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No Direct Association of Myelin Oligodendrocyte Glycoprotein (MOG) Gene Polymorphism (Val142leu) in Genetic Susceptibility to Migraine

Miyelin Oligodendrosit Glikoprotein (MOG) Gen Polimorfizminin, (Val142Leu) Migrene Genetik Duyarlılık ile Doğrudan Bir İlişkisi Yoktur

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Abstract

Objective: Genes which are involved in immune response portray possible candidate genes in migraine. One of those genes is that myelin oligodendrocyte glycoprotein (MOG) that plays an important role in mediating the complement cascade. The purpose of our study is to show the effect of MOG G511C (Val142Leu; rs2857766) polymorphism in migraine attack frequency.

Materials and Methods: In the cohort of 101 Turkish migraine patients and in a control group of 101 healthy subjects, MOG Val142Leu alleles' distribution was examined. Restriction fragment length polymorphism (RFLP) was carried out to genotype this polymorphism.

Results: Although MOG Leu allele frequency was determined as under-represented in migraine patients, any significant difference between the patient and control groups' genotype, and allele frequencies were not obtained [OR=0.47 (0.21-1.08), p=0.053 for genotypes; OR=0.50 (0.23-1.11), p=0.060 for alleles]. However, a statistically significant relationship between MOG G511C (Val142Leu) polymorphism and the decreased migraine attack frequency was determined [OR=11.71 (1.32-103.77), p=0.013]. Val/Leu genotype frequency increrased in migraine patients with two or fewer attacks per month.

Conclusion: Migraine attack frequency might be related with MOG Val142Leu heterozygote genotype. So we think that MOG gene might be related to genetic susceptibility to migraine in the human leukocyte antigen (HLA) region.

Keywords: Migraine, Myelin oligodendrocyte glycoprotein, Polymorphism, HLA, Val142Leu

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Öz

Amaç: İmmün yanıtta yer alan genler, migrende olası aday genleri gösterir. Bu genlerden biri, kompleman kaskadına aracılık etmede önemli bir rol oynayan miyelin oligodendrosit glikoprotein genidir (MOG). Çalışmamızın amacı; migren atak sıklığında MOG G511C (Val142Leu; rs2857766) polimorfizminin etkisini göstermektir.

Gereç ve Yöntemler: 101 Türk migren hastası kohortunda ve 101 sağlıklı denekten oluşan kontrol grubunda MOG Val142Leu alellerinin dağılımı incelendi. Bu polimorfizmi genotiplemek için restriksiyon fragman uzunluk polimorfizmi (RFLP) yapıldı.

Bulgular: MOG Leu allel frekansının, migren hastalarında yetersiz temsil edildiğinin belirlenmesine rağmen hasta ve kontrol grubu genotipleri ve allel frekansları arasında anlamlı bir farklılık elde edilemedi [OR=0,47 (0,21-1,08), genotipler için p=0,053; OR=0,50 (0,23-1,11), aleller için p=0,060]. Ancak MOG G511C (Val142Leu) polimorfizmi ile azalmış migren atak sıklığı arasında istatistiksel olarak anlamlı bir ilişki saptandı [OR=11,71 (1,32-103,77), p=0,013]. Ayda iki veya daha az atak geçiren migren hastalarında Val/Leu genotip sıklığı artmıştır.

Sonuç: Migren atak sıklığı, MOG Val142Leu heterozigot genotipi ile ilişkili olabilir. Dolayısıyla MOG geminin, insan lökosit antijeni (HLA) bölgesinde migrene genetik yatkınlıkla ilişkili olabileceğini öngörmekteyiz.

