ORIGINAL RESEARCH

CYP2C19 polymorphism frequency in Russian patients in Central Russia and Siberia with acute coronary syndrome

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Purpose: The aim of this study is to investigate the frequency of *CYP2C19*2, *3* allelic variants, associated with poor response to clopidogrel, and *CYP2C19*17*, associated with excessive response to clopidogrel, in patients with acute coronary syndrome (ACS) from Siberia and Moscow regions of Russia.

Patients and methods: The study included 512 ACS patients who were subsequently treated with coronary arterial stenting. The subjects assigned were from the cities of Central (Novosibirsk, Kemerovo), Eastern (Irkutsk), Northern (Surgut) Siberia regions and from Moscow region. The mean age of patients enrolled was 63.9 ± 10.9 years. Among the assigned subjects, the proportion of men accounted for 80% and women 20%.

Results: According to the results obtained in the present study, from 16% up to 27.5% of patients in different regions of Russia have at least one *CYP2C19* "poor metabolizer" (PM) allele variant affecting clopidogrel metabolism and, therefore, suppressing its antiplatelet activity. *CYP2C19*17* allele variant was identified with the frequency of 15.4% up to 33.3%. The study revealed the presence of statistically significant differences in *CYP2C19*3* allele frequency between the Russian ethnic group patients from Eastern and Central Siberia ($p=0.001$; odds ratio=1.05 [95% confidence interval 1.01–1.09]).

Conclusion: The study revealed statistically significant differences between the allele frequencies in Eastern and Central Siberia, which can probably be caused by a considerable number of Buryats inhabiting Eastern Siberia.

Keywords: P2Y12 receptor inhibitors, clopidogrel resistance, dual antiplatelet therapy

Introduction

Over the recent decade, coronary heart disease (CHD) has been a leading cause of mortality as reported by the World Health Organization in 2014.[1] An estimated 7.4 million people died from CHD in 2012, accounting for 13.2% of the total number of deaths. A major concern of contemporary cardiology practice is considered to be prevention of stent thrombosis in patients with acute coronary syndrome (ACS). The stented patients are treated with antiplatelet therapy aimed at preventing stent occlusion.[2] Plavix (clopidogrel), as a part of dual antiplatelet therapy, is the most commonly used agent in Russian practice. Obviously, it is due to its affordability and generic versions availability, which reduces the treatment costs. However, according to European Society of Cardiology Guidelines, clopidogrel can no longer be recognized as a first-line therapy drug because of diminished response demonstrated by a number of patients. This resistance has been associated with genetic polymorphisms of *CYP2C19* affecting clopidogrel metabolism.[3] Therefore, it is crucial for antiplatelet therapy implementation to determine

the frequencies of important alleles of cytochrome *CYP2C19* gene. These polymorphism frequencies have not been much studied in Russian population, still less in Siberian region.

The allele of *CYP2C19* gene is classified into the so-called "poor" and "rapid" alleles affecting clopidogrel metabolism. Allele variants that affect *CYP2C19* isoenzyme metabolic activity the most are *CYP2C19*2* and *CYP2C19*3* (*Gly681Ala* and *Gly636Ala*, respectively). They were observed to be associated with reduced cytochrome activity,[4,5] while *CYP2C19*17 (Cys806Thr)* polymorphism is known to cause augmented substrate metabolism.[6]

It has been observed that carriers of at least one "poor metabolizer" (PM) allele of *CYP2C19* demonstrate higher residual platelet reactivity when on clopidogrel, which indicates poor clinical outcome in stented patients and higher risk of postoperative stent thrombosis.[7,8] Prevalence of carriers of two polymorphic *CYP2C19* alleles, affecting metabolism, is 15% and 35% in Caucasians and South and Central Asia population, respectively,[9] which is considered to be significant for Siberian heterogenetic population.[10]

This article is the first to present data on frequency of *CYP2C19*2, *3,* and *17* allele variants in patients with ACS from Siberian and Moscow regions of Russia.

Patients and methods

The study included 512 ACS patients from Russian ethnic groups who were subsequently treated with coronary arterial stenting. The subjects assigned were from the cities of Central (Novosibirsk, Kemerovo), Eastern (Irkutsk), Northern (Surgut) Siberia regions and from Moscow region.

