



# Association of GABRA1 Polymorphisms with Migraine with Aura: A Preliminary Case–Control Study in a Turkish Cohort

## GABRA1 Polimorfizmlerinin Auralı Migren ile İlişkisi: Türk Kohortunda Ön Vaka-Kontrol Çalışması

●Oğuzhan Yaralı<sup>1</sup>, ●Ebru Marzioglu Ozdemir<sup>2</sup>, ●Cigdem Yuce Kahraman<sup>3</sup>,  
●Gokhan Ozdemir<sup>4</sup>, ●Mustafa Can Guler<sup>5</sup>, ●Abdulgani Tatar<sup>3</sup>

<sup>1</sup>Department of Medical Genetics, Erzurum Regional Training and Research Hospital, Erzurum, Türkiye

<sup>2</sup>Department of Medical Genetics, Faculty of Medicine, Selcuk University, Konya, Türkiye

<sup>3</sup>Department of Medical Genetics, Faculty of Medicine, Ataturk University, Erzurum, Türkiye

<sup>4</sup>Department of Neurology, Faculty of Medicine, Selcuk University, Konya, Türkiye

<sup>5</sup>Department of Physiology, Training and Research Hospital, Ataturk University, Erzurum, Türkiye

### Abstract

**Aim:** The objective of this study is to ascertain the association between two prevalent GABRA1 polymorphisms (rs12658835, rs35166395) and migraine with aura. In addition, the investigation will encompass the clinical characteristics of the condition, including trigger patterns and family history.

**Material and Method:** 108 persons with clinically proven migraine with aura and 107 demographically matched healthy controls were enrolled in a multicenter case-control study (Ataturk University Faculty of Medicine Neurology Department and Palandöken State Hospital Neurology Outpatient Clinic; 01 Feb–01 Jun 2013). Sociodemographics, migraine characteristics, triggers, and family history were recorded through structured in-person interviews. A sample of peripheral blood was used to extract genomic DNA. SNP genotyping was performed using a validated real-time PCR allelic discrimination kit for GABRA1 rs12658835 and rs35166395. The case/control status was hidden from the lab staff.

**Results:** The migraine with aura cohort was predominantly female (82.4%) with a mean age of 33.8±12.4 years; the control group exhibited a similar distribution of sex and age (both  $p > 0.05$ , Mann–Whitney U for age). rs12658835 exhibited an excess of mutant genotype in migraine with aura (7.4%, 8/108) in comparison to the control group (0%, 0/107),  $p = 0.007$ . The genotype distributions of rs35166395 (wild/mutant/heterozygous: 60/16/24% in migraine with aura vs. 65/13/22% in controls) did not differ ( $p > 0.05$ ). In the context of migraine with aura cases, a family history of migraine was associated with an elevated probability of activity-impairing attacks (69.4% overall; OR ≈ 2.06;  $p = 0.02$ ) and pain exacerbation during physical activity ( $p = 0.02$ ). No substantial gender-based disparities were observed in other clinical characteristics.

**Conclusion:** In this Turkish cohort, the GABRA1 rs12658835 variant may be associated with migraine with aura, whereas the rs35166395 variant is not. Familial predisposition has been linked to more debilitating attacks and exertional exacerbation. This highlights the genetic factors that contribute to the severity of the phenotype, as well as the potential GABAergic mechanisms involved in the pathophysiology of migraine with aura.

**Keywords:** Migraine, polymorphism, GABRA1

### Öz

**Amaç:** Bu çalışmanın amacı, GABRA1 genindeki iki yaygın polimorfizmin (rs12658835, rs35166395) auralı migren ile ilişkisini saptamaktır. Ayrıca tetikleyici paternler ve aile öyküsü dâhil olmak üzere klinik özellikler incelenmiştir.

**Gereç ve Yöntem:** Çok merkezli olgu–kontrol tasarımında (Ataturk Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı ve Palandöken Devlet Hastanesi Nöroloji Polikliniği; 01.02.2013–01.06.2013) klinik olarak doğrulanmış auralı migren tanılı 108 birey ve demografik olarak eşleştirilmiş 107 sağlıklı kontrol çalışmaya alındı. Yapılandırılmış yüz yüze görüşmelerle sosyodemografik veriler, migren özellikleri, tetikleyiciler ve aile öyküsü kaydedildi. Periferik kandan genomik DNA izole edildi. GABRA1 rs12658835 ve rs35166395 için gerçek zamanlı PCR alel-ayırımı kiti kullanılarak SNP genotipleme yapıldı. Laboratuvar personeli olgu/kontrol durumuna körlendi.

