GALAXY INTERNATIONAL INTERDISCIPLINARY RESEARCH JOURNAL (GIIRJ)
ISSN (E): 2347-6915
Vol. 12, Issue 5 May (2024)

GENE-GENE INTERACTION OF POLYMORPHISMS 5A/6A OF THE MMP3 GENE AND 1562 C/T OF THE MMP9 GENE IN PATIENTS WITH CEPHALGIC SYNDROME WITH AND WITHOUT CEREBRAL VASCULAR ANOMALIES

Rakhmatullayeva Gulnora, Dustmukhamedova Risolat
Tashkent Medical Academy. Department of Neurology and
Medical Genetics. Tashkent, Uzbekistan

ABSTRACT

One of the possible causes of headaches is abnormalities of cerebral vascular development. In this regard, the study of molecular-genetic manifestations of gene-gene interactions is highly relevant. Therefore, in the course of analyzing the data of molecular-genetic studies, we studied gene-gene interaction of polymorphisms 5a/6a of MMP3 gene and 1562 C/T of MMP9 gene in patients with cephalgic syndrome with and without cerebral vascular anomalies. The study of which showed certain changes characteristic for these interactions. The analysis of "gene-gene interactions" in the studied groups revealed a number of genotypic combinations. The combination of two "unfavorable genotypes" was found in 15 patients (22.7%) and 8 healthy individuals (12.3%).

Keywords: cephalgic syndrome, vessels, pathological tortuosity, molecular genetics.

INTRODUCTION

Currently, there are probably no pathologies in the genesis of which the role of gene mutations could not be seen. According to the literature, recent studies have demonstrated that matrix metalloproteinases play a key role in the initiation of angiogenesis, invasion, and metastasis [1,2]. The essence of angiogenesis processes consists in the fact that after vascular dilation and increase of vascular permeability there is a constriction of endothelial cells and a decrease in the density of intercellular contacts. As a result, the basal membrane is destroyed by some proteases, including MMP. [3]. For example, gene-gene interaction polymorphisms 5a/6a of the MMP3 gene and 1562 C/T of the MMP9 gene may increase the risk of cerebral vascular pathology, which in turn may be the cause of cephalgic syndromes with the development of various CVDs.

Research objective: to study the role of gene-gene interactions in the development of vascular anomalies.

MATERIALS AND METHODS

We examined 66 (50.4%) patients with cephalgic syndrome, as well as 65 (49.6%) practically healthy individuals who constituted the control group.

All patients underwent clinical and neurological, neuroimaging: duplex scanning of brachiocephalic arteries, brain MSCT with angiography or MRI with angioregime, as well as molecular genetic studies of metalloproteinase gene MMP3, MMP9 with the study of gene-gene interactions.

Results: Analysis of "gene-gene interactions" in the studied groups revealed a number of genotypic combinations. The combination of two "unfavorable genotypes" was found in 15 patients (22.7%) and 8 healthy individuals (12.3%). At the same time, the relative risk of disease development in carriers of "unfavorable genotypes" was OR =2.1. However, in pairwise comparison of frequencies of these combinations, the difference did not reach statistical significance ($\chi 2=2.5$; P=0.1; 95%CI 0.8207, 5.35), which does not allow us to draw an unambiguous conclusion. Despite the existence of statistically unreliable differences, the lower limit of 95%CI (confidence interval) of the relative risk is close to unity, so in this case we consider it appropriate to interpret the obtained indicators as a trend rather than a pattern. In this case, it is necessary to increase the sample size, which will allow us to obtain more reliable results. Fig.1, 2.

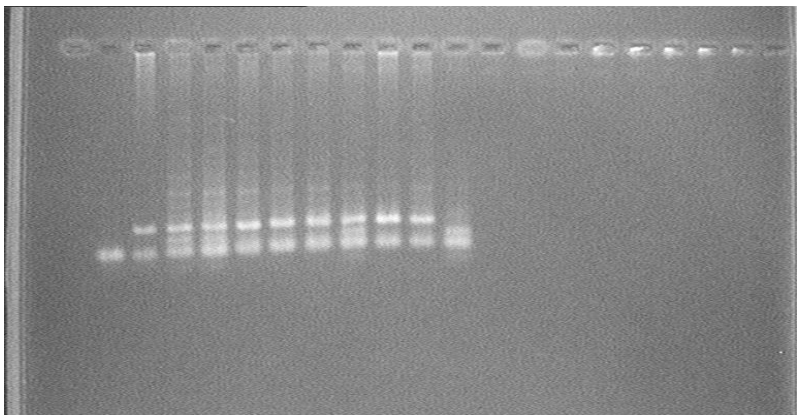

Figure 1: Results of MMP3 gene analysis in patients on DNA samples from 9 patients

