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FREQUENCIES OF CYP2C9 AND VKORC1 GENE'S VARIANTS IN STROKE PATIENTS OF ASIAN AND CAUCASIAN RACES IN YAKUTIA

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Abstract

The frequencies of allelic and genotypes variants of polymorphisms *CYP2C9* *1 (wild-type), *CYP2C9* *2 (rs1799853), *CYP2C9* *3 (rs1057910) of *CYP2C9* gene; polymorphism -1639G> A of *VKORC1* gene (rs9923231) were studied among stroke patients requiring the prolonged warfarin anticoagulation (n=117) in different racial groups of Yakutia. It was found that the frequency of AA genotype of polymorphism -1639G> A *VKORC1* gene (rs9923231) is higher among Asians compared to the Caucasians. The frequency of investigated *CYP2C9* alleles and genotypes had no significant differences between two racial groups. These findings may have practical value for optimization of warfarin therapy for stoke prevention taking into account racial and pharmacogenetic characteristics.

Key words. *CYP2C9* gene, *VKORC1* gene, polymorphisms, warfarin, pharmacogenetics, atrial fibrillation, stroke

Introduction.

Anticoagulant therapy has been prescribed widely for prevention of stroke and other thromboembolic events in patients with atrial fibrillation and prosthetic heart valves. Warfarin is most common used oral anticoagulant medication. There are racial features in warfarin requiring dosage. For example, it was found that a lower dose of warfarin required for Asians compared to Caucasians [7].

The carriage of certain polymorphisms of *CYP2C9* and *VKORC1* genes mainly determines the individual sensitivity to warfarin [7, 9, 12]. *CYP2C9* is the cytochrome P-450 gene, and *VKORC1* is vitamin K epoxide reductase subunit 1 gene. Polymorphisms *CYP2C9* *2 and *CYP2C9* *3 are associated with the warfarin metabolism's reducing and lower dose requirement compared to most common polymorphism *CYP2C9* *1 [9]. Polymorphism −1639G>A in the *VKORC1* gene was shown to affect the warfarin sensitivity. Carriers with genotypes −1639GG and −1639GA required higher warfarin doses compared to carriers with −1639AA genotype [19].

There are the features in frequencies of *CYP2C9* and *VKORC1* variants between racial groups that determine the different requiring warfarin dosage [1, 7, 9, 11, 13, 14, 17]. Furthermore, the allelic frequent's differences exists among ethnic groups within the same racial group [4, 9, 10]. Thus, the investigation of the frequencies of genetic variants determining warfarin sensitivity in different racial and ethnic groups is very actual task for the optimization of requiring dosage especially in initiation therapy period. The population of Yakutia consists mainly with two racial groups: Caucasians and Asians. The *CYP2C9* and *VKORC1* allelic frequency not been studied clearly in Yakutia's population.

Purpose. To evaluate the allelic and genotype's frequencies of *CYP2C9* and *VKORC1* polymorphisms among stroke patients in different racial groups of Yakutia.

Materials and Methods. It was provided the study in the group of 117 patients hospitalized in the Regional Vascular Center in 2012–2014. All patients had got acute ischemic stroke due to the atrial fibrillation and were required the prolonged warfarin anticoagulation. The studied group included two racial groups: Asians (1^{st} group) and Caucasians (2^{nd} group). 1^{st} group consist of the patients belonging to indigenous ethnicity (Yakut, Even, Evenk); 2^{nd} group consist of patients belonging to Russians, Ukrainian, Byelorussians, Pole. Ethnicity was self-reported.

It was conducted molecular genetic study for carriage of polymorphisms *CYP2C9* *1 (wild-type), *CYP2C9* *2 (rs1799853), *CYP2C9* *3 (rs 1057910) of *CYP2C9* gene; polymorphism -1639G> A of *VKORC1* gene (rs9923231). A genetic study was conducted in Genomic scientific laboratory of NEFU Medical Institute (Yakutsk). DNA extraction was performed using a set ExtraGene (Germany) and phenol-chloroform method. Genetic typing of *CYP2C9* *2 (rs1799853), *CYP2C9* *3 (rs1057910) and *VKORC1* -1639G> A (rs9923231) conducted with PCR kits SPC "Liteh" (Moscow). The patient's informed consents for genetic research were given in every case.