Anahtar Kelimeler: Migren, Miyelin oligodendrosit glikoprotein, Polimorfizm, HLA, Val142Leu

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Introduction

Migraine is a common episodic brain disorder in which environmental and genetic factors involved in its pathophysiology (1). The disease affects 15% of population worldwide. The migraine frequency is three times more common in females (15-18%) than in males (6%). It has been reported that the higher prevalence in women is typically due to hormonal fluctuations or estrogen withdrawal (2). The International Headache Society (IHS) categorized different types of headache [i.e. migraine with aura (MA) and without aura (MO)] based on the aura (1). It is widely believed that cortical spreading depression (CSD) is the pathophysiological mechanism of the aura. Cortical spreading depression is a slowly propagating wave characterized by the loss of all spontaneous or evoked synaptic activity, and activation potentials resulting in near complete depolarization of neuron and glial cells for migraine aura (3).

In heredity studies, the heritability of migraine was approximately determined as 42% (3). Since familial hemiplegic migraine (FHM) is an autosomal dominant inherited disease caused by mutations in three genes encoding ion channels (CACNA1A, ATP1A2 and SCN1A), it is pathophysiologically accepted as a model of hemifegic migraine with aura. With genome-wide association studies, 38 migraine-related ion channel and non-ion channel coding genes were also identified with highly related to common migraine (4). However, etiology and pathophsiology of the migraine is not known well.

In migraine patients, immune system disregulation is supported with the presence of immune activation caused by patients' peripheral blood and cerebrospinal fluids' aberrant amount of proinflammatory cytokines and receptors (4). For normal development of central nervous system (CNS) along with many neuropsychiatric disorder pathogenesis, cytokines are required. The cytokine molecules can change neurotransmitter and neuropeptide systems in addition to affecting nerve cells (5, 6). The human leukocyte antigen (HLA) gene region contains a wide range of highly polymorphic closely linked genes. An increase in shared HLA haplotypes in eight households was showed by investigating the patients with MO. So, this indicates the potential linkage between heredity of migraine and HLA (6). For polymorphisms of three genes [i.e. tumor necrosis factor alpha (TNF-α), tumor necrosis factor beta (TNF-β) and the *16 allele of DRB1] and migraine, an important association was detected (7-9). Myelin oligodendrocyte glycoprotein (MOG) gene is only detected in the mammalian CNS and mapped to 6p21.3-6p22 within 60-kilobase telomeric region of HLA-F locus. The gene polymorphisms have a linkage disequilibrium with other migraine susceptibility genes in HLA region (10). The protein is compromised 245 amino acids, synthesized in the endoplasmic reticulum (ER) in oligodentrocytes and subsequently transfered to the membrane surface of the oligodentrocyte (OL) cell, and outer surface of myelin sheath in the CNS (11). MOG protein is a cellular adhesion molecule, complement sytem activator, regulator of stability of the oligodendrocyte microtubules and mediates associations between myelin, and the immune system. Variants of the MOG gene may affect the advance of autoimmune disorders via mechanisms such as amino acid substitutions and altered gene expression (12). In pathophysiology of migraine with and without aura, responsible genes are still unknown; however, sterile inflammation might play a significant role in cranial vasculature endothelial stage (13). Linkage analysis has localized MOG gene located at 6p21.3 in the major histocompatibility complex (MHC) region which was intensively investigated in migraine. Thus, MOG gene was selected as a candidate (7).

Important polymorphisms identified in the gene include G15A (0.14), CTC repeat in exon 1 (0.04), Val142Leu (0.191), Val145Ile (0.057) in exon 3, 551168A→G (0.131) and 551177C→T (0.02) in intron 4. Although the effect of the identified polymorphisms on the protein structure or function is not known, it was preferred among the known MOG gene polymorphisms in the current study due to the high frequency of polymorphic variants in the population and the presence of a conserved amino acid substitution in the transmembrane domain. There are also various examples of diseases cited as the cause of the migraine including V/L mutations in the transmembrane domains of the proteins encoded by CFTR, ABC7, PSEN1, TSHR, ACHR and KORC1 genes (14, 15). For this step, we used case-control approach to determine the contribution of the MOG variants to migraine.

