used with *Mbl* (Fermantas) restriction endonuclease and the genotypes were determined as G/G with 163 bp (undigested), G/C with 163, 101, 62 bp and C/C with 101, 62 fragments.

Statistical analysis

Statistical analysis was performed by running a packaged program of IBM SPSS Statistics 20 software. Comparison of the categorical variables (such as: gender, genotype, allele…) between groups were performed with Pearson Chi Square Test, Yates' Chi Square Test, Fisher's Exact Test, One Proportion Exact p Value and Chi Square Goodness of Fit Test analyses. On the other hand, continuous variables (such as: age, height, weight…) were compared between groups with Mann–Whitney U Test for the non-normal variables and Student's t Test for the normally distributed variables. We compared parameter values between two groups by means of two independent sample t test and Mann–Whitney U test. Furthermore we used Shapiro–Wilk Test for the normality. The p values less than 0.05 were accepted as significant.

Results

Basic characteristics of the HT patients selected for this study are listed in Table 1. There were statistically significant differences between the control group and patients group with respect to gender distribution ($p = 0{,}00$), smoking ($p = 0{,}02$), diabetes mellitus (DM) ($p = 0{,}00$), myocardial infarction (MI) ($p = 0{,}00$), body mass index (BMI) ($p = 0{,}00$),

Table 1 Comparison of baseline characteristics of case patients (HT) and the controls

Risk factors	Controls (n = 108) mean ± SD	HT (n = 111) mean ± SD	*p* value
Age (years)	56.878 ± 10.528	56.111 ± 11.090	**0.579**
Gender (female/male)	43 (39.8 %)/65 (60.2 %)	80 (72.07 %)/31(27.93 %)	0.00*
BMI (kg/m^2)	30.099 ± 4.432	26.863 ± 3.741	0.00*
Systolic BP (mmHg)	143.635 ± 17.494	124.351 ± 11.562	0.00*
Diastolic BP (mmHg)	87.785 ± 9.237	78.222 ± 9.512	0.00*
Total cholesterol, mg/dL	192.308 ± 39.423	197.055 ± 36.970	0.335
HDL cholesterol, mg/dL	42.242 ± 10.306	46.564 ± 13.297	0.04*
LDL cholesterol; mg/dL	115.630 ± 36.239	118.487 ± 40.812	0.561
Triglyceride, mg/dL	205.975 ± 149.938	181.527 ± 112.071	0.158
IL6 (ng/ml)	0.139 ± 0.257	0.118 ± 0.179	0.471
CRP, mg/L	5.830 ± 10.010	6.815 ± 18.364	0.590
Smoking (±) n (%)	13 (11.81 %)/98 (88.19 %)	7 (6.5 %)/101 (93.5 %)	0.02
Alcohol (±) n (%)	4(3.6 %)/107 (96.4 %)	5(4.6 %)/103(95.4 %)	0.674
DM (±) n (%)	22(19.81 %)/89(80.19 %)	6(5.6 %)/102(94.4 %)	0.00*
MI (±) n (%)	11 (9.90 %)/100(90.1 %)	2(1.8 %)/106(98.2)	0.00*
Stroke (±) n (%)	4 (3.6 %)/107(96.4 %)	0 (0 %)/108 (100 %)	0.077

Mean: average, *SD* standard deviation

BMI body mass index, *BP* blood pressure, *HDL* high-density lipoprotein, *LDL* low density lipoprotein, *IL-6* Interleukin -6, *CRP* C-reactive protein, *DM* diabetes mellitus, *MI* myocardial infarction

* $p < 0.05$

HDL ($p = 0{,}04$), SBP ($p = 0{,}00$), DBP ($p = 0{,}00$). On the other hand, no significant statistical differences were found in terms of age ($p = 0{,}579$), alcohol consumption ($p = 0{,}674$), stroke ($p = 0{,}077$), total cholesterol ($p = 0{,}335$), low density lipoproteins (LDL) ($p = 0{,}561$), triglyceride ($p = 0{,}158$). In comparison to IL-6 and CRP levels between control and HT groups no significant statistical differences were found (Table 1).

