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VARIATIONS IN THE FREQUENCY OF ALLELIC AND GENOTYPIC FORMS OF THE RS522616 POLYMORPHISM IN THE MMP3 GENE AMONG PATIENTS WITH AVM

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Abstract
This study investigates the distribution of allelic and genotypic forms of the rs522616 polymorphism in the MMP3 gene among patients diagnosed with cerebral arteriovenous malformations (AVMs) and a control group of healthy individuals. AVMs are congenital vascular anomalies of the brain, characterized by abnormal arterial-venous connections that bypass the capillary system. Although the condition is relatively rare, it carries significant risk due to complications such as intracranial hemorrhage and seizures.
The rs522616 polymorphism (A/G) in the MMP3 gene may influence the expression of matrix metalloproteinase-3, an enzyme involved in vascular remodeling and extracellular matrix degradation. This study analyzed 154 individuals, including 94 AVM patients and 60 healthy controls, to assess the prevalence and potential pathological relevance of the polymorphism. The genotypic and allelic distributions were evaluated using standard case-control statistical methods, including Hardy-Weinberg equilibrium testing and chi-square analysis.
The results revealed that the A allele was predominant in both groups, while the G allele—considered potentially unfavorable—was slightly more common among AVM patients, particularly those with hemorrhagic complications. Although the differences were not statistically significant, trends suggested that individuals with the homozygous G/G genotype may have a higher predisposition to severe clinical manifestations such as hemorrhage. Subgroup analyses (hemorrhage, seizure, and other neurological deficits) further supported these observations.
This study contributes to the limited but growing body of literature on the genetic basis of AVMs and highlights the potential role of the rs522616 polymorphism in MMP3 as a genetic marker of susceptibility and disease severity. While preliminary, the findings underscore the need for further large-scale investigations in diverse populations to validate the role of this polymorphism and its interaction with clinical phenotypes.

Keywords: Cerebral arteriovenous malformation (AVM), MMP3 gene, rs522616 polymorphism, genetic susceptibility, hemorrhagic complications, genotype-phenotype association.

Introduction

Cerebral arteriovenous malformation (AVM) is a congenital pathology of the vascular system of the brain, characterized by the formation of abnormal connections between arteries and veins, bypassing the capillary network. It was first described by Luschka and Virchow in the mid-19th century. Vascular formation disorders (angiogenesis) in the central nervous system occur between the 4th and 13th week of fetal embryonic development. The disease can manifest at any age; however, it most commonly affects individuals between 20 and 40 years old. It is more frequent in men than in women. Throughout life, AVMs may present with intracranial hemorrhages, epileptic seizures, and cephalic syndrome. In some cases, asymptomatic malformations are detected.

The focal nature of vascular abnormalities suggests that AVM formation may result from other factors initiating a pathological process in the area of the future malformation (1). These can include environmental factors; mechanical factors that stimulate angiogenesis; angiogenic factors; and inflammatory cytokines. As a result of hemodynamic influences such as intravascular pressure, tension and stretch of the vascular wall, and high blood flow, a type of blood circulation is created that activates molecular mechanisms in the smooth muscle and endothelial cells of the brain, leading to proliferation and vascular remodeling. Recent studies support the hypothesis that genetic factors play a role in the pathogenesis of sporadic AVMs, further substantiated by reports of familial cases of the disease and its association with known systemic genetic disorders (2).

Our study included 154 individuals, of whom the main group consisted of 94 patients with a confirmed diagnosis of cerebral arteriovenous malformation (AVM), and the control group included 60 conditionally healthy individuals without signs of cerebrovascular pathology. Thus, the main group accounted for 61.0% (95% CI: 52.9–68.8), while the control group made up 39.0% (95% CI: 31.2–47.1).

Analysis of the gender composition of the main group revealed a significant predominance of males. Among the 94 patients with cerebral arteriovenous malformations, males constituted 70.2% (95% confidence interval: 59.9–79.2), whereas the proportion of females was significantly lower — 29.8% (95% CI: 20.8–40.1). This marked male predominance in the study cohort supports epidemiological research data indicating a higher prevalence or clinical manifestation of AVM in males. This may be due to hormonal and vascular-regulatory differences, as well as variations in risk factor profiles, including blood pressure levels, physical activity, and neuroendocrine mechanisms of vascular reactivity.

Given the significant role of the rs522616 polymorphism in the disruption of MMP3 enzyme expression, we conducted an analysis of the allele and genotype frequency distribution of this locus in a cohort of AVM patients and a control sample of Uzbek nationality. The rs522616 polymorphism of the MMP3 gene represents a single nucleotide substitution A/G (https://www.snpedia.com/index.php/Rs522616) and may lead to a significant increase in the activity of the corresponding protein (3).

