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ORIGINAL ARTICLE

Genetic Polymorphisms of Cytochrome P450 Enzymes and Transport Proteins in a Russian Population and Three Ethnic Groups of Dagestan

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Aim: The objective of this study was to investigate the prevalence of polymorphic markers of the *CYP2C19*, *CYP2C9*, *CYP2D6*, *SLCO1B1*, and *ABCB1* genes among the three ethnic groups in Dagestan and compare it with the carrier frequency of these markers among the Russian population living in Moscow.
Methods: The study involved 186 healthy, unrelated, and chronic medication-free volunteers (53 males and 133 females) of the three ethnic groups in the Dagestan Republic: 46 Laks, 90 Avars, and 50 Dargins. Genotyping was performed using real-time polymerase chain reaction-based methods. The allelic prevalences of the three Dagestan people were compared with ethnic Russians from the Moscow region.
Results: Statistically significant differences for the following gene polymorphisms: *CYP2C19*17*, *CYP2C9*3*, *ABCB1 (C3435T)*, *SLCO1B1*5* were found between the Russian population and three ethnic groups of the Dagestan republic.
Conclusion: The data obtained from this study will help to assess the priority of implementation of genotyping in the region.

Keywords: the P450 cytochrome, ethnic groups, pharmacogenetics, P-glycoprotein, Russians, Dargins, Avars, Laks

Introduction

In recent years, progress in the field of pharmacogenetics has made a significant contribution to the development of personalized medicine. The use of genotyping in relation to other clinical, laboratory, and demographic factors enables to optimize pharmacotherapy in terms of drug safety and efficacy (Liou *et al.*, 2012). Polymorphism of genes encoding components of the pharmacokinetic pathways is a universal factor that has an impact on the efficacy and safety of many drugs. The most clinically significant are genes encoding cytochrome P450 enzymes—CYP2C9, CYP2D6, CYP2B6, CYP3A4, CYP3A5, and CYP2C19 (which are responsible for the metabolism of almost half of all drug classes: antiplatelet agents, anticoagulants, antihypertensive, antianginal, lipid-lowering, antiarrhythmic, psychotropic, antidiabetic, antitumor, and other drugs) (Maier *et al.*, 2016) and genes encoding transport proteins—ABCB1 (P-glycoprotein) and SLCO1B1 (gene of OATP1B1 transporter protein) (Weber, 2008; Valdes and Yin, 2016) (Table 1). Studies among different ethnic groups show marked inter-racial and interethnic differences in drug sensitivity (Kalow, 2005). For example, allelic variants *CYP2D6 * 3*, ** 6*, ** 7*, and ** 8* are present only among Caucasians, while the *CYP2D6 * 17* allele variant is present only among the Negroid population (Masimirembwa *et al.*, 1996). Additionally, the prevalence of *CYP2D6* (gene allelic variant, encoding formation of CYP2D6 isozyme with low metabolic activity) varies considerably among different African populations, that is, among ethnic groups within one race: 2–19% (Masimirembwa *et al.*, 1996). Most pharmacogenetic studies have been conducted on Caucasians, making it difficult to extrapolate the results to other ethnic groups. That is why the study of polymorphic gene carrier frequency is especially important for such a multinational country as Russia. There is a current insufficiency of studies on the prevalence of major pharmacogenetic predictive markers of increased drug sensitivity among the many indigenous ethnic groups of the Caucasus region. Studies on Caucasus nations have shown the same genetic variety as in studies on European and the Middle Eastern ethnic groups (Nasidze *et al.*, 2001; Bulayeva *et al.*, 2003; Yunusbayev *et al.*, 2012).

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Table 1. Characterization of the Polymorphisms

Gene	*SNP*	*rs*	*Drug*
CYP2C19	*CYP2C19*2, +681G>A*	rs4244285	Clopidogrel, proton pump inhibitors, selective serotonin reuptake inhibitor, voriconazole
	*CYP2C19*3, +636G>A*	rs498693	
	*CYP2C19*17, –806C>T*	rs 12248560	
CYP2C9	*CYP2C9*3, +1075A>C*	rs1057910	Warfarin, acenocoumarol, phenytoin
CYP2D6	*CYP2D6*4, +1846G>A*	rs3892097	Codeine, doxepin, tricyclic antidepressants
SLCO1B1	*SLCO1B1*5, +521T>C*	rs4149056	Statins
ABCB1	*ABCB1, 3435C>T*	rs1045642	Statins, clopidogrel, new oral anticoagulants, haloperidol

