DOI: 10.20514/2226-6704-2021-12-2-123-128 УДК [616.092.6:575.174.015.3]:616.34-085](571.54/.55)

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КЛИНИЧЕСКАЯ ЗНАЧИМОСТЬ ПОЛИМОРФИЗМА ГЕНА ЦИТОХРОМА P4502C19(681G/A) У ЖИТЕЛЕЙ ЗАБАЙКАЛЬСКОГО КРАЯ ПРИ ЛЕЧЕНИИ КИСЛОТО-ЗАВИСИМЫХ ЗАБОЛЕВАНИЙ

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Clinical Significance of Cytochrome P4502C19 (681G/A) Gene Polymorphism in Residents of the Trans-Baikal Territory in Treatment of Acid-Dependent Diseases

Резюме

Цель исследования. Изучить полиморфизм CYP2C19(681A/G) среди населения Забайкальского края в сравнении с данными в других регионах мира и России. **Материалы и методы.** Проведено генетическое типирование CYP2C19(G681A) у 132 человек (81 женщина и 53 мужчины) проживающих на территории Забайкальского края, медиана возраста составила 47 (18; 72) лет. Отклонения распределений генотипов изученного полиморфного локуса от распределения Харди-Вайнберга оценено с использованием критерия хи-квадрат. Сравнительный анализ полученных данных проведен с помощью критерия Фишера. Различия считали значимыми при p <0,05. **Результаты.** Распространенность CYP2C19(681G/G) составила 105 человек (79,6%), CYP2C19(681G/A) — 25 лиц (18,9%) и CYP2C19(681A/A) — 2 участника (1,5%). Аллель А гена CYP2C19 в 681 положении встречался в 14,2%. Аллель А реже встречается в популяции Забайкальского края, по сравнению с азиатами (Китай p <0,001; Япония p=0,015) и не отличался в распространенности от коренных американцев, латиноамериканцев, афроамериканцев, жителей Московской, Воронежской, Иркутской областей и Саха-Якутии. CYP2C19(681A/A) чаще встречался в азиатской популяции, чем среди забайкальцев, p=0,003. Распространенность генотипа CYP2C19(681A/A) не отличалась между популяцией Забайкальского края афроамериканцами, европеоидами, населением Московской и Воронежской области. **Заключение.** Распространенность аллеля А полиморфного локуса 681G/A CYP2C19 в популяции Забайкальского края составила 14,2% и оказалась сопоставимой с европеоидами, но встречалась реже, чем у китайцев и в японской популяции. Распространенность генотипа CYP2C19(681A/A) составила 1,5%, что соответствовало мировым данным среди европеоидных популяций и встречалась реже, чем у азиатов.

Ключевые слова: *полиморфизм, цитохром P450, аллель, CYP2C19(681A/G)*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов.

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 31.05.2021 г.

Принята к публикации 25.11.2021 г.

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Для цитирования: Жилина А.А., Ларева Н.В., Лузина Е.В. и др. КЛИНИЧЕСКАЯ ЗНАЧИМОСТЬ ПОЛИМОРФИЗМА ГЕНА ЦИТОХРОМА P4502C19(681G/A) У ЖИТЕЛЕЙ ЗАБАЙКАЛЬСКОГО КРАЯ ПРИ ЛЕЧЕНИИ КИСЛОТО-ЗАВИСИМЫХ ЗАБОЛЕВАНИЙ. Архивъ внутренней медицины. 2022; 12(2): 123-128. DOI: 10.20514/2226-6704-2021-12-2-123-128

Abstract

Aims. To study the CYP2C19(681A/G) polymorphism among the population of the Trans-Baikal Territory in comparison with data in other regions of Russia and the world. **Materials and methods.** The study involved 132 people (81 women and 53 men). The median age was 47 (18; 72) years. Genotyping of the 681G/A polymorphic locus of the CYP2C19 gene was performed by polymerase chain reaction. **Results.** The prevalence of CYP2C19(681G/G) was 105 people (79.6%), CYP2C19(681G/A) — 25 people (18.9%) and CYP2C19(681A/A) — 2 participants (1.5%). Allele A of the CYP2C19 gene in position 681 was found in 14.2%. Allele A is less common in the population of the Trans-Baikal Territory, compared with Asians (China, p <0.001; Japan, p = 0.015) and did not differ in prevalence from Native Americans, Hispanics, African Americans, residents of Moscow, Voronezh, Irkutsk regions and Sakha-Yakutia. CYP2C19(681A/A) was more common in the Asian population than among the Transbaikalians, p = 0.003. The prevalence of the CYP2C19(681A/A) genotype did not differ between the population of the Trans-Baikal Territory, African Americans, Caucasians, and the population of the Moscow and Voronezh regions. **Conclusions.** The prevalence of the allele A in the population of the Trans-Baikal Territory was 14.2% and was comparable to the Caucasians, but less common than in the Asian population. The prevalence of the CYP2C19(681A/A) was 1.5%, which was consistent with world data among Caucasoid populations and was less common than in Asians.