**Bulgular:** Auralı migren grubu çoğunlukla kadındı (%82,4) ve ortalama yaş 33,8±12,4 yıld; kontrol grubunda yaş ve cinsiyet dağılımı benzerdi (her ikisi için  $p > 0,05$ , yaş için Mann–Whitney U). rs12658835 için auralı migren grubunda mutant genotip fazlalığı saptandı (%7,4; 8/108) ve bu fark kontrol grubuna kıyasla anlamlıydı (%0; 0/107;  $p = 0,007$ ). rs35166395 genotip dağılımları (auralı migrende sırasıyla %60/%16/%24; kontrollerde %65/%13/%22) arasında anlamlı fark yoktu ( $p > 0,05$ ). Auralı migren olgularında ailede migren öyküsü, aktiviteyi kısıtlayan ataklarla (toplam %69,4; OR ≈ 2,06;  $p = 0,02$ ) ve fiziksel aktivite ile ağrı artışıyla ( $p = 0,02$ ) ilişkili bulundu; diğer klinik özelliklerde cinsiyete göre belirgin fark saptanmadı.

**Sonuç:** Bu Türk kohortunda GABRA1 rs12658835 varyantı auralı migren ile ilişkili bulunurken, rs35166395 ile ilişki izlenmedi. Ailevi yatkınlığın daha yıkıcı ataklar ve eforla alevlenme ile ilişkisi, fenotip şiddetine katkıda bulunan genetik etmenleri ve auralı migrenin patofizyolojisinde olası GABAerjik mekanizmaları desteklemektedir.

**Anahtar Kelimeler:** Migren, polimorfizm, GABRA1



## INTRODUCTION

Recurrent and frequently incapacitating headache attacks lasting from a few hours to several days are the hallmark of migraine, a common and disabling neurological disorder. Although migraine-like attacks may also occur in several neurological and vascular conditions,<sup>[1–4]</sup> migraine with aura (MwA) is primarily approached as a neurobiological disorder characterized by altered cortical excitability and inhibitory–excitatory imbalance.<sup>[1–3]</sup>

The prevalence of migraine without aura is estimated to be approximately 6–10%, whereas migraine with aura affects about 3–6% of the population.<sup>[4]</sup> Hemiplegic migraine is a rare subtype that may mimic acute vascular events, highlighting the clinical importance of recognizing aura symptoms.<sup>[5]</sup>

Aura symptoms can mimic acute cerebrovascular events in clinical practice, underscoring the importance of understanding biological factors contributing to MwA.<sup>[6]</sup> Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system and helps regulate neuronal excitability. Altered inhibitory–excitatory balance has been implicated in MwA pathophysiology. GABRA1 encodes the  $\alpha 1$  subunit of the GABA<sub>A</sub> receptor, a key mediator of fast synaptic inhibition; thus, common variation in GABRA1 may influence MwA vulnerability.<sup>[7]</sup>

Twin and family studies support a substantial heritable component in migraine, with higher concordance rates in monozygotic than dizygotic twins and consistent familial aggregation, suggesting that genetic factors contribute meaningfully alongside environmental influences.<sup>[8]</sup> Overall, these findings are consistent with a complex, polygenic architecture that may differ between MwA and migraine without aura.<sup>[9]</sup>

From a broader standpoint, the interaction between genetic and environmental factors has become a pivotal area for further research. It is evident that both genetic predispositions and environmental factors have a considerable impact on the manifestation of migraine-related issues. This demonstrates how environmental factors can significantly impact the frequency and intensity of migraine attacks, even while hereditary factors establish a propensity.<sup>[10]</sup> The distinction between migraine with aura and migraine without aura underscores the complexity of these subtypes, suggesting that their genetic underpinnings may be distinct, potentially indicating unique environmental triggers and hereditary pathways.<sup>[9]</sup>