This is best illustrated in the case of Dagestan Republic, where more than 26 of the 50 autochthonous ethnic groups of Caucasus live (Marchani *et al.*, 2008). The main indigenous ethnic groups of the Dagestan Republic are the Avars, Dargins, Laks, Lezgins, Kumyks, Tabasarans, Rutuls, and Aguls, etc. (Mirzaev *et al.*, 2014). Despite the small territory of the Dagestan Republic, there is a high degree of isolation of each group in the region (this is due to terrain features, the high frequency of inbreeding, relatively constant population size, and patrilocality), which leads to differences in the prevalence of polymorphic markers among close ethnic groups (Bulayeva, 2006).

Materials and Methods

Study population

The study involved 186 healthy, unrelated, and chronic medication-free volunteers (53 males and 133 females) of the three ethnic groups in the Dagestan Republic: 46 Laks (15 males and 31 females), 90 Avars (28 males and 62 females), and 50 Dargins (10 males and 40 females). The mean age of volunteers enrolled was 22.6 ± 7.2 years. Belonging to a particular ethnic group was determined as described in the literature, a generally accepted method—self-identification. The study has been performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before entering the study. The study has been approved by the Russian Medical Academy of Continuous Professional Education. The study was approved by the Research and Ethics Committee both at the Russian Medical Academy of Continuous Professional Education and Dagestan State Medical University. Recruitment of a set of volunteers was carried out on the basis of the Department of Hospital Therapy №1 FSBEI HE «Dagestan State Medical University» of the Ministry of Healthcare of the Russian Federation (Makhachkala, Russia) and Republican Clinical Hospital Republic of Dagestan. The prevalence of allelic variants *CYP2C19*2* (*681G>A*, rs4244285), *CYP2C19*3* (*636G >A*, rs4986893), *CYP2C19*17* (*–806C>T*, rs12248560), *CYP2C9*3* (*1075A>C*, rs1057910), *CYP2D6*4* (*1846G>A*, rs3892097), and *SLCO1B1*5* (*521C>T*, rs4149056) *u ABCB1* (*3435C>T*, rs1045642) was compared with Russian nationals from the Moscow region as the representatives of the largest ethnic group (Gaikovitch *et al.*, 2003; Sychev *et al.*, 2015, 2016).

Genotyping

A venous blood sample (4 mL) was collected from all participants in EDTA (ethylenediaminetetraacetic acid) tubes and kept on ice during transportation to the laboratory. Genomic DNA was extracted from whole blood using kits of CJSC «Syntol» (Moscow, Russian Federation). Gene carriership was determined by real-time polymerase chain reaction (real-time polymerase chain reaction [PCR]) using kits «SNP-Screen» of CJSC «Syntol» (Moscow, Russian Federation). Base numbering and allele definitions follow the nomenclature of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee (www.cypalleles.ki.se). The genotypes were determined with a TaqMan® Single-Nucleotide Polymorphism Genotyping Assay kit and TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA), according to the manufacturer's instructions, using an ABI PRISM® Sequence Detector 7000 (Applied Biosystems). Genotype polymorphisms were detected using Real-Time CFX96 Touch (Bio-Rad Laboratories, Inc.).

Statistics

Genotype frequencies were tested for deviations from Hardy–Weinberg equilibrium (HWE) through chi-square analysis at www.oege.org/software/hwe-mr-calc.shtml (Rodriguez *et al.*, 2009). Statistical significance was assessed by chi-square test to compare differences between studied groups. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistic 20.

Results

Genotype distribution of *CYP2C19*2*, *CYP2C19*17*, *CYP2C9*3*, *CYP2D6*4*, *ABCB1* (*C3435T*), and *SLCO1B1*5* was in the HWE in all analyzed ethnic groups (Tables 2 and 3). Genotype and allele distribution of *CYP2C19*3* was not in the HWE in Avars and Dargins.

In Table 4, it is genotypes' distribution among Russians that was the control group in the present research.

CYP2C19

There were no statistically significant differences in *CYP2C19*2* and *CYP2C19*3* allele frequencies between Russians and Avars. However, there were statistically significant differences in the *CYP2C19*17* allele frequency observed between these ethnic groups (Table 5). *CYP2C19*17* allele frequency in Russians was higher than in Avars (27.3% vs. 20%, $p = 0.04$). There were no statistically significant differences in *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* allele frequencies between Russians and Dargins and Laks (Tables 6 and 7).

