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# The Role of Matrix Metalloproteinase-1 (-1607 1G/2G) Gene Variation in Ischemic Stroke Development

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ABSTRACT

**Objective:** The matrix metalloproteinase (MMP) family is a potential genetic risk factor for the development of cerebrovascular disease, including ischemic stroke. MMP-1 (-1607 1G/2G) gene variation can lead to excessive MMP-1 protein production and MMP-1 enzyme activity. MMPs have an important role in the pathophysiology ischemic stroke pathophysiology and clinical outcome. Thus, the sensitivity to ischemic stroke may vary according to genetic characteristics. The objective of this study was to investigate the effect of MMP-1 (-1607 1G/2G) gene variation in the development of ischemic stroke disease in the population of Thrace, Turkey.

**Materials and Methods:** In all, 87 ischemic stroke patients and 80 healthy controls were enrolled in the study. Polymerase chain reaction and restriction fragment length polymorphism methods were used to determine the genotype distribution of MMP-1 (-1607 1G/2G) gene variations.

**Results:** There were more 1G/1G genotype (56.9%) and 1G/2G genotypes (55.1%) of MMP-1 (-1607 1G/2G) gene variations in the patient group than in the control group. However, no significant difference was determined between the groups in the distribution of MMP-1 (-1607 1G/2G) gene variation genotypes (p=0.127). The allele frequency of MMP-1 (-1607 1G/2G) gene variation in the ischemic stroke patient and healthy control groups was not significantly different from the Hardy-Weinberg distribution (p=0.6556 and p=0.0501, respectively).

**Conclusion:** The 1G/1G and 1G/2G genotypes of MMP-1 (-1607 1G/2G) gene variation were observed more frequently in the ischemic stroke group compared with the healthy control group. However, the MMP-1 (-1607 1G/2G) gene variation was not determined to be a genetic risk factor for the development of ischemic stroke in the population of Thrace region of Turkey.

**Keywords:** Ischemic stroke, matrix metalloproteinases, polymerase chain reaction, polymorphism, restriction fragment length

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## INTRODUCTION

Cerebrovascular disease (CVD) includes focal and global neurological symptoms that develop as a result of pathological processes associated with cerebral blood vessels. Stroke is a neurodegenerative disorder that can occur due to CVD (1, 2). Stroke is classified in 2 groups: ischemic stroke and hemorrhagic stroke (1).

Ischemic stroke is a neurological disease characterized by cell damage resulting from decreased cerebral blood flow (1). The levels of oxygen and glucose required for the brain fall below critical values. Pathophysiologically, cerebral blood flow is interrupted or blocked, and ischemic cascade and irreversible neuronal death occurs in the brain cells (3). Disruption of the blood-brain barrier in ischemic stroke has been associated with a variety of neurological complications (4).

The etiology of ischemic stroke has not been fully elucidated. Hypertension, hyperlipidemia or dyslipidemia, diabetes mellitus, smoking, alcohol consumption, atherothrombosis, atrial fibrillation, hypercholesterolemia, and chronic inflammation are important risk factors underlying ischemic stroke development (1, 5). Chronic inflammation promotes atherosclerotic plaque formation and plaque rupture, and thus can lead to the development of ischemic stroke (6). Clinical, environmental, and demographic risk factors have been associated with the development and pathogenesis of ischemic stroke (7). Ischemic stroke is accepted as a multifactorial disease in which genetic and environmental factors both play a role in the pathogenesis (5, 6). Various studies have been performed in different populations to investigate the relationship between genetic factors that may play a role in susceptibility and the risk of developing ischemic stroke (8, 9).

MMPs are calcium-dependent endopeptidases containing zinc that play an important role in the extracellular matrix degradation of blood vessels. MMPs produced by endothelial cells, neurons, microglia, and astrocytes can have an effect on various physiological processes. Blockage of the activity of MMPs has been associated with the brain damage that often occurs in ischemic stroke (2, 10). MMPs are endopeptidases that

can be expressed everywhere and contribute to innate immunity against various pathogens. MMP-1, MMP-2, MMP-3, MMP-9, and MMP-12 play an important role in the pathophysiology of ischemic stroke. A significant relationship has been reported between matrix degradation by MMPs and plaque stability, rupture, and ischemic stroke (2, 10–12).