In order to address the unique obstacles associated with identifying disease-causing mutations in non-Mendelian illnesses, such as migraine, particular methodological techniques are required. It is evident that classical parametric linkage analysis is frequently inappropriate for conditions dependent on an exact genetic model, on which the analysis is predicated. This is particularly problematic given the diverse genomic architecture observed in non-Mendelian illnesses. Sutherland and Griffith advocate for the notion that non-

parametric or model-free linkage analyses are to be preferred, as they empower researchers to investigate linkage without the necessity of a predetermined genetic framework.<sup>[11]</sup>

Therefore, we aimed to investigate whether GABRA1 rs12658835 and rs35166395 polymorphisms are associated with migraine with aura in a Turkish case–control cohort, and to explore the relationship between family history and clinical severity.

## MATERIAL AND METHOD

### Study Design and Participants

This study was carried out with the approval of the University of Health Sciences Erzurum Faculty of Medicine Scientific Research Ethics Committee (Date: 10.07.2025, Approval No: 2025/07-171, Meeting No: 07), including the retrospective reuse of data collected in 2013. All procedures were conducted in accordance with ethical standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

This multicentre observational case–control study was conducted between 1 February and 1 June 2013 at two sites: the Neurology Outpatient Clinic of Palandöken State Hospital and the Neurology Department of Atatürk University Faculty of Medicine. Consecutive patients with migraine aged  $\geq 16$  years were screened. Diagnoses were established by board-certified neurologists using the then-current International Classification of Headache Disorders (ICHD) criteria. The study comprised two groups: 108 individuals with MwA and 107 healthy controls who were frequency-matched to the MwA group by salient sociodemographic characteristics and sex.

### Inclusion/Exclusion Criteria

**Inclusion criteria:** Clinical diagnosis of MwA according to ICHD, Capacity to provide informed consent.

**Exclusion criteria:** Pregnancy, Active systemic inflammatory/autoimmune disease, Known structural CNS disease, Previous stroke or transient ischemic attack (TIA), Chronic anticoagulant, antiepileptic, or vasoactive therapy that could confound vascular phenotypes, Inability to complete the questionnaire.

**Controls:** Controls had no history of migraine or other primary headache disorders and no major neurological disease. They were frequency-matched to the MwA group by key sociodemographic characteristics and sex.

### Recruitment, Consent, and Data Collection

During routine visits, participants were recruited one after the other, and signed informed consent was acquired. Sex, age, education/income proxies, migraine characteristics (age at onset, attack frequency/duration, aura features, triggers), family history, comorbidities, and medication use were all recorded using a structured interviewer-administered questionnaire. Interviews took place in person on the day of enrollment.

## Genetic Analysis

Genomic DNA was isolated from peripheral blood leukocytes using a silica-membrane method and stored at  $-20^{\circ}\text{C}$  until analysis. Two GABRA1 SNPs (rs12658835 and rs35166395) were genotyped using a dual-color probe-based real-time PCR allelic discrimination assay (PrimerDesign®). All runs included negative controls and internal kit controls; a subset of samples was repeated as blinded duplicates for quality assurance. Genotype calls were made using the manufacturer's software according to the instructions for use.

## Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 29.0 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Kolmogorov–Smirnov test. Categorical variables were compared using Chi-square or Fisher's exact tests; continuous variables using Student's t test or Mann–Whitney U, as appropriate. Effect sizes are presented as odds ratios (ORs) with 95% confidence intervals where applicable. All tests were two-tailed with  $\alpha = 0.05$ . Hardy–Weinberg equilibrium was assessed in the control group for each SNP using an exact test. Given the number of clinical variables and triggers evaluated, these analyses were considered exploratory; therefore, p-values for clinical comparisons were interpreted descriptively and were not adjusted for multiple comparisons.

## RESULT

Our study included a total of 215 participants: 108 patients clinically diagnosed with migraine with aura and 107 healthy controls.

