Global Science Research Journals

Available online at
www.globalscienceresearchjournals.org

Global Journal of Medicine and Medical Sciences

Full Length Research Paper | Open Access

ISSN: 2449-1888, Vol. 7 (7). Pp. 489-493
October, 2019

Study of the role of the rs2010963 polymorphism of the VEGFA gene in the formation of predisposition to immune microthrombovasculitis (Schönlein - Henochpurpura) in persons of Uzbek nationality

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Accepted 11 October, 2019

Abstract

Genetic polymorphism rs2010963 of the VEGF gene has been detected in unrelated patients with immune microthrombovasculitis (Schönlein-Henoch purpura). A significant difference was found in the distribution of the G allele (p = 0.0003) and the C / G genotype (p = 0.0002) of the VEGFA gene (rs2010963) between the main group of patients with immune microthrombovasculitis and the control group. An assessment of the risk of developing the disease showed its association with the G allele (31.3% versus 13.7%; χ2 = 13.14; P = 0.0003; OR = 2.87; 95% CI 1.60-5.16) and the C / G genotype (χ2 = 13.8; P = 0.0002; OR = 3.85; 95% CI 1.86-7.98). Our results show that the polymorphism rs2010963 of the VEGFA gene is associated with the development of immune microthrombovasculitis in people of Uzbek nationality.

Keywords: rs2010963 polymorphism of the VEGFA gene, immune micro-thrombovasculitis (Shönlein-Henochpurpura), carriage, predisposition, persons of Uzbek nationality

INTRODUCTION

Immune microtrombovasculitis (Schönlein-Henochpurpura) is a systemic vasculitis with small vessels (mainly capillaries, venules and arterioles), characterized by deposition of immune complexes containing class A immunoglobulins on the basal membrane [8]. In recent years, there has been a general trend towards an increase in the incidence of immune microtrombovasculitis with an increase in its prevalence among the adult population [3]. Along with this, there is a tendency to chronicity of the process, an increase in patients with severe mixed forms of the disease (abdominal and renal), which occur with severe disorders and terrible complications [1,4,6].

The development and widespread introduction of molecular genetic methods in medicine, has allowed to expand the understanding of the mechanisms of formation of many diseases. Some progress was made in the study of the immune microtrombovasculitis, but many pathogenic mechanisms underlying destruction of the vascular wall in the immune mikrotrombovaskulite still [2,12] have not been fully disclosed.Thus, in the literature there are data from a number of studies showing that different genes can play an important role in the development of a disease [5,7] in interaction with the environment [12]. These data indicate that genetic polymorphisms are one of the important factors in the formation of immune microthrombuscovulitis. Considering that this disease is an immune-dependent pathology, some scientists, based on the results of their research, suggest that vascular endothelial growth factor (VEGFA) being a cytokine with angiogenic activity may be associated with the development of immune microtrombovasculitis [13, 14].The complexity and lack of knowledge of the mechanisms of damage to the vascular

endothelium in immune microthrombovasculitis have determined our goal to study the possible association of the rs2010963 polymorphism of the VEGFA gene with the formation of susceptibility to the immune microtrombovasculitis.

MATERIAL AND METHODS

The study included 75 adults (the main group) of unrelated patients of Uzbek nationality with an established diagnosis of immune microthrombovasculitis according to modern classification criteria of EULAR, PRINTO and PreS (2010) [11]. Of these, 41 patients were in the midst of a crisis (subgroup “A”) and 34 patients were in remission (subgroup “B”) of the disease.The average age of patients was 43.5 ± 3.8 years. All patients were observed at 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.

DNA isolation from leukocytes was performed in accordance with the standard protocol [9]. Detection of rs2010963 polymorphism of the VEGFA gene was carried out 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 package “OpenEpi 2009, Version 9.3”.

RESULTS AND DISCUSSION

Taking into account the data indicating that vascular endothelial growth factor (VEGFA) may be associated with the development of immune microthrombovasculitis, we performed typing of the polymorphism of the VEGFA gene (rs2010963) in the group of patients with immune microthrombus vasculitis and in relatively healthy individuals in the control group (Table1).