MMP-1 is a 53-kilodalton protein that plays an active role in the degradation of interstitial collagen types I, II, III, and neuronal cell death (2). The synthesis and release of MMPs such as MMP-1 are regulated by complex signaling pathways, the protein transport networks. Genetic variations defined in the promoter region of the MMP-1 gene are associated with inherited differences in MMP-1 expression and susceptibility to disease pathologies, such as ischemic stroke (13). The MMP-1 (-1607 1G/2G) gene variation identified in the promoter region of the MMP-1 gene is a genetic variation characterized by guanine insertion/deletion (1G/2G). The 2G allele of the MMP-1 (-1607 1G/2G) gene variation forms the (5'-GGA-3') binding site for the transcription factor ETS. This binding site is associated with increased MMP-1 transcription, and as a result of increased MMP-1 gene expression, excessive MMP-1 protein production occurs and MMP-1 activity increases (14).

Previous studies have examined Serbian, Tunisian, Malaysian, and Chinese populations with the aim of investigating the relationship between MMP-1 (-1607 1G/2G) gene variation and ischemic stroke. Turkey is situated between Europe and Asia, and is characterized by different ethnic populations and varied geographic environments. The present study was conducted with participants from the Thrace region of Turkey. This population may exhibit a similar profile to European and Asian populations in terms of allele distribution. Genetic variability can reflect ethnic and racial characteristics. Therefore, the results of analysis of genetic variations may differ in people of different ethnic origins or race. Inherited differences in MMP-1 expression that may affect susceptibility to various disease pathologies may be due genetic variations in the promoter region of the MMP-1 gene. Targeting specific proteins that regulate MMP-1 expression and activity could represent an important avenue for a therapeutic approach to ischemic stroke (2, 10, 13, 15). Therefore, this research was designed to determine the association between MMP-1 (-1607 1G/2G) gene variation and development of ischemic stroke in a population from Thrace, Turkey.

## MATERIALS and METHODS

Ethics committee approval was obtained from the Trakya University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (TÜTF-BAEK no: 2018/281). Signed, informed consent was provided by all members of the patient group with ischemic stroke and the healthy control group.

This study was carried out at the Trakya University Faculty of Medicine Department of Biophysics and Department of Neurology. A total of 87 ischemic stroke patients and 80 healthy controls were enrolled. The patient group consisted of adult patients diagnosed with ischemic stroke and included patients hospitalized during acute stroke or patients who came to the outpatient clinic for tests in the chronic stage of ischemic stroke. Ischemic stroke was diagnosed based on a neurological examination and imaging data, including cerebral magnetic resonance imaging, and computed tomography imaging. Patients younger than 18 years of age or those who were pregnant, breastfeeding, or with a history of malignancy were excluded. In addition, patients with any other neurodegenerative disease associated with the central nervous system were excluded from the study. Patients with a hemorrhagic stroke, cardioembolic stroke due to atrial fibrillation or heart valve replacement, transient ischemic attack, or with cranial imaging studies that did not reveal ischemia, or those with simultaneous myocardial infarction and stroke were also excluded. The control group consisted of healthy volunteers without a history of CVD. Members of the ischemic stroke patient group and the healthy control group were selected from Edirne province and the surrounding area. Participant blood pressure was measured after 12 hours of fasting. Patients with a systolic and diastolic blood pressure of ≥140/90 mmHg were diagnosed with hypertension. Those with biochemical analysis results of a fasting blood glucose level >126 mg/dL were diagnosed with diabetes mellitus. The studies to determine the genetic predisposition to ischemic stroke were carried out in the Trakya University Faculty of Medicine Department of Biophysics. The flow diagram for participants is presented in Figure 1.