Of the patients with MWA, 89 (82.4%) were female and 19 (17.6%) were male. In the control group, 85 (79.4%) were female and 22 (20.6%) were male. There was no significant difference between the patient and control groups. It was investigated whether there was a difference in gender among the relatives of individuals with migraine with aura. No statistical relationship was found between gender and the presence or absence of migraine in relatives. The overall mean age of those with migraine with aura was  $33.75 \pm 12.37$ , while it was  $35.02 \pm 12.26$  for women and  $27.78 \pm 11.38$  for men. Based on data obtained from pedigree analysis, the number of patients with migraine with aura who had migraine in their family was 72 (66.9%). Sixty female patients (67.4%) had a family history of migraine, while 12 male patients (29.3%) had a family history of migraine. The patients' educational status, age ranges, and occupations were queried, and the data obtained are presented in **Table 1**. There was no statistical difference between these values ( $p > 0.05$ ).

The clinical characteristics of patients with aura migraine were examined according to gender. Within this framework, the severity of migraine headache, the character of the pain, the localisation of the headache, the frequency of the pain, whether it increased with physical activity, and accompanying symptoms (nausea, vomiting, photophobia, phonophobia,

smell sensitivity) were investigated. No statistically significant differences were found between the values shown in **Table 2**. ( $p > 0.05$ ). Because multiple clinical variables were assessed, these comparisons are presented descriptively/exploratorily.

The severity of migraine headache, the nature of the pain, the location of the headache, the frequency of the pain, whether it increases with physical activity, and accompanying symptoms were examined in individuals with MWA, comparing those with and without a family history of migraine. In this study, when the severity of the headache was assessed, 69.4% of all individuals with migraine with aura stated that the pain hindered their daily activities, while 30.6% stated that the pain did not hinder their daily activities. When considering those with a family history of migraine, 79.2% of these individuals stated that their daily activities were impaired, while 20.8% stated that their daily activities were not impaired. Among those without migraine in their family, 18 (50%) reported that their daily activities were impaired, while the other 18 (50%) stated that their daily activities were not impaired. This difference was statistically significant ( $p = 0.02$ ). When risk calculations were performed, it was determined that the impairment of daily activities was 2.06 times higher among those with a family history of migraine. Another significant parameter was whether patients experienced an increase in pain intensity with physical activity; 67.6% of patients responded yes, while 32.4% responded no. When those with a family history of migraine were evaluated, 79.2% of these patients reported an increase in pain intensity with physical activity, while 42.8% reported no increase. When those without a family history of migraine were evaluated, 20.8% of patients reported an increase in pain intensity with physical activity, while 57.2% reported no increase. This finding was statistically significant ( $p = 0.02$ ). There was no statistical significance among the other parameters ( $p > 0.05$ ).

**Table 1. Sociodemographic Characteristics of Migraine Patients with Aural Symptoms According to Gender**

	Total (%)	Women (%)	Men (%)
Number of patients participating in the study (%)	108 (100%)	89 (82.4%)	19 (17.6%)
Average age of patients participating in the study (years)	$33.75 \pm 12.37$	$35.02 \pm 12.26$	$27.78 \pm 11.38$
Number of patients with migraine in their family	72 (66.9%)	60 (67.4%)	12 (29.3%)
Number of patients without migraine in their family	36 (33.3%)	29 (16.7%)	7 (17.1%)
Level of education (%)			
1. None	60 (55.6%)	58 (65.2%)	2 (10.5%)
2. Primary school	13 (12.0%)	9 (10.1%)	4 (21.1%)
3. Middle school	27 (25.0%)	16 (18.0%)	11 (57.9%)
4. High school	8 (7.4%)	6 (6.7%)	2 (10.5%)
5. University college	8 (7.4%)	6 (6.7%)	2 (10.5%)
Age ranges (years)			
1. 18-29 Years	43 (39.8%)	31 (34.8%)	12 (63.2%)
2. 30-39 Years	34 (31.5%)	31 (34.8%)	3 (15.8%)
3. 40-49 Years	23 (21.3%)	20 (22.5%)	3 (15.8%)
4. 50 Years of age and over	8 (7.4%)	7 (7.9%)	1 (5.3%)
Profession			
1. Housewife/unemployed	76 (70.4%)	76 (85.4%)	----
2. Student	18 (16.7%)	11 (12.4%)	7 (27.8%)
3. Active worker	14 (13.0%)	2 (2.2%)	12 (63.2%)