Materials and Methods

Population of Study

After the approval of Non-Interventional Research Ethics Committee of Firat University (session number: 2021/02-45, dated February 4, 2021) was obtained, the study was carried out by obtaining verbal and written consents of the families. The protocol of this study was approved by ethics committee and informed consent form was signed by all participants. In addition, the principles of the Declaration of Helsinki were taken into account throughout our study. 101 migraineurs and 101 controls were recruited from Elazig province and its surroundings. 90 females and 11 males, and 82 females and 19 males were present in patient and control group, respectively. Diagnosis of the migraine was carried out after six months' follow up according to the International Classification of Headache Disorders (ICHD-II) criteria (16). An experienced neurologist examined all participants. Patients were interviewed to determine their age, gender, family history, intensity and frequency of migraine attacks in the previous 12 months, age of onset, and other clinical features. Details of the clinical symptoms seen in participants were obtained from the daily surveys. For this study, patients with comorbid diseases (e.g. vascular, hormonal and neurological disorders, and genetically transmitted disease); with nonmigrainous headaches, complicated and uncooperative by mental illnesses or other cognitive disfunctions such as in the heart, kidney, liver, or other important organs were excluded. Patients were divided into two groups which were composed of 64 MO patients (ICHD-II code 1.1), and 37 MA patients (ICHD-II code 1.2), respectively. Migraine patients were divided into three subgroups according to the headache attack frequency. First group has at least two, second group has three to five and third group has more than five attacks per month in the past year. Intensity of the pain was scaled as: Low pain=Did not put back daily activities; Tolerable pain=Puts back daily activities; Vigorous pain=Disrupts daily activities. Control subjects were randomly selected from healthy volunteers who had a routine medical examination at the hospital, had no history of migraine or a family history of migraine, and were similar in their age and gender. To exclude the migraine and cluster headaches, a neurologist specializing in headaches screened healthy volunteers.

Genotyping

From peripheral blood, genomic DNA was isolated by using the Wizard Genomic DNA Exraction Kit (Promega, Madison, WI, USA). In the third exon, MOG G511C (Val142Leu) polymorphism was genotyped by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) (15). MOG gene spesific primers were: Forward primer 5′-TGCTCCTCCTGCAGATGACT-3′ and reverse primer 5′-GCTCCAAGAAGCCAGCTCAT-3′ (IDT, USA). PCR cycles were carried out at 95 °C for 5 min, 35 cycles at 95 °C 30 sec, 58 °C for 30 sec, 72 °C for 30 sec and 72 °C for 5 min, respectively. Briefly, the PCR reaction mixture was prepared by using 50 ng of genomic DNA (30 µl final volume), 3 µl of 2.5 mM dNTPs (Fermentas, Waltham, MA, USA), 3 µl of MgCl2, 1 µl of NH4 buffer, 0.2 µl of Taq polymerase (Fermentas, Waltham, MA, USA) and 1 µl 10 pmol of each primers per well. To minimize the partial digests, 15 µl aliquot of the product was digested with the 0.5 U Hinf-I (Fermentas, Waltham, MA, USA) restriction enzyme at 37°C overnight. On a 3.5% agarose gel which contained 10 mg/ml ethidium bromide, digested products were run at 120 V for 40 min. Gel screening was performed by using a gel electrophoresis visualization system (Vilber Lourmat, France). After screening, it was determined that Val allele had 121 bp fragments and the Leu allele had 104 bp + 17 bp fragments (Figure 1). Two reviewers scored independently the results of genotyping.

Statistical Analyses

The statistical analyses in this study were performed by using IBM's the Statistical Package for the Social Sciences (SPSS) 22.0 software package (193.255.124.131; SPSS, Chicago, IL, USA). Pearson $\chi 2$ test (Fisher's Exact Test), confidence interval (CI) and Hardy-Weinberg equilibrium (HWE) were used for case-control analyses. The relationship between clinical, demographic features and genotype was examined by using

Pearson's correlation test and Mann Whitney U test. Odds ratios and P values of the variables were calculated at 95% confidence level. In this study, P<0.05 was considered as statistically significant.