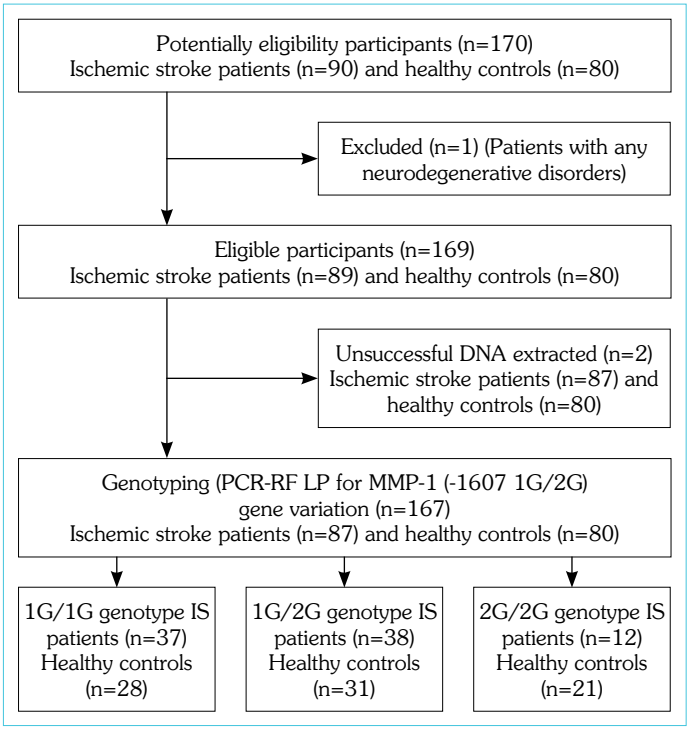


**Figure 1. Flow diagram of ischemic stroke patients and healthy controls**

IS: Ischemic stroke; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism

### DNA Isolation

The DNA of the ischemic stroke patient and healthy control groups was isolated from peripheral blood in tubes containing ethylenediaminetetraacetic acid. The purity and quality of the isolated DNA was determined using a nanodrop spectrophotometer and all of the samples were checked using 0.8% agarose gel electrophoresis.

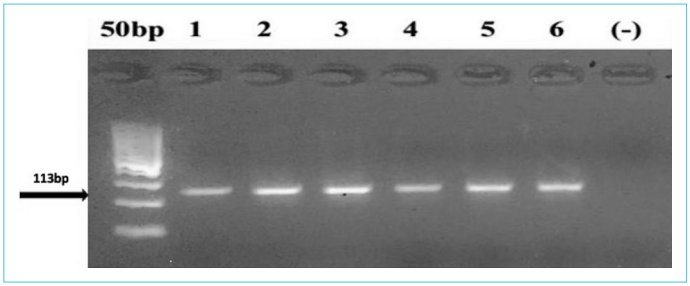


**Figure 2.** **Polymerase chain reaction samples of patient and control groups for MMP-1 (-1607 1G/2G) gene variation (113 bp, 50 bp marker)**

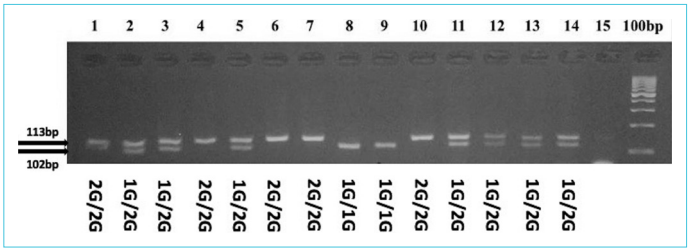


**Figure 3.** **Restriction fragment length polymorphism samples of patient and control groups for MMP-1 (-1607 1G/2G) gene variation: 1G/1G genotype (102 bp and 11 bp; Lanes 8 and 9 numbered bands), 1G/2G genotype (113 bp, 102 bp and 11 bp; Lane 2, 3, 5, 11, 12, 13 and 14 numbered bands) and 2G/2G genotype (113 bp; Lane 1, 4, 6 and 10 numbered bands). Note: 11 bp is not observed; 100 bp marker**

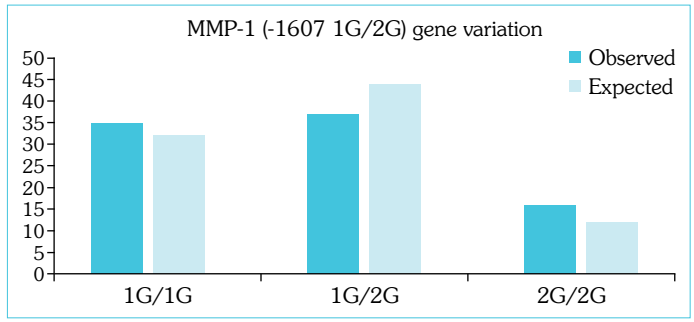


**Figure 4.** **Observed and expected genotype frequency of MMP-1 (-1607 1G/2G) gene variation (Ischemic stroke patients and healthy control group, N=167)**