Key words: *polymorphism, cytochrome P450, allele, CYP2C19(681A/G)*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 31.05.2021

Accepted for publication on 25.11.2021

For citation: Zhilina A.A., Lareva N.V., Luzina E.V. et al. Clinical Significance of Cytochrome P4502C19 (681G/A) Gene Polymorphism in Residents of the Trans-Baikal Territory in Treatment of Acid-Dependent Diseases. The Russian Archives of Internal Medicine. 2022; 12(2): 123-128. DOI: 10.20514/2226-6704-2021-12-2-123-128

ADDs — acid-dependent diseases, CYP — cytochrome P450, GERD — gastroesophageal reflux disease, PPIs — proton pump inhibitors

One of the reasons for adverse drug reactions is the differences in the mechanisms of drug interactions mediated by various enzymes of the cytochrome P450 (CYP) family [2]. Cytochrome P450 is a superfamily of enzymes that catalyze the metabolism of medications and other substances. Genetic polymorphism in CYP is the main reason for individual differences in drug responses ranging from side effects to lack of efficacy. Of the 50 cytochrome P450 isoenzymes identified, more than 20 are functionally polymorphic (e.g., CYP2A6, CYP2C9, CYP 2C19, CYP2D9, CYP1B1 and CYP1A2). CYP2C19 is the most polymorphic member of the CYP2C subfamily. It catalyzes the metabolism of medications, including proton pump inhibitors [1]. One of the most common and potentially dangerous diseases today is gastroesophageal reflux disease (GERD); the prevalence of this disease tends to increase and significantly worsens the quality of life of patients. GERD is based on the reflux of stomach contents into the esophagus, i.e. gastroesophageal reflux. Proton pump inhibitors (PPIs) are the drugs of choice to relieve reflux symptoms and epithelialize erosions on the esophageal mucosa [2]. Despite that, these medications are far from "perfect" antisecretory agents, they have the most significant and long-term acid-suppressive capacity compared to antacids and H2 blockers of histamine receptors [2]. Cytochrome P450 2C19 (CYP2C19) plays a key role in PPI metabolism [3]. It particularly determines the rate of PPI metabolism, which varies in different ethnic groups due to the phenomenon of genetic polymorphism. There are currently 27 allele variants of CYP2C19; among them, CYP2C19*2, CYP2C19*3 and CYP2C19*17 alleles are described in the most detail [3]. The prevalence of mutant alleles in the population of patients with acid-dependent diseases can affect the outcome of treatment [4].

Genetic polymorphism of CYP2C19 results in individual differences in enzyme expression and metabolic activity. Allelic variation classifies the population according to CYP2C19 catalytic activity into slow, extensive and ultra-rapid drug clearance phenotypes [1]. Among all nonfunctional alleles, CYP2C19*2 (681G/A) is the most significant [3]. Patient genotyping for this gene can optimize the management of acid-dependent diseases (ADDs). It is known that the prevalence of polymorphic alleles varies in different populations [1]. To date, there are no data on the prevalence of the 681G/A polymorphic locus of CYP2C19 gene in the population of Trans-Baikal Territory, which does not allow us to assess the need for genotyping this gene in order to improve the quality of treatment for patients with acid-dependent diseases.

Objective of the Study

To analyze the prevalence of genotypes and alleles of the 681G/A polymorphic locus of the CYP2C19 gene among the population of Trans-Baikal Territory in comparison with data from other regions of Russia and the world; to assess the need for genotyping this polymorphic locus in clinical practice for patients with ADDs.

