Cytoschrome 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 2003 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%).

Conclusion: The results of the investigation will be beneficial for developing guidelines for CYP2C19 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

Individuals’ 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 and 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 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-mephentoin. Later in 1993 Wrington et al. [6] found that S-mafenitoin 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 (10q4.1-24.3).

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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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/*1); 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 allelic variations and frequencies for different ethnic groups in Russian Federation. A literature review was conducted using the following databases: MEDLINE and eLIBRARY.

Table 1: Allele and genotype frequencies of CYP2C19 gene in different ethnic groups in Russia.

<table>
<thead>
<tr>
<th>Ethnic groups</th>
<th>Region Of Russian Federation</th>
<th>n</th>
<th>Polymorphic marker</th>
<th>Population characteristics</th>
<th>Genotypes</th>
<th>Allelic variants</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russians</td>
<td>Tomsk</td>
<td>130</td>
<td>*2</td>
<td>Allergic diseases</td>
<td>81 (66.9)</td>
<td>0.83</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td>Tomsk</td>
<td>62</td>
<td>*2,*3</td>
<td>lymphoproliferative disorders</td>
<td>n.d.</td>
<td>0.86</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Moscow and the Moscow Region</td>
<td>395</td>
<td>*2</td>
<td>Ischemic heart disease</td>
<td>288 (72.7)</td>
<td>0.85</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td>Moscow and the Moscow Region</td>
<td>40</td>
<td>*2,*3,*17</td>
<td>Ischemic heart disease</td>
<td>20 (50.0)</td>
<td>0.71</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>Tomsk</td>
<td>146</td>
<td>*2</td>
<td>Healthy</td>
<td>111 (76.1)</td>
<td>0.83</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Tomsk</td>
<td>82</td>
<td>*2</td>
<td>Healthy</td>
<td>64 (78.0)</td>
<td>0.88</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Astrakhan</td>
<td>52</td>
<td>*2</td>
<td>Healthy</td>
<td>40 (77.0)</td>
<td>0.85</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Voronezh</td>
<td>290</td>
<td>*2,*3</td>
<td>Healthy</td>
<td>228 (78.7)</td>
<td>0.86</td>
<td>[38]</td>
</tr>
<tr>
<td>Tatars</td>
<td>Kazan</td>
<td>97</td>
<td>*2</td>
<td>Ischemic heart disease</td>
<td>76 (78.4)</td>
<td>0.86</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td>Astrakhan</td>
<td>50</td>
<td>*2</td>
<td>Healthy</td>
<td>40 (80.0)</td>
<td>0.87</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Astrakhan</td>
<td>50</td>
<td>*2</td>
<td>Healthy</td>
<td>31 (62.0)</td>
<td>0.85</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>The Republic of Tuva</td>
<td>88</td>
<td>*3</td>
<td>Healthy</td>
<td>84 (95.4)</td>
<td>0.98</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>The Republic of Buryatiya</td>
<td>88</td>
<td>*2</td>
<td>Healthy</td>
<td>54 (61.3)</td>
<td>0.79</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>The Republic of Buryatiya</td>
<td>88</td>
<td>*3</td>
<td>Healthy</td>
<td>77 (87.5)</td>
<td>0.93</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>The Sakha Republic (Yakutia)</td>
<td>88</td>
<td>*2</td>
<td>Healthy</td>
<td>54 (61.3)</td>
<td>0.77</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Altai Republic</td>
<td>87</td>
<td>*2</td>
<td>Healthy</td>
<td>64 (73.5)</td>
<td>0.85</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Altai Republic</td>
<td>87</td>
<td>*3</td>
<td>Healthy</td>
<td>80 (92.0)</td>
<td>0.96</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Chechens</td>
<td>50</td>
<td>*2</td>
<td>Healthy</td>
<td>41 (82.0)</td>
<td>0.87</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Carachays</td>
<td>125</td>
<td>*2</td>
<td>Healthy</td>
<td>92 (73.6)</td>
<td>0.86</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Circassians</td>
<td>77</td>
<td>*2</td>
<td>Healthy</td>
<td>55 (68.8)</td>
<td>0.81</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Ingushes</td>
<td>50</td>
<td>*2</td>
<td>Healthy</td>
<td>44 (88.0)</td>
<td>0.92</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Dagestans (Laks, Dargins, Avars)</td>
<td>30</td>
<td>*2</td>
<td>Healthy</td>
<td>26 (86.7)</td>
<td>0.93</td>
<td>[32]</td>
</tr>
</tbody>
</table>

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
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, 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, Kalmuks 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 Kalmuks – 25%; 11.0% in Chechens; 14% in Tatars; 8.0% in Ingushes.

The difference between CYP2C19 genotype (Table 1) frequencies among Kalmuks and Ingushes (χ²=5.765, p=0.0163) as well as between the Kalmuks and the Chechens (χ²=3.6, p=0.0289) were statistically significant. Relatively high allele and genotype CYP2C19*2 frequencies in Kalmuks are natural, as Kalmuks belong to Mongolian race. The cause of low incidence of the CYP2C19*2 allele 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 prevalence was higher among the Asian population, with the highest rate in Kalmuks - 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, Kalmuks, Yakuts, Tuvinians, 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 multinatinality. 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.

- 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.

References