Written informed consent was obtained from all participants before entering the study. The research has been approved by the local ethics committees (of State-Financed Health Institution "Irkutsk Regional Badge of Honour Clinical Hospital," Federal State-Financed Institution "Research Institute for Complex Issues of Cardiovascular Diseases" of Siberian Branch of the Russian Academy of Sciences, State-Financed Health Institution of Novosibirsk region "City Clinical Hospital № 1," State-Financed Institution of Khanty-Mansi Autonomous Okrug-Yugra District Cardiologic Dispensary "Center of Diagnostics and Cardiovascular Surgery," Institute of Chemical Biology and Fundamental Medicine of Siberian Branch of the Russian Academy of Sciences, Federal State-Financed Institution of Further Professional Education "Russian Medical Academy of Postgraduate Education" of Ministry of Health of the Russian Federation, Pirogov City Clinical Hospital № 1).

The mean age of patients enrolled was 63.9±10.9 years. Among the assigned subjects, the proportion of men accounted for 80% and women 20%. All the patients were administered dual antiplatelet therapy – clopidogrel (300 mg – loading dose, 75 mg – maintenance dose) as a part of complex medication therapy. The subjects were also given pharmacogenetic testing provided by Pharmacogenomics Laboratory of the Institute of Chemical Biology and Fundamental Medicine, SB RAS and the Research Center of Federal State-financed Institution of Further Professional Education "Russian Medical Academy of Postgraduate Education" of Ministry of Health of the Russian Federation.

CYP2C19 genotyping

The study was conducted on the blood samples (4 mL) collected from the veins of the bend of the elbow with ethylene diamine tetraacetate vacutainer tubes VACUETTE® (Greiner Bio-One, Austria). This procedure was performed on the 3rd–5th days as of hospitalization date. DNA extraction from leukocytes was carried out using laboratory reagents kit "DNA – EKSTRAN-1" (ZAO Syntol, Russia). Isolated DNA was then being stored at –80°C. Genotyping of *CYP2C19*2, CYP2C19*3,* and *CYP2C19*17* allele variants was performed with "Pharmacogenetics Clopidogrel" (DNA-Technology Ltd, Russia). Genotyping for *CYP2C19* was performed with the use of an oligonucleotide ligation assay after initial specific amplification by means of a polymerase chain reaction (PCR) involving three primers for the major variant alleles *CYP2C19*2 (c.G681A; rs4244285), CYP2C19*3 (c.G636A;rs4986893)*, and *CYP2C19*17 (c.C806T; rs12248560)*. Primers: 5′-GATATGCAATAATTTTCCCAC-TATCATTG-3′ and 5′-GGTGTTCTTTTACTTTCTC-CAAAATATCAC-3′ were used to amplify sequence of the *CYP2C19*2* 681G.A (rs4244285) in exon 5; for *CYP2C19*3* (c.636G>; rs4986893), we used 5′-CACCCT-GTGATCCCACTTTC-3′ and 5′-ACTTCAGGGCTTG-GTCAATA-3′; for *CYP2C19*17* (c.C806T; rs12248560), we used 5′-AAATTTGTGTCTTCTGTTCTCAAA-3′ and 5′-AATCCCAGTTCTGCCAGCTA-3′. The sequence of the G allele-specific probe was 5′-FAM-TTATTTCCC-GGGAACC-3′, and the sequence of the A allele-specific probe was 5′-VIC-ATTATTTCCCAGGAACC-3′.

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 a TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's instructions, using an ABI PRISM® Sequence Detector 7000 (Applied Biosystems). All the PCR reactions were carried

out in a 10-μL reaction volume containing genomic DNA 10 ng, oligonucleotide primers 0.5 pM, 1 μL 10 PCR buffer, deoxynucleotides (dNTPs) 250 μM, magnesium chloride 3 mM, and DNA polymerase 0.25 U. The cycling program involved preliminary denaturation at 95°C for 10 min, followed by 30 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 60 s, and elongation at 72°C for 60 s, followed by a final elongation step at 72°C for 7 min (18). *CYP2C19 *1/*1* carriers are designated as "extensive metabolizers," *CYP2C19*2* or *CYP2C19*3* carriers *(*2/*2, *2/*3, *3/*3)* as "PMs," and *CYP2C19 (*1/*2, *1/*3, *2/*17, *3/*17)* carriers as "intermediate metabolizers" (IMs). *CYP2C19*17 (*1/*17, *17/*17)* carriers are designated as "ultra-rapid metabolizers" (UMs).

