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Cytochrome 2C19 Enzyme Polymorphism Frequency in Different Indigenous Ethnic Groups in Russian Federation: A Systematic Review

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Abstract

Background and objective: Genetically determined diversity in the activity of cytochrome P450 (CYP) – enzyme regulating the biotransformation of drugs and xenobiotics – is one of the main causes of interindividual differences in response to pharmacotherapy. The objective of this review is to analyze the prevalence of polymorphic markers of gene *CYP2C19,* associated with the violation of the pharmacological response to clopidogrel among the various ethnic groups living in the Russian Federation.

Methods: A literature review was conducted using the following databases: MEDLINE and eLIBRARY.RU. Russian language articles published between 20032003 (the first publication in Russians) and 2014 were reviewed.

Results: The authors detected 11 original research studies on *CYP2C19* gene in 11 indigenous ethnic groups of Russian Federation. According to the research data, the frequency of *CYP2C19*2* and *CYP2C19*3* markers prevalence is higher in the Mongolian race (with maximum *CYP2C19*2* frequency in the Kalmyks - 25, 0 % and *CYP2C19*3* in Tatars – 21,0 %). *CYP2C19*17* allele has been studied only in Russians, and was about the same as in the Caucasian race (14,0 %).

Conclusion: The results of the investigation will be beneficial for developing guidelines for *CYPC19* genotype–directed antiplatelet therapy for each region of Russia.

Keywords: *CYP2C19* Polymorphism; Pharmacogenetics; Ethnic differences of *CYP2C19*2; CYP2C19*3; CYP2C19*17*; Clopidogrel resistance

Introduction

Individual's response to specific drugs is a great issue for medicine in the twenty-first century. Genetically determined diversity in the activity of cytochrome P450 (CYP) – enzyme regulating the biotransformation of drugs and xenobiotics – is one of the main causes of the interindividual differences in response to pharmacotherapy.

Cytochrome P450 was first described in 1958 by Klingenberg [1] and Garfinkel [2]. The known clinically relevant cytochromes include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 и CYP3A4. Some of these isoforms exhibit genetic polymorphisms. The frequency of these polymorphisms differs markedly between ethnic groups. These genetic differences mean some people have an enzyme with reduced or no activity. Patients who are 'slow metabolisers' may have an increased risk of adverse reactions to a drug metabolised by the affected enzyme. It is estimated that genetics can account for 20 to 50 percent of variability in drug disposition and effects [3].

CYP2C19 appears to be one of the main CYP2C isoform found in the human. CYP2C19 hydroxylates a wide a wide variety of drugs (clopidogrel, barbiturates, diazepam, lansoprazole, nelfinavir, clonazepam, cyclophosphamide, omeprazole, etc.) [4].

Genetic polymorphism was discovered at Vanderbilt University by Kupfer et al. [5] in 1979 when conducting the research 4'-hydroxylation of the anticonvulsant S-mephenytoin. Later in 1993 Wrington et al. [6] found out that S-mefenitoin was the substrate of CYP2C19 enzyme. In 1994, Goldstein and de Morais [7] found that *CYP2C19* gene polymorphisms are associated with the loss of heterozygosity on chromosomes 10q (10q.1-24.3).

There is about 34 *CYP2C19* alleles including *CYP2C19*1*, *CYP2C19*2* and *CYP2C19*3, CYP2C19*17* (http://www.cypalleles.ki.se/cyp2c19.htm). Among functional defective alleles *CYP2C19*2* contributes 75% [8] in Asians and 93% [9] in Caucasians. 25% of defective alleles in Asians [10] is the *CYP2C19*3*, which is very rare in Caucasians (less than 1%) [11]. These pharmacogenetic variations lead to inappropriate concentrations of drugs and drug metabolites, which may contribute towards the toxicity and risk of adverse drug reactions or lack of therapeutic benefit. In contrast, the pro-drugs such as clopidogrel may be less effective in reducing the rate of cardiovascular events among persons who are carriers of loss-of-function CYP2C19 alleles that are associated with reduced conversion of clopidogrel to its active metabolite.

Several studies have examined the frequency of various *CYP2C19* alleles worldwide. The reported allele frequency of *CYP2C9*2* was about 50% in Asians, 18% in Caucasians, 34% in Africans and 19% in American populations [12-15]. The allele frequency of CYP2C9*3 among the Caucasian, African and Asian populations was <1 %, <1 % and 7 %, respectively [16]. The *CYP2C19*17* genotype was found in 25,7 % of the Germans [17], 22,0 % of the Norse [18], 20,0 % of the Swedes [19], 0,3 % of the Koreans [19], 4,0 % of the Chinese [20], 1,3 % of the Japanese [21].