Table 1: The frequency distribution of alleles and genotypes of the rs2010963 polymorphism of the VEGFA gene in the groups of patients and controls

Group	N	Allele distribution frequency				Genotype distribution frequency					
		C		G		C/C		C/G		G/G	
		n	%	N	%	n	%	n	%	n	%
The main group, (n = 75) of them:	75	103	68.7	47	31.3	33	44.0	37	49.3	5	6.7
"A" subgroup, (n = 41)	41	56	68.3	26	31.7	17	41.4	22	53.7	2	4.9
"B" subgroup, (n = 34)	34	47	69.1	21	30.9	16	47.1	15	44.1	3	8.8
Control group, (n = 73)	73	126	86.3	20	13.7	55	75.3	16	21.9	2	2.7

During the study, in the main group of patients with respect to the control group, a significant decrease in the carrier status of the favorable allele C was found (68.7% versus 86.3%) and an increase in the percentage of carriers of the unfavorable allele G almost 3 times (31.4% versus 13.7%; $\chi 2 = 13.14$; $p = 0.0003$; OR = 2.875; 95% CI: 1.602– 5.157) (Table 2).

As an inevitable consequence of an increase in the carriage share of the allele G in the main group compared with the control group, there is a decrease in carriers of the C / C genotype and a significant increase in the detection of the heterozygous C / G genotype. Along with this, it should be noted that in the main and control groups, a carrier of the rare G / G genotype was found.

Table 2: Frequency distribution of alleles and genotypes of VEGFA gene polymorphism (rs2010963) in the groups of patients and controls

Polymorphism		Alleles and genotypes	Control group, (n=73)		The main group, (n = 75)		Credibility
			n	%	n	%	
C634G gene VEGFA	Alleles	C	126	86.3	103	68.7	χ^2=13.14; p=0.0003; OR=2.875; 95%CI:1.602-5.157
		G	20	13.7	47	31.3	
	Genotypes	C/C	55	75.3	33	44.0	χ^2=15.1; P=0.0001; OR=0.26; 95% CI 0.13-0.52
		C/G	16	21.9	37	49.3	χ^2=13.8; P=0.0002; OR=3.85; 95%CI 1.86-7.98
		G/G	2	2.7	5	6.7	χ^2=3.11; P=0.08; OR=4.17; 95%CI 0.76-22.7

The decrease in the proportion of carriers of the C / C genotype in the main group of patients (44.0% versus 75.3%; χ2 = 15.1; P = 0.0001; OR = 0.26; 95% CI 0.13-0.52) indirectly indicates the protective role of homozygous C / C genotype in the pathogenesis of immune microthrombovasculitis.

Amid a decrease in the carriage of the protective homozygous C/C genotype (p = 0.0001), the proportion of carriers of the heterozygous C / G genotype in patients in the main group was significantly higher (49.3% versus 21.9%; χ2 = 13.8; P = 0.0002; OR = 3.85; 95 % CI 1.86-7.98), which clearly indicates the presence of a significant association between the heterozygous C / G genotype of the rs2010963 polymorphism of the VEGFA gene with the development of an immune microthrombovasculitis.

The carrier of the functionally unfavorable homozygous genotype G / G (χ2 = 3.11; P = 0.08; OR = 4.17; 95% CI 0.76-22.7), according to the calculated odds ratio, 4.17 times statistically insignificantly increases the risk of developing immune microthrombovasculitis.

Approximately the same features were observed in the "A" and "B" subgroups of patients. Thus, in the “A” subgroup, compared with the control group, the share of allele C was lower (68.3% versus 86.3%), whereas the G allele exceeded 2.9 times (31.3% versus 13.7%; χ2 = 10.57; p = 0.001; OR = 2.925; 95% CI: 1.508-5.673). In the “B” subgroup, the frequency of the favorable allele C (69.1% versus 86.3%) was lower, and the negative G allele was higher than the control by 2, 8 times (30.9% versus 13.7%; χ2 = 8.8; p = 0.003; OR = 2.8; 95% CI: 1.401-5.657). The revealed facts indicate the association of the G allele with a high risk of developing immune microthrombovasculitis.