Materials and Methods

The study involved 132 subjects (81 females and 53 males). The study group included 79 patients with gastroesophageal reflux disease (30 males and 49 females), median age 44.5 (33; 57). The patients were examined and treated by a gastroenterologist at the diagnostic local clinic of the Federal State Budgetary Educational Institution of Higher Education Chita State Medical Academy of the Russian Ministry of Health from 2018 to 2020. GERD was diagnosed in patients based on the data of daily pH-impedancemetry and endoscopic examination of the upper gastrointestinal tract, according to the clinical guidelines of the Russian Gastroenterological Association (2017) [5].

We carried out a prospective single-center study. Patients with other chronic non-communicable diseases were excluded from the study. *It was decided to expand the cohort of participants based on a control group (apparently healthy individuals) who underwent a preventive medical examination at the diagnostic local clinic* — Federal State Budgetary Educational Institution of Higher Education Chita State Medical Academy of the Ministry of Health of Russia ═53 subjects (24 males and 29 females), age 45 (28; 62) because, as a result of statistical data processing, no differences were found in the prevalence of polymorphic variants of the CYP2C19*2 gene. All respondents who agreed to take part in the study were born and have lived in Zabaykalsky Krai for at least three generations and described themselves as Caucasians. Therefore, a group of 132 individuals (54 males and 78 females) was formed, median age was 47 (18; 62). This study followed the ethical principles of the Declaration of Helsinki. The study was approved by the local Ethics Committee at the Chita State Medical Academy, Chita, protocol No. 83, dated October 22, 2016.

Genotyping of the 681G/A polymorphic locus of the CYP2C19 gene was carried out by polymerase chain reaction. DNA samples isolated from peripheral venous blood WBC were the material for genetic analysis. Visualization of the amplification products was performed by electrophoresis in 3% agar gel with the addition of ethidium bromide with UV detection. We used standard kits for the studied SNPs manufactured by Litekh Research and Production Company (Moscow). Genetic tests were performed in the molecular genetics laboratory of the Research Institute of Molecular Medicine of the Chita State Medical Academy of the Ministry of Health of Russia.

Data were collected using MS Excel. Calculations were carried out using the online Hardy-Weinberg equilibrium calculator, Statistica 10.0. Statistical processing was carried out according to the principles of the International Committee of Medical Journal Editors (ICMJE) and the recommendations of "Statistical Analysis and Methods in the Published Literature (SAMPL)" [4]. Nominal data were described with the indication of absolute values and percentages in groups. Normality of the trait distribution was assessed using the Shapiro-Wilk test. In all cases, the hypothesis of normality was rejected. Therefore, the results are presented as a median and interquartile interval (Me (25%; 75%)). Assessment of the deviation in the distributions of genotypes of the studied polymorphic locus from the Hardy-Weinberg distribution was carried out using a modified Pearson's chi-square test. Comparative analysis of the data obtained was carried out using the Fisher test. Statistical significance of the relative odds was estimated based on the 95% confidence interval (95% CI). Differences were considered significant at $p < 0.05$.

Results

As a result of genotyping the 681G/A polymorphic locus of the CYP2C19 gene, three genotypes (G/G, G/A, A/A) were identified. The CYP2C19(681G/G) genotype had the highest prevalence — 105 (79.5%) individuals, the heterozygous variant of CYP2C19(681G/A) was less common — 25 (18.9%) respondents, and only 2 (1.5%) participants had the A/A genotype (see Table 1). It was established that the distribution of frequencies of genotypes and alleles of the polymorphic locus 681 G/A of the CYP2C19 gene corresponded to the distribution according to Hardy-Weinberg law, $p = 0.8843$ and $p = 0.1157$, respectively, suggesting the obtained results could be extrapolated to the population.

Table 1. *Frequency of genotypes and alleles of the CYP2C19 gene at the 681G/A position in the population of the Trans-Baikal Territory*

Genotypes and Alleles	Frequency (%)
G/G	79,6
G/A	18,9
A/A	1,5
G	85,8
A	14,2

A comparative analysis of the prevalence of the non-functional CYP2C19*2 allele in the population of Trans-Baikal Territory was carried out using world data and the results of studies performed by other Russian authors [2, 5, 6, 7, 8]. Statistically significant differences were obtained relative to Asian populations. In the Chinese population, the A allele was more prevalent than in the population of Trans-Baikal Territory (OR = 6.365, 95% CI 3.209; 12.625, $p < 0.001$). The prevalence of the non-functional CYP2C19 allele at position 681 in the Japanese population was also significantly higher than in our study (OR = 2.468; 95% CI 1.215; 5.012, $p = 0.015$). When comparing our data with the results obtained by other Russian authors, there were no statistically significant differences in the prevalence of this allele (see Table 2).