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Ethnic groups	Region Of Russian Federation	n	Polymorphic marker	Population characteristics	Genotypes n (%)				Allelic variants				References
					EM	IM	PM	UP	*1	*2	*3	*17	
Russians	Tomsk	130	*2	Allergic diseases	81 (66,9)	38(31,4)	2 (1,7)	n.d.	0,83	0,17	n.d.	n.d.	[28]
	Tomsk	62	*2,*3	lymphoproliferative disorders	n.d.[1]	n.d.	n.d.	n.d.	0,86	0,14	0,0	n.d.	[37]
	Moscow and the Moscow Region	395	*2	Ischemic heart disease	288 (72,7)	101(25,5)	7 (1,8)	n.d.	0,85	0,15	n.d.	n.d.	[36]
	Moscow and the Moscow Region	40	*2,*3,*17	Ischemic heart disease	20 (50,0)	12 (30,0)	0 (0,0)	8 (20,0)	0,71	0,15	0,0	0,14	[35]
		146	*2	Healthy	111 (76,1)	31 (21,2)	4 (2,7)	n.d.	0,83	0,13	n.d.	n.d.	
	Tomsk	82	*2	Healthy	64 (78,0)	16 (19,5)	0 (0,0)	n.d.	0,88	0,12	n.d.	n.d.	[34][2]
		87	*3	Healthy	87 (100,0)	0 (0,0)	0 (0,0)	n.d.	1	n.d.	0,0	n.d.	
	Astrakhan	52	*2	Healthy	40(77,0)	8 (16,0)	4(7,0)	n.d.	0,85	0,15	n.d.	n.d.	[30]
	Voronezh	290	*2,*3	Healthy	228 (78,7)	56 (19,3)	6 (2,0)	n.d.	0,86	0,11	0,03	n.d.	[38]
Tatars	Kazan	97	*2	Ischemic heart disease	76 (78,4)	20 (20,6)	1 (1,0)	n.d.	0,86	0,14	n.d.	n.d.	[39]
	The Republic of Tatarstan	130	*2,*3	Acid-related disorders	56 (43,1)	62 (47,7)	12 (9,2)	n.d.	0,67	0,12	0,21	n.d.	[40]
	Astrakhan	50	*2	Healthy	40 (80,0)	7 (14,0)	3 (6,0)	n.d.	0,87	0,13	n.d.	n.d.	[30]
Kalmyks	Astrakhan	50	*2	Healthy	31 (62,0)	13 (26,0)	6 (12,0)	n.d.	0,85	0,15	n.d.	n.d.	[30]
Tuvinians	The Republic of Tuva	88	*2	Healthy	63 (71,7)	24 (27,2)	1 (1,1)	n.d.	0,85	0,15	n.d.	n.d.	[34]
		88	*3	Healthy	84 (95,4)	4 (4,6)	0 (0,0)	n.d.	0,98	n.d.	0,02	n.d.	
Buryats	The Republic of Buryatia	88	*2	Healthy	54 (61,3)	31 (35,2)	3 (3,5)	n.d.	0,79	0,21	n.d.	n.d.	[34]
		88	*3	Healthy	77 (87,5)	10 (11,4)	1 (1,1)	n.d.	0,93	n.d.	0,07	n.d.	
Yakuts	The Sakha Republic (Yakutia)	88	*2	Healthy	54 (61,3)	27 (30,6)	7 (7,9)	n.d.	0,77	0,23	n.d.	n.d.	[34]
		87	*3	Healthy	79 (90,8)	8 (9,2)	0 (0,0)	n.d.	0,95	n.d.	0,05	n.d.	
Altayans	Altai Republic	87	*2	Healthy	64 (73,5)	20 (23,0)	3 (3,5)	n.d.	0,85	0,15	n.d.	n.d.	[34]
		87	*3	Healthy	80 (92,0)	7 (8,0)	0 (0,0)	n.d.	0,96	n.d.	0,04	n.d.	
Chechens	Astrakhan	50	*2	Healthy	41(82,0)	7 (14,0)	2 (6,0)	n.d.	0,87	0,13	n.d.	n.d.	[30]
Carachays	The Republic of Karachay-Cherkessia	125	*2	Healthy	92 (73,6)	31 (24,8)	2 (1,6)	n.d.	0,86	0,14	n.d.	n.d.	[31]
Circassians		77	*2	Healthy	53 (68,8)	19 (24,7)	5 (6,5)	n.d.	0,81	0,19	n.d.	n.d.	[31]
Ingushes	Astrakhan	50	*2	Healthy	44 (88,0)	4 (8,0)	2 (4,0)	n.d.	0,92	0,08	n.d.	n.d.	[30]
Dagestans (Laks, Dargins, Avars)	Makhachkala	30	*2	Healthy	26 (86,7)	4 (13,3)	n.d.	n.d.	0,93	0,07	n.d.	n.d.	[32]

