Clinical and Experimental Health Sciences

Investigation of *TRPM8* Gene Variations in a Turkish Population with Migraine

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ABSTRACT

Objective: A migraine is a type of headache that occurs in attacks. The rs10166942 single-nucleotide polymorphism (SNP) in the eighth member of the subfamily melastin of the potential transition receptor channel (transient receptor potential cation channel, subfamily M, member 8) (TRPM8) genes is thought to play a role in the etiology of migraine. Migraine shares certain characteristics with neuropathic pain, and TRPM8 has been identified as a potential target for treating neuropathic pain in animal models.

This study aimed to determine the frequency of TRPM8 polymorphisms and their association with migraine in a Turkish population.

Methods: The study included 68 unrelated migraine patients and 59 healthy individuals as the control group. The TRPM8 rs10166942 gene polymorphism was identified using the Real Time Polymerase Chain Reaction Melting Curve Analysis system.

Results: A significant difference in the TRPM8 rs10166942 variant was observed between migraine patients and controls. The TRPM8 genotype distribution differed significantly in the patient group (TT=72 %; TC=26.4%; CC=1.5 %) and control group (TT=64.4 %; TC=25.4 %; CC=10.2 %). In the control and migraine patient groups, the frequencies of the C and T alleles were 22.8% and 77.1%, respectively, and 14.7% and 85.3%, respectively.

Conclusion: The TRPM8 rs10166942 gene polymorphism was found to be associated with migraine in female patients in the Turkish population.

Keywords: Migraine; TRPM8; polymorphism; family history; headache

1. INTRODUCTION

Migraine, defined as a neurovascular disease, is the most studied type of pain in the primary headache group (1). Migraine is a common neurological disease characterized by severe, typically unilateral headache attacks with nausea, vomiting, and phono and/or photophobia (2). Migraine is considered a multifactorial disorder influenced by both environmental and genetic components. The prevalence of migraine is higher among individuals of European descent compared to those of African or Asian descent (3). In 2008, the overall frequency of migraine in Turkey was 16.4%, with a frequency of 8.5% in men and 24.6% in women (4). In another study, migraine prevalence was 29.3% in females and 9.3% in males (5). Studies examining the hereditary pathophysiology of migraine suggest that genetic susceptibility is higher among first-degree relatives than in the general population, with the risk rate varying between 34 and 57% (6,7). Therefore, migraine often affects multiple members within the same family.

A screening study showed that the rate of migraine in other family members ranges between 1.5 and 19.3 % (8). The genetic transmission in migraine with aura is higher than without aura (9).

There are 6 types of migraine. These are migraine without aura, migraine with aura, periodic syndromes of childhood with cyclic migraine precursors, retinal migraine, migraine complications, and possible migraine (10). The pathophysiology of migraine is complex. According to the trigeminovascular theory, migraine involves both the vascular and nervous systems (11,12). There are different mechanisms in the triggering of migraine headaches in the second stage after the symptoms. In contrast, the cortical

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spreading depolarization theory suggests that the aura may result from nitric oxide generation triggered by nitroglycerin, which in turn induces migraine.

Other theories postulate that the central nervous system neuromodulator and neurotransmitter serotonin plays a role (13-15).

The International Headache Genetics Consortium published the first genome-wide association study (GWAS) of migraine in 2010 (16). GWAS identified rs2651899, rs10166942, and rs11172173 as possible associated variants in the domains of the *PRDM16*, *TRPM8*, and *LRP1* genes (17). A GWAS focusing on MO patients (migraine without aura) reported 12 nominally important signals in the discovery stage, two of which are in the *LRP1* and *TRPM8* genes, and these gene regions were also identified in a previous study (18). The present study examined the rs10166942 polymorphism in the *TRMP8* gene.

