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Role of Genetic Markers of Disorder Plate Line of Hemostasis (ITGB3 and ITGA2) in Pathogenesis Ischemic Stroke

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Abstract: ***In the course of the study, in 35 patients with ischemic stroke, the associative relationship of the Leu33Pro polymorphism in the integrin beta3 gene (ITGB3) and the polymorphic marker C807T in the integrin alpha-2 gene (ITGA2) in the formation of IS was analyzed. During the study in patients with IS, a significant relationship was established between the risk of developing this pathology and the distribution of predisposing / protective variants of the ITGB3 and ITGA2 polymorphism genotypes. In the studied groups, the actual distribution of genotypes polymorphism Leu33Pro in the gene for integrin beta-3 (ITGB3) and C807T in the gene for integrin alpha-2 (ITGA2) corresponded to those expected at Hardy-Weinberg equilibrium (RHB) (p <0.05).***

Keywords: ischemic stroke, Leu33Pro ITGB3 genetic polymorphism, C807T marker in the integrin alpha-2 gene (ITGA2).

1. Relevance

In recent years, there has been an increase in the proportion of ischemic strokes (IS) among young people - about 20% of all strokes [1, 6, 13]. The incidence, according to various sources, varies from 3 to 23 per 100,000 people [3]. As a provocateur in these situations, hereditary thrombophilia can most often be considered, since in some patients the examination reveals occlusion of cerebral arteries due to intravascular thrombosis [2, 11, 10]. Thrombophilia is defined as a violation of hemostasis and hemorheology, characterized by an increased tendency to develop thrombosis or intravascular coagulation, which is based on acquired and genetically determined disorders in various links of hemostasis and hemorheology [8, 9, 5]. Among the factors that increase the risk of thrombosis, platelet receptor genes are very important. In this case, the analysis of the genetic marker of the platelet receptor gene for collagen (ITGA2 807C> T) and fibrinogen (ITGB31565T> C) is carried out. With a defect in the receptor gene for collagen, the adhesion of platelets to the vascular endothelium and to each other increases, which leads to increased thrombus formation. When analyzing the genetic marker ITGB31565T> C, it is possible to reveal the effectiveness or ineffectiveness of antiplatelet therapy with aspirin. With disorders caused by mutations in these genes, the risk of thrombosis, myocardial infarction, ischemic stroke increases [12, 7]. When analyzing the genetic marker ITGB31565T> C, it is possible to reveal the efficacy or ineffectiveness of antiplatelet therapy with aspirin. With disorders caused by mutations in these genes, the risk of thrombosis, myocardial infarction, ischemic stroke increases [12, 7]. When analyzing the genetic marker ITGB31565T> C, it is possible to reveal the efficacy or ineffectiveness of antiplatelet therapy with aspirin. With disorders caused by mutations in these genes, the risk of thrombosis, myocardial infarction, ischemic stroke increases [12, 7].

Ability to regularly identify hereditary genetic a predisposition to thrombosis (polymorphism associated with mutations or disease) can significantly contribute to early diagnosis and enable early intervention and prevention of thrombotic incidents [4, 14].

2. Material and Research Methods

During the genetic study, we examined 35 patients with IS who were in the neurological department of the clinic of the Andijan State Medical Institute. The diagnosis of IS was carried out in accordance with the currently accepted clinical guidelines. Isolation of the DNA molecule from peripheral blood was performed using the Ampli Prime RIBO_prep kit. Genotyping of the Leu33Pro ITGB3 polymorphism and the rs1126643 polymorphic locus of the ITGA2 gene was performed on based on the method of Tag Man-probes on the Rotor-Gene Q amplifier (Quagen, Germany), using a commercial test kit of OOO Litekh (Russia).

Statistical processing of the results was performed using the standard OpenEpi V.9.2 software package. Analysis of the deviation of the empirical frequencies of genotypes from the theoretically expected Hardy – Weinberg distribution was carried out using the Statistical 6.0 software package.

The purpose research is, study of the frequency of distribution and assessment of the relationship of polymorphism Leu33Pro in the gene integrin beta-3 (ITGB3) and polymorphic locus rs1126643 of the ITGA2 gene in patients with IS.

3. Results Obtained and their Discussion

The frequencies of both alleles and genotypes of Leu33Pro ITGB3 and C807T ITGA2 are presented as absolute numbers and percentages. Accordingly, the differences

between the groups were assessed using the χ test2. Moreover, to quantify the effect of each option on disease risk, univariate odds ratios (OR) were calculated with corresponding 95% confidence intervals (95% CI).

During the study, in patients in the subgroup with IS and in the control group, the proportion of the wild Leu allele and the unfavorable Pro allele in the integrin beta-3 gene (ITGB3) was 88.6% and 11.4% versus 95.6% and 4.4%, respectively. Statistical processing revealed a significant decrease in the frequency of the favorable Leu allele in the study group of patients (88.6% versus 95.6% in the control group with $\chi2$ =4.5; P = 0.03; OR = 0.3; 95% CI: 0.13 - 0.96). (Table 1). In the presence of this allele, the risk of developing IS is absent; accordingly, the presence of the wild Leu allele indicates a possible protective effect against the formation of IS. A significant increase in the dominant, mutant Pro allele was revealed in patients with IS compared to conventionally healthy donors (11.4% versus 4.4%). The calculated odds ratio showed that the chance of detecting a functional of the unfavorable Pro allele in the respondents with IS increased 2.8 times as compared to the control group ($\chi2$ =4.5; P = 0.03; OR = 2.8; 95% CI: 1.05-7.63). (Table 1).

