ORIGINAL INVESTIGATIONS

# Structure of the distribution of genetic determinants of the efficacy and safety of non-steroidal anti-inflammatory drugs in the Russian population: focus on *CYP2C8*, *PTGS1* and *PTGS2*

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*The efficacy and safety of non-steroidal anti-inflammatory drugs (NSAIDs) may be determined by the polymorphic nature of the CYP2C8, PTGS1 and PTGS2 genes.*

***Objective:*** *to analyze the nature of the distribution of CYP2C8*3 (rs10509681), CYP2C8*3 (rs11572080), PTGS1 (rs10306135), PTGS1 (rs12353214) and PTGS2 (rs20417) among residents of the North Caucasus.*

***Patients and methods.*** *The study involved 676 volunteers from Russian, Balkar, Kabardian and Ossetian ethnic groups. Carriage of polymorphic markers CYP2C8, PTGS1 and PTGS2 was determined using real-time polymerase chain reaction.*

***Results and discussion.*** *There were no significant differences between the groups in the rs10509681 and rs11572080 variants of the CYP2C8 gene. In all groups, the carriage of a combination of CYP2C8 and CYP2C9 alleles, encoding the phenotype of normal metabolizers, prevailed with a frequency of about 75% or more. The rs10306135 variant of the PTGS1 gene was found in 5.9% of Russians, 1.1% of Balkars, 5.3% of Kabardians, and 10.6% of Ossetians; variant rs12353214 – in 19.1; 9.4; 10.8 and 9.2%, rs20417 polymorphism of the PTGS2 gene in 0.4; 5; 2.8 and 3.1% respectively.*

***Conclusion.*** *The data obtained can be used to develop a more rational approach to the prescription of NSAIDs, taking into account the genetic characteristics of the local population in ethnic regions.*

***Keywords:*** *pharmacogenetics; ethnic groups; CYP2C8; PTGS1; PTGS2; non-steroidal anti-inflammatory drugs.*

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Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common group of medicines used for pain relief in various areas of clinical medicine, accounting for 5–10% of all drugs prescribed annually [1]. However, the reasons for the possible ineffectiveness of NSAIDs and a high frequency of adverse reactions during their use in certain groups of patients have not yet been studied.

NSAIDs are metabolized by *CYP450* family enzymes, mainly CYP2C8 and CYP2C9 [2, 3]. Some variants of *CYP2C8* and *CYP2C9* genes have been shown to significantly affect the cytochrome activity profile and pharmacokinetic parameters of NSAIDs [2]. *CYP2C8* and *CYP2C9* genes are highly polymorphic, with 18 polymorphisms and over 70 allelic variants for each gene described to date. The allelic variants of the genes affect the enzymatic activity of CYP450, and their combination determines four different metabolic phenotypes: ultrafast, extensive (normal), intermediate and poor metabolizers [2, 3]. The phenotypic manifestations of the combinations of *CYP2C8* and *CYP2C9* genes variants may be among the markers of variability in the therapeutic effect and safety of NSAIDs.

The second component of this variability may be genetic variants of two enzymes – prostaglandin-endoperoxide synthetase 1 and 2 (PTGS1 and PTGS2), which determine their interaction with NSAIDs. Polymorphisms of *PTGS1* and *PTGS2* genes that modify their activity affect the pharmacodynamic effect of NSAIDs. Recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) include adjusting the regimen and dose of NSAIDs according to *CYP2C9* genetic variants. The recommendations consider *CYP2C8*, *PTGS1* and *PTGS2* genes as potential markers. However, the need to expand their evidence base is emphasized [4].

Given a high genetic heterogeneity of Russia's multinational population [5], identifying the pattern of the carriage of pharmacogenetic markers in ethnic groups remains an important task, especially in the context of the transition to personalized medicine.

CYP2C9 isoenzymes significantly affect the biotransformation rate of many NSAIDs. Carriage of *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910) variants has been shown to slow down NSAID metabolism that leads to increased plasma drug concentrations and an increased risk of gastrointestinal bleeding (GIB) [2, 6]. The prevalence of *CYP2C9*2* and *CYP2C9*3* in some Russian ethnic groups has been studied previously [7, 8], but the distribution of *CYP2C8* gene variants has not been characterized.