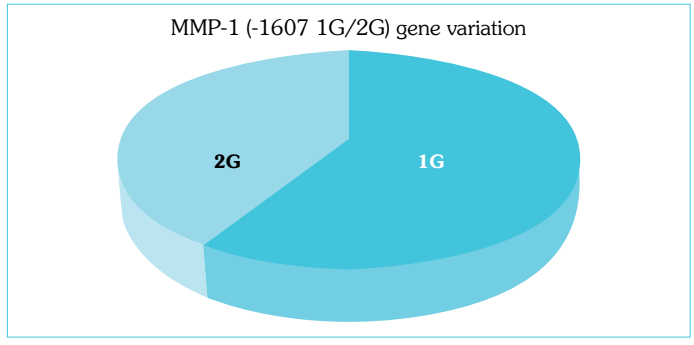


**Figure 5.** **Allele frequency of MMP-1 (-1607 1G/2G) gene variation (ischemic stroke patients and healthy control group, N=167)**

**Table 1.** Comparison of clinical findings of the patient group with ischemic stroke and the healthy control group

| Clinical findings | Patient group (n=87) | | Control group (n=80) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Age (years) | 61.84±12.003 | | 61.03±10.968 | | 0.649[a] |
| Gender | | | | | |
| Female | 36 | 49.3 | 37 | 50.7 | 0.526[b*] |
| Male | 51 | 54.3 | 43 | 45.7 | |
| Hypertension | 52 | 70.3 | 22 | 29.7 | **<0.001**[b*] |
| Diabetes mellitus | 29 | 70.7 | 12 | 29.3 | **0.010**[b*] |
| Alcohol use | 23 | 52.3 | 21 | 47.7 | 1.000[b] |
| Smoking | 39 | 63.9 | 22 | 36.1 | **0.020**[b*] |
| Heart disease | 24 | 92.3 | 2 | 7.7 | **<0.001**[b*] |
| Cerebrovascular disease history | 16 | 100.0 | 0 | 0.0 | **<0.001**[b*] |

a: Student t-test; b: Chi-squared test; *: Significance (p<0.05)

## Polymerase Chain Reaction Method

A preparation of 25 µL of polymerase chain reaction (PCR) mixture containing 50 ng of isolated DNA, 0.2 mM deoxyribose nucleotide triphosphate for forward and reverse primers (Invitrogen, Waltham, MA, USA), 1xPCR buffer, 3 mM magnesium chloride, and 1.25 U Taq DNA polymerase was created. 5'-TCGTGAGAATGTCTTCCCATT-3' forward and 5'-TCTTGGATTGATTTGAGATAAGTCATATC-3' reverse primers were used. For MMP-1 (-1607 1G/2G) gene variation analysis, amplification was performed with denaturation for 5 minutes at 94°C, followed by 35 cycles with denaturation for 20 seconds at 94°C, annealing for 20 seconds at 55°C, and extension for 20 seconds at 72°C, followed by 5 minutes of extension at 72°C. Electrophoresis with 2% agarose gel was used to check the MMP-1 (-1607 1G/2G) gene variation (Fig. 2).

## Restriction Fragment Length Polymorphism Method

The restriction fragment length polymorphism method, using 1x Tango buffer, PCR reaction products, distilled water, and 5U of

**Table 2.** Comparison of genotype distribution in the patient group with ischemic stroke and the healthy control group

| Genotype distribution | Patient group (n=87) | | Control group (n=80) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| MMP-1 (-1607 1G/2G) | | | | | |
| 1G/1G | 37 | 56.9 | 28 | 43.1 | |
| 1G/2G | 38 | 55.1 | 31 | 44.9 | 0.127[a] |
| 2G/2G | 12 | 36.4 | 21 | 63.6 | |

1G/1G; 1G/2G; 2G/2G: Guanine-guanine. a: Chi-squared test; *: Significance (p<0.05)

**Table 4.** Risk estimate statistics in the patients with ischemic stroke and the healthy control group

| Risk estimate | Value | 95% CI | |
|---|---|---|---|
| | | Lower | Upper |
| Odds ratio for gender | 1.219 | 0.661 | 2.249 |
| Odds ratio for smoking | 2.142 | 1.121 | 4.093 |
| Odds ratio for alcohol use | 1.010 | 0.507 | 2.012 |
| Odds ratio for hypertension | 3.917 | 2.042 | 7.514 |
| Odds ratio for diabetes mellitus | 2.833 | 1.327 | 6.049 |
| Odds ratio for heart disease | 14.857 | 3.381 | 65.280 |

