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Association between rs1800795 (-174 G/C) Polymorphism in the Promoter of *IL6* Gene and Risk of Relapsing-Remitting Multiple Sclerosis (RRMS) in Isfahan Population

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Abstract

Multiple sclerosis (MS) is an inflammatory demyelinating disease of central nervous system (CNS) that mostly affects young adults. The etiology of MS includes both genetic and environmental factors. A single nucleotide polymorphism (SNP) linked with autoimmune disorders predisposition, identified by Genome-Wide Association Study (GWAS) among genes which immunologically related are considerably over signified. The goal of the current study is investigation of the association between rs1800795 (-174 G/C) polymorphism in the promoter of *IL6* gene variant with the risk of RRMS in a subset of Iranian population. In this case-control study, 110 healthy subjects and 110 patients with RRMS were included. DNA was extracted from blood samples and polymerase chain reaction (PCR) was used to amplify the fragment of interest contain rs1800795 SNP, restriction fragment length polymorphism (RFLP) method was performed for genotyping of the DNA samples with a specific restriction enzyme (*NlaIII*). SPSS for Windows software (version 18.0; SPSS, Chicago, IL) was used for statistical analysis. No significant differences were found between RRMS patients and healthy controls with respect to the distribution of the cytokine gene polymorphism investigated. Odds ratio adjusted for age, sex, and blood groups (except A blood group) has displayed similar outcomes. These results indicate that the rs1800795 SNP is not a susceptibility gene variant for development of RRMS in the Isfahan population. Further studies using new data on complex transcriptional interactions between IL-6 polymorphic sites are necessary to determine IL-6 haplotype influence on susceptibility to RRMS.

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Keywords

Multiple Sclerosis (RRMS), GWAS, *IL6* Gene, Polymorphism

1. Introduction

Multiple sclerosis (MS) is considered a chronic inflammatory neurodegenerative disease of the central nervous system (CNS) that leads to important disability including mental, physical, and occasionally psychiatric complications and mostly affects young adults [1] [2]. The fast growing in prevalence of MS has been a leading public health crisis globally, including Iran [3]. The cause of MS is still unknown, it is generally believed to be an autoimmune disease and both intricate genetic factors with many predisposing-conferring genes as well as environmental factors have been identified as important causes [4]. Genetic susceptibility to MS is likely to be under a polygenic manner, but the majority of the genes involved is yet to be identified [5] [6]. Over the past decade, many efforts have been invested in the exploration for genes predisposing to autoimmune disease such as MS [7] [8]. Recently, notable advance was made in detection of susceptible genes in which single nucleotide polymorphisms (SNPs) involved in autoimmune diseases. Thus, many association studies of polymorphic immune-associated genes described for autoimmune disorders. Most of these genes are investigated because they are supposed to be related to the pathogenesis of diseases based on the function of the gene [8] [9]. One of the susceptibility genetic variants that related to autoimmune diseases is rs1800795 SNP in the IL-6 gene. Several studies have investigated whether a promoter region polymorphism in the gene encoding interleukin 6 (IL-6), might enhance susceptibility to some autoimmune disorders [10]-[13]. It was demonstrated that polymorphisms within the critical promoter or other regulatory regions of several cytokine genes can modify the activity of transcription resulting in inter-individual differences in the levels of cytokine production. These variations may influence the outcome of infections and increase susceptibility to autoimmune disorders. As MS is considered as a chronic immune-mediated neurodegenerative disease, polymorphism in inflammatory cytokines seems to be reasonable candidates for investigation [14]. Increased levels of IL-6 have been detected in the brain tissue of patients with MS [15] and in mononuclear cells in the blood and cerebrospinal fluid (CSF) [16] [17]. IL-6 is a multifunctional Th2 cytokine involved in acute inflammation by the production of acute phase proteins and by the modulation of specific immune responses [18]. IL-6 can promote migration, survival and differentiation of oligodendrocytes precursors into Myelin Basic Protein-positive cells [19] and together with TNF-α can trigger the release of brain-derived neurotrophic factor (BDNF) which is an essential mediator of neuronal survival and synaptic plasticity in the CNS [20]. It is known that IL-6 enhances humoral immune response, so the up-regulated IL-6 system might be involved in antibody-mediated demyelinatin pathways [19]. Recent studies have demonstrated that IL-6 is involved in regulating the balance between IL-17 producing TH17 cells and T-reg cells [21]. -174 G/C in the promoter of *IL*6 gene polymorphism has been positively correlated with some autoimmune diseases and other authors have investigated this polymorphism in respect to type 2 diabetes [10], systemic lupus erythematosus [11], systemic sclerosis [7], and MS [13]. Given complex genetic effects and multifaceted gene-environment interaction nature of MS, frequencies of genetic SNP polymorphisms are different among ethnic populations [8]. Therefore it is especially important to investigate its association in Isfahan population, where the number of cases with MS is rising rapidly [3]. Thus, the purpose of this study is to specify whether the rs1800795 SNP in the IL-6 gene have been studied in other autoimmune disease is associated with the susceptibility to MS in Isfahan population.