**Table 2. Distribution of Clinical Characteristics of Migraine with Aura According to Gender**

	Total (%)	Women (%)	Men (%)
Migraine headache localisation			
1-Unilateral	83 (76.9%)	68 (76.4%)	15 (78.9%)
2-Double-sided	25 (23.1%)	21 (23.6%)	4 (21.1%)
Characteristics of migraine			
1-Pulsating (throbbing)	94 (87.0%)	79 (88.8%)	15 (78.9%)
2-Other types	14 (13.0%)	10 (11.2%)	4 (21.1%)
Migraine severity			
1-Moderate	9 (8.3%)	4 (4.5%)	5 (26.3%)
2-Severe	24 (22.4%)	22 (24.7%)	2 (10.5%)
3-Impairs daily activities	75 (69.4%)	63 (70.8%)	12 (63.2%)
Frequency of migraine			
1-Every day	20 (18.5%)	19 (21.3%)	1 (5.3%)
2-More than 15 times a month	17 (15.7%)	15 (16.9%)	2 (10.5%)
3-Between 1 and 15 times a month	71 (65.7%)	55 (61.8%)	16 (84.2%)
Worsening with physical activity			
1-Present	73 (67.6%)	61 (68.5%)	12 (63.2%)
2-Absent	35 (32.4%)	28 (31.5%)	7 (36.8%)
Accompanying symptoms			
1-Nausea	81 (75.0%)	73 (82.0%)	8 (42.1%)
2-Vomiting	42 (38.9%)	34 (38.2%)	8 (42.1%)
3-Photophobia	85 (78.7%)	72 (80.9%)	13 (68.4%)
4-Sensitivity to smell	74 (68.5%)	67 (75.3%)	7 (36.8%)
5-Sensitivity to sound	97 (89.8%)	81 (91.0%)	16 (84.2%)

Individuals with MwA were questioned about triggering factors such as mental tension and stress, sleep irregularities, noise, hunger, bright light, menstruation, weather changes (hot-cold), and whether any food or drink triggered pain. The responses received were grouped and analysed according to gender.

Based on the information obtained from the family trees drawn up following interviews with individuals with a family history of migraine, the number of individuals with migraine among these individuals' relatives and the gender distribution were examined. Genetic degrees of kinship were defined as follows:

1st degree: mother, father, children, siblings

2nd degree: uncle, aunt, grandmother, grandfather

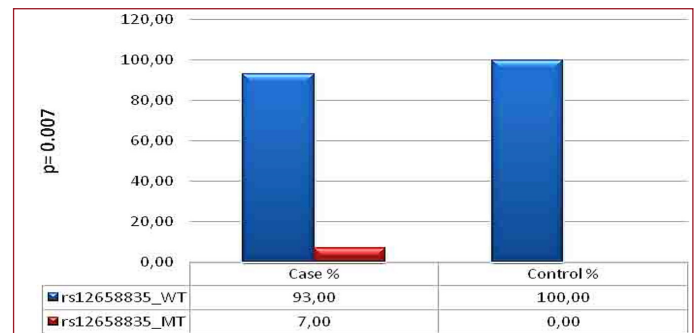
3rd degree: cousins and more distant relatives

were determined, and **Table 3** was created using the data obtained from the patients. No statistical significance was detected in the created grouping ( $p > 0.05$ ).

**Table 3. Assessment of the Degree of Kinship and Gender in MwA**

		General	Women with Aural Migraine	Men with Aural Migraine
First-degree relatives	Average number of female relatives	0.9±1.3	1.01±1.3	0.5±0.6
	Average number of male relatives	0.4±0.8	0.5±0.8	0.2±0.5
Second-degree relatives	Average number of female relatives	0.2±0.5	0.2±0.5	0.3±0.7
	Average number of male relatives	0.1±0.4	0.1±0.4	0.2±0.5
Third-degree relatives	Average number of female relatives	0.03±0.2	0.03±0.2	0.05±0.2
	Average number of male relatives	0.05±0.2	0.04±0.2	0.1±0.2