IL-6 gene −174 G/C and −572 G/C genotype distribution and allelic frequencies of controls and patients with HT are listed in Table 2. No statistically significant differences were found between control and patient groups in terms of genotype distribution and allelic frequencies of IL-6 gene −174 G/C ($p = 0{,}215$, $p = 0{,}573$) and −572 G/C polymorphisms ($p = 0{,}508$, $p = 0{,}698$). Genotype frequencies of −174 G/C polymorphism were determined as 63.9 % GG, 31.5 % GC and 4.6 % CC in control subjects whereas they were 52.3 % GG, 42.3 % GC and 5.4 % CC in patients group. For −572 G/C polymorphism 76.6 % GG, 20.4 % GC and 0 % CC were found in control subjects whereas 77.5 % GG, 21.6 % GC and 0.9 % CC in patients group. No CC genotype was found in control subjects for −572 G/C polymorphism (Table 2). Genotype distributions were in Hardy–Weinberg equilibrium for both −174 G/C ($p = 0.758$ for control subjects and $p = 0.370$ patients group) and −572 G/C ($p = 0.238$ for control subjects and $p = 0.261$ for patients group) polymorphisms.

In comparison to plasma IL-6 and CRP levels between two groups according to genotype distributions of −174 G/C and −572 G/C polymorphisms no statistically significant differences were found ($p > 0.05$) (Table 3).

Discussion

In the present study we have investigated the effects of IL-6 gene −174 G/C and −572 G/C polymorphisms on plasma IL-6 and CRP levels and their possible effects on hypertension etiopathogenesis. Hypertension is a complex genetic disease influenced by both genetic and environmental factors and characterized by high

Table 2 Genotype distributions and allele frequencies of IL-6 −174 G/C and −572 G/C polymorphisms in HT patients and Controls

	Control (n = 108)	HT (n = 111)	*p*	OR (95 %)
IL-6 −174 Genotypes				
GG	69 (63.9 %)	58 (52.3 %)	0.215	1
GC	34 (31.5 %)	47 (42.3 %)		0.682 (0.196–2.371)
CC	5 (4.6 %)	6 (5.4 %)		
IL-6 −174 Alleles				
G	172 (79.63 %)	163 (73.42 %)	0.573	1.100 (0.308–3.936)
C	44 (20.37 %)	59 (26.58 %)		
IL-6 −572 Genotypes				
GG	86 (76.6 %)	86 (77.5 %)	0.508	1
GC	22 (20.4 %)	24 (21.6 %)		0.000 (0.000–0.000)
CC	0 (0 %)	1 (0.9 %)		0.000 (0.000–0.000)
IL-6-572 Alleles				
G	194 (89.82 %)	196 (89 %)	0.698	1
C	22 (10.18 %)	26 (11 %)		0.880 (0.461–1.679)

Table 3 IL-6 and CRP plasma levels according to distributions of IL-6 −174 G/C and −572 G/C polymorphisms in HT patients and controls

Genotype	Control			HT		
	n	IL-6 (pg/l) (mean ± SD)	CRP (mg/l) (mean ± SD)	n	IL-6 (pg/l) (mean ± SD)	CRP (mg/l) (mean ± SD)
−174 G/C						
GG	69	0.122 ± 0.219	4.52 ± 10.94	58	0.130 ± 0.191	6.72 ± 11.92
GC	34	0.110 ± 0.066	10.01 ± 27.10	47	0.159 ± 0.351	3.81 ± 4.30
CC	5	0.125 ± 0.074	16.58 ± 25.07	6	0.097 ± 0.031	10.67 ± 13.58
p		0.946	0.173		0.749	0.126
−572 G/C						
GG	86	0.125 ± 0.200	8.00 ± 20.40	86	0.120 ± 0.175	5.15 ± 9.51
GC	22	0.092 ± 0.018	2.17 ± 2.30	24	0.177 ± 0.424	7.70 ± 11.42
CC	0	–	–	1	0.080	12.72 ± 0
p		0.437	0.186		0.614	0.346

Mean average, *SD* standard deviation

blood pressure (Yamada et al. 2006; Tabassum and Ahmad 2011). Age, gender, life style (sedative life, obesity, excessive alcohol consumption, salty diet and stress), metabolic diseases such as diabetes mellitus are important factors influencing HT development (Grundy et al. 1999). We have found associations between HT and some individual properties such as gender (more in women than men), smoking, and diabetes, MI, BMI, and low HDL ($p < 0.05$). The summarized results are shown in Table 1. In concordance with our results HT prevalence has been found to be increased in men than women in early adulthood whereas it has been found to be increased in women than man in late adulthood and older age (Özcan 1995). SBP shows a sharper increase with age more in women than man. This means increase in blood pressure and HT prevalence in elderly women (Mancia et al. 2007; Mosca et al. 2011). Acute increase in blood pressure just 15–30 min after cigarette smoking shows that smoking is an important risk factor for hypertension (Öksüz 2004; Suheil 2007). Suheil showed that the influence of BMI on HT. They have suggested that hypertension rate was 3 % in normal weight, 15.9 % in overweight, 33.3 % in obese individuals (Suheil 2007).