2. Materials and Methods

2.1. Study Subjects

The case-control study was conducted to assess the association between rs1800795 SNP and RRMS on Isfahan population, a city located in the central region of Iran. The studied population including 110 RRMS patients that referred to MS clinic of Alzahra hospital and 110 matched healthy control subjects who referred to Isfahan Transfusion Organization (control group). The healthy subjects had no history of MS or other autoimmune disorders. All patients had clinically diagnosed RRMS according to the McDonald criteria that were assigned to a

"Relapsing-Remitting" group. The patient and healthy samples were composed of 83 (75.5%) women and 27 (24.5%) men. Written informed consent was obtained from all patients and controls and the study protocol was approved by the *Ethics Committee of Isfahan* University *of Medical Sciences*.

2.2. Statistical Analysis

SPSS for Windows software (version 18.0; SPSS, Chicago, IL) was used for statistical analysis. Frequencies of allele and genotype were tested for Hardy-Weinberg equilibrium using the χ^2 analysis. Logistic regression analysis was applied to calculate distributions and risk allele/genotype-specific odds ratios (ORs), 95% confidential intervals (CIs), and analogous P values after adjustment for gender, age, as covariates between cases. All continuous variables were expressed as the mean ± standard deviation (SD). Student's t-test was used to compare the continuous variables between the RRMS and control groups. Pearson's v2 test was used to evaluate the difference in the prevalence of RRMS among genotypes. $P < 0.05$ was considered as a significant association.

2.3. DNA Extraction and SNP Genotyping

Peripheral blood samples of patient and control groups were collected in tubes containing EDTA as anticoagulant, and then according to the manufacturer's instructions, DNA was extracted from whole-blood samples using the DNG plus DNA extraction Kit (Cinnagen. Tehran, Iran). DNA quality was analyzed by agarose gel electrophoresis and by UV absorption at 260 and 280 nm. Genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The following primers were used for PCR amplification: Forward: 5'-TGACTTCAGCTTTACTCTTTG-3', Reverse: 5'-CTGATTGGAAACCTTATTAAG-3' (Pishgam. Tehran, Iran). These specific PCR primers amplified a 198-bp fragment in which there is a specific restriction site to determine the different alleles of the rs1800795 SNP. PCR was carried out on an Eppendorf thermal cycler (Eppendorf, Hamburg, Germany) under the following conditions: 95˚C for 5 min followed by 35 cycles of 95˚C for 30 s, 52˚C for 30 s, 72˚C for 45 s, and a final extension of 72˚C for 5 min. PCR products were then digested with 1 U of *NlaIII* restriction enzyme (Reaction Volume15 ML) (Fermentas, Lithuania). After 4-h incubation at 37˚C, the enzyme cut the 198 bp PCR product into four fragments 168, 119, 49 and 30 bp in length (**Figure 1** and **Figure 2**). The resulting products were visualized by 3.5% agarose gel electrophoresis. Fragments size of 119 and 49 bp indicated the presence of a wild-type homozygous CC genotype, two 168 bp and 30 bp fragments displayed the presence of homozygous GG genotype (Due to limitation of agarosegelin detection of fragments that are smaller than 50 bp, 30 bp fragment was invisible) and three fragments of 168, 119 and 49 bp indicated the presence of heterozygous CG genotype. In the last step, the products were visualized with Ultraviolet light. To determine genotyping error rate, we performed both random duplications in 20% of the samples.