The aim of this study was to determine the frequency of allelic variants of *CYP2C8*3* (*c.1196A>G*, rs10509681), *CYP2C8*3* (*c.416G>A*, rs11572080), *PTGS1* (*c.-262A>T*, rs10306135), *PTGS1* (rs12353214) and *PTGS2* (*c.-765 G>C*, rs20417) in Russian ethnic group as the most numerous group in Russia and in ethnic groups living in the North Caucasus – Balkars, Kabardins and Ossetians.

## Patients and methods

*Study population*. The study involved 676 healthy volunteers from four ethnic groups living in Russia: Balkars, Kabardins and Ossetians (180 people each), and 136 Russians.

Ethnicity was determined by self-identification of the participants and their parents. Previously, H. Tang et al. [9] noted a high correlation between the self-identification method used and determination of microsatellite markers of ethnicity. Therefore, descendants of mixed marriages were not included in the present study.

The study was approved by the Ethics Committee of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of Russia. All participants signed an informed consent for participation in the study, collection and storage of their biological material.

The prevalence of *CYP2C8*3* (*c.1196A>G*, rs10509681), *CYP2C8*3* (*c.416G>A*, rs11572080), *PTGS1* (*c.-262A>T*, rs10306135), *PTGS1* (rs12353214) and *PTGS2* (*c.-765G>C*, rs20417) was assessed in each group, and a pairwise comparison of allele frequencies was performed. The analysis of co-carriage of the allelic variants of CYP2C8 and CYP2C9 genes was also performed.

*Genotyping*. DNA was isolated from venous blood (4 ml) collected in tubes with EDTA (Vacuette, Greiner Bio-One GmbH, Austria). Reagent kit DNA-Extran-1 (Syntol, Russia) was used to extract DNA. Carriage of polymorphic markers was determined using TaqMan® kits (Applied Biosystems, USA) on a Real-Time CFX96 Touch amplifier (Bio-Rad Laboratories Inc., USA) according to the manufacturer's instructions.

*Statistics*. The allele frequencies were estimated by gene counting, and the Hardy–Weinberg equilibrium was tested using the $\chi^2$-test. Differences in allele frequencies between ethnic groups were measured using Fisher's exact test. With Bonferroni correction, differences were considered statistically significant at $p<0.01$. Statistical analysis was performed using GraphPad software. The SNPStats resource [10] was used to analyze combinations of allelic variants.

**Results.** The pattern of frequency distribution of polymorphic marker genotypes *CYP2C8*3* (rs10509681), *CYP2C8*3* (rs11572080), *PTGS1* (rs10306135), *PTGS1* (rs12353214) and *PTGS2* (rs20417) determined in ethnic groups mostly corresponded to the Hardy–Weinberg equilibrium distribution ($p>0.05$). The exceptions were *PTGS1* (rs10306135), *PTGS2* (rs20417) genotypes in Balkars, *PTGS2* (rs20417) in Kabardins, and *PTGS1* (rs10306135) in Russians (Table 1). In all groups, allele frequencies for all studied markers were compared in pairs (see Tables 1 and 2).

The rs10509681 variant of the *CYP2C8* gene was found with a frequency of 6.6%; 12.5%; 10.6% and 7.5% in Russians, Balkars, Kabardins, and Ossetians, respectively. In the analysis of the second polymorphic marker rs11572080 of the *CYP2C8* gene, the following group distribution was obtained: 7.0%; 11.4%; 10.6% and 6.9%, respectively. No significant differences in the distribution of the two variants were found.

The lowest frequency of rs10306135 of the PTGS1 gene was detected in Balkars – 1.1%, in Russians it was 5.9% ($p=0.0009$), in Kabardins – 5.3% ($p=0.0022$) and in Ossetians – 10.6% ($p=0.001$), the differences were significant compared with all other groups. Comparison of the groups of Russians, Kabardins and Ossetians showed no differences.