CI: Confidence interval

**Table 3.** Allele frequency of MMP-1 (-1607 1G/2G) in the patients with ischemic stroke and the healthy control group

| Gene variations | Patient group (n=87) | | | | Control group (n=80) | | | |
|---|---|---|---|---|---|---|---|---|
| | Allele | Case | Frequency | Std. Error | Allele | Case | Frequency | Std. Error |
| MMP-1 (-1607 1G/2G) | 1G | 112 | 0.6437 | 0.0372 | 1G | 87 | 0.5437 | 0.0435 |
| | 2G | 62 | 0.3563 | 0.0372 | 2G | 73 | 0.4562 | 0.0435 |
| | Total | 174 | 1.0000 | | Total | 160 | 1.0000 | |
| | Hardy - Weinberg equilibrium test: Pearson chi$^2$=0.199 Pr=0.6556[a] | | | | Hardy - Weinberg equilibrium test: Pearson chi$^2$=3.838 Pr=0.0501[a] | | | |

a: Hardy-Weinberg equilibrium test; *: Significance (p<0.05)

restriction enzyme, was employed to determine the genotype distributions of the MMP-1 (-1607 1G/2G) gene variation. The PCR products were digested at 37°C for 3 hours with Xmn I restriction enzyme. Electrophoresis with 2% agarose gel was used to check the MMP-1 (-1607 1G/2G) distribution (Fig. 3).

### Statistical Analysis

An independent samples test was used to compare the age variable between the patient and control groups. A chi-squared test was used to compare the variables of gender, smoking, alcohol use, CVD history, hypertension, diabetes mellitus, and heart disease between the groups. A chi-squared test was also used in a comparison of the genotype distributions of the MMP-1 (-1607 1G/2G) gene variation between the patient and control groups. The Hardy-Weinberg distribution was used to determine allele frequency of the MMP-1 (-1607 1G/2G) gene variation in the ischemic stroke patients and healthy controls. Odds ratio values were calculated for the clinical findings with a 95% confidence interval. The results were expressed as number (percentage) or mean±SD. Statistical significance was accepted at p<0.05. The statistical analysis of the data was performed using IBM SPSS Statistics for Windows, Version 20.0 software (IBM Corp., Armonk, NY, USA).

## RESULTS

The findings indicated a significant difference in the smoking, diabetes mellitus, heart disease, (pre-stroke myocardial infarction, congestive heart failure), CVD history, and hypertension variables between the patient and control groups (p<0.05). No significant difference was found between the patients with ischemic stroke and the healthy control group related to the age, gender, or alcohol variables (p>0.05) (Table 1). The 1G/1G homozygous and 1G/2G heterozygous genotypes of the MMP-1 (-1607 1G/2G) gene variation were observed more frequently in the ischemic stroke group; however, without significant difference (p>0.05) (Table 2). In addition, the 1G and 2G allele frequency of the MMP-1 (-1607 1G/2G) gene variation in the ischemic stroke patient and the healthy control groups did not significantly differ from the Hardy-Weinberg distribution (p>0.05) (Table 3). Risk estimate statistics were computed for both groups and odds ratio values were calculated with a 95% confidence interval (Table 4). In our study population (N=167), the genotype frequency of 1G/1G was 39%, 41% for 1G/2G, and 20% for 2G/2G, while the expected genotype frequency was 1G/1G: 36%, 1G/2G: 48% and 2G/2G: 16%. Since the chi-squared value (3.26) calculated on the basis of the observed and expected genotype frequency was <3.84, which is the 0.05 significance limit, the population was determined to be within the Hardy-Weinberg model (Fig. 4). The allele frequency in the study population (patients with ischemic stroke and healthy controls, N=167) of the 1G allele was 59% and 41% for the 2G allele (Fig. 5).

## DISCUSSION

Ischemic stroke is a multifactorial process that can lead to death of neuronal cells and hypoxia and neurological damage in brain cells. Ischemic stroke has been associated with various envi-

ronmental risk factors, such as hypertension, smoking, alcohol use, diabetes mellitus, and chronic inflammation. Genetic factors may also contribute to the development of ischemic stroke. Therefore, ischemic stroke is known as a polygenic disease caused by the combination of environmental and genetic factors. Previous research has examined relationships between genetic variations and ischemic stroke in different races and populations (2, 3, 6, 16, 17).

There is an important relationship between the risk of ischemic stroke and the inflammatory response. Proteins in inflammatory pathways play an important role in the pathogenesis of ischemic stroke and inflammatory mediators may affect the development of ischemic stroke. MMPs, associated with chronic inflammation, are important genetic factors that may be involved in the pathogenesis of ischemic stroke. In some experimental brain injury models, it was observed that MMP regulation was disrupted after ischemia. Investigation of the effects of MMP gene variations in various diseases with acute brain damage revealed a significant relationship between genetic variations and changes in the level of MMP enzyme expression (7, 17).