Table 2. Genotype Frequencies of *CYP2C19*, *CYP2C9*, *CYP2D6*, *ABCB1*, and *SLCO1B1* Gene Polymorphisms in Different Ethnic Groups

		Ethnic groups					
SNP	*Genotype*	*Avars,* n *(%)*	*Expected Hardy–Weinberg test* (n)	*Laks,* n *(%)*	*Expected Hardy–Weinberg test* (n)	*Dargins,* n *(%)*	*Expected Hardy–Weinberg test* (n)
*CYP2C19*2 (+681G>A)*	*1/*1	69 (77)	69	34 (74)	33.9	45 (90)	45.1
	*1/*2	20 (22)	19.3	11 (24)	11.2	5 (10)	4.75
	*2/*2	1 (1)	1.3	1 (2)	0.9	0 (0)	0.1
*CYP2C19*3 (+636G>A)*	*1/*1	90 (100)	90	44 (96)	44	50 (100)	50
	*1/*3	0 (0)	0	2 (4)	2	0 (0)	0
	*3/*3	0 (0)	0	0 (0)	0	0 (0)	0
*CYP2C19*17 (–806C>T)*	*1/*1	57 (63)	57.6	28 (61)	29	27 (54)	28.9
	*1/*17	30 (33)	28.8	17 (37)	15.1	22 (44)	18.2
	*17/*17	3 (4)	3.6	1 (2)	2	1 (2)	2.9
*CYP2C9*3 (+1075A>C)*	*1/*1	65 (72)	64.2	31 (67)	29.8	34 (68)	34.5
	*1/*3	22 (24)	23.6	12 (26)	14.5	15 (30)	11.1
	*3/*3	3 (4)	2.2	3 (7)	1.8	1 (2)	1.5
*CYP2D6*4 (+1846G>A)*	*1/*1	67 (74)	68.5	29 (63)	30.6	31 (62)	32.8
	*1/*4	23 (26)	20.1	17 (37)	13.9	19 (38)	15.4
	*4/*4	0 (0)	1.47	0 (0)	1.6	0 (0)	1.9
*SLCO1B1*5 (+521T>C)*	*1/*1	64 (71)	65.9	38 (83)	37.4	41 (82)	40.5
	*1/*5	26 (29)	22.2	7 (15)	8.1	8 (16)	9
	*5/*5	0 (0)	1.9	1 (2)	0.4	1 (2)	0.5
ABCB1 (3435C>T)	CC	16 (18)	17.8	4 (8)	4.6	8 (16)	6.9
	CT	48 (53)	44.4	21 (46)	19.9	21 (42)	23.3
	TT	26 (29)	27.8	21 (46)	21.6	21 (42)	19.9

Table 3. Correspondence of the Distribution of the Genotype Frequencies to the Hardy–Weinberg Equilibrium

SNP	CYP2C19*2	CYP2C19*3	CYP2C19*17	CYP2C9*3	CYP2D6*4	ABCB1 (C3435T)	SLCO1B1*5
Avars							
P	0.73	None	0.7	0.5	0.16	0.4	0.1
χ^2 test	0.1	None	0.15	0.4	1.9	0.5	2.5
Laks							
P	0.9	0.8	0.4	0.24	0.1	0.7	0.34
χ^2 test	0.009	0.02	0.74	1.3	2.36	0.15	0.8
Dargins							
P	0.7	None	0.14	0.65	0.09	0.48	0.43
χ^2 test	0.13	None	2.1	0.2	2.75	0.5	0.6

CYP2D6*4

There were no statistically significant differences in *CYP2D6* allele frequencies between the Russian population and three ethnic groups of the Dagestan Republic (Avars, Dargins, and Laks) (Tables 5–7).

CYP2C9*3

*CYP2C9*3* prevalence was the lowest in Russians and accounts for 6.7%, while it was 19.57% ($p=0.0008$), 17% ($p=0.001$), and 15.5% ($p=0.0002$) in Avars, Dargins, and Laks, respectively (Tables 5–7). There was the absence of *CYP2C9*3* allele in Dargins and Avars.