TRP (Transient Receptor Potential) channels are involved in many cellular processes (19), including the perception of cold in mammals (20). The multi-membered *TRP* channel *TRPM8* appears to play an important role as a pain transmission mediator in neuropathic and inflammatory pain, and therefore is a potential therapeutic target for the treatment of various painful conditions (21). In the temperature range of approximately 15°C to 30°C, *TRPM8* allows the passage of an inward cationic current that is inversely proportional to the temperature. Interestingly, *TRPM8* is also activated by natural ligands such as menthol and mediates the local cooling sensation associated with mint-containing products (22, 23). The rs10166942 variant is phenotypically important because its ancestral allele is protective against migraine. Adaptation to cold could play a role in the reported variation in migraine prevalence (24). The migraine-associated *TRPM8* rs10166942 variant is located at 3p24 (17, 25).

The low-density lipoprotein (*LDL*) receptor–associated protein *LRP1* is the second cloned member of the *LDL* receptor family (26). The rs11172113 variant is the third SNP localized to 12q13.3 in the first intron of the *LRP1* gene region (27). *LRP1* exhibits activity in numerous cell types and is expressed in the brain and tissues containing vessels, where it regulates synaptic transmission and serves as an extracellular sensor (28). *LRP1* also mediates signal transmission required for the regulation of vascular permeability, and therefore, it is thought to be associated with migraine (28). Although studies have demonstrated associations between migraine and the *TRPM8* rs10166942 and *LRP1* rs1172113 allele polymorphisms and differences depending on race, the mechanisms underlying these associations remain unclear. The present study investigated whether there is a link between the *TRPM8* rs10166942 polymorphism and migraine in a Turkish population.

2. MATERIALS & METHODS

1. Subjects

The study enrolled 68 individuals with migraine diagnosis as the patient group and 59 healthy individuals as the control group. Approval for the study was obtained from the Clinical Research Ethics Committee of Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital (101-20.062014). Peripheral venous blood samples were collected from migraine patients (65 females, 3 males; age range 38.17±1.476 years) who presented to the Neurology Department of Medeniyet University Training and Research Hospital. The control group consisted of volunteers (46 females, 13 males; age range 35±1.236 years) without neurological disease or migraine diagnosis.

In our study, the number of female participants was higher than that of male participants, reflecting the higher rate of female admissions to the hospital.

Detailed information was collected regarding gender, age, family history, smoking status, frequency of headaches, causes of headaches, patient medical history, and whether drugs were used for treatment. Signed information consent forms were obtained from all patients and controls.

2. DNA Isolation

Peripheral venous blood samples were collected from migraine patients and healthy controls and stored at −30°C in 5ml EDTA tubes until used for DNA isolation. DNA was isolated according to the protocol of the DNA isolation kit for mammalian blood (Roche Diagnostics, USA). The amount and purity of the isolated DNA were determined by UV spectrophotometry at 260/280 nm. In addition, DNA quality was assessed by 0.4 % agarose gel electrophoresis.

3. SNP Selection and Genotyping

The SNP chosen for genotyping was rs10166942 (*TRPM8*), based on a previous GWAS study.

The *TRPM8* rs10166942 polymorphism was genotyped using Taqman-based real – time PCR, and consequent melting curve analysis was performed on a LightCycler 96 Instrument (Roche Applied Science, Germany).

Real-time PCR analysis was performed using the *TRPM8* High Pure PCR Template Preparation kit (Roche Diagnostics, USA) with a fluorochrome-labeled TaqMan probe.

The probes were used for RT-PCR and array-specific bicolor fluorescence resonance energy transfer. The primer and probe sequences were as follows:

Primers

Sense 5′-CTACTTACTACCTAACACTTGGC-3′;

Antisense5′

CTGAAAGGAAGGATAGGGTTG-3′;

Probes

probe 5′-FAM-AGAAAACCCCCTTGACAAAGAGAGAC-3′; and

probe 5′-TGCAGAAAGCATGTTCAATTCAAG-ROX-3′.