The second variant rs12353214 of the *PTGS1* gene was found most frequently in Russian (19.1%) and significantly less frequently in the Caucasian ethnic groups: 9.4% of Balkars ($p=0.0006$), 10.8% of Kabardins ($p=0.0041$), and 9.2% of Ossetians ($p=0.0004$). The Caucasian groups did not differ significantly in the frequency of this allele.

The prevalence of rs20417 of the *PTGS2* gene was lowest in the Russian, 0.4%, but significant differences were only detected compared with the Balkars (5.0%; $p=0.0005$). The frequency of rs20417 was 2.8% in Kabardins and 3.1% in Ossetians.

In addition, we analyzed the pattern of co-carriage of CYP2C8 and CYP2C9 gene variants in Caucasian ethnic groups. Data on the carriage of allelic variants CYP2C9*2 (c.430C>T, rs1799853) and CYP2C9*3 (c.1075A>C, rs1057910) in the ethnic groups were taken from our previously published works [7, 8]. The results are shown in Table 3.

As the analysis showed, in all groups the carriage of a combination of variants of *CYP2C8* and *CYP2C9* genes encoding the phenotype of normal (extensive) metabolizers with a frequency of about 75% or more was predominant. The other most frequent combinations of *CYP2C8* and *CYP2C9* gene alleles encoded the phenotype of intermediate metabolizers.

**Discussion.** The adverse effects of NSAIDs are a major concern. The situation is further aggravated by the fact that these drugs are sold without prescription and a large proportion of consumers

**Table 1. Frequency of genotypes for the studied polymorphisms in ethnic groups and their correspondence to the Hardy-Weinberg distribution**

| Marker | Genotype | Balkars | | | | | Kabardins | | | | | Ossetians | | | | | Russians | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OF | EF | % | $\chi^2$ | p | OF | EF | % | $\chi^2$ | p | OF | EF | % | $\chi^2$ | p | OF | EF | % | $\chi^2$ | p |
| *CYP2C8*3* (rs10509681) | CC | 4 | 2.8 | 2.2 | 0.671 | 0.7150 | 0 | 2.0 | 0.0 | 2.498 | 0.2867 | 2 | 1.0 | 1.1 | 1.166 | 0.5581 | 0 | 0.6 | 0.0 | 0.689 | 0.7087 |
| | CT | 37 | 39.4 | 20.6 | | | 38 | 34.0 | 21.1 | | | 23 | 25.0 | 12.8 | | | 18 | 16.8 | 13.2 | | |
| | TT | 139 | 137.8 | 77.2 | | | 142 | 144.0 | 78.9 | | | 155 | 154.0 | 86.1 | | | 118 | 118.6 | 86.8 | | |
| *CYP2C8*3* (rs11572080) | CC | 139 | 141.3 | 77.2 | 3.046 | 0.2181 | 142 | 144.0 | 78.9 | 2.498 | 0.2867 | 155 | 155.8 | 86.1 | 1.028 | 0.5981 | 117 | 177.67 | 86.0 | 0.764 | 0.6825 |
| | CT | 41 | 36.3 | 22.8 | | | 38 | 34.0 | 21.1 | | | 25 | 23.3 | 13.9 | | | 19 | 17.67 | 14.0 | | |
| | TT | 0 | 2.4 | 0.0 | | | 0 | 2.0 | 0.0 | | | 0 | 0.9 | 0 | | | 0 | 0.66 | 0.0 | | |
| *PTGS1* (rs10306135) | AA | 177 | 176.02 | 98.3 | 48.996 | 0.0001 | 162 | 161.5 | 90.0 | 0.557 | 0.7569 | 148 | 144.0 | 82.3 | 9.993 | 0.0068 | 126 | 120.47 | 92.6 | 73.442 | 0.0001 |
| | AT | 2 | 3.96 | 1.1 | | | 17 | 18.0 | 9.4 | | | 26 | 34.0 | 14.4 | | | 4 | 15.06 | 2.9 | | |
| | TT | 1 | 0.02 | 0.6 | | | 1 | 0.5 | 0.6 | | | 6 | 2.0 | 3.3 | | | 6 | 0.47 | 4.4 | | |
| *PTGS1* (rs12353214) | CC | 148 | 147.6 | 82.2 | 0.122 | 0.9409 | 142 | 143.1 | 78.9 | 0.724 | 0.6964 | 148 | 148.5 | 82.2 | 0.202 | 0.9041 | 90 | 88.97 | 66.2 | 0.326 | 0.8495 |
| | CT | 30 | 30.8 | 16.7 | | | 37 | 34.8 | 20.6 | | | 31 | 30.0 | 17.2 | | | 40 | 42.06 | 29.4 | | |
| | TT | 2 | 1.6 | 1.1 | | | 1 | 2.1 | 0.6 | | | 1 | 1.5 | 0.6 | | | 6 | 4.97 | 4.4 | | |
| *PTGS2* (rs20417) | CC | 171 | 162.4 | 95.0 | 162.055 | 0.0001 | 175 | 170.1 | 97.2 | 125.041 | 0.0001 | 169 | 169.1 | 93.9 | 0.208 | 0.9010 | 135 | 135.0 | 99.3 | 0.002 | 0.9990 |
| | CG | 0 | 17.1 | 0.0 | | | 0 | 9.7 | 0.0 | | | 11 | 10.7 | 6.1 | | | 1 | 1.0 | 0.7 | | |
| | GG | 9 | 0.5 | 5.0 | | | 5 | 0.2 | 2.8 | | | 0 | 0.2 | 0.0 | | | 0 | 0.0 | 0.0 | | |