Statistical analysis

Statistical processing of the results was performed using the GraphPad InStat (GraphPad). Mean values are presented as M±SD, where M is mean and SD is standard deviation. To determine distinctions in categorical variables between groups, the Pearson's chi-squared (χ^2) test was used. To check on compliance with the Hardy–Weinberg equilibrium, the Fisher's exact test was applied. Differences with $p < 0.05$ were regarded as significant.

Results

The present study was designed to investigate the frequency of *CYP2C19* "PM" allele variants (*CYP2C19*2, CYP2C19*3*) associated with increased risk of stent thrombosis and frequency of "rapid metabolizer" allele variants (*CYP2C19*17*), associated with increased risk of clopidogrel-induced bleedings. Five hundred and twelve Russian ethnic group patients from Central Russia (Moscow region), Northern, Central, and Eastern Siberia, presented with ACS, were enrolled in the study. The frequencies of the alleles and genotypes analyzed are shown in Table 1.

Among the 87 cardiac patients from Northern Siberia, frequencies of "PM" allele variants (*CYP2C19*2, CYP2C19*3*) were 14.9% and 0.5%, respectively. At the same time, almost one-third (27.5%) of the patients carried at least one *CYP2C19*2 (*1/*2+*2/*2)* allele. Frequency of *CYP2C19*17* allele variant 33.3%, and almost half of the patients (49.4%) carried at least one *CYP2C19*17 (*1/*17+*17/*17)* allele. The genotype distribution presented in Table 1 showed no deviation from the Hardy–Weinberg equilibrium for "PM" allele variants (*2: χ^2=0.002, p=0.96; *3: χ^2=0.002, p=0.95), though there was deviation revealed for "extensive metabolizer" ones (*17: χ^2=6.6, p=0.01).

In 222 Russian ethnic group patients from Central Siberia, the frequency of the most common "PM" allele variant *CYP2C19*2* was 11.05%. No subject with the rarer allele variant *CYP2C19*3* was detected. Carriers of at least one *CYP2C19*2 (*1/*2+*2/*2)* allele amounted to 22.1% of the patients studied. Frequency of "extensive metabolizer" allele variant *CYP2C19*17* was 17.1% of patients with one-third of them (31.1%) carrying at least one *CYP2C19*17 (*1/*17+*17/*17)* allele. The genotype distribution (Table 1) showed no deviation from Hardy–Weinberg's equilibrium (*2: χ^2=3.4, p=0.06; *17: χ^2=0.05, p=0.08).

In 122 Russian ethnic group patients from Eastern Siberia, the frequencies of *CYP2C19*2* and *CYP2C19*3* allele variants were 10.6% and 2.85%, respectively. Nearly quarter of the patients (20.5%) carried at least one *CYP2C19*2 (*1/*2+*2/*2)* allele. The *CYP2C19*17* allele frequency was 22.2%, with 40.1% of the patients carrying at least one *CYP2C19*17 (*1/*17+*17/*17)* allele. The genotype distribution showed no deviation from Hardy–Weinberg's equilibrium for *CYP2C19*2* (χ^2=0.13, p=0.71) and *CYP2C19*17* (χ^2=0.01, p=0.91), though there was deviation revealed for *CYP2C19*3* (χ^2=8.5, p=0.003).

In 81 ACS patients of Russian ethnic group (Central Russia [Moscow region]), the *CYP2C19*2* frequency was 8.0%. No subject with *CYP2C19*3* allele variant was detected in this group. Carriers of at least one *CYP2C19*2* allele variant amounted to less than quarter of the patients (16.0%). The *CYP2C19*17* allele variant frequency was 15.4%, with almost one-third of the patients (29.6%) carrying at least one *CYP2C19*17 (*1/*17+*17/*17)* allele. The allele and genotype distribution showed no deviation from Hardy–Weinberg's equilibrium: (*2: χ^2=0.61, p=0.43; *17: χ^2=0.42, p=0.42).