The PCR mix was prepared using Lightcycler Taqman Master Mix (Roche; catalog number 03 003 248 001) *TRPM8* and Light Snip rs10166942 containing Taqman probe. The reaction mixture for genotyping consisted of H_2O (nuclease free) 10-14.4 µl, reagent mix (Snip) 1 µl, Fast Start DNA master mix 2 µl, $MgCl_2$ (25mM)1.6 µl final concentration 3mM, genomic DNA 1-5 µl (50 ng).

The LightCycler 96 PCR system automatically calculated the negative derivative of the fluorescence change and generated a melting curve for each sample. In this study, *TRPM8* genotyping was carried out based on rs10166942-*TRPM8* melting curves and peaks. Real-time PCR analysis of the *TRPM8* gene was performed in three stages.

First, during the denaturation stage, samples were heated at 95°C for 45 cycles of 10 seconds, followed by an extension at 72°C for 2 to 7 minutes.

Melting curve analysis was then performed in steps of 95°C for 30 seconds, 40°C for 2 minutes, 75°C for 1 second, and finally 40°C for 30 seconds.

In the final cooling stage, samples were held at 40°C for 30 seconds.

4. Statistical Analysis

Unpaired *t*-tests were used to evaluate the significance of differences between the patient and control groups. Hardy-Weinberg equilibrium was applied to the polymorphisms using the χ^2 test. Comparisons were made to determine the relationship between the allelic frequency distribution and phenotypes of the polymorphisms. $p \leq .05$ was considered statistically significant.

3. RESULTS

Demographic and clinical characteristics of the patients and controls are summarized. The clinical features of migraine patients are summarized. The clinical features of migraine patients varied: 30.8% had a family history, while 69.1% did not. Attacks were most frequently observed once a week (47%) and twice a week (32.3%). Discontinuation-vomiting was observed in 42.6 % of patients, and photophobia or odor characteristics were observed in 88.2%. Attack duration lasted four hours (66.1%). The rate of interference with daily activities was 94.1%. Additionally, 1.47%of patients had diabetes, 4.41% had thyroid disease, and 14.7% had a history of smoking.

We genotyped the *TRPM8* rs10166942 marker selected from a previous GWAS of 68 migraine patients and 59 controls in Turkey. Real-time PCR was used to analyze the presence of the *TRPM8* rs10166942 polymorphism in migraine patients and controls. The characteristics of the patient and control groups are shown in Table IV. The patient group consisted of 65 women and 3 men, with an age range of 38.17±1.476 years, whereas the control group consisted of 46 women and 13 men, with an age range of 35±1.236 years. Migraine patients and healthy controls did not significantly differ in terms of age.

TRPM8 Polymorphism

Analysis of the genotype distribution of the *TRPM8* rs10166942 polymorphism between the control and patient groups revealed that the rate was higher only among female migraine patients.

TRPM8 polymorphism was found to be significant in women (Tablo I).

Table 1. *Genotype distributions of the TRPM8 polymorphism between the control and patient groups.*

TRPM8 Genotype & Alleles	Controls (%)	Patients (%)	P[b] (1x/3x)
CC	6 (10.16)	1 (1.47)	0.1168/0.001***
CT	15 (25.42)	18 (26.47)	
TT	38 (64.40)	49 (72.05)	
C/T	27/91 (22.98/77.1)	20/116 (14.7/85.3)	0.106/0.0049**
Total	59	68	P<.05

Pb: The calculations were repeated after tripling the size of the population and statistical analysis was performed.

A comparison of the frequency of the TT allele between the 68 migraine patients and 59 controls revealed a statistically significant difference, with a higher frequency in patients (p< 0.005).

Isolated DNA samples were amplified by real-time PCR using *TRPM8*-specific primers and primer-specific Taqman probe (Light Snip), and rs10166942 melting curves and peaks were obtained. The form of generated melting curves allowed for allelic discrimination relying on the corresponding peaks on the negative first derivative of the fluorescence-versus-temperature plots.

