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ORIGINAL RESEARCH

Comparison of *CYP2C9*, *CYP2C19*, *CYP2D6*, *ABCB1*, and *SLCO1B1* gene-polymorphism frequency in Russian and Nanai populations

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Background: The efficiency and safety of drug therapy depends on the peculiarities of functioning of the P450 cytochrome group and transporting proteins. There are significant differences for single-nucleotide polymorphism (SNP) frequency.

Materials and methods: We studied the peculiarities of P450 cytochrome polymorphisms, SLCO1B1 transporting protein, and P-glycoprotein carriage in healthy volunteers in the Nanai ethnic group living in Russia, and compared them to the carriage of SNPs in the Russian population according to literature data.

Results: After performing the real-time polymerase chain reactions on the samples from 70 healthy volunteers from the Nanai group, for the *CYP2C9*2*^{C430T} polymorphism we determined 70 CC-genotype carriers. As for the *CYP2C9*3*^{A1075C} polymorphism, we found 62 AA-genotype carriers and eight AC-genotype carriers. For the *CYP2C19*2*^{G681A} polymorphism, we determined 39 GG-genotype carriers and 28 GA-genotype carriers, for the *CYP2C19*3*^{G636A} polymorphism 58 GG-genotype carriers and 12 GA-genotype carriers, and for the *CYP2C19*17*^{C806T} polymorphism 67 CC-genotype carriers and three CT-genotype carriers. For the *CYP2D6*4*^{G1846A} polymorphism, the GG genotype had 68 carriers, and the GA genotype two carriers. For the *ABCB1*6*^{C3435T} polymorphism, there were 19 CC-genotype carriers and 39 CT-genotype carriers. For the *SLCO1B1*5*^{T521C} polymorphism, the TT genotype had 41 carriers and the CT genotype 25 carriers. The distribution of genotypes fitted the Hardy–Weinberg equilibrium for all the polymorphisms, except those of *CYP2C9*2*. There were also significant differences in allele frequencies for some polymorphisms between the Nanais and the Russians.

Conclusion: In the Nanai population, there are polymorphisms connected with the decrease in safety and efficiency of drug therapy. Studying the ethnic differences might influence the determination of priority in the introduction of pharmacogenetic tests in clinical practice in different regions of Russia.

Keywords: pharmacogenetics, ethnicity, Asians, Europeans, SNP, P450 cytochrome, ethnic group, P-glycoprotein

Introduction

The efficacy and safety of pharmacological therapy depends on the peculiarities of absorption, metabolism, and excretion of the drugs. The metabolism of drugs is mostly determined by the effect of enzymes of the cytochrome P450 group. The best-known agents determining the absorption and excretion of drugs are solute carrier transporters and P-glycoprotein.[1] 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

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(antiplatelet, anticoagulant, antihypertensive, antianginal, lipid-lowering, antiarrhythmic, psychotropic, antidiabetic, antitumor, and other drugs) and genes encoding transport proteins: *ABCB1* (P-glycoprotein) and *SLCO1B1* (OATP1B1-transporter protein).[2–4] Studying the influence of different single-nucleotide polymorphisms (SNPs) on the absorption, distribution, metabolism, and excretion of drugs may help in reducing the problems of the variability of drug responses, potentially resulting in a decrease in prevalence of treatment failure and adverse events.[5] However, some SNP frequencies have significant variance in different ethnic groups. For example, *CYP2C19*17* was 42- and 24-fold more frequent in Mediterranean–South Europeans and those from the Middle East than in East Asians ($P<0.001$, in both cases).[6] 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. In the present research, we identified frequencies of some of the polymorphisms of genes *CYP2C9*, *CYP2C19*, *CYP2D6*, *ABCB1*, *SLCO1B1* in the Nanai ethnic group (the Nanai is a small native population in the Russian Far East, living along the middle reaches of the Amur River Valley).[7]

Materials and methods

Sample

A total of 70 healthy volunteers (14 men [20%] and 56 women [80%]) with an average age of 43.5 (22–70) years living in Khabarovsk territory in the Russian Far East were engaged in the research. All the volunteers were informed about the objectives and methods of the research. They also gave informed consent to participate in the research and provided the researchers the right to extract their genetic material. The study was approved by the local ethical committee of the Russian Medical Academy of Continuing Professional Education (record 12, December 8, 2015). Written consent was obtained from all study participants. The criteria for inclusion were no consanguinity among the analyzed individuals and belonging to the Nanai ethnic group, which was determined by volunteers' and their parents' self-identification.[8] The criteria for exclusion were relatives and descendants of other ethnic groups.