Differences in the frequencies of *CYP2C19* "poor" and "rapid metabolizer" allele variants between four different groups of patients were measured by Fisher's exact test. Statistically significant difference was found only between Central and Eastern Siberia patients (*p*=0.001; Table 1).

Discussion

As cytochrome enzymes (CYP2C9, CYP2D6, CYP2B6, CYP3A4, CYP3A5, and CYP2C19) 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. Particularly, knowing the *CYP2C19* phenotype ("extensive metabolizers," "PMs," "IMs," and "UMs") of a patient may help in prescribing optimum dose

Table 1 Allele and genotype frequencies and comparison between Russian acute coronary syndrome patients according to geographical region: Moscow region, Northern, Central, and Eastern Siberia (Fisher's exact test)

Allele and genotype n (%)	Geographical region of residence			
CYP2C19*2	Northern Siberia	Central Siberia	Eastern Siberia	Moscow region
N	87	222	122	81
*1/*1	63 (72.4)	173 (77.9)	97 (79.5)	68 (84.0)
*1/*2	22 (25.3)	49 (22.1)	24 (19.7)	13 (16.0)
*2/*2	2 (2.3)	0 (0.0)	1 (0.8)	0 (0.0)
*2 (%)	14.9	11.5	10.6	8.0
Central Siberia	p=0.307; OR=0.92 (95% CI 0.8–1.07)[a]	NA	NA	NA
Eastern Siberia	p=0.24; OR=0.91 (95% CI 0.77–1.06)	p=0.78; OR=0.98 (95% CI 0.87–1.09)	NA	NA
Moscow region	p=0.09; OR=0.86 (95% CI 0.73–1.01)	p=0.33; OR=0.92 (95% CI 0.82–1.04)	p=0.46; OR=0.94 (95% CI 0.83–1.08)	NA
CYP2C19*3	–	–	–	–
*1/*1	86 (98.9)	222 (100.0)	116 (95.1)	81 (100.0)
*1/*3	1 (1.1)	0 (0.0)	5 (4.1)	0 (0.0)
*3/*3	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
*3 (%)	0.5	0.0	2.8	0.0
Central Siberia	p=0.28; OR=0.98 (95% CI 0.96–1.01)	NA	NA	NA
Eastern Siberia	p=0.24; OR=1.01 (95% CI 0.99–1.08)	p=0.001; OR=1.05 (95% CI 1.01–1.09)	NA	NA
Moscow region	p=1.0; OR=0.98 (95% CI 0.96–1.01)	Comparison impossible	p=0.46; OR=0.94 (95% CI 0.83–1.08)	NA
CYP2C19*17	–	–	–	–
*1/*1	44 (50.6)	153 (68.9)	73 (59.8)	57 (70.4)
*1/*17	28 (32.2)	62 (27.9)	43 (35.2)	23 (28.4)
*17/*17	15 (17.2)	7 (3.2)	6 (4.9)	1 (1.2)
*17 (%)	33.3	17.1	22.2	15.4
Central Siberia	p=0.07; OR=0.82 (95% CI 0.67–1.02)	NA	NA	NA
Eastern Siberia	p=0.76; OR=0.95 (95% CI 0.74–1.21)	p=0.09; OR=1.15 (95% CI 0.97–1.36)	NA	NA
Moscow region	p=0.09; OR=0.81 (95% CI 0.63–1.03)	p=0.88; OR=0.97 (95% CI 0.82–1.15)	p=0.13; OR=0.85 (95% CI 0.69–1.04)	NA

Note: [a]Fisher's exact test not applicable.
Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

of drug and in predicting the increased risk of adverse reactions to achieve better therapeutic outcomes. This gives the possibility to predict both individual and population risk of clopidogrel-induced adverse cardiovascular events and treatment inefficiency. The evaluation of the interindividual differences in the prevalence of CYP2C19 gene polymorphisms is very important in the countries such as Russian Federation because of the high multinationality. The results of the pharmacogenetic investigation may be beneficial for developing guidelines for CYP2C19 genotype-directed antiplatelet therapy for each region of the Russian Federation.

