

# Evaluation of Polymorphism Gene AGTR1 (rs5186) in the Pathogenesis of Immune Microtrombovasculitis

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**Abstract** The AGTR1 gene rs5186 genetic polymorphism was detected among non-relatives of patients with immune microtrombovasculitis (Schenlein-Genoch purpura). In the main group of patients, compared with the control group, a slight decrease in the A / C genotype was noted (41.3% versus 49.3%). Along with this, the presence of the C / C homozygous genotype (20.0% versus 17.8%) was also detected in both groups. The frequency distribution of genotypes was statistically insignificant ( $\chi^2 = 0.96$ ;  $df = 2$ ,  $p = 0.62$ ). The results suggest that the carriage of the polymorphic variant of the AGTR1 gene (rs5186) is not associated with the risk of developing immune microtrombovasculitis in people of Uzbek nationality.

**Keywords** rs5186 polymorphism of the AGTR1 gene, Immune microtrombovasculitis (purpura of Shenlein-Genoch), Carriage, Predisposition, People of Uzbek nationality

## 1. Introduction

Studies aimed at studying the pathogenetic mechanisms of immune microtrombovasculitis (IMTV) have proven that the disease is associated with a variety of factors, which allows it to be defined as multifactorial [8,9].

Among the variety of these factors, a special place in the risk of IMTV formation is given to genetic components, which are based on the polymorphism of genes [3].

According to literary data, the genes of the renin-angiotensin system, which play a key role in enhancing pro-inflammatory processes, are important for the development of IMTV [2,10].

It is known that the renin-angiotensin system (RAS), along with the regulation of sodium homeostasis, blood pressure, is also involved in the process of inflammation [1].

Considering that IMTV is a disease characterized by lesions of the blood vessels of the microvasculature and associated with the activation of endothelial cells, then there are opinions that RAS by participating in vascular tone modulation, possibly directly or through various factors, can also affect the vascular structure, in particular endothelin and nitric oxide [6]. Therefore, RAS may be

involved in the pathogenesis of IMTV.

The results of a number of studies have shown that polymorphisms of the PAC genes, in particular angiotensin II receptor 1 (AGT, AGTR1A, AT1R), are involved in the progression of nephropathy and proteinuria in IMTV [4]. It is assumed that polymorphisms of the RAS genes may be associated with the risk of developing IMTV due to their effect on the level of angiotensin [5].

Considering the absence of any convincing evidence "for" or "against" the various proposed hypotheses about the pathogenesis of IMTV, we conducted a study to examine the role of the genetic polymorphism AGTR1 (rs5186) in the development of IMTV in people of Uzbek nationality.

## 2. Main Body

### 2.1. The Purpose of Our Research

To study the role of the polymorphic variant of the AGTR1 gene (rs5186) in the occurrence of immune microthrombovasculitis in people of Uzbek nationality.

### 2.2. Material and Methods of Study

The study included 75 adults aged from 16 to 80 years (the main group) of unrelated Uzbek patients with an established diagnosis of immune microthrombovasculitis (Shenlein-Henoch purpura) according to the modern classification criteria of EULAR, PRINTO and PreS (2010) [7].

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Published online at <http://journal.sapub.org/ajmms>

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Of these, 41 patients were in the midst of a crisis (subgroup “A”) and 34 - in remission (subgroup “B”) of the disease. All patients were observed in the consultative and diagnostic clinic of the Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan in the period from 2017 to 2018. The control group consisted of 73 healthy unrelated persons of Uzbek nationality who had no history of inflammatory, allergic, systemic and renal diseases, matched by gender and age with the examined group of patients.

Detection of AGTR1 polymorphism (rs5186) was performed using SNP-PCR on a programmable thermal cycler from Applied Biosystems 2720 (USA), using test systems from Litex (Russia), according to the manufacturer’s instructions.

Statistical analysis of the results was carried out using the statistical software package "OpenEpi 2009, Version 9.3".