Sample preparation

A 5 mL sample of each volunteer's blood was extracted to determine the SNPs. This was put into vacuum tubes with ethylenediaminetetraacetic acid. Extraction was executed in December 2015 at the Troitskaya Central District Hospital clinic of the Ministry of Healthcare of Khabarovsk territory in Najhin village. The frozen samples were delivered to the Russian Medical Academy of Continuous Professional Education research center in Moscow, where DNA was extracted from the leukocytes.

The extracted DNA was tested for carriage of the SNPs *CYP2C9*2*^{C430T} rs1799853, *CYP2C9*3*^{A1075C} rs1057910, *CYP2C19*2*^{G681A} rs4244285, *CYP2C19*3*^{G636A} rs4986893 or rs57081121, *CYP2C19*17*^{C806T} rs12248560, *CYP2D6*4*^{G1846A} rs3892097, *ABCB1*6*^{C3435T} rs1045642, and *SLCO1B1*5*^{T521C} rs4149056 using real-time polymerase chain reaction with the help of a commercial set provided by Syntol (Moscow, Russia) and a CFX96 Touch (Bio-Rad Laboratories, Hercules, CA, USA). The program included preliminary denaturation at 95°C, which lasted 3 minutes, then 40 cycles of 15 seconds' denaturation at 95°C, then annealing at 63°C for 40 seconds. We used Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for interpretation of genotypes.[9–11]

CYP2C9

The carriers of the *1/*1 genotype were designated extensive metabolizers, carriers of the *CYP2C9*2* and *CYP2C9*3* alleles in a heterozygous state (*1/*2, *1/*3) designated intermediate metabolizers, and those carrying both the alleles simultaneously (*2/*3) poor metabolizers.[9]

CYP2C19

Carriers of the *1/*1 genotype were designated extensive metabolizers, with two alleles of *CYP2C19*2* or *CYP2C19*3* (*2/*2, *2/*3, *3/*3) poor metabolizers, and those carrying *CYP2C19*2* or *CYP2C19*3* or carrying *CYP2C19*17* with one allele of *CYP2C19*2* (*1/*2, *1/*3, *2/*17) intermediate metabolizers. Carriers of *CYP2C19*17* alleles in homozygous and heterozygous states (*1/*17, *17/*17) were designated ultrarapid metabolizers.[10]

CYP2D6

Carriers of *1/*1 and *1/*4 genotypes were designated extensive metabolizers, and those with the *CYP2D6*4* allele in a homozygous state (*4/*4) poor metabolizers.[10]

ABCB1 (C435T)

Carriers of the CC genotype have a "normal activity" transporter. The T allele is associated with abnormality pharmacokinetics.[12]

SLCO1B1

Carriers of *1/*1 genotype have a "normal activity" transporter; *SLCO1B1*5* allele in heterozygous state

(*1/*5) – "intermediate activity"; *5/*5 homozygotes – "low activity".[11]

Comparison group

A population of Russians was chosen as the comparison group, as this is the largest ethnic group in Russia. The control group was arranged according to data in the literature (we used PubMed as the main source), with high priority given to research on healthy volunteers. If there were no groups of healthy volunteers, the priority was given to the research with large numbers of patients. Groups with insignificant differences in allele frequencies on Hardy–Weinberg equilibrium were involved in the research.