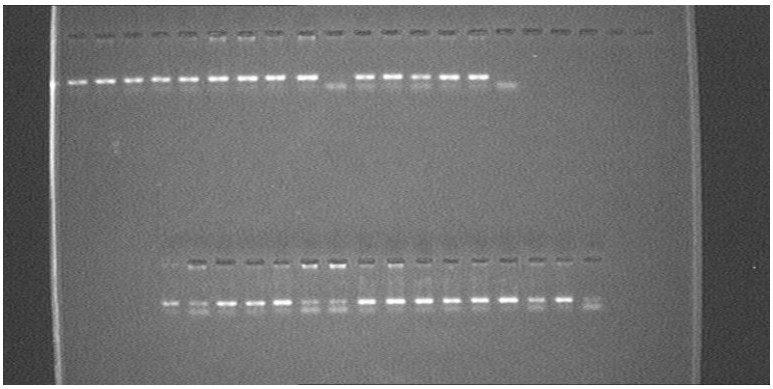

Figure 2: Results of MMP9 gene analysis in patients on DNA samples from 15 patients

Table 1. Frequency of genotypes in patients with cephalgia and healthy controls

№	groups	Genotype frequencies							
		Heterozygote+ heterozygote (+/- and +/-)		Homozygote + heterozygote (+/+ and +/-)		Homozygote +Homozygote (+/+ and +/+)		Patients with normal or single mutant genotypes	
		N	%	n	%	n	%	n	%
1	patients n=66	9	13.6	4	6.1	2	3.0	51	77.3
2	control n=65	4	6.2	4	6.2	0	0.0	57	87.7

Carriage or absence of the corresponding allele was labeled as "+" or "-".
Overall (genotypic variants): $\chi 2$ =2.5; P=0.1; OR =2.1; 95%CI 0.8207, 5.35.
Genotypes:
+/- and +/- (allelic variants): $\chi 2$ =4.1; P=0.04; OR =2.4; 95%CI 1.008, 5.753
+/- and +/- (genotypic variants): $\chi 2$ =2.1; P=0.1; OR =2.4; 95%CI 0.7025, 8.253.
+/+ and +/+ (allelic variants): $\chi 2$ =8.1; P=0.004; OR =4.0 +/+ and +/+ genotypic variant: $\chi 2$ =2.0; P=0.2; OR =2.0
Cumulative (genotypic variants) $\chi 2$ =3.6; P=0.056; OR =3.05; 95%CI 0.9178, 10.14
Cumulative (allelic variants): $\chi 2$ =10.6; P=0.001; OR =3.7; 95%CI 1.625, 8.613
As a result of the comparative analysis of combinations of "functionally unfavorable" genotypic variants in the groups of patients and controls, the key variants of intergenic interactions determining the development of pathological deformations of cerebral vessels were identified. These were carriers of "double heterozygotes" and "double homozygotes" genotypic variants.
Carriers of "double heterozygotes" polymorphisms 5a/6a of the MMP3 gene and 1562 C/T of the MMP9 gene were almost 2.4 times more frequent among the patients than in the control group. Despite $\chi 2$ =2.1; P=0.1; 95%CI 0.7025, 8.25, nevertheless, we do not exclude a possible contribution of this genotypic variant to the formation and course of cephalgic syndrome. The accumulation of this unfavorable genotype in one individual is a risk factor for the development of vascular anomalies.
The genotypic variant "homozygote+homozygote" was detected exclusively in the group of patients and with a very low frequency of 3.0% ($\chi 2$ =2.0; P=0.2; OR =2.0). This may be associated with a high risk of development of various severe complications in patients with possible further elimination of such intergenic combination (natural selection) (certain genotypic combinations in adaptation of each particular organism to environmental conditions). Unfortunately, we cannot say unequivocally that there is an associative relationship between the combination of "unfavorable genotypes" and the risk of disease formation. However, judging by our own data, there is a tendency to increase the frequency of "functionally impaired" double homozygotes among the examined patients.
It is quite unexpected, but the fact that the combination of "homozygote and heterozygote" occurred with almost equal frequency in patients and in the corresponding individuals of the control group (6.1% and 6.2%, respectively), which casts doubt on the independent role of such a variant as a risk factor for the development of pathological deformities.

CONCLUSION

Thus, due to the low frequency of carriage of the most significant combinations of "functionally impaired genotypes" of polymorphisms 5a/6a of the MMP3 gene and MMP9 gene, we did not reveal a clear correlation between these genotypic variants and the risk of vascular anomalies. However, based on the important independent role of polymorphisms 5a/6a of the MMP3 gene and 1562 C/T of the MMP9 gene in the formation of cerebrovascular diseases, it can be assumed that the combination of polymorphic variants of these genes also affect the risk of pathologic deformations, which may not strictly determine the development of the disease, but reliably determine the degree of its risk.

REFERENCES

1. Metalloprotinases as regulators of neoangiogenesis in malignant neoplasms./Spirina L.V., Kondakova I.V., Klishko E.V., Kakurirna G.V., Shishkin D.A.//Sib.onkol. journal.-2007-T21, No.1-C. 67-71
2. Biological role and regulation of matrix metalloprotinases in cancer /Davidson B., Reich R., Risberg B., Nesland L.M.//Arch.pathol.-2002-T.64, №3.-P. 47-53.
3. Hotko A.A. Role of matrix metalloprotinases in the development of psoriasis and associated comorbidity (review)//Saratov Scientific Medical Journal. 2003.T.9, №3. C.582-584.