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POLYMORPHISM RS522616 OF THE MMP3 GENE IN THE GROUP OF PATIENTS WITH AVM AND IN THE CONTROL GROUP

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Abstract
Arteriovenous malformation (AVM) of the brain is a congenital vascular anomaly characterized by abnormal connections between arteries and veins, often leading to hemorrhage, seizures, or neurological deficits. Recent studies have focused on genetic predispositions that may influence the development and clinical manifestations of AVM. Among these, the matrix metalloproteinase 3 (MMP3) gene plays a key role in extracellular matrix remodeling and vascular wall integrity. The rs522616 polymorphism of the MMP3 gene, representing a single A/G nucleotide substitution, has been hypothesized to influence enzyme activity and, consequently, AVM pathogenesis.
This study investigated the distribution of allelic and genotypic variants of rs522616 in 95 patients with AVM and 60 control individuals of Uzbek nationality. Genotyping revealed no statistically significant differences in allele (A vs. G) or genotype (A/A, A/G, G/G) frequencies between the AVM and control groups, indicating that the polymorphism is not a direct determinant of AVM susceptibility. However, subgroup analyses demonstrated a higher prevalence of the unfavorable G allele and particularly the homozygous G/G genotype among patients with hemorrhagic AVM, suggesting a potential genetic predisposition to severe clinical outcomes. Although statistical significance was not reached, the observed trend highlights the possible contribution of rs522616 polymorphism to AVM progression and complications.
These findings suggest that rs522616 polymorphism of the MMP3 gene may serve as a candidate genetic marker for predicting hemorrhagic risk in AVM patients. Further large-scale, multi-ethnic studies are necessary to validate the observed associations and to better understand the role of MMP3 polymorphisms in cerebrovascular pathologies. Ultimately, genetic profiling may contribute to the development of personalized approaches for prognosis and management of AVM complications.

Keywords: Arteriovenous malformation (AVM), MMP3 gene, rs522616 polymorphism, genetic predisposition, hemorrhage risk, Cerebrovascular genetics.

Introduction

One congenital vascular condition of the brain known as arteriovenous malformation (AVM). The existence of arteriovenous shunts that constitute the so-called malformation node is the primary characteristic of cerebral AVMs' angioarchitectonics. The development of a tangle of linked vessels

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is a characteristic of AVMs. Throughout life, AVMs can present as either a hemorrhagic form, which affects 50–70% of cases, or a torpid form, which is represented by localized neurological deficiency, cephalgia, epileptic convulsions, and chronic cerebral circulatory insufficiency. Sometimes an abnormality that shows no symptoms is found. Magnetic resonance imaging (MRI) and cerebral angiography (CAG) are used to confirm the diagnosis. Multispiral computed tomography (MSCT) or magnetic resonance imaging (MRI) of the brain might occasionally reveal an asymptomatic abnormality. The most extensive research has been done in the past few years on the genomics of many complex disorders. The candidate gene method and genome-wide linkage and association analysis (genome-wide association studies, GWA study, GWAS) are two techniques used to seek for genetic factors of predisposition to AVM. (1,2).

MMPs, or matrix metalloproteinases. The family of matrix-disrupting enzymes known as human MMPs. Neutrophils, monocytes, macrophages, fibroblasts, osteoclasts, chondrocytes, keratinocytes, endothelium, and epithelial cells are among the normal or altered cells that produce metalloproteinases. AVM vessel walls are damaged by the proteolytic enzymes secreted by these cells, including metalloproteinases, myeloperoxidases, cytokines, and others, which results in rupture foci. By secreting myeloperoxidase, metalloproteinase, cytokines, and other proteolytic enzymes, MMPs can break down nearly every extracellular matrix component present in connective tissues, including collagen, fibronectin, laminin, proteoglycans, etc.

The extracellular matrix becomes less unstable when matrix metalloproteinases' natural inhibitors, known as tissue inhibitors of matrix metalloproteinases, or TIMPs, inhibit their activity. A number of malignant tumors had altered MMP and TIMP. The gene MMP3 is a major activator of other MMPs, and its level is much higher in AVM. MMP3 is produced in extremely modest amounts by several connective tissue cells and is a member of the stromyelisi 1 class. However, MMP3 synthesis is dramatically stimulated when these cells are exposed to cytokines such TNF-a, b, IL-1, IL-6, growth factors, and oncogenes. MMP-2, -3, -7, and -9 help to activate transforming growth factor β, which releases monocytes from the matrix and acts as a chemoattractant. MMPs are often present in tissues in trace levels (3).

The MMP3 gene's rs522616 polymorphism, which is a single A/G nucleotide substitution (https://www.snpedia.com/index.php/Rs522616), may cause the associated protein's activity to significantly increase. We examined the frequency of distribution of allelic and genotypic variants of this locus in a cohort of patients with AVM and a control sample of Uzbek nationality, given the significant function of the rs522616 polymorphism in the disruption of MMP3 enzyme production (4,5).