### 2.3. Results of the Study

The results of a molecular genetic study of the polymorphic variant of the AGTR1 gene (rs 5186) showed that the frequency of allele A for conditionally healthy individuals in the control group was 57.5%, for the main group of patients IMTV - 59.3%. The share of allele C for conditionally healthy individuals was 42.3%, and among patients with IMTV in the main group it was 40.7% (Table 1). Differences between groups were statistically insignificant ( $\chi^2 = 0.099$ ;  $p = 0.75$ ; OR = 0.93; 95% CI: 0.5848-1.474). At the same time, the risk of IMTV in individuals in whom the polymorphism of the AGTR1 gene (rs 5186) was detected was less than one.

**Table 1.** The frequency of distribution of alleles and genotypes of the polymorphism of the AGTR1 gene (rs 5186) in the control group and in patients with IMTV

Frequency distribution		Groups			
		Main	“A”	“B”	Control
<i>n:</i>		75	41	34	73
<i>Alleles</i>					
A	abs	89	54	35	84
	%	59.3	65.9	51.5	57.5
C	abs	61	28	33	62
	%	40.7	34.1	48.5	42.3
<i>Genotypes</i>					
A/A	abs	29	20	9	24
	%	38.7	48.8	26.5	32.9
A/C	abs	31	14	17	36
	%	41.3	34.1	50.0	49.3
C/C	abs	15	7	8	13
	%	20.0	17.1	23.5	17.8

According to the data obtained from the study of the AGTR1 gene polymorphism (rs 5186), shown in Table 1, it is obvious that in the main group of patients, in comparison with the control group, a slight increase in the frequency of

the wild A / A genotype was observed (38.7% versus 32.9%) and a decrease in the heterozygous A / C genotype (41.3% versus 49.3%). In both groups studied, the presence of a mutant homozygous C / C genotype was also detected (20.0% versus 17.8%). The frequency distribution of genotypes was statistically insignificant ( $\chi^2 = 0.96$ ;  $df = 2$ ,  $p = 0.62$ ) (table 2).

**Table 2.** The difference in the frequency distribution of alleles and genotypes of the polymorphism of the AGTR1 gene (rs 5186) in the control group and in patients of IMTV

Frequency distribution		Groups		Statistical significance			
		Control	Main				
<i>n:</i>		73	75				
<i>Alleles</i>				$\chi^2$	P	OR	95% CI:
A	abs	84	89	0.099	0.75	0.93	0.5848 - 1.474
	%	57.5	59.3				
C	abs	62	61				
	%	42.3	40.7				
<i>Genotypes</i>				$\chi^2$	df	P	
A/A	abs	24	29	0.96	0.96	0.62	
	%	32.9	38.7				
A/C	abs	36	31				
	%	49.3	41.3				
C/C	abs	13	15				
	%	17.8	20.0				

The absence of statistically significant differences in the carriage of alleles and genotypes of the AGTR1 gene polymorphism (rs 5186) in the studied groups indicates the absence of an associative relationship in the distribution of the studied polymorphism with the risk of UTI.

The results of a comparative analysis of the frequency distribution of alleles and genotypes between the two subgroups of the main group and the control group shows that the proportion of the carrier A allele was 65.9% and 51.5%, and the allele C was 34.1% and 48.5% ( $\chi^2 = 1.521$ ;  $p = 0.2179$ ; OR = 0.7025; 95% CI: 0.4004-1.232) and  $\chi^2 = 0.691$ ;  $p = 0.4058$ ; OR = 1.277; 95% CI: 0.7168-2.276). The proportion of genotypes A/A, A/C and C/C was 48.8% and 26.5%; 34.1 and 50.0; 17.1 and 23.5% ( $\chi^2 = 3.11$ ;  $df = 2$ ,  $p = 0.212$  and  $\chi^2 = 0.6977$ ;  $df = 2$ ,  $p = 0.7055$ ). Analysis of the obtained data indicates the absence of a statistically significant difference in the distribution of alleles and genotypes of polymorphism rs5186 of the AGTR1 gene between the compared groups of patients in the acute stage and in the remission stage of BMI (table 3 and 4).