Statistical analysis

We performed Hardy–Weinberg tests to confirm the independence of allele distribution in studied polymorphisms. Fisher's exact test was used to estimate differences between frequencies of allele mutations of Russian and Nanai ethnic groups. Statistical data were processed using InStat software. $P<0.05$ was considered statistically significant for all tests.

Results

We determined polymorphisms of *CYP2C19*, *CYP2C9*, *CYP2D6*, *ABCB1*, and *SLCO1B1* of 70 healthy volunteers from the Nanai ethnic group. For the *CYP2C9* gene, we discovered zero frequency of the T allele of the *CYP2C9*2*^{C430T} polymorphism, so it was impossible to calculate χ^2 value for Hardy–Weinberg proportions, and 5.7% frequency of the C allele of the *CYP2C9*3*^{A1075C} polymorphism.

For the *CYP2C19* gene, frequency of the A allele of the *CYP2C19*2*^{G681A} polymorphism was 24.3%, frequency of the A allele of the *CYP2C19*3*^{G636A} polymorphism was 8.6%, frequency of the T allele of the *CYP2C19*17*^{C806T} polymorphism was 2.1%. For the *CYP2D6* gene, frequency of the A allele of the *CYP2D6*4*^{G1846A} polymorphism was 1.4%. For the *ABCB1* gene, frequency of the T allele of the *ABCB1*6*^{C3435T} polymorphism was 45%. The frequency of the C allele of the *SLCO1B1*5*^{T521C} polymorphism was 23.6%. Genotype frequencies did not deviate significantly from Hardy–Weinberg equilibrium. The results are presented in Table 1.

We compared the frequency of alleles in the Nanai ethnic group to frequency in the Russian group, and the results are presented in Table 2. We did not discover any significant differences in frequency of the *CYP2C9*3*, *ABCB1*, or *SLCO1B1*5* polymorphism between Nanais and Russians. However, polymorphisms of the *CYP2C19* gene were found with significantly different frequency: the *CYP2C19*2*

Table 1 Results of genotyping the Nanai ethnic group

Polymorphism	*CYP2C9*2*^{C430T}, rs1799853	*CYP2C9*3*^{A1075C}, rs1057910	*CYP2C19*2*^{G681A}, rs4244285	*CYP2C19*3*^{G636A}, rs4986893/rs57081121	*CYP2C19*17*^{C806T}, rs12248560	*CYP2D6*4*^{G1846A}, rs3892097	*ABCB1*^{C3435T}, rs1045642	*SLCO1B1*5*^{T521C}, rs4149056
Subjects, n/alleles, n	70/140	70/140	70/140	70/140	70/140	70/140	70/140	70/140
*1/*1, n (%)	70 (100)	62 (88.6)	39 (55.7)	58 (82.9)	67 (95.7)	68 (97.1)	19 (27.1)	41 (58.6)
*1/*X, n (%)	0	8 (11.4)	28 (40)	12 (17.1)	3 (4.3)	2 (2.9)	39 (55.7)	25 (35.7)
*X/*X, n (%)	0	0	3 (4.3)	0	0	0	12 (17.1)	4 (5.7)
*1, n (%)	140 (100)	132 (94.3)	106 (75.7)	128 (91.4)	137 (97.9)	138 (98.6)	77 (55)	107 (76.4)
*X, n (%)	0	8 (5.7)	34 (24.3)	12 (8.6)	3 (2.1)	2 (1.4)	63 (45)	33 (23.6)
χ^2 (Hardy–Weinberg)	-	0.26	0.54	0.62	0.03	0.01	1.1	0.005
P	-	0.6	0.46	0.43	0.85	0.9	0.29	0.9

Notes: *1, nonmutant allele of the cytochrome/transporter; *X, minor-allele frequency; *1/*1, "wild" genotype; *1/*X, heterozygous genotype; *X/*X, mutant homozygous allele genotype. Differences significant at $P<0.05$.