Materials and Methods

The study included overall 154 patients, 95 with brain AVMs. The average age of patients at the period of manifestation was 33.8 ± 13.5 years. The control group consisted of 60 individuals (mean age: 33.0 ± 11.2) without AVMs. Magnetic resonance imaging and cerebral angiography were performed in the Republican Scientific Center of Neurosurgery under the Ministry of Health of the Republic of Uzbekistan and the Republican Specialized Hematology Scientific and Practical Medical Center.

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The distribution of genotypic variants of the MMP3 gene polymorphism rs522616 in the control group and the examined cohort of AVM patients was analyzed, and the results indicated that the empirical-actual genotype distribution matched the Hardy-Weinberg equilibrium (p>0.05). These findings suggest that the patient and control cohorts under study are representative enough for additional research.

The "case-control" model was used to compare two samples in order to do the association analysis. The A allele slightly exceeded the G allele in the main group of patients, with a frequency of 23.8% versus 22.5%, respectively (χ2=0.1; p=0.91; OR=1.1; 95%CI:0,56-1,86), and the A allele slightly outnumbered the control group, with a frequency of 77.5% versus 76.2% (χ2=0.1; p=0.91; RR=1.0; 95%CI:0.56-1.74; OR=0.9; 95%CI:0.51-1.69). (Table 1).

Table 1 The frequency of distribution of alleles and genotypes of the rs522616 polymorphism in the MMP3 gene in the main group and in the control group

N	Group	Frequency of alleles				Frequency of genotype distribution					
		A		G		A/A		A/G		G/G	
		n	%	n	%	n	%	n	%	n	%
1	The main group n=61	93	76.23	29	23.77	39	63.9	15	24.6	7	11.5
a	A subgroup with hemorrhage n=21	30	71.43	12	28.57	12	57.14	6	28.57	3	14.29
b	A subgroup with seizures n=20	31	77.5	9	22.5	14	70.0	3	15.0	3	15.0
c	Subgroup with other neurological deficits n=20	32	80.0	8	20.0	13	65.0	6	30.0	1	5.0
4	The control group (n=60)	93	77.5	27	22.5	38	63.3	17	28.3	5	8.3

The major patient group and the control sample had genotypic variations A/A, A/G, and G/G of the MMP3 gene rs522616 polymorphism at frequencies of 63.9% and 24.6% and 11.5%, respectively, compared to 63.3%, 28.3%, and 8.3%, respectively (Table 2). Patients in the main group and the control group shared the A/A genotype at equal rates (63.9% vs. 63.3%, respectively; χ2=0.0; p=0.92; OR=1.0; 95%CI:0.49-2.15). Patients in the main group and the control group had the same prevalence of heterozygous genotype A/G (24.6% vs. 28.3%, respectively χ2=0.2; p=0.77 OR=0.8; 95%CI:0.37-1.85). The main group's percentage of unfavorable homozygous G/G genotypes tended to be higher than that of the control group (11.5% versus 8.3%, respectively). The odds ratio indicates that the likelihood of having AVM. The odds ratio indicates that there is no significant 1.4-fold increase in the likelihood of getting AVM with the G/G genotype (χ2=0.3; P=0.69).

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Table 2 Frequency of distribution of alleles and genotypes of polymorphism rs522616 of MMP3 gene in the main group and in the control group

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	The main group		The control group							
	n	%	n	%						
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

The frequency distribution of genotypic and allelic variants of the MMP3 gene's rs522616 polymorphism was compared, and the results showed a strong correlation with the unfavorable G allele's direct dependence on the frequency of occurrence.

The prevalence of genotypes and alleles of the MMP3 gene polymorphism rs522616 in the group of patients who experienced seizures and bleeding.

The frequency of distribution of alleles of the rs522616 polymorphism of the MMP3 gene was examined for differences in distribution between the hemorrhage and seizure groups (Table 3). The results showed that wild allele A slightly outperformed the seizure group, with a frequency of 77.5% versus 71.4% (χ2=0.4; p=0.9; RR=0.9; 95%CI:0.38-2.23; OR=0.7; 95%CI:0.27-1.97). In the subgroup, the group with hemorrhage had a slightly higher prevalence of the unfavorable G allele than the group with seizures (28.6% vs. 22.5%, respectively; χ2=0.4; p=0.72; OR=1.4; 95%CI:0.52-3.74).

Table 3 The frequency of distribution of alleles and genotypes of the MMP3 polymorphism rs522616 in the subgroup with hemorrhage and in the subgroup with seizures

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	A subgroup with hemorrhage		A subgroup with seizures							
	n	%	n	%						
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

The frequency of distribution of MMP3 polymorphism rs522616 genotypes and alleles in the bleeding and other neurological impairment subgroups.

Table 4 show the findings of the investigation of the frequency of distribution of alleles of the rs522616 polymorphism of the MMP3 gene for variations in their distribution in the groups with bleeding and other neurological impairments.