In the comparison groups on the polymorphism of the AGTR1 gene (rs 5186), the data obtained were also checked for Hardy-Weinberg equilibrium, which showed in the control and main groups that the distribution of the genotypes of the observed frequency and the theoretically expected Hardy-Weinberg equilibrium ( $p > 0.05$ ).

The frequency of the study of the genotype of the polymorphism of the AGTR1 gene (rs 5186) observed in

patients of IMTV and in the control group A/A genotype was detected in 38.7% and 32.9% of cases, while the expected results were 35.2% and 33, 1%, and A/C genotype was observed in 41.3% and 49.3% of cases, while it was expected in 48.26% and 48.86% of cases.

In our studies, the C/C genotype was observed in 20.0% of IMTV patients and 17.8% of patients examined in the control group, and the expected frequency was 16.54% and 18.03%, respectively. The difference of results was not significant ( $\chi^2 = 1.54$ ;  $df = 2$ ;  $p = 0.214$  and  $\chi^2 = 0.01$ ;  $df = 2$ ;  $p = 0.9372$ ).

**Table 3.** The difference in the frequency distribution of alleles and genotypes of the polymorphism of the AGTR1 gene (rs 5186) in the control group and in the "A" subgroup of patients IMTV

Frequency distribution		Groups		Statistical significance			
		Control	“A”				
n:		73	41				
Alleles				$\chi^2$	P	OR	95% CI:
A	abs	84	54	1.521	0.2179	0.7025	0.4004 - 1.232
	%	57.5	65.9				
C	abs	62	28				
	%	42.3	34.1				
Genotypes				$\chi^2$	df	P	
A/A	abs	24	20	3.11	2.0	0.212	
	%	32.9	48.8				
A/C	abs	36	14				
	%	49.3	34.1				
C/C	abs	13	7				
	%	17.8	17.1				

**Table 4.** The difference in the frequency distribution of alleles and genotypes of the polymorphism of the gene AGTR1 (rs 5186) in the control group and in the "B" subgroup of patients IMTV

Frequency distribution		Groups		Statistical significance			
		Control	“B”				
n:		73	34				
Alleles				$\chi^2$	P	OR	95% CI:
A	abs	84	35	0,691	0.4058	1,2777	0.7168 - 2.276
	%	57.5	51.5				
C	abs	62	33				
	%	42.3	48.5				
Genotypes				$\chi^2$	df	P	
A/A	abs	24	9	0,6977	2.0	0.7055	
	%	32.9	26.5				
A/C	abs	36	17				
	%	49.3	50.0				
C/C	abs	13	8				
	%	17.8	23.5				

Thus, in our study, we studied the characteristics of the frequency distribution of alleles and genotypes of the polymorphic variant rs5186 of the AGTR1 gene among patients with BMI and conditionally healthy individuals of Uzbek nationality. An analysis of the results showed the

absence of significant differences in the proportion of carriage of alleles and genotypes between the main group of patients with BMI and the control group, which indicates the absence of the role of rs5186 polymorphism of the AGTR1 gene as an independent genetic marker in the risk of developing BMI in people of Uzbek nationality.

### 3. Conclusions

Immune microtrombovasculitis is a multifactorial disease, in the formation of which an important role is played by genetic factors, which often determine its course [8,9]. The literature contains studies on the role of the genes of the renin-angiotensin system (RAS) in the development and course of IMTV [1,2,9]. The results of these studies suggest that due to the effect on the inflammatory processes in the body, polymorphisms of the ASD genes can be associated with the development of BMI.

This study examined the genetic association between the development of IMTV and the AGTR1 (rs5186) gene polymorphism. The results of our studies showed that in the main group of patients, in comparison with the control group, there was an insignificant decrease in the detection rate of the A/C genotype (41.3% versus 49.3%). In addition, the homozygous C/C genotype was detected in both studied groups (20.0% vs. 17.8%). The distribution of genotype frequencies was statistically insignificant ( $\chi^2 = 0.96$ ;  $df = 2$ ,  $p = 0.62$ ). The obtained results suggest that the carriage of the polymorphic variant of the AGTR1 gene (rs5186) is not associated with the risk of developing immune microthrombovasculitis in people of Uzbek nationality.

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