Table 1: Allele and genotype frequencies of CYP2C19 gene in different ethnic groups in Russia.
[1]n.d. = Not determined for the study population by authors.
[2]In the study by Makeeva et al. [34] prevalence of *CYP2C19*2* and *CYP2C19*3* was studied in separate groups

Determining the *CYP2C19* genotype can help by determining the metabolizer phenotype. Normal *CYP2C19* enzyme activity is expected when two *CYP2C19*1* alleles are considered to be present *(CYP2C19*1/*2)*; *CYP2C19* Intermediate Metabolizer (IM) phenotype is suggested by the presence of one *CYP2C19* allele with decreased function and one *CYP2C19* allele with normal function or one *CYP2C19* allele with decreased function and one *CYP2C19* allele with increased function *(CYP2C19*1/*2, *1/*3, *2/*17, *3/*17)*; *CYP2C19* Poor Metabolizer (PM) phenotype is suggested by the presence of two CYP2C19 non-functional alleles *CYP2C19*2* or *CYP2C19*3* (*CYP2C19*2/*2, *2/*3, *3/*3*). Heterozygosity or homozygosity for the increased function *CYP2C19*17* allele is associated with increased CYP2C19 activity and an ultra-rapid metabolizer phenotype (UM) (http://www.pharmgkb.org/).

Approximately 3% of the European population, 4-7% of the African population [4], 12-16 % of the Koreans [22,23], 18-23 % of the Japanese [24,25], 15-17 % of the Chinese [26] are CYP2C19-poor metabolizers.

Extensive and intermediate metabolizers phenotypes are the most common in humans, because *CYP2C19* poor-metabolizer phenotypes behave as autosomal recessive traits [8].

Since cytochrome enzymes are responsible for metabolizing over half of all drugs on the market today, it is important for a physician to have valuable information to determine whether a patient's specific genotype may impact their drug response. Moreover, knowing the *CYP2C19* phenotype of a patient may help in prescribing optimum dose of drug to achieve better therapeutic outcome.

The Russian Federation is a geographically huge country with a vast variety of ethnic groups. Nowadays, there is a lack of publications referred to *CYP2C19* gene polymorphisms prevalence among the different ethnicities in the Russian Federation (except Russians). Therefore, the aim of this study was: (1) to analyze the prevalence of polymorphic markers of gene *CYP2C19* in various ethnic groups living in the Russian Federation and (2) acquaint foreign researchers with the this data.

Materials and Methods

We conducted a systematic literature review to identify published studies of *CYP2C19* allelic variations and frequencies for different indigenous ethnic groups in Russian Federation. A literature review was conducted using the following databases: MEDLINE and eLIBRARY.RU. Russian language articles published between 2003 and 2014 were reviewed.

Search terms "Cytochrome P450", "*CYP2C19*", "*CYP2C19*2*", "*CYP2C19*3*", "*CYP2C19*17*", "Genetic polymorphism of CYP2C19", "Pharmacogenetics" were used.

Included studies had to meet the following inclusion criteria: (1) *CYP2C19* genotyping performed in all patients, (2) there is an indication of the ethnicity of participants in all studies, (3) original studies published between 2003 (the first publication in Russians) and 2014. Exclusion criteria: review articles.

The following data were abstracted: population characteristics (healthy or patients), number of subjects, ethnicity, frequency of alleles and genotypes, region of population residence.

There were no restrictions of inclusion on the basis of patient characteristics, publication type (journal article, abstract or conference proceedings), or publication language.

Results and Discussion

We detected 11 original research studies on *CYP2C19* gene in 11 indigenous ethnic groups in Russian Federation (Table 1). These data may confer important benefits in terms of determination of appropriate strategies of drug therapy, clinical safety and for best decision-making in public health about the rational use of CYP2C19 substrates in different indigenous ethnic groups in Russian Federation. However, lack of information about frequency of *CYP2C19* alleles could create a barrier to the use of pharmacogenetic testing in these populations [27].

Ethnic distribution of CYP2C19 alleles and genotypes was studied among Russians, Tatars, Karachays, Circassians, Ingushes, Chechens, Kalmuks and Dagestan's people (Laks, Dargins, Avars). The ethnicity was identified on the basis of patient's ethnic self-identification. In some cases the researchers surveyed the parents of the trial subjects in order to identify ethnicity.