As can be observed, allele G slightly outperformed allele A in the group of patients with hemorrhage, with an incidence of 28.6% versus 20.0%, respectively (χ2=0.8; p=0.52; RR=1.1; 95%CI:0.35-3.55; OR=1.6; 95%CI:0.58-4.44), and allele A slightly outperformed the group with

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neurological deficiency, with a frequency of 80.0% versus 71.4% ($\chi2$=0.8; p=0.52; RR=0.9; 95%CI:0.38-2.12; OR=0.6; 95%CI:0.23-1.73).

Table 4 Alleles and genotypes of the MMP3 gene polymorphism rs522616 were more often distributed in the bleeding group than in the group with other neurological impairments.

Alleles and genotypes	Number of alleles and genotypes examined				$\chi2$	p	RR	95%CI	OR	95%CI
	A subgroup with hemorrhage		A subgroup with other neurological deficits							
	n	%	n	%						
A	30	71,4	32	80,0	0,8	0,52	0,9	0,38 - 2,12	0,6	0,23 - 1,73
G	12	28,6	8	20,0	0,8	0,52	1,1	0,35 - 3,55	1,6	0,58 - 4,44
A/A	12	57,1	13	65,0	0,3	0,81	0,9	0,27 - 2,82	0,7	0,2 - 2,53
A/G	6	28,6	6	30,0	0,0	0,94	1,0	0,26 - 3,51	0,9	0,24 - 3,58
G/G	3	14,3	1	5,0	1,0	0,57	2,9	0,79 - 10,32	3,2	0,33 - 30,21

The frequency of homozygous G/G genotype was significantly higher in the bleeding group than in the neurological deficit group (14.3% versus 5.0%, respectively). The odds ratio indicates that having this genotype raises the likelihood of acquiring this kind of glaucoma by more than three times ($\chi2$=1.0; P=0.57).

The following findings were derived from a thorough examination of the data on the frequency of alleles and genotypes of the MMP3 gene's rs522616 polymorphism in patients with arteriovenous malformations. Allelic variant frequency analysis showed that allele A is prevalent in both the control sample and the major patient group, with no discernible differences between the two groups. Patients with AVM had a slightly higher incidence of occurrence of the unfavorable G allele, particularly in the bleeding category. The distribution of the A/A genotype in the main and control groups was nearly comparable, according to genotypic analysis. Additionally, there were no notable changes between the groups for the heterozygous A/G genotype. Nonetheless, individuals with AVM were more likely to have a homozygous unfavorable G/G genotype, particularly in the bleeding category. This difference is not statistically supported, but it does appear to be trending.

The subgroup of patients who experienced hemorrhages had a higher frequency of carrying the unfavorable G allele and, particularly, the homozygous G/G genotype, according to a comparative analysis of clinical subgroups. This could suggest that the genotype may play a part in the risk of hemorrhages. While the heterozygous variant was more frequently observed in patients with various neurological impairments, the A/A genotype and the unfavorable homozygous G/G genotype were more prevalent among patients with seizures. The subgroup with neurological deficit and no serious consequences had the highest incidence of the advantageous allele A.

As a result, the MMP3 gene polymorphism rs522616 shows a possible correlation with a number of clinical signs of AVM, particularly in relation to the risk of seizures and bleeding. The homozygous G/G genotype is more prevalent in patients with more severe clinical forms of the disease and may be a genetic marker of a greater risk of complications, particularly hemorrhages, even though it is not supported by statistically significant differences. However, the heterozygous A/G genotype did not significantly correlate with severe manifestations of the disease, and the A/A genotype has a

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neutral profile, being equally distributed in the control and study groups without noticeable consequences (6).

The findings indicate that information on the MMP3 gene's rs522616 polymorphism may be useful in clinical practice for predicting which patients are most likely to experience AVM complications. This information will aid in the creation of tailored strategies for the management and avoidance of these complications. The importance of the found correlations, however, has to be further verified within the context of larger-scale research projects with more participants.

Our study's findings show that the MMP3 gene polymorphism rs522616 may be linked to clinical types of arteriovenous malformations, particularly when hemorrhages and convulsive syndrome are involved. The G/G genotype and unfavorable G allele were found to be more common in patients with severe AVM consequences, including hemorrhages and epileptic seizures. It should be noted, although, that the relationships found have not attained statistical significance and are merely displayed as trends, which need to be verified in bigger samples.

However, there is currently little information in the literature on the contribution of a particular polymorphism, rs522616, of the MMP3 gene to the onset and progression of AVM. Regarding this polymorphism in brain AVM, there are no direct investigations in the scientific literature that support or contradict our hypothesis and the findings. The majority of research on MMP3's function focuses on neurodegenerative illnesses and other pathologies such ischemic and hemorrhagic strokes (7).

Therefore, our findings improve our knowledge of the genetic components of AVM development and progression, but future studies with a larger sample size and a wider range of ethnic groups are needed. The role of the MMP3 gene will be clarified by additional research involving more variants and a broader variety of clinical manifestations. Additionally, prognostically significant genetic indicators for clinical practice will be suggested..

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