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Original Article:

Association of IL–10 and F2 and F5 Blood Clotting Factors Genes Polymorphisms with Pre-Eclampsia Risk

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Abstract: Background: The article presents the influence evaluation results of the anti-inflammatory cytokine — IL10 and blood clotting factors - F2 and F5 genes polymorphism on the formation of hereditary predisposition to the development of preeclampsia in women of the Rostov region. Patients and methods: In this case-control setting, we included 101 pregnant women at 24 to 36 weeks of gestation, who were divided into two groups: the group of women with preeclampsia and the control group. All women were tested for mutations of interleukin–10 gene (IL-10), the blood coagulation factors F2 and F5 genes. Results: During the analysis of the IL-10 -592A>C (rs1800872) and -819T>C (rs3021097); F2 20210G-A (rs1799963) and F5 1691G-A (rs6025) polymorphisms contribution to genetic predisposition to preeclampsia, it was detected that carriers of the homozygous genotype of the IL-10 -592A>C polymorphic locus have an increased risk of developing this complication of pregnancy (OR=3,39; 95%CI 1.13–10.22), however, no statistically significant differences were found for the other studied loci. Conclusion: The current study results inconsistent with previous studies; showed that the IL-10 -592A>C polymorphism, but not IL-10 -819T>C, F2 20210G-A and F5 1691G-A polymorphisms, may be contributed to the susceptibility of preeclampsia in Rostov population.
Key Words: Preeclampsia, polymorphism of gene, F2, F5, blood clotting factor, IL-10, anti-inflammatory cytokine

Introduction:
Preeclampsia (PE) is a pregnancy complication characterized by the presence of hypertension and proteinuria and is a leading cause of maternal and perinatal morbidity and mortality.(1) Hypertensive disorders of pregnancy, which include PE, affect about 10% of all pregnant women around the world.(2) Opinions on the etiology and pathogenesis of PE are diverse, and sometimes completely opposite, which is the main reason initiating the search for new markers predicting the development of this pathology. Numerous studies have shown a significant contribution of the hereditary component to the structure of predisposition to PE, the proportion of which varies in different ethnic groups. More than 100 candidate genes are known to form the genetic risk of PE, among which the genes of anti-inflammatory cytokines and the genes of blood clotting factors are.(3, 4)
Interleukin–10 (IL-10) is an anti-inflammatory cytokine, which plasma levels are believed to decrease in patients with PE. It was indicated that the IL-10 -592A>C (rs1800872) and -819T>C (rs3021097) polymorphisms were associated with preeclampsia.(5) On the contrary, it was suggested that the IL-10 -592A>C and -819T>C polymorphisms are unlikely to be important in susceptibility to pre-eclampsia.(6)
Blood coagulation system disorders are common complications in PE. Most authors note that the blood coagulation factors F2 (rs1799963) and F5 (rs6025) genes polymorphisms lead to thrombosis, violate trophoblast invasion and transform uteroplacental blood flow into a system with high peripheral resistance, resulting in the development of PE.(7) However, in some populations no difference was found in the prevalence of the genetic risk factors for thrombosis in women with PE compared with control subjects.(8,9)
Thus the aim of this study was to investigate whether IL-10 and F2 and F5 blood clotting factors genes polymorphisms are associated with susceptibility to PE in a group of women from Rostov region.

Materials and Methods
In this case-control setting, we included 101 pregnant women from Rostov region at 24 to 36 weeks of gestation, who were divided into two groups: the group of women with preeclampsia and the control group. Criteria for the PE diagnosis confirmation were presence of arterial hypertension

after the 20th week of pregnancy (systolic blood pressure ≥140 mm Hg) and clinically significant proteinuria (protein presence in urine ≥0.3 g/l in a daily sample or in two samples taken at 6 hours intervals). The control group consisted of women without preeclampsia symptoms. All subjects participating in this study gave their written informed consent, and the protocol was approved by the ethics committee of the Academy of biology and biotechnology.

Genomic DNA was isolated from peripheral blood samples using a "Proba-Rapid-Genetika" kit ("DNA-Technology", LLC, Russia) following manufacturer's protocol. The IL-10 -592A>C (rs1800872) and -819T>C (rs3021097) genotypes were determined using a "Reagents kit for genetic polymorphisms detection by real-time PCR method" ("DNA-Technology", LLC, Russia) using DTlite Real-Time PCR System ("DNA-Technology", LLC, Russia) following manufacturer's protocol. The F2 20210G-A (rs1799963) and F5 1691G-A (rs6025) genotypes were determined using a "Kardio Genetika Thrombophilia" ("DNA-Technology", LLC, Russia) using DTlite Real-Time PCR System ("DNA-Technology", LLC, Russia) following manufacturer's protocol.

Statistical analysis: Both groups were tested for Hardy-Weinberg equilibrium using the Hardy–Weinberg equilibrium calculator (www.oege.org/software/Hardy-Weinberg). Odd ratios (OR) and 95% confidence intervals (95%CI) were calculated using online calculator for calculating statistics in case-control studies (http://gen-exp.ru/calculator_or.php). $P < 0.05$ was considered statistically significant. The multifactor dimensionality reduction (MDR) open-source software package (http://www.multifactordimensionalityreduction.org/) was used to explore gene–gene interactions.

Results and Discussion

The results of the study of IL10 gene -592A>C polymorphic variant alleles and genotypes frequencies are presented in Table 1. The distribution of genotypes and alleles frequencies of the studied polymorphism in both groups of women corresponds to the Hardy–Weinberg equilibrium.