Note: OF- observed frequency; EF - expected frequency.

**Table 2. Pairwise comparison of the carriage of the alleles of the polymorphisms studied in populations of Balkars, Kabardins, Ossetians and Russians**

| Marker | Ethnic groups | n/N (alleles) | Minor allele frequency, % | Kabardins | Ossetians | Russians |
|---|---|---|---|---|---|---|
| | | | | | p | |
| *CYP2C8*3* (rs10509681) | Balkars | 45/360 | 12,5 | 0.4840 | 0.0341 | 0.0156 |
| | Kabardins | 38/360 | 10,6 | - | 0.1931 | 0.0911 |
| | Ossetians | 27/360 | 7,5 | - | - | 0.7555 |
| | Russians | 18/272 | 6,6 | - | - | - |
| | | | | | | |
| *CYP2C8*3* (rs11572080) | Balkars | 41/360 | 11,4 | 0.8117 | 0.0520 | 0.0744 |
| | Kabardins | 38/360 | 10,6 | - | 0.1129 | 0.1257 |
| | Ossetians | 25/360 | 6,9 | - | - | 1.0000 |
| | Russians | 19/272 | 7,0 | - | - | - |
| | | | | | | |
| *PTGS1* (rs10306135) | Balkars | 4/360 | 1,1 | 0.0022 | 0.0001 | 0.0009 |
| | Kabardins | 19/360 | 5,3 | - | 0.0124 | 0.8609 |
| | Ossetians | 38/360 | 10,6 | - | - | 0.0439 |
| | Russians | 16/272 | 5,9 | - | - | - |
| | | | | | | |
| *PTGS1* (rs12353214) | Balkars | 34/360 | 9,4 | 0.6216 | 1.0000 | 0.0006 |
| | Kabardins | 39/360 | 10,8 | - | 0.5348 | 0.0041 |
| | Ossetians | 33/360 | 9,2 | - | - | 0.0004 |
| | Russians | 52/272 | 19,1 | - | - | - |
| | | | | | | |
| *PTGS2* (rs20417) | Balkars | 18/360 | 5,0 | 0.1763 | 0.2551 | 0.0005 |
| | Kabardins | 10/360 | 2,8 | - | 1.0000 | 0.0282 |
| | Ossetians | 11/360 | 3,1 | - | - | 0.0161 |
| | Russians | 1/272 | 0,4 | - | - | - |

Note. Statistically significant differences - $p<0.01$; n/N (alleles) - number of minor alleles of the gene / total number of alleles.