Together with the indicated peculiarities in the frequency distribution of alleles C and G, the corresponding changes were also established in relation to the frequencies of genotypes of the VEGFA gene polymorphism (rs2010963). It should be noted that in both subgroups of patients, there was a carrier of all three variants of genotypes, including the rare mutant genotype G / G. In accordance with the increase in the G carrier allele among patients of both subgroups, there was a significant decrease in carriers of the C / C genotype (41.4% versus 75.3% and 47.1% versus 75.3%), and an increase in the proportion of the C / G genotype (53.7% versus 21.9%; χ2 = 12.8; P = 0.0003; OR = 4.45; 95% CI: 1.91-10.3 and 44.1% vs. 21.9%; χ2 = 6.82; P = 0.009; OR = 3.22; 95% CI: 1.31-7.91) and also the genotype G / G (4.9% vs. 2.7%; χ2 = 1.41; P = 0.23; OR = 3.24; 95% CI: 0.42-24.7 and 8.8% against 2.7%; χ2 = 3.5; P = 0.06; OR = 5.16; 95% CI: 0.79-33.6).

The above data, namely, a significant reduction in the frequency of carriers of the C / C genotype in the main group of patients and in both subgroups "A" and "B" indicate its protective role in the pathogenesis of damage to the endothelium of microvessels in immune microthrombovasculitis disease. While a significant increase in the proportion of carriers of the heterozygous C / G genotype and the mutant G / G genotype, at the expense of patients in both subgroups, it is convincingly indicative of the high association of VEGFA gene polymorphism (rs2010963) with the development of immune microtrombovasculitis.

It should be noted that the identified frequency (Hobs) of the distribution of VEGFA polymorphism genotypes (rs2010963) in the main group of patients and in the control group of donors corresponded to the expected distribution (Hexp) according to the Hardy-Weinberg equation (P> 0.05).

In order to determine the effectiveness of this genetic marker, we calculated the sensitivity (SE), specificity (SP),

and the probability index of the patient being distinguished from healthy polymorphism rs2010963 of the VEGFA AUC gene (Area Under Curve). The predictive value was determined as follows: markers were considered as a random classifier if AUS <0.5, poor <0.5 AUS <0.6, average 0.6 <AUS <0.7, good 0.7 <AUS <0.8 and excellent AUS> 0.8. Determination of the prognostic value of the C / G heterozygous genotype (AUS = 0.65 in the main group, AUS = 0.67 in the A group, and AUS = 0.63 in the B group) showed that it acts as a marker of the average classifier in the formation of an immune microtrombovasculitis.

Thus, the results of a comparative analysis of the frequency and proportion of the carrier of the polymorphism of the VEGFA gene (rs2010963) in the main group relative to the control group of conditionally healthy individuals convincingly prove its involvement in the pathogenesis of the development of immune microthrombovasculitis.

CONCLUSION

Immune microtrombovasculitis is a multifactorial disease, in the formation of which an important role is given to genetic factors that often determine its course [7]. The literature contains studies on the role of the vascular endothelial growth factor (VEGFA) gene in the pathogenesis of immune microtrombovasculitis [10,14, 15].

In this study, the genetic association between the development of immune microtrombovasculitis and the polymorphism of the VEGFA gene (rs2010963) was studied. The results of our studies showed that the frequency of occurrence of the heterozygous C / G genotype of the VEGFA gene (rs2010963) in the group of patients with immune microthrombovasculitis (49.3%) is significantly higher in comparison with the control group (21.9%). The results suggest that the functionally unfavorable allele G and the heterozygous genotype C / G of the rs2010963 polymorphism of the VEGFA gene are significant markers of an increased risk of the formation of immune microtrombovasculitis in people of Uzbek nationality.

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How to cite this paper::

D.S. Matkarimova (2019). Study of the role of the rs2010963 polymorphism of the VEGFA gene in the formation of predisposition to immune microthrombovasculitis (Schönlein -Henochpurpura) in persons of Uzbek nationality. Glob. J. Med. Med. Sci. 7(7). Pp. 483-485 http://www.globalscienceresearchjournals.org/gjmms/