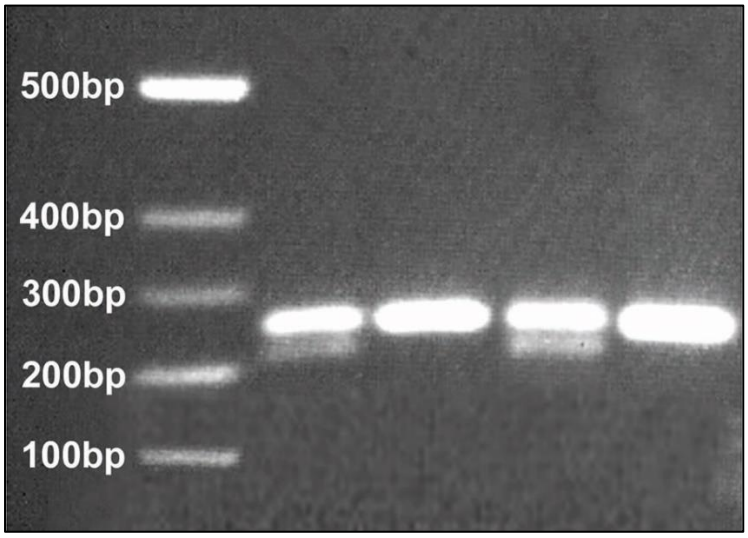

Figure 1. Agarose gel electrophoresis of the PCR products after digestion with Hinf I restriction enzyme showing the presence of Val142Leu polymorphisms of the MOG gene. 3.5% agarose gel electrophoresis, ethidium bromide staining and UV transillumination were performed. M: Molecular weight marker (100 bp each). Lane 1, 2: Bands of 121 bp and 17 bp indicating heterozygote Val/Leu genotype; Lane 3 and 4: Band of 121 bp indicating wild type Val/Val genotype.

Results

Mean ages were calculated as 33.40±9.34 and 34.13±8.4 for patient and control groups, respectively. Thirteen (13.13%) of the patients were receiving paracetamol, seventeen (17.17%) of them were taking non-steroidal anti-inflammatory (NSAII) drugs and seventy one (71.17%) were receiving analgesic-triptan combination therapy during attack. Prophylactically, patients received treatment with amitriptyline or proparapanol. While 83 of the patients had a triggering effect, 18 patients could not identify any trigger. The order in which enviromental agravation factors as the triggers was defined as emotional stress (72/83), physical activity (56/83), and menstruation (22/83). No statistically significant differences between patients and controls were found in terms of the distribution frequency of gender, age, smoking, and drinking status (P>0.05). When MO and MA patients were compared within the patient group, no significant difference was observed in terms of age, gender, age of migraine onset, presence of migraine in relatives, time of pain, frequency of attacks per mounth, intensity of pain, side of pain, aggravation of headache by environmental exposure, therapy, resistance of standard therapy, smoking and drinking parameters (P>0.05). Demographic and clinical characteristics of the patients are shown in Table 1. RFLP method which was used to determine Val142Leu polymorphism is completely appropriate. Agarose gel electrophoresis image are shown in Figure. Genotyping counts determined at polymorphic loci were in Hardy–Weinberg equilibrium for both controls (χ2=1, PHW=0.2) and patients (χ2=0.2, PHW =0.6) (P>0.05). For Val142Leu polymorphism between patients and controls, there was no difference in the genotype and allele distribution [OR=0.47 (0.21-1.08), P=0.053 for genotypes; OR=0.50 (0.23-1.11), P=0.060 for alleles]. The frequency of the Val142Leu genotype was found to be lower than that in controls despite of statistically insignificance in migraine patients. A significant difference was not observed in MA versus MO at the genotypic level (Val/Val) [P=0.53; OR=1.17 (0.30-4.45)] as well as the allelic one [P=0.53; OR=1.16 (0.31-4.25)]. A significant difference was found between the headache attacks frequency and Val142Leu polymorphism (P=0.026) according to Pearson χ2 test. Allelic and genotypic frequencies of polymorphisms are shown in Table 2. The headache attack frequency according to genotypes is presented in Table 3. No significant association was observed among other clinical features such as age, gender, presence of aura, age of migraine onset (years), presence of migraine in relatives, duration of headache attack (hours/attack), pain