When analyzing the prevalence of the non-functional homozygous genotype of cytochrome P450, the CYP2C19(681A/A) genotype was found to be more common in Asians than the population of Trans-Baikal Territory (OR = 10.513, 95% CI 1.902; 58.106, $p = 0.003$) and did not differ from other populations in the world and in Russia ($p > 0.05$), see Table 3.

Table 2. Comparative analysis of the prevalence of the cytochrome P450 allele-A of the 681G/A polymorphic locus in populations around the world and in various regions of Russia

Population	Allele A (%)	p
Native Americans (n=1133) [8]	9,75	0,515
Hispanics (n=1898) [9]	10,77	0,67
Afro-Latinos (n=82) [9]	18,29	0,563
Argentine Ashken Jews (n=163) [9]	13,64	1,000
Chinese (n=267)[9]	51,3	0,001
Japanese (n=186)[4]	29	0,015
Russian Federation		
Moscow region, Caucasian nationality (n=1912) [10]	14,0	1,000
Voronezh region (n=580) [10]	11,4	0,67
Sakha-Yakutia (n=206) [11] Caucasians	13,49	1,000
Sakha-Yakutia (n=409) [11] Yakuts	14,54	1,000
Irkutsk region (n=89) [4]	11,3	0,67
Trans-Baikal Territory, own data (n=132)	14,2	-

Note: n — number of subjects; p — significance level

Table 3. Comparative analysis of the prevalence of the CYP2C19(681A/A) genotype in populations of the world and Russia

Population (n)	Allele A/A (%)	p
African American (n=966) [12]	3,7	0,683
Asians (n=573) [12]	13,8	0,003
Caucasians (n=1356) [12]	2,1	1,00
Russian Federation		
Moscow region, Caucasian nationality (n=971) [10]	1,4	1,00
Voronezh region (n=290) [10]	1,7	1,00
Own data (n=132)	1,5	-

Note: χ^2 — Pearson chi square, n — number of subjects; p — significance level

Discussion

The main tasks of pharmacogenetics are the search for an optimal drug for a particular patient, the determination of the required and sufficient dose, the optimization of side effects by analyzing the individual set of genes involved both in the implementation of the mechanism of drug action and in its metabolism.

PPI metabolism occurs with the participation of the CYP2C19 isoenzyme, and its genetic polymorphism impacts the antisecretory activity of these drugs [13]. Poor metabolizers are characterized by the decline in microsomal hydroxylation processes in the liver, leading to an increase in the area under the curve (AUC) by 5–12 times compared to extensive metabolizers. Individuals who are heterozygous for variant alleles demonstrate AUC values 2–4 times higher than those of extensive metabolizers. Enhanced pharmacokinetics leads to improved pharmacodynamics. Average 24-hour values of intragastric pH indicate the status of a metabolizer: the highest pH (and PPI effect) is in "poor" metabolizers, intermediate pH — in heterozygotes and lowest pH — in "extensive" metabolizers [14]. Patients with the CYP2C19(681G/G) genotype are defined as rapid metabolizers of proton pump inhibitors, and patients with the CYP2C19(681G/A) and CYP2C19(681A/A) genotype have slow drug metabolism [15]. In our study, about 80% of respondents had the CYP2C19(681G/G) genotype, indicating the predominance of "extensive" metabolizers in the population of Trans-Baikal Territory.

To improve the effectiveness of treatment of patients with GERD, it should be determined whether the genotype of a rapid metabolizer of cytochrome P450 2C19 is a risk factor for the failure of therapy with proton pump inhibitors [3]. In particular, the clinical efficacy of PPIs in eradication therapy for H. pylori-associated diseases and in the management of gastroesophageal reflux disease in "slow" metabolizers is more than double than that in "extensive" metabolizers. These differences primarily relate to omeprazole and lansoprazole, whose metabolism depends on CUPC19, and are not significant for rabeprazole and pantoprazole, which are metabolized to a lesser extent by this enzyme [13]. In a meta-analysis, Hitomi Ichikawa et al. (2016) showed that the effectiveness of PPI therapy in GERD, including reflux esophagitis and non-erosive reflux disease, was 56.4% (95% CI; 53.9–58.9%, 870/1543). Treatment response rates