Analysis of the genotype distribution of the rs522616 polymorphism of the MMP3 gene in the studied AVM patient cohort and control group showed that the observed empirical distribution of genotypes corresponds to the expected distribution under Hardy-Weinberg equilibrium ($p > 0.05$). These data indicate the representativeness of the patient and control cohorts for further study.

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An association analysis was conducted by comparing two samples using the case-control model. As a result of our investigation into the frequency distribution of alleles of the rs522616 polymorphism of the MMP3 gene for differences in distribution between the main group of AVM patients and the control group (Table 1), allele A was found to be slightly more frequent in the control group (77.5%) compared to 76.2% in the AVM group (χ^2=0.1; p=0.91; RR=1.0; 95% CI: 0.56–1.74; OR=0.9; 95% CI: 0.51–1.69). Conversely, allele G was slightly more frequent in the patient group (23.8%) compared to 22.5% in the control group (χ^2=0.1; p=0.91; OR=1.1; 95% CI: 0.56–1.86).

Table 1 Allele and genotype frequency distribution of the rs522616 polymorphism in the MMP3 gene in the main and control groups

No.	Group	Allele Frequency	Genotype Distribution Frequency
		A (%)	G (%)
1	Main group (n=61)	93 (76.23)	29 (23.77)
a	Subgroup with hemorrhage (n=21)	30 (71.43)	12 (28.57)
b	Subgroup with seizures (n=20)	31 (77.5)	9 (22.5)
c	Subgroup with other neurological deficits (n=20)	32 (80.0)	8 (20.0)
2	Control group (n=60)	93 (77.5)	27 (22.5)

The genotype frequency distribution of A/A, A/G, and G/G in the rs522616 polymorphism in the MMP3 gene for the patient and control groups was 63.9%, 24.6%, and 11.5% in the main group, compared to 63.3%, 28.3%, and 8.3% in the control group, respectively (Table 2). The A/A genotype was found equally in both groups (63.9% vs. 63.3%; χ^2=0.0; p=0.92; OR=1.0; 95% CI: 0.49–2.15). The heterozygous A/G genotype also showed similar frequencies between the groups (24.6% vs. 28.3%; χ^2=0.2; p=0.77; OR=0.8; 95% CI: 0.37–1.85). A trend was observed toward a higher proportion of the unfavorable homozygous G/G genotype in the patient group (11.5%) compared to the control group (8.3%), although this difference was not statistically significant. The odds ratio indicated that the risk of developing AVM with the G/G genotype increased 1.4-fold (χ^2=0.3; p=0.69), which was also not statistically significant.

Table 2 Allele and genotype frequency distribution of rs522616 of the MMP3 gene in the main and control groups

Alleles and Genotypes	Main Group	Control Group	χ^2	p	RR	95% CI	OR	95% CI
A	93 (76.2%)	93 (77.5%)	0.1	0.91	1.0	0.56–1.74	0.9	0.51–1.69
G	29 (23.8%)	27 (22.5%)	0.1	0.91	1.0	0.56–1.86	1.1	0.59–1.95
A/A	39 (63.9%)	38 (63.3%)	0.0	0.92	1.0	0.49–2.08	1.0	0.49–2.15
A/G	15 (24.6%)	17 (28.3%)	0.2	0.77	0.9	0.38–1.98	0.8	0.37–1.85
G/G	7 (11.5%)	5 (8.3%)	0.3	0.69	1.4	0.5–3.77	1.4	0.43–4.75

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Comparative analysis of allele and genotype frequency distributions of the rs522616 polymorphism of the MMP3 gene revealed a clear trend toward a direct association with the frequency of the unfavorable G allele.

Frequency Distribution in Hemorrhage and Seizure Subgroups

In the analysis of allele distribution between the hemorrhage subgroup and the seizure subgroup (Table 3), the wild-type A allele was slightly more frequent in the seizure subgroup (77.5% vs. 71.4%; χ^2=0.4; p=0.72; RR=0.9; 95% CI: 0.38–2.23; OR=0.7; 95% CI: 0.27–1.97). The unfavorable G allele was slightly more frequent in the hemorrhage subgroup (28.6%) compared to the seizure subgroup (22.5%), though this difference was also not statistically significant (χ^2=0.4; p=0.72; OR=1.4; 95% CI: 0.52–3.74).