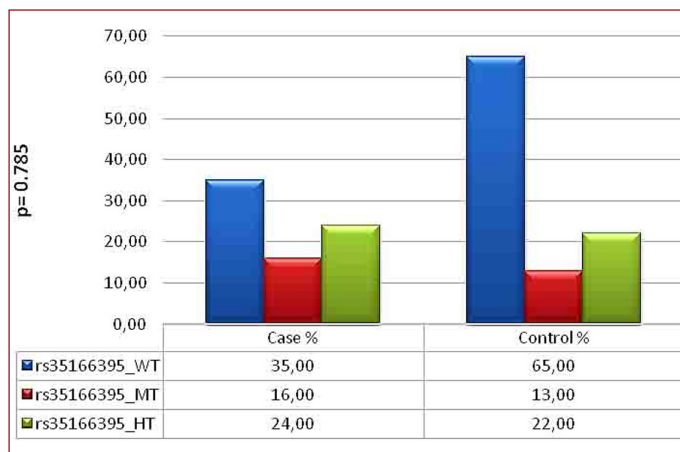
The rs12658835 and rs35166395 polymorphisms in the GABRA1 gene were investigated in DNA obtained from blood samples taken from individuals with aura migraine and from the control group. In the rs12658835 analysis, 8 (7%) mutant genotypes and 100 (93%) homozygous wild genotypes were detected in the patient group. All individuals in the control group had the wild-type homozygous genotype. When the patient and control groups were compared, the p-value was 0.007, indicating a significant difference in favour of the patient group ( $p < 0.05$ ) (**Figure 1**). Because of the zero count in controls, the odds ratio was estimated using the Haldane–Anscombe correction (OR=18.18, 95% CI 1.04–319.16; Fisher's exact  $p = 0.0068$ ), indicating an imprecise effect estimate due to the low number of carriers.

**Figure 1. rs12658835 Polymorphism Assessment**

In the analysis conducted for rs35166395, 65 (60%) wild-type genotypes, 17 (16%) mutant-type genotypes, and 26 (24%) heterozygous-type genotypes were detected in the patient group. In the control groups, 69 (65%) wild-type genotypes, 14 (13%) mutant-type genotypes, and 24 (22%) heterozygous-type genotypes were detected (**Table 4**). There was no statistically significant difference between the patient and control groups (dominant model AB+BB vs AA: OR=1.20, 95% CI 0.69–2.09; Fisher's exact  $p = 0.574$ ). Allele frequencies were similar (minor allele frequency: 0.278 in cases vs 0.243 in controls; allelic OR=1.20, 95% CI 0.78–1.84;  $p = 0.443$ ) (**Figure 2**). Hardy–Weinberg equilibrium testing in controls was not informative for rs12658835 (no variant allele observed), whereas rs35166395 deviated from HWE (exact  $p = 0.00012$ ).

**Table 4. Statistical evaluation of rs12658835 and rs35166395**

	Case	Control	Total
rs12658835	Wild type	100	107
	Mutant type	8	0
	Total	108	107
rs35166395	Wild type	65	69
	Mutant type	17	14
	Heterozygote type	26	24
Total	108	107	215



**Figure 2.** rs35166395 Polymorphism Assessment

## DISCUSSION

To date, much evidence has been presented showing that migraine is a hereditary disease. Experiments conducted on large populations have shown that the relative risk of migraine in the families of migraine sufferers is three times higher than in control groups without migraine.<sup>[12]</sup> Records of twins from different countries, collected on a national scale, have demonstrated a high degree of concordance for migraine in both monozygotic and dizygotic twins.<sup>[13]</sup> In addition, two population-based studies have been published showing that genetic interaction is stronger in migraine with aura than in migraine without aura.<sup>[14,15]</sup> However, subsequent studies have identified candidate gene variants for both aural and non-aural migraine. Although factors such as incomplete penetrance and high variability in expressivity have caused considerable confusion in many studies in the past, segregation analyses of most migraine carriers in common forms have failed to identify any Mendelian pattern.