Table 1: Association between Leu33Pro polymorphism in the integrin beta-3 gene (ITGB3) in patient and control groups

The investigated group	Alleles and genotypes	Statistical difference in relation to the control group					
		Relative risk		Odds ratio		$\chi2$	p-value
		RR	95% CI:	OR	95% CI:		
Ischemic stroke (n = 35)	Leu	0.51	0.29 - 0.88	0.3	0.13 - 0.96	4.5	0.03 *
	Pro	1.97	1.14 - 3.40	2.8	1.05 - 7.63		
	Leu / Leu	0.52	0.28 - 1.0	0.4	0.13 - 1.12	3.2	0.07 *
	Leu / Pro	1.74	0.87 - 3.51	2.2	0.73 - 6.83	2.1	0.1
	Pro / Pro	4.36	3.15 - 6.03	* * * *	* * * *	3.3	0.07 *

Frequencies Leu / Leu, Leu / Pro, Pro / Pro genotypes Leu33Pro in the integrin beta-3 gene (ITGB3) in the studied groups of patients with IS and controls were: 80.0%, 17.1% and 2.9% versus 91.3%, 8.7% and 0.0%, respectively. As can be seen, the frequency of the wild genotype Leu / Leu and the mutant marker Pro / Pro among patients with IS were insignificant than in the control group ($\chi2$ =3.2; P = 0.07; OR = 0.4; 95% CI: 0.13–1.12 and $\chi2$ =3.3; P = 0.07). There was a tendency to an increase in the number of the heterozygous Leu / Pro genotype in patients with IS (17.1% versus 8.7% with $\chi2$ =2.1; P = 0.1; OR = 2.2; 95% CI: 0.73 - 6.83). (Table 1). The calculated relative risk of developing IS in the presence of an unfavorable marker Leu / Pro increases 2.2 times.

In patients with IS, as can be seen from Table 2, in the studied groups of patients and controls, the proportion of C and T alleles rs1126643 of the ITGA2 gene was 55.7% and 44.3% versus 70.9% and 29.1%, respectively. The calculated odds ratio showed that the chance of detecting a functional unfavorable allele T rs1126643 of the ITGA2 gene in respondents with IS significantly increased (1.9 times more) compared with representatives of the control group ($\chi2$ =5.4; p = 0.02; OR = 1.9; 95% CI 1.11-3.38). (Table 2).

Table 2: Association between C807T polymorphism in the integrin alpha-2 gene (ITGA2) in patient and control groups

The investigated group	Alleles and genotypes	Statistical difference in relation to the control group				$\chi2$	p-value
		Relative risk		Odds ratio			
		RR	95% CI:	OR	95% CI:		
Ischemic stroke	C	0.62	0.42 - 0.92	0.5	0.30 - 0.90	5.4	0.02 *
	T	1.62	1.08 - 2.41	1.9	1.11 - 3.38		
(n = 35)	C / C	0.62	0.34 - 1.15	0.5	0.24 - 1.18	2.4	0.1
	C / T	1.33	0.68 - 2.61	1.4	0.61 - 3.42	0.7	0.4
	T / T	2.63	1.29 - 5.32	4.2	1.33 - 13.62	6.5	0.01 *

Frequencies C807C, C807T, T807T of genotypes rs1126643 gene ITGA2 in the studied subgroup of patients with IS and controls were: 34.3%, 42.9% and 22.9% versus 49.5%, 42.7% and 7.8%, respectively. As can be seen, the frequency of the ancestral genotype C807C among patients with IS was also slightly lower than in the control group ($\chi2$ =2.4; p = 0.1; OR = 0.5; 95% CI 0.24-1.18). A significant increase (4.2 times) in the number of unfavorable homozygous T807T genotype in patients with IS compared with the control group was revealed - 22.9% versus 7.8%, respectively ($\chi2$ = 6.5; p = 0.01; OR = 4.2; 95% CI 1.33-13.62; RR = 2.6; 95% CI 1.29-5.32). (Table 2). This can be considered as a predictive marker of an increased risk of developing IS. **Conclusion.** Thus, the analyzed data of the study showed that the presence of the wild Leu allele indicates a possible protective effect in relation to the formation of IS. When an unfavorable Pro allele is identified in respondents with IS, the risk of developing this pathology increases sharply by 2.8 times. And also when a heterozygous Leu / Pro genotype was detected in the main group, the risk of developing IS was low.

The study revealed that in patients with IS, the frequency of the unfavorable T allele and the mutant T / T marker of the rs1126643 polymorphic locus of the ITGA2 gene were significant compared to the control. This indicates that in the presence of the above allele and genotype, the risk of developing this disease increases sharply.

Thus, we can conclude that unfavorable genotypic variants of Leu33Pro polymorphism in the gene integrin beta-3 (ITGB3) and polymorphic locus rs1126643 of the ITGA2 gene may play a role in the development of thromboembolic diseases like IS.

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