index (intensity of pain; visual analog scale), site of pain, agravation of headache by enviromental exposure, therapy, resistance to standard therapy, smoking, drinking when the patients with the Val142Val genotype were compared with the patients with Val142Leu genotype ($p>0.05$). Table 3 presents the characteristics and symptoms of migraine in carriers of Val142Val or Val142Leu. With the post-hoc analyzes made using the G power 3.1 program, 70% power was obtained in the current sampling. The effect size (W) of the study is 0.226.

Table 1
Demographic Characteristics of Study Participants

Parameters	Controls (n=101)	MO (n=64)	MA (n=37)
Age (years)	34.13±8.45	33.2 ± 6.0	32.9 ± 11.2
Familial history	–	54.6	56.7
Sex			
Female /Male	82/19	58/6	30/7
Frequency			
1–3/month	–	18	9
3–5/month	–	16	16
5–10/month	–	30	12
Intensity			
Low	–	2	2
Moderate	–	26	16
Severe	–	36	19
Duration			
12 h	–	9	8
12–24 h	–	21	18
<24 h	–	34	11
Smoking status			
Smoker	18	7	4
Non-smoker	83	57	33
Drinking status			
Drinker	2	1	0
Non-drinker	99	63	37

*MO: Migraine without aura, MA: Migraine with aura, Values are the mean±SD or percentage number of subjects. Pain severity was graded as follows: Low pain=Did not interfere with daily activities; Moderate pain=Interferes with daily activities; Severe pain=Impedes daily activities.

Table 2

MOG genotype and allele distribution in controls and patients of migraine

Genotypes	Patients (n=101)	Controls (n=101)	Odds ratio	P-value
Val/Val	91 (90.09%)	82 (81.18%)		
Val/Leu	10 (0.99%)	19 (18.81%)	0.47 (0.21-1.08)	0.053
Leu/Leu	0 (0%)	0 (0%)		
Allele				
Val	0.9 (95,04%)	0.8 (90,59%)	0,50 (0.23-1.11)	0.060
Leu	0.1 (4.95%)	0.2 (9.40%)		

Table 3

The frequency of attacks according to *MOG* genotypes

The headache attacks frequency per month	Val/Val	Val/Leu	Odds ratio	P-value
Two (a)	21	6	a vs b 2.761 (0.62-12.32) a vs c 11.714 (1.32-103.77)	0.157 **0.013***
Three-Five (b)	29	3	b vs c 4.241 (0.42-42.84)	0.212
More than five (c)	41	1		

*P<0.05; a vs.b, a vs. c and b vs. c odds ratios were calculated as 2.761 (0.619-12.321), 11.714 FF (1.322-103.773) and 4.241 (0.419-42.842), respectively.