ABCB1

When comparing the distribution of allele frequencies between the Avars, Laks, Dargins, and Russians in the current study, statistically significant differences were found only between the Laks and Russians. Prevalence of T allele was higher among the Laks and amounted to 68.48%, while it was 54.3% in the Russian population ($p=0.01$) (Table 6).

Table 4. Genotype Distributions Among Russians Considered as Control Group in the Present Research

SNP	*Genotype*	n	*Reference*
*CYP2C9*3*	*1/*1	252	Gaikovitch
	*1/*3	37	*et al.* (2003)
	*3/*3	1	
*CYP2C19*2*	*1/*1	229	Gaikovitch
	*1/*2	56	*et al.* (2003)
	*2/*2	5	
*CYP2C19*17*	*1/*1	506	Sychev
	*1/*17	399	*et al.* (2015)
	*17/*17	66	
*CYP2D6*4*	*1/*1	194	Gaikovitch
	*1/*4	87	*et al.* (2003)
	*4/*4	9	
ABCB1 3435C>T	CC	62	Gaikovitch
	CT	141	*et al.* (2003)
	TT	87	
*SLCO1B1*5*	*1/*1	665	Sychev
	*1/*5	346	*et al.* (2016)
	*5/*5	60	

SLCO1B1*5

Statistically significant differences in *SLCO1B1*5* prevalence were found between Russians and three ethnic groups of Caucasus (Avars, Laks, and Dargins).

*SLCO1B1*5* prevalence was the highest in Russians and accounts for 21.8%, while it was 14.4% ($p=0.02$), 10% ($p=0.007$), and 9.78% ($p=0.008$) in Avars, Dargins, and Laks, respectively (Tables 5–7).

Discussion

Since 1998, there is a special guide for the implementation of the drug in a new region—ICH E5 (Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use [ICH] E5 guideline).

This guide provides information about implementation of the ethnically sensitive drug (i.e., the use of this drug has to be accompanied by reporting of genetically determined pharmacokinetic and pharmacodynamic characteristics of the ethnic group). In this case, extrapolation is to be conducted in a new region. For example, the maximum recommended dose for 32% of medicines registered in the period from 2001 to 2007 in the United States was nearly two times more than the recommended dose of these drugs in Japan (Arnold *et al.*, 2010). Proteins of cytochrome P450 as well as transport proteins play a key role in the metabolism and transport of drugs. Knowledge of the prevalence of polymorphisms of genes encoding these proteins among different ethnic groups will help to increase the drug efficacy and reduce the number of adverse drug reactions.

CYP2C19

The most common *CYP2C19* polymorphisms are *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* (Beitelshees *et al.*, 2011). Carriers of *CYP2C19*2* and *CYP2C19*3* polymorphisms are poor metabolizers, that is, they have decreased activity of liver enzymes and reduced biotransformation. Carriers of *CYP2C19*17* polymorphism are ultrarapid metabolizers (Mirzaev *et al.*, 2013). About 50% of the Mongoloid population, 34% of Negroid population, and 18% of Caucasians are *CYP2C19*2* carriers (Mega *et al.*, 2009; Bonello *et al.*, 2010). *CYP2C19*3* allele frequency is less than 1% in Caucasians and the Negroid population and

Table 5. Results of Comparison of Genotype Frequencies of *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17*, *CYP2C9*3*, *CYP2D6*4*, *ABCB1* (*C3435T*), and *SLCO1B1*5* Gene Polymorphisms in Avars and Russian Population

SNP	Total (n/allele)		Allele, n (%)		Odds ratio	95% confidence interval	p	Reference
	Avars	Russians	Avars	Russians				
*CYP2C19*2*	90/180	290/580	22 (12.7)	66 (11.4)	1.08	0.64–1.81	0.78	Gaikovitch *et al.* (2003)
*CYP2C19*3*	90/180	290/580	0 (0.0)	2 (0.3)	0.78	0.03–16.43	1	Gaikovitch *et al.* (2003)
*CYP2C19*17*	90/180	971/1942	36 (20.0)	531 (27.3)	0.66	0.45–0.97	0.04	Sychev *et al.* (2016)
*CYP2C9*3*	90/180	290/580	28 (15.5)	39 (6.7)	2.55	1.52–4.28	0.0008	Gaikovitch *et al.* (2003)
*CYP2D6*4*	90/180	290/580	23 (12.8)	105 (18.1)	0.66	0.40–1.07	0.11	Gaikovitch *et al.* (2003)
ABCB1 (C3435T)	90/180	290/580	100 (55.5)	315 (54.3)	1.05	0.75–1.47	0.79	Gaikovitch *et al.* (2003)
*SLCO1B1*5*	90/180	1071/2142	26 (14.4)	466 (21.8)	0.6	0.39–0.93	0.02	Sychev *et al.* (2016)