Statistical analysis was performed using software packages STATISTICA 8. Study of the interrelationship between the pairs of discrete qualitative characteristics was performed using the paired analysis of conjugation tables. In addition to Fisher's exact test the strength of evaluations analyzed associations was described using relative risk values (OR) and 95 % confidence intervals (CI).

Results. The study group (n = 117) included 70 males (59.8 %). Mean age was 67.3 years (min – 34; max – 80). According to the ethnicity patients were distributed as follows: indigenous ethnicity of Asian race – n = 61 (52.1 %) (1^{st} group), Caucasians – n = 56 (47.8 %) (2^{nd} group). The results of the comparative analysis of the *CYP2C9* and *VKORC1* allelic and genotype's frequencies between racial groups are presented in the Table.

Table: *CYP2C9* and *VKORC*1 allelic and genotype's frequencies depending on race.

	Asians (n=61)	Caucasians (n=56)	*p**	OR (95% CI) for significant values
polymorphism ***CYP2C9***				
allele's carriers (n, %)				
*1	60 (98.3)	52 (92.8)	0.192	
*2	7 (11.4)	13 (23.2)	0.139	
*3	15 (24.6)	19 (33.9)	0.311	
genotype's carriers (n, %)				
*1/*1	40 (65.6)	28 (50)	0.096	
*1/*2	6 (9.8)	9 (16.1)	0.409	
*1/*3	14 (22.9)	15 (26.8)	0.673	
*2/*3	1 (1.6)	4 (7.1)	0.92	
polymorphism -1639G> A ***VKORC1***				
allele's carriers (n, %)				
G	17 (27.9)	48 (85.7)	< 0.0001	0.064 (0.022 – 0.178)
A	58 (95.1)	50 (89.2)	0.308	
genotype's carriers (n, %)				
GG	3 (4.9)	6 (10.7)	0.308	
GA	14 (22.9)	42 (75)	< 0.0001	0.099 (0.038 – 0.251)
AA	44 (72.1)	8 (14.3)	< 0.0001	15.529 (5.610 – 44.586)

* Fisher's exact test

In the 1st group (n = 61) there were 60 carriers with allele *CYP2C9* *1 (98.3 %), 7 carriers with allele *CYP2C9* *2 (11.4 %), 15 carriers with allele *CYP2C9* *3 (24.6 %).

In the 2nd group (n = 56) there were 52 carriers (92.8 %), 13 carriers (23.2 %) and 19 carriers (33.9 %) with alleles *CYP2C9* *1, *CYP2C9* * 2, *CYP2C9* *3, respectively.

No significant differences in number of *CYP2C9* *1, *CYP2C9* *2, *CYP2C9* *3 allelic carriers were found between the two studied groups (p = 0.192; p = 0.139; p = 0.311, respectively).

The number of carriers with 1/1 *CYP2C9* genotype was n = 40 (65.6 %) in 1st group, and n = 28 (50 %) in 2nd group (p = 0.096). The number of carriers with 1/2 *CYP2C9* genotype was n = 6 (9.8 %) in 1st group, n = 9 (16.1 %) in 2nd group and this differences were not significant (p = 0.409). The number of carriers with 1/3 *CYP2C9* genotype was n = 14 (22.9 %) in 1st group, while among Caucasians – 15 (26.8 %) (p = 0.673). The number of carriers with 2/3 *CYP2C9* genotype was n = 1 (1.6 %) in 1st group, in 2nd group – n = 4 (7.1 %) (p = 0.192). There were no carriers

with 2/2 *CYP2C9* genotype and with 3/3 *CYP2C9* genotype in both groups. Thus, there were no significant differences in number of allelic carriers of *CYP2C9* gene between the Asian and Caucasian groups, as well as in genotype's frequencies of this gene.