MMPs have been associated with various physiological and pathological processes. For example, tissue damage has been associated with extracellular matrix degradation (14). MMP-1 is an important member of the MMP family and plays an important role in the degradation of matrix components. MMP-1 transcription is regulated by the combined effects of factors such as cytokines, hormones, and growth factors. In other research, the 2G allele of the MMP-1 (-1607 1G/2G) gene variation was reported to demonstrate significantly greater transcription activity than the 1G allele (14).

Other studies have investigated the relationship between MMP gene variations and the development of ischemic stroke with varied results. In a meta-analysis study, the 2G allele of the MMP-1 (-1607 1G/2G) gene variation was determined to be a genetic risk factor for ischemic stroke. A study of a Serbian population observed a significant relationship between the MMP-1 (-1607 1G/2G) gene variation and carotid plaque formation (2). In a study performed with a Tunisian population, the MMP-1 (-1607 1G/2G) gene variation was not found to be a genetic risk factor for ischemic stroke patients with Type 2 diabetes mellitus. The same study also found that the MMP-1 (-1607 1G/2G) gene variation was not an important biomarker for CVD, such as ischemic stroke, in diabetic patients (18). Results of research conducted with a Malaysian population indicated that the MMP-1 (-1607 1G/2G) gene variation was not a genetic risk factor for the development of essential hypertension in male patients (8).

Our study was carried out with a group from the Thrace region of northwestern Turkey. Previous studies have been performed to determine the role of several genetic variations in the development of ischemic stroke in this population. The results of analysis of genetic variations may differ according to ethnicity and race. This study was designed to investigate the possible role of MMP-1 gene variation in the development of ischemic stroke in the population of Thrace, which will provide valuable information related to the demographic characteristics of the region.

In our study, the 1G/1G and 1G/2G genotypes of the MMP-1 (-1607 1G/2G) gene variation were observed with greater frequency in the ischemic stroke patient group than in the healthy control group; however, without reaching the level of statistical ($p>0.05$). Consequently, the MMP-1 (-1607 1G/2G) gene variation was not determined to represent a genetic risk factor for ischemic stroke. The 1G and 2G allele frequency of the MMP-1 (-1607 1G/2G) gene variation in the ischemic stroke patient and healthy control groups did not vary significantly from the Hardy-Weinberg distribution ($p<0.05$).

Some limitations of our study should be pointed out. First, the sample size was relatively small. The limited statistical power may have contributed to the lack of a significant correlation between MMP-1 (-1607 1G/2G) gene variation and ischemic stroke risk. Second, comparison of the genotype distribution of the MMP-1 (-1607 1G/2G) gene variation in ischemic stroke subgroups could provide more detailed results. Furthermore, different selection criteria can lead to different results. Finally, modified Rankin score values measuring disability and the prognosis of stroke patients were not examined, which could provide information about clinical outcomes and associations with different alleles. Additional, larger, and more comprehensive studies are needed to further investigate the relationship between MMP-1 (-1607 1G/2G) gene variation and ischemic stroke.

## CONCLUSION

Several limited studies have been conducted with different populations to investigate the relationship between MMP-1 (-1607 1G/2G) gene variations and ischemic stroke development that have yielded different results. The differences may stem from different selection criteria as well as genetic variation in different populations. In our study of a population from Thrace, Turkey, MMP-1 (-1607 1G/2G) gene variation was not determined to be a genetic risk factor for ischemic stroke. In addition, the 1G and 2G allele frequency of the MMP-1 (-1607 1G/2G) gene variation in ischemic stroke patients and the healthy control group did not vary significantly from the Hardy-Weinberg distribution.

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**Ethics Committee Approval:** The Trakya University Faculty of Medicine Non-Invasive Clinical Investigations Local Ethics Committee granted approval for this study (date: 07.08.2018, number: TÜTF-BAEK 2018/281).

**Informed Consent:** Signed informed consent forms were obtained from each of the individuals ischemic stroke patients and healthy control groups.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – NA, AA; Design – NA, AA; Supervision – NA, AA; Resource – NA, AA; Materials – NA, AA; Data Collection and/or Processing – AA, SK; Analysis and/or Interpretation – NA, AA; Literature Search – NA, AA; Writing – NA; Critical Reviews – NA.

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

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