Table 2 Comparison of frequencies of SNPs between Nanai and Russian groups

	Subjects, n/alleles, n		*X, n (%)		*P*-value[+]	OR	95% CI
	Nanai	Russian	Nanai	Russian			
*CYP2C9*3*	70/140	642/1,284[27,28]	8 (5.7)	74 (5.8)	1	0.99	0.47–2.1
*CYP2C19*2*	70/140	642/1,284[27,28]	34 (24.3)	158 (12.3)	0.0002	2.29	1.5–3.48
*CYP2C19*3*	70/140	290/580[27]	12 (8.6)	2 (0.3)	<0.0001	27.1	5.98–122.59
*CYP2C19*17*	70/140	971/1,942[29]	3 (2.1)	531 (27.3)	<0.0001	0.06	0.02–0.18
*CYP2D6*4*	70/140	642/1,284[27,28]	2 (1.4)	224 (17.4)	<0.0001	0.07	0.02–0.28
ABCB1	70/140	290/580[27]	63 (45)	315 (54.3)	0.059	0.69	0.48–0.99
*SLCO1B1*5*	70/140	1,071/2,142[15]	33 (23.6)	466 (21.8)	0.69	1.11	0.74–1.66

Notes: *X, minor allele frequency; [+]frequencies of Nanai vs Russian alleles compared using accurate Fisher criterion. Differences significant at $P<0.05$.
Abbreviations: CI, confidence interval; OR, odds ratio; SNPs, single nucleotide polymorphisms.

polymorphism was found more often in the Nanai group (24.3% vs 12.3% in the Russian population, $P=0.0002$); *CYP2C19*3* was also found more often in the Nanai group (8.3% vs 0.3% in the Russian population, $P<0.0001$); and *CYP2C19*17* was found more often in the Russian group (27.3% vs 2.1% in the Nanai group, $P<0.0001$). Besides, the *CYP2D6*4* polymorphism was found significant more rarely in the Nanai group than in the Russian one – 1.4% vs 17.4%. We made a likely functional characteristic of cytochrome activity for the Nanai and Russian populations for *CYP2C19*, *CYP2C19* and *CYP2D6* using CPIC guidelines (Table 3).[9,10]

Discussion

It is known that drug dosages are different for different ethnic groups. For example, the maximum recommended dose for 32% of medicines registered in the period 2001–2007 in the US was nearly twice that of the recommended dose of these drugs in Japan.[13] 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 drug efficacy and reduce the number of adverse drug reactions. This might help in determination of priorities in the introduction of pharmacogenetic testing to clinical practice in different regions of Russia, and could also reveal the peculiarities of prevalence of genetic predictors of heightened race/ethnic sensitivity to drugs.

There are a lot of native ethnic groups living in Russia comprising Asians and Caucasians. Studying the carriage of mutant alleles in different populations seems to be up to date, as far as optimization of the implementation of pharmacogenetic testing in clinical practice in different regions of Russia is concerned. Today, we have some data about the existence of polymorphisms in the Yakut population, a large ethnic group living in the Asian part of Russia; it is known that the frequency of *CYP2C19*2* is 18.1%, *CYP2C19*3* 3.1%, *CYP2C9*2* 5.1%, *CYP2C9*3* 6.7%, *SLCO1B1*5* 14%, and *VKORC1*^{G1639A} 83.2%.[14,15] Tatars and Bashkirs, ethnic groups living in the European part of Russia, have frequencies of *CYP2C9*2* of 5.1% and 6%, *CYP2C9*3* of 5.4% and 6.2%, and *CYP2D6*4* of 9.5% and 7.1%, respectively.[16,17] The Nenets have a frequency of *CYP2D6*4* of 7.3%.[18] However, we do not have any pharmacogenetic data for many ethnic groups in Russia, and we do not have such data for the Nanai people. We compared this to the frequency of the alleles of the studied polymorphisms in the Russian ethnic group.