Number of carriers with allele G of the polymorphism -1639G> A *VKORC1* gene (rs9923231) consisted n = 17 (27.9 %) in 1st group, while in the 2nd group – n = 48 (85.7 %). Differences in number of carriers with this allele between the groups were significant ($p < 0.0001$; OR = 0.064; 95 % CI: 0.022 - 0.178).

Number of carriers with allele A of this polymorphism in 1st group was n = 58 (95.1 %), in 2nd group was n = 50 (89.2 %). Differences in this allelic frequency between the groups were not significant ($p = 0.308$).

Number of GG genotype's carriers was n = 3 (4.9 %) in 1st group, and n = 6 (10.7 %) in 2nd group ($p = 0.308$). The analysis of GA and AA genotype's frequencies established significant differences between groups. Thus, the account of carriers with GA genotype was n = 14 (22.9 %) in 1st group, while one was n = 42 (75 %) in 2nd group ($p < 0.0001$; OR = 0.099; 95 % CI: 0.038 - 0.251). The number of carriers with AA genotype was n = 44 (72.1 %) in 1st group, while one was n = 8 (14.3 %) in 2nd group ($p < 0.0001$; OR = 15.529; 95 % CI: 5.610 - 44.586).

Discussion. This study was performed for the investigation of allelic and genotype's frequencies of *CYP2C9* and *VKORC1* polymorphisms in the two racial groups in Yakutia. The study was conducted in the group of patients with acute stroke needed for further long-term anticoagulant therapy for secondary prevention of stroke. This study has practical importance because of the fact that the account of persons permanently receiving anticoagulant therapy to prevent trombembolic events in the population is growing rapidly. On the other hand, the distribution of gene's polymorphisms affecting the susceptibility to the most commonly used anticoagulant warfarin in Yakutia's population understood poorly. Previously, it was conducted a pilot study of the ethnic characteristics of the distribution of *CYP2C9* and *VKORC1* gene's polymorphisms in the group of cardioembolic stroke patients among Asian indigenous ethnicity and Caucasians in Yakutia [2]. Features of *CYP2C9* genotype's distribution were investigated in the children with epilepsy among Yakut and Tuva ethnic groups in comparison with Russians. It was determined that the *CYP2C9* *1 / *1 genotype predominated among Yakuts (88.9 %) and Tuvinians (81.5 %) compared with Russians (65.0 %). Heterozygous genotypes *CYP2C9* *1 / *2 and CYP2C9 *1 / *3 prevailed among Russians (18.0 % and 15.0 %, respectively) compared Yakuts (7.4 % and 3.7 %, respectively) and Tuvinians (6.0 % and 12.5 %, respectively) [3]. The study provided in group of 229 unrelated healthy Yakut individuals had been shown that there are the frequency difference in the polymorphism *VKORC1* - 1639G > A between the Yakut and Russian groups ($\chi 2 = 62.15$, P <