The melting peaks were 51.89±5 °C for the T allele and 60.81 for the C allele, and two peaks were observed at 51.89±5°C and 60.81°C for the heterozygous TC allele. *TRPM8* polymorphism analysis with Light Snip rs10166942 and Fast Start DNA master kit was performed and interpreted based on the melting curve analysis, as described in the kit instructions. One case out of a total of 68 migraine cases (1.47%) was determined as CC, whereas 18 cases were determined as CT (26.47%), and 49 cases were determined as TT (72.05%) (Figure I).

The *TRPM8* rs10166942 polymorphism was also evaluated with respect to gender, family history of migraine, impact on daily work, and sensitivity to light and smell.

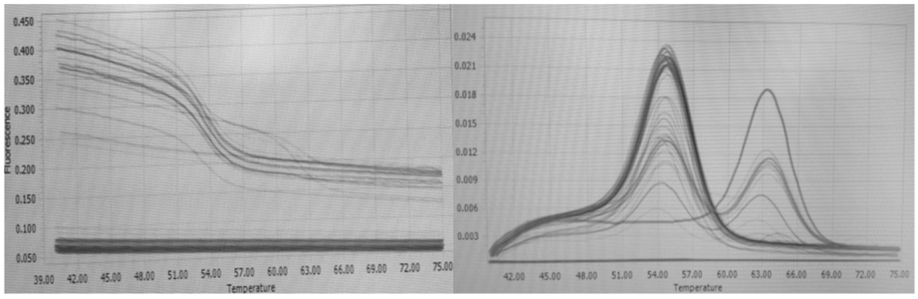

Figure 1. *Representative melting curve analysis and melting peaks. Representative melting curve analysis specific to the TRPM8 rs10166942 polymorphism in the migraine and control groups is shown on the left, and melting peaks are shown on the right. T allele Tm grade 51.89±5°C; heterozygous C allele Tm grade 60.81±5°C. For the heterozygous TC allele, two peaks were observed, at Tm grade 51.89±5°C and 60.81±5°C.*

Table 2. *Genotype and allele frequencies of the TRPM8 rs10166942 polymorphism by sex.*

Genotype	Control Female	Patient Female	P[b] (1x/3x)	Control Male	Patient Male	P[b] (1x/3x*)
CC	4	1	0.138/0.037**	2	-	0.751/0.424
CT	8	16		7	2	
TT	28	47		10	2	
Allele	**Frequency**					
T	64	110	0.335/0.058	*27*	6	0.821/0.806
C	16	18		*11*	2	

** Pb: Statistical analysis was repeated the calculations were repeated after tripling the size of the population (P<.005).*

Table 3. *Genotype and allele frequencies of the TRPM8 rs10166942 polymorphism by sex.*

Genotype	With Family History	No Family History	P[b] (1x/3x*)
CC	-	-	0.390/0.035
CT	7	9	0.390/0.035
TT	12	35	0.390/0.035
C	7	9	0.204/0.028
T	31	79	0.204/0.028

** Pb: Statistical analysis was repeated after the calculations were repeated after tripling the size of the population (P<.005)*

Table 4. *TRPM8 polymorphism according to gender, family history, impact on daily work, and sensitivity to light and smell.*

PATIENT																	CONTROL			
ALLELE	WOMAN								MALE								WOMAN		MALE	
	Number	(%)	A	(%)	G	(%)	I	(%)	Number	(%)	A	(%)	G	(%)	I	(%)	Number	(%)	Number	(%)
CC	1	1,47	-	-	1	1,47	1	1,47	-	-	-	-	-	-	-	-	4	6,77	2	3,3
CT	16	23,5	7	10,2	15	22	15	22	2	2,94	2	2,94	2	2,94	1	1,47	8	13,5	7	11,8
TT	47	69,1	12	17,6	44	64,7	42	61,7	2	2,4	1	1,47	2	2,94	1	1,47	28	47,4	10	16,9
Total	64	94,1	19	27,9	60	88,2	58	85,2	4	5,88	3	4,41	4	5,88	2	2,94	40	67,7	19	32,2

A: Family story, G: Influenceing day-to-day work, I: Light and odor sensitivity

Table 5. *Allele and genotype distributions among female patients according to light/smell sensitivity , family history and according to daily activity restrictions.*