CYP2C9

The *CYP2C9*2* polymorphism was not present in this sample, so χ^2 by Hardy–Weinberg was not calculated. In the Russian population, the frequency of this polymorphism

Table 3 Likely phenotypes in Nanai and Russian ethnic groups

	CYP2C9		*CYP2C19*		*CYP2D6*	
	Nanai	Russian[27,28]	Nanai	Russian[29]	Nanai	Russian[27,28]
EM	62 (88.6%)	440 (68.5%)	28 (40%)	317 (32.6%)	70 (100%)	619 (96.4%)
IM	8 (11.4%)	185 (28.8)	36 (51.4%)	251 (25.8%)	–	–
PM	0	17 (2.6%)	5 (7.1%)	17 (1.8%)	0	23 (3.6%)
UM	–	–	1 (1.4%)	386 (39.8%)	–	–
Total	70 (100%)	642 (100%)	70 (100%)	971 (100%)	70 (100%)	642 (100%)

Note: We used CPIC guidelines for interpretation of pharmacogenetic information.[9,10]
Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

was 11%. The frequency of the *CYP2C9*3* polymorphism in the Nanai population was 5.7% vs 5.8% in Russian population, but differences were not significant (P=1; Table 2). The differences in likely phenotypes of the *CYP2C9* gene were found, ie, slow metabolizers (intermediate metabolizer + poor metabolizer) were significantly rarer among the Nanai population: 2.7 times less than in the Russian population (odds ratio [OR] 0.28, 95% confidence interval [CI] 0.1–0.6; P=0.0003; Table 3). Peculiarities in ethnic differences in frequency of *CYP2C9*2* and *CYP2C9*3* polymorphisms have been described in the literature as Caucasians in Europe (12.1%–14.7% and 6.2%–8.4%) and Asians (0.6%–7.3% and 3.4%-11.7%), respectively.[19] Today, there are dosing guidelines by the CPIC and Dutch Pharmacogenetics Working Group (DPWG) for pharmacogenetic testing on the *CYP2C9* gene for the personalization of anticoagulant therapy, hypoglycemic therapy, and for some other drugs.[20]

CYP2C19

According to the results of the research, the frequency of the *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* polymorphisms in the Nanai ethnic group (24.3%, 8.6%, and 2.1%, respectively) significantly differed from that in the Russian ethnic group. Polymorphisms associated with slow activity (*CYP2C19*2* and *CYP2C19*3*) were found 1.9 (P=0.0002) and 28.6 (P<0.0001) times, respectively, more often in the Nanai population, and the *CYP2C19*17* polymorphism, associated with accelerated metabolism, was found 12.9 (P<0.0001) times more rarely (Table 2). Moreover, the "slow" (IM + PM)-likely phenotypes were found 2.1 times (OR 3.7, 95% CI 2.3–6.1; P<0.0001) more often and a "fast"-likely phenotype (ultrarapid metabolizer) found 28.4 times more rarely (OR 0.02, 95% CI 2.3–6.1; P<0.0001) in the Nanai group (Table 3). There are some ethnic differences in known polymorphism frequency, eg, Caucasians have frequencies of *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17* of 13.3%–16.2%, 0.1%–0.6%, and 20.1%–42%, and Asians of 18.5%–30.3%, 0.5%–6.9%, and 0.96%–13.7%, respectively.[6] Today, there are dosing guidelines from the CPIC and DPWG on pharmacogenetic testing on the *CYP2C19* gene for the personalization of clopidogrel, antidepressants, proton-pump inhibitors, and other drug therapies.[21]

CYP2D6

We studied the *CYP2D6*4* polymorphism, which was found 12.2 times more rarely in the Nanai population than in the Russian one (P<0.0001; Table 2). However, we did not find significant differences in likely phenotypes between the Russians and the Nanais (OR 0.19, 95% CI 0.01–3.1; P=0.15; Table 3). There are ethnic differences in polymorphism frequencies, eg, Caucasians have *CYP2D6*4* frequency of 18.5%–26.3% and Asians 0.42%–7.7%.[22] Today there are dosing guidelines from the CPIC, DPWG, and Canadian Pharmacogenomics Network for Drug Safety on pharmacogenetic testing on the *CYP2D6* gene for the personalization of tamoxifen, narcotic analgesics, antipsychotics, and some other drug therapies.[23]