Studies on migraine genetics are quite complex due to the distinct complex characteristics of the migraine with aura and migraine without aura groups. Both patient groups experience nausea without vomiting, sensitivity to light and sound, and severe recurrent headaches lasting 4 hours or more. However, patients with migraine with aura may experience attacks that include transient episodes of focal neurological dysfunction. More commonly, migraine with aura is characterised by bimodal flashing lights or starburst patterns, followed by loss of vision in the same part of both visual fields, lasting between 5 and 60 minutes. Less commonly, patients with migraine with aura may experience speech disorders, unilateral extremity weakness, and episodes of unilateral paraesthesia followed by fatigue. At this point, there is no clear distinction as to whether the genes suspected for migraine with aura and migraine without aura are the same or different. However, there are currently very important clinical studies on both separate and shared characteristics that include similar approaches for appropriate treatment.<sup>[16]</sup>

In a study conducted by Plummer and colleagues on GABA genes, downregulation was observed in GABA genes in migraine patients.<sup>[17]</sup> This situation raises the idea of using GABA receptor agonists in migraine treatment, and the binding of related drugs to GABA A receptors may affect the migraine process.<sup>[18]</sup> In another study conducted by Plummer and colleagues, expression changes in two GABA receptor genes were identified in individuals with migraine. This study suggested that expression changes in the GABRA3 and GABBR2 genes in particular may play a role in the pathophysiology of migraine and that these genes could be used as biomarkers in individuals with migraine.<sup>[19,20]</sup> If such individuals can be identified through testing, trialling GABA agonists in these patients could be very beneficial.<sup>[17]</sup>

In our study, Single Nucleotide Polymorphisms (SNPs) that were found to be significant in terms of the GABRA1 gene in patients with aura migraine were also selected as suspects; the aim was to investigate gene polymorphism and examine the relationship between the results obtained and the disease. In our study, the rs12658835 and rs35166395 polymorphisms in the GABRA1 gene were investigated in DNA obtained from blood samples taken from individuals with MwA and from the control group. In the rs12658835 investigation, the mutant genotype was detected in 7% of the patient group and the homozygous wild genotype in 93%. All individuals in the control group had the wild-type homozygous genotype. When comparing the patient and control groups, the p-value (0.007) was found to be significant for the patient group. In the rs35166395 analysis, 60% of the patient group had the wild-type genotype, 16% had the mutant-type genotype, and 24% had the heterozygous-type genotype. In the control group, 65% wild-type genotype, 13% mutant-type genotype, and 22% heterozygous-type genotype were detected. When comparing the patient and control groups, no statistical difference was found ( $p > 0.05$ ). It can be stated that the rs35166395 polymorphic structure is not associated with the phenotype in patients with aura migraine. In addition, it can be stated that the rs12658835 polymorphic structure is associated with aura migraine. SNPs affecting the domains that provide the folding regions of proteins or their relationship to the target region lead to phenotypic effects. Here, it is highly probable that SNP rs12658835 is localised in a region affecting protein function. A key limitation of this study is the low number of rs12658835 variant carriers (8 cases vs 0 controls), which results in wide confidence intervals and a fragile effect estimate. Therefore, the observed association should be interpreted as preliminary and requires replication in larger, independent cohorts. In addition, the analyses of multiple clinical variables were exploratory and were not adjusted for multiple comparisons, which may increase the risk of type I error. Given the rarity of the variant and the modest sample size, the study is underpowered to detect small-to-moderate genetic effects.

## CONCLUSION

This multicentre case-control study found that the GABRA1 rs12658835 variant was associated with migraine with aura, whereas the rs35166395 variant showed no significant relationship with case status. A positive family history was associated with a greater functional impact and exertional worsening, suggesting a genetic influence on both susceptibility and phenotype. These findings implicate GABA-A receptor pathways in migraine with aura, highlighting the need to evaluate genotype-informed risk stratification and GABA-modulating prophylaxis.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of University of Health Sciences Erzurum Faculty of Medicine Scientific Research Ethics Committee (Date: 10.07.2025, Decision No: BAEK 2025/07-171)

**Informed Consent:** All participants (patients and controls) provided written informed consent prior to enrollment and data collection (face-to-face interviews on the day of inclusion).

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

**Acknowledgements:** The authors thank the Atatürk University Faculty of Medicine, Department of Neurology and the Palandöken State Hospital Neurology Outpatient Clinic for their support in patient recruitment and clinical coordination, and the medical genetics laboratories for technical assistance during genotyping.