Freidin's et al. was investigated 130 Russians living in Russian city of Tomsk were enrolled (median age 39 ± 13, 5 years, 67 women and 63 men) [28]. *CYP2C19*2* allele frequency was 14,7%, *CYP2C19*1/*1, CYP2C19*1/*2* and *CYP2C19*2/*2* genotype frequencies – 66,9 % (81 participants), 31,4 % (38 participants) и 1,7 % (2 participants) respectively. The results shown in this work confirmed the data of studies conducted among Caucasians [29], at the same time *CYP2C19*2* frequency is remarkably lower than that in the Mongolian race [8].

Kantemirova B.I. et al. identified *CYP2C19*2* among Russians, Chechens, Tatars, Kalmyks and Ingushes. The study included 208 healthy children aged from 1 to 18 years [30]. According to the study, for functional deficient *CYP2C19*2*, allele frequency is highest among Kalmyks – 25%; 11,0% in Chechens; 14% in Tatars; 8,0% in Ingushes.

The difference between *CYP2C19* genotype (Table 1) frequencies among Kalmyks and Ingushes (χ^2=5,765, p=0,0163) as well as between the Kalmyks and the Chechens (χ^2=3,6, p=0,0289) were statistically significant. Relatively high allele and genotype *CYP2C19*2* frequencies in Kalmyks are natural, as Kalmyks belong to Mongolian race. The cause of low incidence of the *CYP2C19*2* allelic variant in the research among Tatars is probably mixing with other ethnic groups and incorrect selection of patients.

The polymorphic marker *CYP2C19*2* has also been identified among other indigenous ethnic groups of the North Caucasus: Karachays and Circassians [31], Laks, Dargins, Avars [32].

Romodanovsky et al. [31] investigated 202 participants: 77 Circassians and 125 Karachays (median age 56 ± 11, 31 men and 46 women). The *CYP2C19*2* allele frequencies among Karachays and Circassians were 18,8 % and 14,0 % respectively.

In Dagestan's peoples (Laks, Dargins, Avars) was observed the lowest rate of *CYP2C19*2* polymorphism in Russian Federation – 6,5 %.

On the whole the *CYP2C19*2* allele frequencies in ethnic groups of the North Caucasus are close to those received earlier among most of the nations of Caucasian (White) race [29], which is natural, as Karachayevs, Cherkesses, Ingushes. Laks, Dargins, Avars belong to Caucasian race (not to be confused "Caucasian" and "Caucasus"!).

The frequency of *CYP2C19*2* polymorphic marker was also studied among Bashkirs [33], Yakuts, Buryats, Altayans and Tuvinians [34] (Table 1). The results are close to those received among the Mongolian race.

In our literature review we have evaluated the prevalence of the *CYP2C19* gene polymorphisms among the 11 ethnicities in the Russian Federation. As it was expected, *CYP2C19*2* allele pevalence was higher among the Asian population, with the highest rate in Kalmyks - 25,0 %., The highest rate of *CYP2C19*3* polymorphism was observed in Tatars - 21,2 %.

However, the high rate of *CYP2C19*3* polymorphism is very uncommon in humans (up to 5-7% in the Asian population and about 1% in the European population [16]) and this phenomenon calls for additional studies. *CYP2C19*17* allele prevalence in the Russian population was observed in one study [35] and it was similar to those in the European population (14,0%).

In general, the *CYP2C19* gene polymorphisms prevalence among the Tatars, Kalmyks, Yakuts, Tuvins, Buryats and Altays was similar to those in mongoloids. The *CYP2C19* gene polymorphisms prevalence among the Russians, Karachayevs, Cherkesses, Ingushes, Laks, Dargins, Avars was similar to those in the European population [36-40].

Conclusion

- The evaluation of the interindividual differences in the prevalence of *CYP2C19* gene polymorphisms is very important in the Russian Federation because of the high multinationality. The results of the pharmacogenetic investigation may be beneficial for developing guidelines for *CYPC19* genotype–directed antiplatelet therapy for each region of the Russian Federation.
- Since cytochrome enzymes are responsible for metabolizing over half of all drugs on the market today, it is important for a physician to have valuable information to determine whether a patient's specific genotype may impact their drug response. Moreover, knowing the CYP2C19 phenotype of a patient may help in prescribing optimum dose of drug and in predicting the increased risk of adverse reactions to achieve better therapeutic outcome.

Competing Interests

The authors declare that they have no competing interests.

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