0.001). The comparison of the frequencies of *CYP2C9* + 430C > T (*CYP2C9 *2*) and *CYP2C9* + 1075A > C (*CYP2C9* *3) found no significant differences between Yakuts and Russians [16]. In our study the differences between the allelic frequencies of *CYP2C9* investigated polymorphisms has not been established between two racial groups. Allele *CYP2C9* *1 (wild-type) is the most common among all ethnic groups all over the world. The prevalence of this allele is higher among the Asian race (98 % – Singapore [8], 95.3 % – Malaysia [14], 97 % – Taiwan [1]. Among Caucasian populations this one is lower – 82 % in Sweden [17], 76 % – in Israel [11], 77.2 % – in Italy [6]. In our study, the frequency of *CYP2C9* *1 allele's carriers was also most common among both groups and it was higher among Asians compared to Caucasians (98.3 % vs. 92.8 %), but these differences did not reach significant values (p = 0,192). It was established that most Asians are homozygous for the *CYP2C9*1* alleles (85 %) [5]. In current study most Asians also were carriers of *CYP2C9*1/CYP2C9*1* genotype (65.5 %), and only 50 % were among Caucasians. Among Asians is practically never encountered *CYP2C9 *2* allele (rs1799853) – 0 % (Singapore [8], Malaysia [14], Taiwan [1], China [13]) while in our study, among Asians this polymorphism is set in 11.5 %. Interestingly, the presence of this allele among Asian race in Yakutia has been found in previous studies [2, 3]. In addition, in our study the *CYP2C9*3* frequency was higher compared to data of many researches according those 5 – 11 % of Caucasians carry *CYP2C9*3* [9, 11, 17] and 2 – 4,7 % of Asians carry this allele [1, 9, 13, 14]. But our data supports trend that Asians have lower frequency of this allele compared to Caucasians (24.6 % vs. 33.9 %). It was suggested the racial differs in allelic frequencies of polymorphism -1639G> A *VKORC1* gene (rs9923231) in current study. Thus, among Asians the number of carriers with G allele of polymorphism -1639G> A *VKORC1* gene (rs9923231) was significantly lower compared to the Caucasians (27.9 % vs. 85.7 %; $p < 0.001$, OR = 0.064; 95 % CI: 0.022 - 0.178). GA genotype of this polymorphism was also significantly lower among Asians compared to Caucasians (22.9 % vs. 75 %; $p < 0.0001$; OR = 0.099; 95 % CI: 0.038-0.251). The share of AA genotype's carriers in 1st group was 72.1 %, while in the 2nd group it was 14.3 % ($p < 0.0001$; OR = 15.529; 95 % CI: 5.610 - 44.586). Our data are identical with data of study [17], which had set that the frequency of AA genotype is 14.9 % in the population of Sweden, as well as study [15] – 16.5 %. According to our study this figure is 14.3 % in the Caucasian population of Yakutia. In our study, in Asians the AA genotype's frequency of polymorphism -1639G> A *VKORC1* gene (rs9923231) is most common (72.1 %) whereas AG genotype accounts 22.9 % and GG genotype accounts 4.9 %. In studies conducted in Chinese populations, it was also confirmed that AA genotype's frequency is prevalent and consists 83.7 % vs. 15.7 % (genotype AG) and 0.6 % (genotype GG) [13] and 85.76 % vs. 13.29 % (genotype AG)

and 0.95 % (genotype GG) [18]. Thus, the distribution of allelic and genotype's frequencies of *VKORC1* (rs9923231) in the population of Yakutia is identical to the data of studies conducted in Asian populations. According to our study, in Yakutia the account of AA genotype of the polymorphism -1639G> A *VKORC1* (rs9923231) was significantly higher among Asians compared to Caucasians, G allele carriers was significantly lower and GA genotype was significantly lower among Asians compared to Caucasians. Finally, our data are consistent with the results of the study [16] among healthy Yakut individuals whereby it was found that there are differences in frequency of polymorphism *VKORC1* -1639G> A between Yakuts and Russians. Thus, our data show that population of Yakutia is characterized with predominate of *CYP2C9*1* allele's and *CYP2C9*1 /CYP2C9*1* genotype's carriage what suggests data from other populations. The features are the higher share of *CYP2C9*2* and *CYP2C9**3 alleles' carriage among Asians and *CYP2C9**3 allele's carriage among Caucasians compared to other populations. Polymorphism *VKORC1* -1639G> A is characterized by common frequency of AA genotype's carriage and rare frequency of GA genotype's carriage among Asians compared to Caucasians. These findings suggest that it is necessary to take into account the racial and ethnic factors combined with pharmacogenetic data for adequate warfarin therapy. Our study has limitations which include the small sample size. Future studies are needed to continue investigations in phamacogenetic aspects of anticoagulant therapy in Yakutia.

Conclusions: Thus, in the Yakutia's population the frequency of AA genotype of polymorphism -1639G> A *VKORC1* gene (rs9923231), which significantly increases the risk of warfarin therapy's hemorrhagic complications, is higher among Asians compared to the Caucasians. The frequency of *CYP2C9* alleles and genotypes had no significant differences between two racial groups. These findings may have practical value for optimization of warfarin therapy for stroke prevention taking into account racial and pharmacogenetic characteristics.

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