## REFERENCES

- Pizza V, Bisogno A, Lamaida E, et al. Migraine and coronary artery disease: an open study on the genetic polymorphism of the 5, 10 methylenetetrahydrofolate (MTHFR) and angiotensin I-converting enzyme (ACE) genes. *Cent Nerv Syst Agents Med Chem*. 2010;10(2):91-6.
- Moy BM, Bertucci HK, Lemma B, Rivas O. Hemiplegic Migraine in a Patient With Neurologic Symptoms After Regadenoson Administration. *Clin Case Rep*. 2025;13(7):e70611.
- Shrimpton M, Gasser YP, Sexton A, Malhotra A. Episodic headaches and cognitive decline: uncovering neuronal intranuclear inclusion disease in a young patient. *BMJ Case Rep*. 2025;18(1):e262351.
- Winsvold BS, Hagen K, Aamodt AH, Stovner LJ, Holmen J, Zwart JA. Headache, migraine and cardiovascular risk factors: the HUNT study. *Eur J Neurol*. 2011;18(3):504-11.
- Vinogradova LV, Suleymanova EM, Medvedeva TM. Transient loss of interhemispheric functional connectivity following unilateral cortical spreading depression in awake rats. *Cephalalgia*. 2021;41(3):353-65.
- Grecco MP, Pieroni M, Otero M, Ferreira JL, Figuerola Mde L. Sporadic hemiplegic migraine and CREST syndrome. *J Headache Pain*. 2010;11(2):171-3.
- Bai YF, Chiu M, Chan ES, et al. Pathophysiology of and therapeutic options for a GABRA1 variant linked to epileptic encephalopathy. *Mol Brain*. 2019;12(1):92.
- Ligthart L, Huijgen A, Willemsen G, de Geus EJC, Boomsma DI. Are Migraine and Tension-Type Headache Genetically Related? An Investigation of Twin Family Data. *Twin Res Hum Genet*. 2018;21(2):112-8.
- Stewart WF, Wood C, Reed ML, Roy J, Lipton RB; AMPP Advisory Group. Cumulative lifetime migraine incidence in women and men. *Cephalalgia*. 2008;28(11):1170-8.
- Gallardo VJ, Gómez-Galván JB, Asskour L, et al. A study of differential microRNA expression profile in migraine: the microMIG exploratory study. *J Headache Pain*. 2023;24(1):11.
- Sutherland HG, Griffiths LR. Genetics of Migraine: Insights into the Molecular Basis of Migraine Disorders. *Headache*. 2017;57(4):537-69.
- Merikangas KR, Risch NJ, Merikangas JR, Weissman MM, Kidd KK. Migraine and depression: association and familial transmission. *J Psychiatr Res*. 1988;22(2):119-29.
- Gervil M, Ulrich V, Kyvik KO, Olesen J, Russell MB. Migraine without aura: a population-based twin study. *Ann Neurol*. 1999;46(4):606-11.
- Russell MB, Iselius L, Olesen J. Inheritance of migraine investigated by complex segregation analysis. *Hum Genet*. 1995;96(6):726-30.
- Stewart WF, Staffa J, Lipton RB, Ottman R. Familial risk of migraine: a population-based study. *Ann Neurol*. 1997;41(2):166-72.
- Cutrer FM, Smith JH. Human studies in the pathophysiology of migraine: genetics and functional neuroimaging. *Headache*. 2013;53(2):401-12.
- Plummer PN, Colson NJ, Lewohl JM, et al. Significant differences in gene expression of GABA receptors in peripheral blood leukocytes of migraineurs. *Gene*. 2011;490(1-2):32-6.
- Cutrer FM, Limmroth V, Moskowitz MA. Possible mechanisms of valproate in migraine prophylaxis. *Cephalalgia*. 1997;17(2):93-100.
- Chaturvedi P, Khan R, Sahu P, Ludhiadch A, Singh G, Munshi A. Role of Omics in Migraine Research and Management: A Narrative Review. *Mol Neurobiol*. 2022;59(9):5809-34.
- García-Martín E, Martínez C, Serrador M, et al. Gamma-Aminobutyric Acid (Gaba) Receptors Rho (Gabbr) Gene Polymorphisms and Risk for Migraine. *Headache*. 2017;57(7):1118-35.