**Table 3: Frequency of the most frequent combinations of polymorphic gene variants associated with altered CYP2C8 and CYP2C9 functional activity**

| № | Variants of the combination | | | | Phenotype variant | Frequency of combination variants | | |
|---|---|---|---|---|---|---|---|---|
| | *CYP2C8*3* (rs1050968) | *CYP2C8*3* (rs11572080) | *CYP2C9*2* (rs1799853) | *CYP2C9*3* (rs1057910) | | Balkars | Kabardins | Ossetians |
| 1 | T | C | C | A | NM | 0,7497 | 0,7466 | 0,7902 |
| 2 | T | C | C | C | IM | 0,1086 | 0,1168 | 0,1206 |
| 3 | C | T | T | A | IM | 0,1039 | 0,0781 | 0,0457 |
| 4 | T | C | T | A | IM | 0,0098 | 0,0234 | 0,0142 |

Note. NM - normal metabolizers; IM - intermediate metabolizers.

take them without first consulting a doctor. In addition, NSAIDs, aspirin and other antiaggregants are used by patients suffering from chronic cardiovascular, immune system diseases, etc. A wide range of indications for prescribing NSAIDs, the need for their long-term use, and lack of medical supervision cause a high incidence of gastroduodenal ulcers and erosions, which without proper treatment can be complicated by the development of GIB [11]. Results from large-scale randomized controlled trials (RCT) show that the incidence of upper gastrointestinal clinical events with non-selective NSAIDs ranged from 2.7% to 4.5% and the incidence of complications, such as GIB or perforations, from 1.0% to 1.5% [12].

Recent advances in pharmacogenetics have identified a number of genetic markers that may be responsible for interindividual variability in the efficacy and safety of some cardiological, antipsychotic and antitumor drugs. At the same time, it has been shown that differences in response to drugs may depend not only on individual reactions of the body, but also on population factors [13]. For example, the distribution of clinically relevant markers of response to pharmacotherapy may determine the frequency of adverse reactions and drug ineffectiveness in different ethnic groups. For Russia, with its regions densely populated by ethnic groups, this issue is of particular interest.

The North Caucasus is a highly multi-ethnic region within Russia. The peculiarities of the local landscape form the structure of the various ethnic groups on its territory. The mountainous isolation and ethno-religious separation of the peoples of the North Caucasus have determined a high degree of their genetic heterogeneity. This phenomenon provides an excellent example for studying the effect of the carriage of certain clinically relevant markers on differences in treatment outcomes at the population level.

In our study, the incidence of potential determinants of efficacy and safety of NSAIDs in the indigenous peoples of the North Caucasus – the Balkars, Kabardins and Ossetians – was analyzed to demonstrate interethnic differences. Understanding such differences lays the foundation for the development of territorial programs and personalization algorithms that take into account the genetics of the local population, which is also important from the economic point of view.

A number of clinically relevant biomarkers have been identified for the NSAID group. For example, E. Garcia-Martin et al. [14] in their study of ibuprofen pharmacokinetics in 130 volunteers depending on the carriage of *CYP2C8* and *CYP2C9* variants found that combination of *CYP2C8*1/*3* and *CYP2C9*1/*2* variants was associated with statistically significant decrease in ibuprofen clearance ($p<0.001$). In homozygous or double heterozygous carriers of the *CYP2C8*3* and *CYP2C9*3* alleles, a decrease in the clearance was even more pronounced than in cases without minor allele carriage. Heterozygous and homozygous carriage of *CYP2C8*3* allele determines a decrease in metabolic clearance of ibuprofen by approximately 62% and 10%, respectively, compared with that in carriers of homozygous *CYP2C8*1* and *CYP2C9*1* genotypes [15]. C.R. Lee et al. [16] showed that in the group of 15 volunteers, in *CYP2C9*1/*3* heterozygotes AUC0-∞ values of flurbiprofen were higher and all clearance values were lower than in *CYP2C9*1/*1* homozygotes. However, no significant differences in the studied parameters were found between *CYP2C9*1/*1* and *CYP2C9*1/*2* volunteers. The effect of *CYP2C9*3* polymorphic marker carriage on the AUC and clearance values was similar for lornoxicam [17]. Slow metabolizers *CYP2C9*3* were also found to have increased exposure and decreased clearance with standard doses of piroxicam [18, 19]. No significant changes in pharmacokinetic parameters depending on *CYP2C9* genotype were found for diclofenac. The *CYP2C9*2* allele variant did not reduce diclofenac clearance [20–22], and the effect of *CYP2C9*3* variant appeared to be very limited: in its heterozygous and homozygous carriers the average clearance was 95% and 85%, respectively [23]. There are no data on the effect of *CYP2C8* variants.