Interleukin-6 gene is a polymorphic gene whose −174 G/C and −572 G/C are the common and the rare polymorphisms identified in its promoter region respectively. Some studies showed association between −174 G/C or −572 G/C or both polymorphisms and HT whereas some other studies showed no relationship (Wang et al. 2011; Humphries et al. 2001; Jenny et al. 2002; Timasheva et al. 2008; Losito et al. 2003; Pola et al. 2002).

In our study we found no relationship between genotype distributions and allelic frequencies of IL-6 gene −174 G/C and −572 G/C polymorphisms and HT in comparison to controls and HT patients group. While we found only one case with CC genotype in HT group we found no CC genotype in control subjects for −572 G/C polymorphism (Table 2). This shows that CC genotype of −572 G/C polymorphism is very rare in the Turkish population in the Adıyaman region consistent with results of Humphries et al. (2011) who studied 2589 healthy and 163 CVD men of UK origin and found very rarely −572 CC genotype (GG/GC/CC 2224/225/9 in controls and 135/19/0 in CVD group) (Humphries et al. 2001).

In accordance to our findings, no significant differences were found between IL-6 −174 G/C and −572 G/C polymorphisms and HT whereas some other studies showed relations between IL-6 −174 G/C polymorphism and HT and also cardiovascular diseases (CVD) (Humphries et al. 2001; Timasheva et al. 2008; Losito et al. 2003; Pola et al. 2002; Wong et al. 2007).

Polymorphisms −174 G/C and −572 G/C were shown to be associated with plasma IL-6 (Humphries et al. 2001; Fishman et al. 1998; Losito et al. 2003) and CRP levels (Humphries et al. 2001; Losito et al. 2003; Wong et al. 2007).

Increased IL-6 levels lead to vascular resistance and hypertension in consequence of endothelial dysfunction (Boos and Lip 2006). IL-6 stimulates release of acute phase reactants such as CRP, fibrinogen, amyloid A, TNF-a and IL-ip. It is known that elevated CRP blood levels enhanced hypertension development by inflammation (Wong et al. 2007; Savoia and Schiffrin 2006).

In this study, in order to investigate the relationship between IL-6 gene −174 G/C and −572 G/C variants and IL- 6 and CRP plasma levels and HT we analyzed and compared both IL-6 gene variants and IL6 and CRP levels in healthy control group and HT patients. We have found no statistically significant differences between IL-6 and CRP levels and −174 G/C and −572 G/C IL-6 gene variants and HT ($p > 0.05$) (Tables 1, 3).

Some studies showed elevated plasma levels of IL-6 associated to −174 G/C polymorphism in patients group (Fishman et al. 1998; Losito et al. 2003) whereas both −174 G/C and −572 G/C polymorphisms were associated with elevated plasma CRP levels (Humphries et al. 2001; Losito et al. 2003; Savoia and Schiffrin 2006). Elevated IL-6 or CRP levels or both were found to be associated with HT. However in some studies no association was found between IL-6 or CRP and HT (Bautista et al. 2005; Sesso et al. 2006; Humphries et al. 2001; Losito et al. 2003).

As it seems, the studies in this area produced contradictory results and discussions. Therefore we investigated in this study the effects of −174 G/C and −572 G/C polymorphisms in the promoter region of the IL-6 gene on plasma IL-6 and CRP levels and their associations with hypertension disease. In our study neither IL-6 and CRP levels nor HT were found significantly associated with −174 G/C and −572 G/C gene variants. This may be because such gene polymorphisms and their effects show broad changes between different populations (Gao et al. 2011) and geographic regions.

In conclusion we found relation to −174 G/C and −572 G/C gene variants between neither IL-6 and CRP levels nor hypertension and −572 G allele and the GG genotype is predominant in the Turkish population in the Adıyaman region whereas the CC genotype is very rare.

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Conflict of interest The authors declare that there is no conflict of interest.

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