Table 3 Allele and genotype frequency distribution of rs522616 in the hemorrhage and seizure subgroups

Alleles and Genotypes	Hemorrhage Subgroup	Seizure Subgroup	χ^2	p	RR	95% CI	OR	95% CI
A	30 (71.4%)	31 (77.5%)	0.4	0.72	0.9	0.38–2.23	0.7	0.27–1.97
G	12 (28.6%)	9 (22.5%)	0.4	0.72	1.1	0.37–3.2	1.4	0.51–3.74
A/A	12 (57.1%)	14 (70.0%)	0.7	0.50	0.8	0.26–2.57	0.6	0.16–2.06
A/G	6 (28.6%)	3 (15.0%)	1.1	0.39	1.9	0.6–6.07	2.3	0.49–10.45
G/G	3 (14.3%)	3 (15.0%)	0.0	0.92	1.0	0.18–5.16	0.9	0.17–5.34

Allele and Genotype Frequency of the rs522616 Polymorphism of the MMP3 Gene in the Seizure Group and the Group with Other Neurological Deficits

As a result of the study on allele frequency distribution of the MMP3 gene rs522616 polymorphism to identify differences between the subgroup with seizures and the group with other neurological deficits, allele **A** was slightly more frequent in the group with neurological deficits compared to the seizure group (χ^2=0.1; p=0.79; RR=1.0; 95% CI: 0.35–2.65; OR=0.9; 95% CI: 0.29–2.52), while the **G** allele was slightly more frequent in the seizure subgroup (22.5% vs. 20.0%; χ^2=0.1; p=0.79; RR=1.0; 95% CI: 0.34–3.09; OR=1.2; 95% CI: 0.4–3.39).

The distribution of the homozygous **A/A** genotype and the heterozygous **A/G** genotype in the seizure subgroup and the group with other neurological deficits was 70.0% and 15.0% vs. 65.0% and 30.0%, respectively. Analysis showed that the wild-type **A/A** genotype occurred slightly more often in the seizure subgroup than in the neurological deficit subgroup (70.0% vs. 65.0%; χ^2=0.1; p=0.84; RR=1.1; 95% CI: 0.28–4.17; OR=1.3; 95% CI: 0.33–4.73). The heterozygous **A/G** genotype was more common in the neurological deficit group (30.0% vs. 15.0%; χ^2=1.3; p=0.43; RR=0.5; 95% CI: 0.07–3.4; OR=0.4; 95% CI: 0.09–1.9). The homozygous **G/G** genotype was more frequently observed in the seizure subgroup than in the group with neurological deficits (15.0% vs. 5.0%; χ^2=1.1; p=0.40; RR=3.0; 95% CI: 0.82–11; OR=3.4; 95% CI: 0.35–31.8).

Based on a comprehensive analysis of allele and genotype frequency data for the rs522616 polymorphism of the MMP3 gene in patients with cerebral arteriovenous malformations (AVMs), the following conclusions were drawn:

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• **Allele A** was predominant in both the patient group and the control group, with no statistically significant differences between them.
• The **unfavorable G allele** showed a slightly increased frequency in AVM patients, particularly in the subgroup with hemorrhages.
• Genotypic analysis revealed nearly identical distribution of the **A/A** genotype in both groups.
• The **A/G** genotype also did not differ significantly between groups.
• However, the **G/G genotype** occurred more frequently among AVM patients, especially in the hemorrhagic subgroup, although this difference was not statistically significant and should be interpreted as a trend.

Comparative analysis of clinical subgroups indicated that:
• The **hemorrhagic subgroup** had a higher frequency of the unfavorable **G allele** and particularly the **G/G** genotype, suggesting its potential role in the risk of hemorrhage.
• Among **seizure patients**, both the **A/A** and **G/G** genotypes were more frequent, while the **A/G** genotype was more commonly observed in patients with other neurological deficits.
• The **highest frequency of the favorable A allele** was seen in the subgroup with neurological deficits without severe complications.

Conclusion

The results of our study suggest a **potential association** of the MMP3 gene rs522616 polymorphism with specific clinical manifestations of AVMs, especially **hemorrhage** and **seizure syndromes**. An increased frequency of the **unfavorable G allele and G/G genotype** was observed in patients with severe AVM complications, although these associations did **not reach statistical significance** and should be regarded as **preliminary trends**, warranting further validation in larger cohorts.

This research highlights the importance of continuing to study this genetic locus, especially considering the known roles of **matrix metalloproteinases (MMPs)**, including **MMP3**, in extracellular matrix remodeling and angiogenesis regulation—critical factors in the pathogenesis of cerebral vascular malformations.

At present, literature on the role of the **rs522616 polymorphism** in the development and clinical course of AVMs is limited. No direct studies confirming or refuting our hypothesis on this polymorphism in cerebral AVMs were identified. Most MMP3-related studies focus on **ischemic and hemorrhagic strokes** or **neurodegenerative diseases**.

Thus, our findings contribute to the understanding of **genetic factors** in AVM formation and progression but highlight the need for **further research**, involving larger, ethnically diverse populations. Investigating additional polymorphisms and a wider range of clinical phenotypes will help clarify the role of MMP3 and potentially identify **genetic markers of prognostic value** for clinical practice.

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