Discussion

According to our literature search, this study is the first report determining the genetic association of MOG gene polymorphisms with Turkish migraine subjects. In our study, there was no association between MOG gene rs2857766 polymorphism and migraine or with migraine subtypes. The possible mechanisms responsible for the effect of this polymorphisms on severity or on the risk of developing migraine are unclear. Migraine overlaps many other conditions including bipolar disorder (BD), multiple sclerosis (MS) and epilepsy (8-10). Some authors have suggested that there is an association between MOG gene polymorphism and some diseases such as multiple sclerosis (MS), reading disability and obsessive compulsive disorder, while others published different results (11-13). We showed that Val142Leu polymorphism was underrepresented in migraine patients despite of statistically insignificance. The frequency of the Val142Leu polymorphism in our study was similar to the study of Gomez-Lira et al (14). In our control population, the frequency of the Leu allele was 20%. This value is consistent with 22% (57/248) in Italian population. The gene expression, protein function or activity effect of Val142Leu amino acid substitutions in exon 3 of MOG gene are not exactly known. Changes in splicing, which were reported by Alfonso et al are associated with common genetic variations including Val142Leu in the MOG gene. However, we detected overrepresented Val142Leu genotype in patients with the decreased migraine attack frequency. There may be a number of possible mechanisms underlying the association between Val142Leu genotype and the decreased attack frequency. First, recent studies have implicated that MOG is a complement system classical pathway activator (15). Johns and Bernard proved the binding ability of MOG to C1q. In an unpaired study; C1, C1s and C4 lower levels during early headache are the signs for activation of complement system (12). Val142Leu genotype may decrease the attack frequency by reducing the activation of the compleman system. Second, the pathogenezis of pure menstrual migraine (MM) apperars to be related to estrogen witdrawal, especially MA (17). Oligodendrocytes synthesize nuclear and membrane estrogen receptor alpha (ER-α) and beta (ER-β) receptor protein as well as MOG protein. The classical estrogen signaling activates pathways that lead to differentiation and myelination of OL through activation of ER-α and -β receptors. In support of this datum, it has been shown that the functional remyelination induced by one of the ER-β agonists Indazole-chloride (Ind-Cl) is based on the anti-inflammatory properties of this molecule, as well as the increase in the number of progenitor and mature OL cells. Patients with Val/Leu genotype may decrease the frequency of attacks depending on estrogen effect. However, it is unknown whether MOG expression is changed depending on the estrogen fluctation during menstrual cycle or whether MOG gene is a direct target of ovarian steroid hormones such as estrogen (18). Another datum to support this hypothesis, increased propensity in the female rodents with CSD is consistent with the significant higher prevalence of migraine in women than in men. The exposure to estrogen has been reported to increase CSD susceptibility, whereas exposure to testesterone has the opposite effect (19). Third, the relationships of higher attack frequency, longer disease duration and the increased white matter abnormalities (WMA) in migraine were found (20, 21). Higher rates of hyperintensities of WM and differences in the myelin, and oligodendrocyte-related genes expression are the most reliable findings. Atmaca et al reported that individuals with obsessive-compulsive disorder (OCD) showed a notably higher entire WM volumes in individuals with the Val/Val genotype than Val/Leu and Leu/Leu genotypes (22). We demonstrated a positive correlation between the decreased attack frequency and the Val142Leu genotype. It could be speculated that Val/Leu genotype may be related to reduced risk of the migraine attack frequency and related to decreased WMA. In addition, the intracellular portion of MOG is more immunogenic than the extracellular portion and a predominant MOG epitope containing amino acids located right next to the 142 residues is recognized by CD4+ T cells. In particular, analysis by computer programs showed that the presence of V or L at position 142 altered class I and class II MHC affinity. As a hypothesis, the L residue may elicit a protective effect for migraine by reducing the immunogenicity of this epitope (15).

There are some limitations in our study. First, migraine and subtype case size were not high enough for detection of the small effects from highly low penetrated genes or single nucleotide polymorphisms (SNPs). Obtained data showed the unrelated circumstance of MOG Val142Leu polymorphism and appearance of the migraine. It should be interesting to evaluate the relationship between WMA and MOG polymorphism or MOG antibody positivity rate in patients with migraine. Additional clinical studies on different MOG gene variants in migraine could help give more accurate results. To confirm these results, further genetic, epidemiological and familial aggregation studies in other populations with larger numbers of patients are required.

Conclusion

In our study, no relationship was found between the Val142Leu (rs2857766) polymorphism in the MOG gene and migraine or migraine subtypes in migraine patients for Turkish population. It was figured out that the Val142Leu polymorphism was not adequately represented in migraine patients. In additon, we determined that the Val142Leu genotype was overrepresented in patients with reduced migraine attack frequency i.e. there was a positive correlation between them.

Ethics Committee Approval: The study was approved by the Non-Interventional Research Ethics Committee of Firat University (date: February 4, 2021 and approval number: 2021/02-45).

Informed Consent: Written consent was obtained from the families.

Conflict of Interest: Authors declared no conflict of interest.

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