According to the results obtained in the present study, from 16% up to 27.5% of patients with ACS in different regions of Russia have at least one CYP2C19 "PM" allele variant (*1/*1+*1/*2) affecting clopidogrel metabolism

and, therefore, suppressing its antiplatelet activity. Thus, it results in increased risk of thrombotic event, in particular stent thrombosis for ACS patients after percutaneous coronary intervention.[11] Frequency of CYP2C19*2 allele variant among Russian ACS patients from Northern, Central, and Eastern Siberia was close to that observed among Russian patients from Moscow region, revealed in other previously published studies on stable ACS patients. The study revealed statistically significant differences between the allele frequencies in Eastern and Central Siberia, which can probably be caused by considerable number of Buryats inhabiting Eastern Siberia. Statistically significant differences between CYP2C19*3 allele frequencies observed in Central Siberia and Eastern Siberia can probably be caused by considerable number of Buryats inhabiting Eastern Siberia: Buryats,

indigenous population of Irkutsk region, account for 2.3% of total Irkutsk population while they hardly exceed 0.09% in Kemerovo and Novosibirsk cities. Furthermore, there are less people of Russian ethnic group living in Irkutsk (87% vs. 94.6% and 92.8% in Kemerovo and Novosibirsk, respectively).[12–14]

CYP2C19 polymorphism in Russians with ACS and stable CHD from various geographical regions

The results obtained from this study on ACS patients were compared with those of the previously published data on frequencies of *CYP2C19* allele variants (*CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17*) in Russian ethnic group patients with CHD.[15–17] *CYP2C19*2* prevalence was observed to be significantly higher in Russian patients with stable coronary heart disease (CHD) from Moscow region,[15] when compared with that in the Central Russian (Moscow region) patients enrolled in the current study (15.05% vs. 8%; *p*=0.03; odds ratio [OR]=1.18 [95% confidence interval {CI} 1.01–1.38]). Similarly, *CYP2C19*3* prevalence was higher in Russian patients in the study conducted by Mirzaev et al as compared to that among the patients from Central Siberia enrolled in the current study (*p*=0.002; OR=1.05 [95% CI 1.006–1.01]). Finally, the prevalence of *CYP2C19*17* allele variant was higher among Russian patients from Northern Siberia, when compared with that observed among Russian CHD patients from Moscow region studied by Komarov et al (33.3% vs. 20.6%; *p*=0.01; OR=0.77 [95% CI 0.62–0.96]).[16] There were no statistically significant differences between *CYP2C19*2* and *CYP2C19*3* allele variants frequencies in the patients of the current study when compared with those in the patients with chronic CHD from Tomsk (Western Siberia) (*p*>0.05).[3] Among Ural ACS patients (Chelyabinsk city), treated with coronary stent implantation, frequencies of *CYP2C19*2* and *CYP2C19*3* allele variants were 12.5% and 0.0%, respectively, and no statistically significant differences compared from the data of this study (*p*>0.05).[18]

Allele frequencies of *CYP2C19* from different ethnic populations in the Russian Federation and other countries

The frequency of *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* polymorphisms differs markedly in human populations (Table 2). According to the published data, the highest frequency of *CYP2C19*2* allele occurs in healthy

Table 2 CYP2C19*2, CYP2C19*3, and CYP2C19*17 frequencies in human populations

CYP2C19 allele (%)	Human populations			
	European[28]	Asian[29]	Hispanic[30]	African[31]
CYP2C19*2	15.1	34.5	12.6	12.6
CYP2C19*3	0.0	9.0	0.0	1.0
CYP2C19*17	25.7	0.5	14.0	17.2

volunteers among Pacific Islands population accounting for 63.3%,[19] while the rarest frequency is observed among Dargins (6%).[20] The highest frequency of *CYP2C19*3* allele variant was observed among the Pacific Islands population – 14.4%.[19] *CYP2C19*17* allele variant prevalence in ethnic groups: 25.7%, 22.0%, and 20.0% among Germans, Norwegians, and Swedes, respectively,[21] but in Chinese and Tai – 2.6% and 4.3%.[22,23] According to the previously published studies, the highest frequency of *CYP2C19*17* allele variant was reported to occur among Lithuanian ACS patients (31%) and Russian patients diagnosed with peptic ulcer (27.4%).[24,25] Our results indicate that *CYP2C19*17* allele variant frequency was 33.3% among Russian ethnic group patients from Northern Siberia, thus exceeding the frequency revealed in the previously published studies.