varied significantly between genotypes: rapid — 52.2% (315/604); intermediate — 56.7% (298/526) and poor metabolizers — 61.3% (138/225), p = 0.047 [15]. Similar data were obtained in a study to analyze the endoscopic treatment of esophagitis eight weeks after the use of PPIs [16]. The effectiveness of therapy for poor metabolizers, heterozygotes and extensive metabolizers was 85–100%, 68–95% and 46–77%, respectively. In H. pylori-infected patients, the wild-type CYP2C19 genotype correlates with a lower response (20% lower cure rate) to combination therapy with a PPI and two antibacterials [1]. In 2006, Ariizumi, Ken et al. conducted a study on the efficacy of 10 mg rabeprazole per day in patients with reflux esophagitis depending on the CYP2C19 polymorphism. This study involved 103 patients who received 10 mg of rabeprazole daily. Treatment control was performed after 4 and 8 weeks using endoscopic examination of esophagus and stomach. Before therapy, a study of CYP2C19 polymorphism was carried out. Four weeks after treatment, the healing rate of esophageal mucosa in extensive, intermediate and poor metabolizers was 83.3% (15/18), 77.3% (17/22) and 88.9 (8/9), respectively. After eight weeks, mucosal healing rates were 86.1% (31/36), 92.0% (46.50) and 82.4 (14/17), respectively. There were no differences in mucosal healing in patients with reflux esophagitis among all three genotypes, either after four or eight weeks. The authors concluded that the effectiveness of rabeprazole to a lesser extent depends on the polymorphism of cytochrome P450 [17]. Considering the predominance of "extensive" metabolizers among the residents of Trans-Baikal Territory, rabeprazole is probably preferable in order to increase the effectiveness of managing acid-dependent diseases.

GERD is a chronic relapsing disease, so it is important to predict the exacerbation of the pathological process after stopping therapy. In the Japanese population, it was established that the recurrence of gastroesophageal reflux disease symptoms in extensive metabolizers of CYP2C19 is higher (38.5%) than in heterozygous extensive (10.9%) or poor (5.6%) metabolizers [1, 18]. Given the low prevalence of heterozygous (18.9%) and poor homozygous genotypes (1.5%) among people living in Trans-Baikal Territory, frequent relapses in patients with GERD can be assumed.

The clinical application of pharmacogenetics should be considered in cases when a genotype predicts side effects and/or non-response in patients; genotyping offers definite advantages over phenotyping; a drug has a narrow "therapeutic window"; an equivalent alternative drug is available; possible development of serious side effects or the consequences of a lack of response; there is a possibility of a negative effect/no response with a "marked" frequency; data from prospective studies demonstrating the benefits of genotyping have been accumulated [1]. The practical implication of genotyping for one in five Chinese or patients with variant CYP2C19 alleles is that standard doses of PPIs may be excessive. In European populations, there is a low prevalence of CYP2C19 polymorphisms, which makes genotyping clinically less significant for reflux esophagitis and peptic ulcer management [12]. Our comparative analysis of the prevalence of CYP2C19(G681A) genotypes yielded similar data. It was revealed that in Caucasian populations, including in Russia and in Trans-Baikal Territory, there is a low variability of the studied polymorphisms with a predominance of rapid metabolizers. This makes genotyping of this locus less significant in the management of reflux esophagitis and dictates the need for more frequent use of metabolically neutral PPIs for management of ADDs in the residents of Trans-Baikal Territory.

Conclusion

The frequency of the A allele of the 681G/A CYP2C19 polymorphic locus in the population of Trans-Baikal Territory was 14.2% and was comparable with Caucasians, but was less common than in the Chinese and Japanese populations ($p < 0.001$ and $p = 0.015$, respectively). The prevalence of the CYP2C19(681A/A) genotype was 1.5%, which matched world data among Caucasian populations; it was less common than in Asians ($p = 0.003$). Given the high prevalence of "extensive" metabolizers in Trans-Baikal Territory, with low variability of the CYP2C19(G681A) genetic polymorphism, it is advisable to use drugs that are less metabolized through this cytochrome without prior genetic testing.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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