3. Results

Demographic and clinical features of the participants selected demographic and clinical features of cases and controls in the studied population and the association with MS are demonstrated in **Table 1**. No major differences were observed between the two groups concerning gender (P = 1), age (31.2 ± 6.4 years for controls and 30.2 ± 7.5 years for cases, (P = 0.258). Blood group status also was not statistically different (P = 0.065) between the two groups (**Table 1**). Genotypes were effectively typed in all subjects and did not deviate from the distribution expected by the Hardy-Weinberg equilibrium. The RFLP detection system is schematized in **Figure 2**. Frequencies of the G/G, G/C, C/C and genotypes of rs1800795 SNP were 59.9%, 33.6% and 7.5% in controls, and 53.6%, 35.5% and 10.9% in cases, respectively, the frequency of the C allele in cases (28.6%) was more than that in the healthy control group (24.1%) (**Table 2**). No statistically significant differences were found between RRMS patients and healthy controls with respect to the -174 G > C genotype or allele distribution. For all of alleles and genotypes of the rs1800795 polymorphism, results were not associated with the risk for RRMS in the population under study (**Table 2**). Our data indicate that the -174 IL-6 genotypes have no role in susceptibility to studied RRMS. In addition, when we compared the GG and GC genotypes against CC genotype as reference, the association between rs1800795 SNP genotypes and RRMS risk was examined in subgroups of both subjects stratified by gender, age (under and over 30 years) and blood groups (**Table 3**). The adjusted OR for the GG and GC + CC genotypes was 0.86 (95% CI: 0.29 - 2.51, P = 0.78) in males, and 1.41 (95% CI: 0.61 - 1.93, P = 0.27) in females, which is indicative of no significant association. Also, we did not find significant relation for

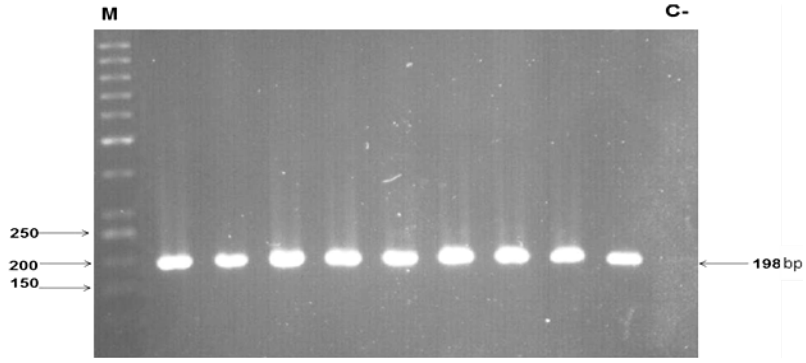

Figure 1. 198 bp PCR product of IL-6 gene polymorphism (rs1800795). Last lane is negative control.

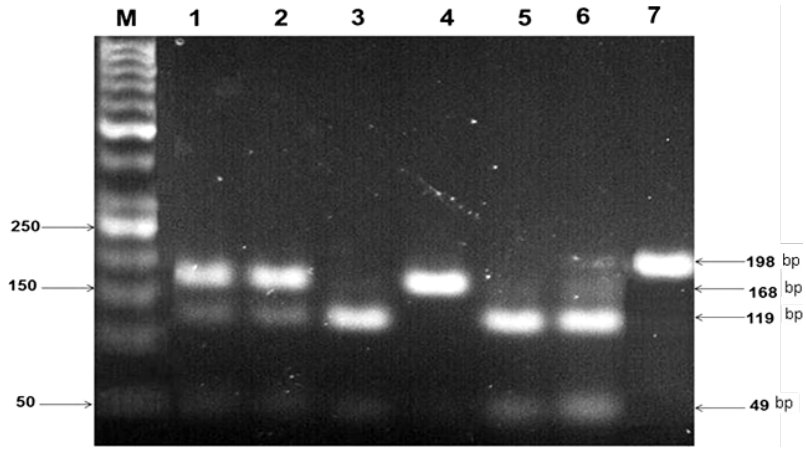

Figure 2. Enzyme digestion. M (50 bp marker); 1, 2, (GC genotypes); 4 (GG genotype); 3, 5, 6 are (CC genotypes) and lane 7 is undigested product.