Genotype	Light/Smell Sensitivity	No Light/ Smell Sensitivity	Pb (1x/3x*)	With Family History	No Family History	Pb (1x/3x*)	With Daily Activity Restrictions	No Daily Activity Restrictions	Pb (1x/3x*)
CC	1	-	0.868/0.563	-	-	0.390/0.035	1	-	0.997/0.902
CT	15	1	0.868/0.563	7	9	0.390/0.035	15	1	0.997/0.902
TT	42	5	0.868/0.563	12	35	0.390/0.035	44	3	0.997/0.902
C	17	1	0.548/0.298	7	9	0.204/0.028	17	1	0.9930/1.0
T	99	11	0.548/0.298	31	79	0.204/0.028	103	6	0.9930/1.0

** Pb: The statistical analysis was repeated that the calculations were repeated after tripling the size of the population (P<0.005).*

Among these, family history was found to be significant among women (Table II-III).

Tables IV and V show *TRPM8* polymorphism allele and genotype distributions according to gender, family history, impact on daily activities, and light and smell sensitivity, particularly in female patients.

According to the Hardy-Weinberg equilibrium analysis results, the *TRPM8* polymorphism was calculated as 4.46 in the control group and 0.1628 in the patient group. This result reveals that the *TRPM8* genotype distribution is closer to the Hardy-Weinberg equilibrium in the control group, while the equilibrium deviates significantly in the patient group.

4. DISCUSSION

In this study, the relationship between the *TRPM8* rs10166942 polymorphism and migraine was investigated in healthy controls and patients diagnosed with migraine in Turkey. The cold and cold-induced burning pain sensor *TPRM8* is expressed in sensory neurons in the dorsal root ganglia (28,29). *TRPM8* has been studied in animal models and found to be particularly associated with neuropathic pain.

Migraine and neuropathic pain share similar characteristics. *TRPM8* may serve as a pathophysiological link between these two types of pain.

Carriers of the rarer allele rs10166942 (CC or C T) have a lower risk of migraine compared to carriers of the two common alleles (TT) (16).

In a sex-related analysis, the *TRPM8* rs10166942 variant was found to be specific to women (30). Xai et al. found no association between the rs10166942 variant in *TPRM8* and migraine in those living in northern China. When they compared the control group and male patients, they found a statistically significant difference (31). However, in our study, sex-related analysis showed that the *TRPM8* rs10166942 variant was specific to women.

Ghosh et al. examined the rs10166942 variant in *TRPM8* in their study in northern India and reported no significant relationship between the migraine and healthy control groups (32). However, a study by Sukhvinder in 2019 in the same country found that the rs10166942 variant could be a potential marker for Migraine with aura **(**MA) in the male subgroup (33).

Ran et al. found no association of the *TRPM8* polymorphism with migraine in their population studies conducted in Switzerland (34). Zafar et al. also found no association for the *TRPM8* polymorphism in their studies. While this association was only at the allelic level, no significant difference was observed at the genotypic level between the case and control groups (35). In the most recent GWAS, a significant correlation was found between the *TPRM8* rs10166942 variant and migraine in German and Dutch MO and MA migraine patients (17). Similarly, a study conducted in Danish and Icelandic populations found that this variant's relationship between MO and MA was significant (36).

The association of this polymorphism with migraine in our population suggests possible regional or ethnic differences in genetic susceptibility between Western and Eastern populations.

However, recent studies in the East have reported a variety of findings regarding the relationship between mutations and migraine (37).

In studies conducted in Taiwan, a relationship between *TPRM8* and chronic migraine was observed (38). In this study, activation of *TRPM8* was observed to reverse heat allodynia in a mouse meningeal inflammation model, indicating that *TRPM8* activation is protective against allodynia in migraine (39). A study conducted in 2017 reported an association of migraine with *TRPM8* positivity in Chinese living in Taiwan (38).