ABCB1 C3435T

Of the Nanais studied, 45% percent had the T allele, the same as in the Russian population(P=0.059; Table 2). According to the literature, the frequency of the T allele in Caucasian and Asian populations is about 50% for each.[24] Today, there are no dosing guidelines from the CPIC, European Medicines Agency, or DPWG on using the $ABCB1*6^{C3435T}$ polymorphism for personalizing therapy for patients, but there has been research devoted to the influence of this SNP on the pharmacokinetics of clopidogrel.[12]

SLCO1B1

We studied the frequency of *SLCO1B1*5*: this was 23.6% in the Nanais vs 21.8% in Russian population (P=0.69; Table 2). There are some ethnic differences in known polymorphism frequency, eg, the frequency of *SLCO1B1*5* in Europe is 14%–23%, while in Asia it is less than 10%.[27] Today, there are dosing guidelines from the CPIC on pharmacogenetic testing for the personalization of statin therapy.[28]

Restrictions of the research

In our research, we compared the frequency of $CYP2C9*2^{C430T}$, $CYP2C9*3^{A1075C}$, $CYP2C19*2^{G681A}$, $CYP2C19*3^{G636A}$, $CYP2C19*17^{C806T}$, $CYP2D6*4^{G1846A}$, $ABCB1*6^{C3435T}$, and $SLCO1B1*5^{T521C}$ polymorphisms in Nanai and Russian ethnic groups. It was impossible to check the frequency of the $CYP2C9*2^{C430T}$ polymorphism against Hardy–Weinberg equilibrium, so we did not compare the frequency of its mutant alleles in Russian or Nanai groups. The Nanai group consisted of healthy volunteers, living on the territory historically occupied by this ethnic group. We chose Russian as the comparison group, as it is the largest ethnic group in the Russian Federation. We sought data on the frequency of the polymorphisms studied, and found two studies on Russian volunteers. The first focused on the $CYP2C9*2^{C430T}$, $CYP2C9*3^{A1075C}$, $CYP2C19*2^{G681A}$, $CYP2C19*3^{G636A}$, $CYP2D6*4^{G1846A}$, and $ABCB1*6^{C3435T}$ polymorphisms (European part of Russia).[29] The second focused

on *CYP2C9*2*^{C430T}, *CYP2C9*3*^{A1075C}, *CYP2C19*2*^{G681A}, and *CYP2D6*4*^{G1846A} (European part of Russia).[27] We combined the data, but neither the first nor the second study provided information on the *CYP2C19*17*^{C806T} and *SLCO1B1*5*^{T521C} polymorphisms. Moreover, we did not find any publications devoted to studying these SNPs among Russian volunteers, so we tried to use only the data of the research with maximal patient numbers where distribution by Hardy–Weinberg equilibrium was not significant. Patients from Moscow with stomach ulcers were included by the *CYP2C19*17*^{C806T} polymorphism, with χ^2 by Hardy–Weinberg of 1.12 (P=0.29).[28] Patients from Moscow with hyperlipidemia were included by the *SLCO1B1*5*^{T521C} polymorphism, with χ^2 by Hardy–Weinberg of 2.8 (P=0.09).[15]

Conclusion

We found *CYP2C9*3*^{A1075C}, *CYP2C19*2*^{G681A}, *CYP2C19*3*^{G636A}, *CYP2C19*17*^{C806T}, *CYP2D6*4*^{G1846A}, *ABCB1*6*^{C3435T}, and *SLCO1B1*5*^{T521C} polymorphisms in the Nanai ethnic group. Patients carrying these polymorphisms require a much more careful approach in choosing drug therapy, due to severe adverse reactions. Moreover, there are significant differences in the carrying of some polymorphisms between the Russians and the Nanais. Data obtained from this study will help to assess the priority of implementation of genotyping in the region. We must study the prevalence of the other polymorphisms among the Nanais and also estimate the frequency of the polymorphisms in other ethnic groups in Russia.

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Disclosure

The authors report no conflicts of interest in this work.

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