Table 1. Demographic features in cases and normal controls.

Variables	Controls (n = 110)	Cases (n = 110)	P value
Age (mean ± SD)	31.2 ± 6.4	30.2 ± 7.5	0.258
Gender			
Male	27 (24.5%)	27 (24.5%)	
Female	83 (75.5%)	83 (75.5%)	1
Blood Group			
A	33 (30%)	28 (25.5%)	
B	29 (26.4%)	20 (18.2%)	
AB	12 (10.9%)	26 (23.6%)	
O	36 (32.7%)	36 (32.7%)	0.065
EDSS			
1		74 (67.3%)	
1.5		19 (17.3%)	
2		13 (11.8%)	
3 - 5		4 (3.6%)	
Symptoms at the onset of MS			
Dizziness		41 (37.3%)	
Numbness in the limbs		35 (31.8%)	
Blurred or double vision		34 (30.9%)	

Table 2. Allele and genotype distribution of rs1800795 SNP in cases and controls and their association with RRMS in this study.

	Controls		Cases		Risk or protective Allele/Genotype	*OR (95% CI)	**P value
	n	%	n	%			
Allele frequency (rs1800795)							
C	53	24.1	63	28.6	---	**1.26 (0.81 - 1.98)**	**0.33**
G	167	75.9	157	71.4			
Genotype frequency							
GG	65	59.9	59	53.6	---	**0.80 (0.47 - 1.36)**	**0.42**
GC	37	33.6	39	35.5	---	**1.08 (0.62 - 1.89)**	**0.77**
CC	8	7.5	12	10.9	---	**1.56 (0.61 - 3.98)**	**0.35**

P value P < 0.05, *the OR with 95% CI shown is for the risk allele/genotype. **P allele is the P value for comparison of the allele distribution between the cases and controls. P genotypeis the P value for comparison of genotype distribution between the cases and controls.

Table 3. Stratification analysis of rs1800795 genotype frequency in cases and controls.

Group		Genotype		OR (95% CI)	*P value
		GG	GC/CC		
Male					
Control		14	13	0.86 (0.29 - 2.51)	0.78
Case		15	12		
Female					
Control		51	32	1.41 (0.61 - 1.93)	0.27
Case		44	39		
Age < 30					
Control		29	22	0.98 (0.46 - 2.07)	0.96
Case		35	26		
Age > 30					
Control		36	23	1.63 (0.76 - 3.51)	0.21
Case		24	25		
Blood Group					
A	Control	23	10	3.55 (1.23 - 10.27)	0.017
	Case	11	17		
B	Control	16	13	0.82 (0.26 - 2.61)	0.74
	Case	12	8		
AB	Control	8	4	1.06 (0.25 - 4.50)	0.94
	Case	17	9		
O	Control	18	18	0.89 (0.36 - 2.26)	0.81
	Case	19	17		

*P value P < 0.05.

under and over 30 years groups (OR = 0.98, 95% CI: 0.46 - 2.07, P = 0.96 and OR = 1.63, 95% CI: 0.76 - 3.51, P = 0.21, respectively), and the genotype distribution. In stratification analysis for blood groups, adjusted OR for the GG and GC + CC genotypes was 3.55 (95% CI: 1.23 - 10.27, P = 0.017) in individuals with A blood group, 0.82 (95% CI: 0.26 - 2.61, P = 0.74) in individuals with B blood group, 1.06 (95% CI: 0.25 - 4.50, P = 0.94) in individuals with AB blood group and 0.89 (95% CI: 0.36 - 2.26, P = 0.81) in individuals with O blood group.