less than 7% in the Mongoloid population (Collet *et al.*, 2009). *CYP2C19*17* was found in 25.7% of Germans (Geisler *et al.*, 2008), 22% of Norwegians (Pedersen *et al.*, 2010), and less than 4% of the Asian population (Korean, Japanese, and Chinese) (Sugimoto *et al.*, 2008). According to obtained data, *CYP2C19*2* polymorphism was less frequent in Dargins, and *CYP2C19*3* was rare both in Russian and Dagestan representatives. All ethnic groups were close to Caucasians by three polymorphism distributions. However, there was significant difference between Russians and Avars by *CYP2C19*17* (Table 5).

CYP2D6*4

CYP2D6 isoenzyme of cytochrome P450 is about 20% of all cytochrome P450 isoenzymes (Zhou, 2009). It participates in the metabolism of more than 25% of all known drugs, including antipsychotics, antidepressants, and so on. *CYP2D6* 1846G>T leads to reduced activity of the CYP2D6 isoenzyme, which in turn causes slowing of the elimination rate of isoenzyme substrates from the body (Zanger *et al.*, 2004).

We have not found any sufficient differences between Russians and Laks, Avars, or Dargins. Therefore, there is no special alertness about drug tolerability among those three Dagestan populations compared with Russians.

CYP2C9*3

Another cytochrome P450 isoenzyme is CYP2C9. It is known that carriers of *CYP2C9*3* (AA/AC+CC) are slow metabolizers, that is, they have decreased metabolism of different drugs (antidiabetics, anticoagulants, and NSAIDs, etc.) (Rost *et al.*, 2005; Sychev *et al.*, 2005). For example, numerous studies showed that to reduce the risk of adverse drug reactions, genotyping for *CYP2C9* (with the *VKORC1* gene) in patients taking warfarin should be performed to initiate with the most matched dose (Rost *et al.*, 2005; Loebstein *et al.*, 2007). Interethnic differences in the prevalence of *CYP2C9* 3* allele have been identified in many studies: the prevalence was 7.4% in Swedes (Yasar *et al.*, 1999), 1.8% in the Japanese (Kimura *et al.*, 1998), and 2.6% in the Chinese (Wang *et al.*, 1995). Statistically significant differences in *CYP2C9*3* prevalence were found between Russians and three ethnic groups of Dagestan (Avars, Laks, and Dargins): they had the *CYP2C9*3* allele at least twice more often than Russians. These data are suitable to literature: *CYP2C9*3* occurs in more cases in Caucasian populations compared with Asians. Of course that was an important finding that must be kept in mind for further research and clinical practice in the Dagestan region.

ABCB1 C3435T

P-glycoprotein is a protein from the ABC family of transporters, which are involved in the transmembrane transport of various substances, including medications.

This protein is encoded by the *ABCB1* gene. Changes in *ABCB1* activity affect the efficiency of different drugs, in particular, antiplatelet agents (clopidogrel) (Aszalos, 2007). According to studies, the incidence of thrombotic events in TT genotype carriers after receiving clopidogrel therapy

Table 6. Results of Comparison of Genotype Frequencies of *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17,* *CYP2C9*3*, *CYP2D6*4*, *ABCB1* (*C3435T*), and *SLCO1B1*5* Gene Polymorphisms in Laks and Russian Population