Table 1: IL10 gene -592A>C polymorphic variant alleles and genotypes frequencies (abs. (%)) in women with pre-eclampsia

Allele/genotype	Preeclampsia n=53	Control n=48	X^2	*p* value	OR	95% CI
IL10 -592A>C						
A-592	**0.491**	**0.323**	5,85	**0.02**	**2,02**	**1.14 – 3.58**
-592C	0.509	0.677			0,5	0.28 – 0.88
AA-592	**15 (28.3)**	**5 (10.4)**	5,22	**0.02**	**3,39**	**1.13 – 10.22**
A-592C	22 (41.5)	21 (43.8)			0,91	0.41 – 2.01
-592CC	16 (30.2)	22 (45.8)			0,51	0.23 – 1.16

Among women with preeclampsia, the proportion of homozygotes for allele A-592 of IL10 gene was increased 3 times. The 3.4 times relative risk of increase of preeclampsia development was revealed for women with this genotype. The distribution of genotype frequencies among women with preeclampsia was statistically significantly different from that in the control group. The frequency of allele A-592 among women with preeclampsia was 0.49, which is statistically significantly higher compared to the control group of women. The level of interleukin-10 production is increased in presence of -592C variant, what leads to a deterioration of the organism response to pathogenic invasions and increased production of antibodies, including immunoglobulin E. The presence of -592C allele causes a reduced organism resistance to pathogens and an increase in the risk of atopic dermatitis, but has protective properties against atherosclerosis, myocardial infarction and premature fetal loss syndrome.(10) In our study -592C allele likely plays the protective role against preeclampsia.

The results of the study of IL10 gene -819T>C polymorphic variant alleles and genotypes frequencies are presented in Table 2. The distribution of genotypes and alleles frequencies of the studied polymorphism in both groups of women corresponds to the Hardy–Weinberg equilibrium.

Table 2: IL10 gene -819T>C polymorphic variant alleles and genotypes frequencies (abs. (%)) in women with pre-eclampsia

Allele/ genotype	Preeclampsia n=59	Control n=48	X^2	*p* value	OR	95% CI
IL10 -819T>C						
T-819	0.703	0.729	0.17	0.68	0.88	0.48 – 1.60
-819C	0.297	0.271			1.14	0.62 – 2.07
TT-819	29 (49.2)	24 (50.0)	0.83	0.66	0.97	0.45 – 2.07
T-819C	25 (42.4)	22 (45.8)			0.87	0.40 – 1.87
-819CC	5 (8.5)	2 (4.2)			2.13	0.39 – 11.50

The frequency of allele T-819 prevails in both groups of women. Among women with preeclampsia, the distribution of IL10 gene 819T>C polymorphism genotype and allele frequencies corresponds to the control group. There were no statistically significant differences between the two groups of women.

The results of the study of F2 gene polymorphic variant 20210G-A alleles and genotypes frequencies are presented in Table 3. The distribution of genotypes and alleles frequencies of the studied polymorphism in both groups of women corresponds to the Hardy–Weinberg equilibrium.

Table 3: F2 gene polymorphic variant 20210G-A alleles and genotypes frequencies (abs. (%)) in women with pre-eclampsia

Allele/ genotype	Preeclampsia n=53	Control n=48	X^2	*p* value	OR	95% CI
F2 20210G-A						
G-20210	0.991	0.979	0.45	0.5	2.23	0.20 – 25.04
20210A	0.009	0.021			0.45	0.04 – 5.02
GG-20210	52 (0.981)	46 (0.958)	0.45	0.8	2.26	0.20 – 25.76
G-20210A	1 (0.019)	2 (0.042)			0.44	0.04 – 5.04
20210AA	0 (0)	0 (0)			0.91	0.02 – 46.58

The frequency of allele G-20210 prevails in both groups of women. Among women with preeclampsia, the distribution of F2 gene 20210G-A polymorphism genotype and allele frequencies corresponds to the control group. There were no statistically significant differences between the two groups of women.

The results of the study of F5 gene polymorphic variant 1691G-A alleles and genotypes frequencies are presented in Table 4. The distribution of genotypes and alleles frequencies of the studied polymorphism in both groups of women corresponds to the Hardy–Weinberg equilibrium.

Table 4: F5 gene polymorphic variant 1691G-A alleles and genotypes frequencies (abs. (%)) in women with pre-eclampsia

Allele/genotype	Preeclampsia	Control	X^2	*p* value	OR	95% CI
	n=53	n=48				
F5 1691G-A						
G-1691	0.962	1.000	3.7	0.05	0.12	0.01 – 2.22
1691-A	0.038	0.000			8.47	0.45 – 159.48
GG-1691	50 (94.3)	48 (100)	2.8	0.25	0.15	0.01 – 2.96
G-1691A	2 (3.8)	0 (0)			4.71	0.22 – 100.59
1691AA	1 (1.9)	0 (0)			2.77	0.11 – 69.67

The frequency of allele G-1691 prevails in both groups of women. Among women with preeclampsia, the distribution of F5 gene 1691G-A polymorphism genotype and allele frequencies corresponds to the control group. There were no statistically significant differences between the two groups of women.

Multifactor-dimensionality reduction reveals no statistically significant interactions among studied genes in preeclampsia.

Conclusion:

The current study results inconsistent with previous studies; showed that the IL-10 -592A>C polymorphism, but not IL-10 -819T>C, F2 20210G-A and F5 1691G-A polymorphisms, may be contributed to the susceptibility of preeclampsia in Rostov population. The -592C allele likely plays the protective role against preeclampsia. The associations for women of the Rostov region identified in this study can be used as genetic markers of predisposition to the formation of preeclampsia, which will allow to form a risk group in a timely manner and to adjust therapeutic and preventive measures.

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Conflict of Interest: None.

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