The ethnic distribution of *CYP2C19* in Russia was investigated among Tatars, Carachays, Circassians, Ingushes, Chechens, Kalmyks, Avars, Laks, Dargins, Bashkirs, Yakuts, Buryats, Altayans, and Tuvinians in previous studies (Table 3).

Table 3 Frequency distribution of *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* allele variants among ethnic groups in Russia

Ethnic groups	Type of subjects	Allele frequencies		
		*2	*3	*17
Russians[15]	CHD	0.12	0.0	0.22
Russians[16]	CHD	0.15	0.0	0.14
Tatars[32]	Healthy	0.12	0.21	n.d.
Kalmyks[33]	Healthy	0.15	n.d.	n.d.
Tuvinians[34]	Healthy	0.15	0.02	n.d.
Buryats[34]	Healthy	0.21	0.07	n.d.
Yakuts[34]	Healthy	0.23	0.05	n.d.
Altayans[34]	Healthy	0.15	0.04	n.d.
Chechens[33]	Healthy	0.13	n.d.	n.d.
Carachays[35]	Healthy	0.14	n.d.	n.d.
Circassians[35]	Healthy	0.19	n.d.	n.d.
Ingushes[33]	Healthy	0.08	n.d.	n.d.
Laks[20]	Healthy	0.14	n.d.	n.d.
Dargins[20]	Healthy	0.05	n.d.	n.d.
Avars[20]	Healthy	0.13	n.d.	n.d.

Abbreviations: CHD, coronary heart disease; n.d., no data.

The results of the study demonstrated that 38.0% of Kalmyks, 23.0% of Russians, 20.0% of Tatars, 18.0% of Chechens, and 12.0% of Ingushes carried at least one *CYP2C19*2* allele variant. Relatively high frequencies of *CYP2C19*2* allele variants and genotypes among Kalmyk population are determined by their Mongoloid origin. The prevalence of *CYP2C19*2* polymorphic marker was not limited to Ingush and Chechen populations but proved to be identified among other five Caucasus populations, such as Carachays, Circassians, Laks, Dargins, and Avars (Table 3). Frequencies of *CYP2C19*2* "PM" allele variant among Carachay and Circassian populations were 18.8% and 14.0%, respectively. According to the results obtained, 31.2% of Circassians and 26.4% of Carachays carried at least one *CYP2C19*2* allele variant, while frequency of this allele variant among Avar, Lak, and Dargin populations accounted to 12.7%, 14.5%, and 5.0%, respectively (Table 3). Frequency of *CYP2C19*2* allele variant among Dargin population was identified as relatively low when compared with other ethnic groups. Therefore, further research on bigger samples is required. *CYP2C19* allele frequency observed in this region was similar to average meanings for most European populations (Table 2). Additionally, *CYP2C19*2,*3* polymorphic marker prevalence has been identified among Bashkirs[26], Yakuts, Buryats, Altayans, and Tuvinians with the results being similar to those on Asian population (Table 2). In the study on 130 Russian subjects from Tomsk city, Freidin et al investigated 67 women and 63 men (with mean age being 39±13.5) diagnosed with allergic disease. The results of the research demonstrated that the frequency of *CYP2C19*2* allele variant was 17.4%, and *CYP2C19*1/*1*, *CYP2C19*1/*2*, and *CYP2C19*2/*2* genotypes distribution accounted for 66.9% (81), 31.4% (38), and 1.7% (2), respectively.[27] *CYP2C19*17* allele variant has been identified in the Central Russia (Moscow city) among patients with peptic ulcer and its frequency accounted for 27.4%,[25] while the result obtained in the present study accounted for 15.4%.

Conclusion

The variability in the distribution of *CYP2C19*2, *3*, and *17* among populations reflects a population-specific pattern, which stresses the need to genotyping these alleles for the patients. The results of the present study will facilitate physicians prescribing clopidogrel by providing an approximate percentage of "poor" and UMs in Russians and may be helpful for development of guidelines for *CYP2C19* genotype-directed antiplatelet therapy in Russian patients with ACS.

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