SNP	Total (n/allele)		Allele, n (%)		Odds ratio	95% Confidence interval	p	Reference
	Laks	Russians	Laks	Russians				
*CYP2C19*2*	46/92	290/580	13 (14.1)	66 (11.4)	1.28	0.67–2.43	0.48	Gaikovitch *et al.* (2003)
*CYP2C19*3*	46/92	290/580	2 (4.3)	2 (0.3)	6.42	0.89–46.19	0.09	Gaikovitch *et al.* (2003)
*CYP2C19*17*	46/92	971/1942	19 (20.6)	531 (27.3)	0.69	0.41–1.15	0.19	Sychev *et al.* (2015)
*CYP2C9*3*	46/92	290/580	18 (19.5)	39 (6.7)	3.37	1.83–6.2	0.0002	Gaikovitch *et al.* (2003)
*CYP2D6*4*	46/92	290/580	17 (18.5)	105 (18.1)	1.02	0.58–1.80	0.88	Gaikovitch *et al.* (2003
ABCB1 (C3435T)	46/92	290/580	63 (68.5)	315 (54.3)	1.82	1.14–2.92	0.01	Gaikovitch *et al.* (2003)
*SLCO1B1*5*	46/92	1071/2142	9 (9.7)	466 (21.8)	0.39	0.19–0.78	0.008	Sychev *et al.* (2016)

Table 7. Results of Comparison of Genotype Frequencies of *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17*, *CYP2C9*3*, *CYP2D6*4*, *ABCB1* (*C3435T*), and *SLCO1B1*5* Gene Polymorphisms in Dargins and Russian Population

SNP	Total (n/allele)		Allele, n (%)		Odds ratio	95% Confidence interval	p	Reference
	Dargins	Russians	Dargins	Russians				
*CYP2C19*2*	50/100	290/580	5 (5.0)	66 (11.4)	0.4	0.16–1.04	0.052	Gaikovitch *et al.* (2003)
*CYP2C19*3*	50/100	290/580	0 (0.0)	2 (0.3)	1.15	0.05–24.17	1	Gaikovitch *et al.* (2003)
*CYP2C19*17*	50/100	971/1942	24 (24.0)	531 (27.3)	0.83	0.52–1.34	0.53	Sychev *et al.* (2015)
*CYP2C9*3*	50/100	290/580	16 (16.0)	39 (6.7)	2.64	1.41–4.94	0.004	Gaikovitch *et al.* (2003)
*CYP2D6*4*	50/100	290/580	19 (19.0)	105 (18.1)	1.06	0.61–1.82	0.88	Gaikovitch *et al.* (2003)
ABCB1 (C3435T)	50/100	290/580	63 (63.0)	315 (54.3)	1.43	0.92–2.21	0.12	Gaikovitch *et al.* (2003)
*SLCO1B1*5*	50/100	1071/2142	10 (10.0)	466 (21.8)	0.39	0.2–0.77	0.007	Sychev *et al.* (2016)

was higher than the incidence of thrombotic events in carriers of CC genotype (Simon *et al.*, 2009). The prevalence of polymorphisms of the *ABCB1* (*C3435T*) gene was studied in different ethnic groups: the prevalence of the T allele was 48% in the Spanish population (Bernal *et al.*, 2003), 28% in Turks, 18% in the Palestinian population (Nassar *et al.*, 2014), and 49% in the Polish population (Mrozikiewicz *et al.*, 2007).

Allele T frequencies in our sample were as expected for Caucasian populations: there were no significant differences between two Dagestan populations and Russians. Only Lak representatives had a higher rate of T allele compared with Russians. That feature could be useful in further research to establish risks of drug tolerability in that ethnic group.

SLCO1B1*5

The *SLCO1B1* gene encodes OATP1B1 (one of the major influx transporting proteins). Genetic variations of the gene may affect the pharmacokinetics of drugs and lead to an increase in adverse events, in particular, increase in events of statin-induced myopathy in hyperlipidemic patients (Canestaro *et al.*, 2014). It has been established that the carriers of the *SLCO1B1*5* (521T> C) allele have reduced transporter protein activity and increased risk of myopathy (Search Collaborative Group *et al.*, 2008). Currently, experts from the European Science Foundation recommend the use of genotyping for *SLCO1B1* to predict the development of myopathy in patients planned to be treated with statin therapy (Becquemont *et al.*, 2011).

In the current sample, we observed that *SLCO1B1*5* was less frequent in Laks, Dargins, and Avars than Russians. Therefore, it might be associated with reduced risk of statin-induced myopathy in those ethnic groups. However, further research is needed to confirm that hypothesis.

Conclusion

Data obtained from this study will help to assess the priority of implementation of genotyping in the region. We found statistically significant differences in the prevalence of polymorphisms of genes among Russian populations and three ethnic groups of the Dagestan Republic. Identifying the most clinically significant polymorphisms may be one of the most important ways to improve the prevention of serious adverse drug reactions and to identify important genetic determinants of hypersensitivity to the drug.

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