When the rs10166942 T allele is examined from an evolutionary point of view, the positive selection of this allele can be explained by *TRPM8* expression, cold-sensing function, and the resulting thermoregulatory heat production. When populations living in warmer climates are examined, it is seen that the ancestral C allele is associated with reduced *TRPM8* function and weakened cold-sensing. Among those living in colder climates, *TRPM8* expression is higher in carriers of the T allele, which may have functionally conferred higher cold-activated sensory capability, which in turn translated into higher thermoregulatory heat production. This may have resulted in positive selection of the allele along the latitudinal kline as an adaptation. The T allele was found to be the risk allele for migraine across all studies (40).

Evolutionary adaptations in the *TRPM8* gene during the transition from warmer to colder climates may have led to mutations associated with migraine susceptibility (23). According to a study conducted in Japan in 2018, no relationship was observed between this variant and migraine (41). A study in Spain found that rs10166942 was correlated only under the recessive model in x^2 comparisons, not in logistic regression analyses, although they captured the most robust replication signals in the x^2 test and logistic regression analysis of *TRPM8* under different genetic models (42). A review by Vasileios et al. indicated that the rs10166942 CT genotype is associated with increased risk of migraine and MO, whereas homozygosity seems to provide a protective effect (43). In our study, a significant difference in the *TRPM8* rs10166942 variant was found between patients diagnosed with migraine and healthy controls in Turkey. The *TRPM8* genotype distributions in patients (TT = 72 %; TC =26.5 %; CC =1.5 %) and controls (TT = 64.4%; TC = 25.4%; CC =10.2%) differed significantly. In the control group, the C allele frequency was 22.8%; the T allele was 77.1 % In the migraine patient group, the T allele frequency was determined to be 85.3% and C allele was 14.7%. For the *TRPM8* rs10166942 variant in women, the difference between the control and patient groups was significant.

In the USA, migraine prevalence has been consistently shown to be higher for European Americans than for African Americans when non-genetic confounding factors are taken into account (44,45). In the American study, carriers of the low migraine risk allele had reduced sensitivity to cold stimuli, providing evidence for a genotype-dependent effect on cold pain sensation, suggesting that TRPM8 acts as a cold thermosensor and cold pain transducer in humans. (46).

Experimental and clinical studies published after 2023 indicate that TRPM8 may play a role in migraine biology not only through genetic predisposition but also through sensory modulation and neuronal excitability. Studies conducted in 2023 and 2024 reported that TRPM8 activation regulates cold perception and allodynia, and that these mechanisms may be important in migraine-associated sensory sensitivity (47,48). Furthermore, a study published in 2025 demonstrated that TRPM8 deficiency may affect pain responses and migraine-related mood symptoms (49). Considering this literature, although no significant genotype-phenotype association was found for rs10166942 in their study, it is thought that TRPM8 may play a functional role in migraine pathophysiology (47–49).

In our study group, no statistically significant differences were found when comparing the effects of daily activity, light/smell sensitivity, and family history with TRPM8 rs10166942 genotypes. These findings are based solely on the analyses conducted in our study.

However, significant associations were found for family history and alleles (genotypes) only in female patients ($p < .005$). The results of this study suggest that the *TRPM8* rs10166942 variant is a risk factor for migraine in Turkey. A larger case – control study is needed to confirm the association of this SNP with migraine susceptibility in Turkey.

5. CONCLUSION

The results of our study suggest that the rs10166942 *TRPM8* gene polymorphism is a risk factor for the development of migraine in Turkey. Limitations of the study in terms of the smaller number of male participants and also that patient groups were not classified according to the type of migraine. Identification of this TRPM8 polymorphism, which was studied for the first time in association with migraine in our country, may contribute to understanding and assessing disease risk.

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Acquisition of data for the study: B. G, F. C , İ.A.
Analysis of data for the study: B.G. ,H.C, B.A, İ.A. , F.C
Interpretation of data for the study: H. C, B. G, B.A.
Drafting the manuscript: H. C, B.G
Revising it critically for important intellectual content: H. C, B.G.
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