4. Discussion

Although etiology of the MS still remains ambiguous, the genetic effect on both predisposition and clinical outcomes is undeniable. Study of potentially key polymorphisms in the some genes of the genome has developed as

a promising approach in understanding of the complicated interaction between genotype of subjects and multifactorial diseases such as MS [4] [22] [23]. It has been demonstrated that IL-6 levels are increased in various autoimmune diseases, including MS and play an important role in MS pathophysiology [7]. It is known that IL-6 enhances humoral immune response, so the up-regulated IL-6 system might be involved in antibody-mediated demyelinating pathways [20]. IL-6 transcription is regulated by different factors binding to the promoter region. This may cause variations in expression levels and may possibly play a role in susceptibility to different autoimmune and inflammatory diseases as well as MS cases [14]. In the present study IL-6 gene polymorphism was examined in order to search for possible association between specific polymorphic profile and RRMS susceptibility. Our results show that, frequency of the C allele (28.6%) and CC genotype (10.9%) in the cases was more than that in the healthy control group (24.1%) and (7.5%) respectively. But, frequency of the G allele (75.9%) and GG genotype (59.9%) in controls was more than that in the case group (71.4%) and (53.6) respectively. So we can consider C allele as a risk allele and G allele as a protective allele in the studied population. Thus, it is suggested that the G allele has a masking effect over the C allele in the heterozygous G/C genotype, which may be due to a complex interaction of both alleles when present co-dominantly. Under such conditions, it is postulated that the G allele induces a protective response that prevents the individuals from developing MS. The rs1800795 polymorphism in IL-6 gene has been positively correlated with some autoimmune diseases and other authors have investigated this polymorphism in respect to type 2 diabetes [10], systemic lupus erythematosus [11], systemic sclerosis [7], and MS [13]. In a study of MS patients carried out on IL-6 promoter polymorphism (rs1800795) by Mirowska-Guzel *et al*. [13], *IL*6-174G > C polymorphism was found to be relevant for population risk of MS. Percentage of C allele carriers was higher in MS group (53%) than in controls (38%) ($P < 0.0001$, OR = 1.88, 95% CI 1.4 - 2.5). *IL*6-174 CC genotype occurred more than twice as often for patients (29.4%) as for healthy controls (12.4%) ($P < 0.00001$, OR = 2.86, 95% CI 1.7 - 4.9). Another study by Sfrent-cornateanu *et al*. [12], carried out on IL-6 promoter polymorphism in systemic sclerosis patients, showed that the GG homozygosis was found to be associated with a higher degree of illness activity and disability in systemic sclerosis patients. In a study of systemic lupus erythematosus (SLE) patients carried out on rs1800795 polymorphism by Chua *et al*. [11], significant association was observed at homozygous G genotype in SLE patients. ($P < 0.00000000625$, OR = 7.33, 95% CI 3.5 - 15.05), whereas the heterozygous G/C genotype was significant in the controls. In another study by Illig *et al*. [10], carried out on rs1800795 polymorphism in type 2 diabetes patients, showed that GG genotype was found to be associated with type 2 diabetes ($P < 0.0096$, OR = 1.51, 95% CI 1.11 - 2.07). In the present investigation, no evidence was obtained to suggest that -174 *IL*6 polymorphism is susceptibility factor for the development of RRMS. Further investigation using new data on transcriptional interactions between IL-6 polymorphic sites are necessary to determine IL-6 haplotype influence on susceptibility to MS.

5. Conclusion

In the present study, however the *IL*6 promoter region polymorphism (rs1800795) did not any significant association with susceptibility to MS. We were unable to reproduce previous studies suggesting that polymorphismat -174 of the *IL*6 promoter region correlate with susceptibility to autoimmune diseases such as MS. The reasons for this could be due to differences in the ethnicity of patients in those studies and the current study, environmental risk profiles, body composition, the sample size used in the studies, or to other factors as yet undetermined. Further evaluation in this area is still needed.

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