T.E. Morozova et al. [24] showed that carriage of the minor allele of the *CYP2C9*3* polymorphism was associated with decreased pain intensity when using ketoprofen in patients after cardiac surgery. The results of another Russian study do not support

the conclusions about the effect of *CYP2C9*3* on the efficacy of post-surgery pain relief with tramadol and ketorolac in patients undergoing laparoscopic cholecystectomy [25]. At the same time, the authors conclude that the efficacy of pain relief with these drugs is associated with *CYP2C9*2*: pain was statistically significantly less severe in carriers of the *CYP2C9*2* minor allele. However, both *CYP2C9* alleles were considered as possible predictors of GIB with ketorolac [25]. Controversial data on the effect of *CYP2C8*3* and *CYP2C9*3* allele carriage on the efficacy of analgesic therapy with NSAIDs were obtained using piroxicam as an example. In 102 volunteers heterozygous for *CYP2C8*3* and *CYP2C9*3*, piroxicam was effective in relieving pain after molar surgery, regardless of CYP polymorphic gene combination variants [26]. However, this work did not assess the risk of adverse reactions to piroxicam in groups depending on the genotype. In addition, a low dose of the drug was administered for a short period, 20 mg once daily for 4 days.

The importance of studying the pharmacogenetics of NSAIDs is also due to their adverse reactions. Although this issue is not well understood, it appears that *CYP2C9*2, CYP2C9*3* alleles, which determine reduced enzyme functional activity, are associated with an increased risk of acute GIB in patients receiving NSAIDs. Variants of *CYP2C8*, in particular *CYP2C8*3*, may also contribute to this risk [2, 18, 27]. According to C. Martinez et al. [28], *CYP2C9*2* and *3 carriage is associated with a 2.5-fold increased risk of GIB after taking NSAIDs such as celecoxib, diclofenac, ibuprofen, indomethacin, lornoxicam, piroxicam or naproxen: *CYP2C9*2* carriers had a relative risk (RR) of GIB – 1.91 (p=0.009), *CYP2C9*2/*3* carriers – 2.67, and *CYP2C9*2/*2* carriers – 4.16 (p=0.078). In another study, the frequency of *CYP2C8*3* and *CYP2C9*2* alleles in the group of patients who had GIB while taking NSAIDs was higher compared with the group of patients without such disorders: the odds ratio (OR) for *CYP2C8*3* was 2.4 (p<0.002) and for *CYP2C9*2* – 2.7 (p<0.013) [29]. A. Pilotto et al. [27] found that patients with endoscopically confirmed NSAID-induced GIB showed a higher frequency of *CYP2C9*1/*3* and **1/*2* genotypes than controls. In this work, the presence of the *CYP2C9*3* allele correlated with a significantly higher risk of bleeding (adjusted OR 7.3). In a meta-analysis by J.A. Agundez et al. [2], *CYP2C9*2* was a risk factor for GIB with all NSAIDs (OR 1.58) and with NSAIDs that are substrates of *CYP2C8* or *CYP2C9* (OR 1.96). The role of *CYP2C9*3* appears to be less significant with any NSAID (OR 1.6) and with NSAIDs of *CYP2C8* or *CYP2C9* substrates (OR 1.74). The pooled OR for both *CYP2C9*2* and *CYP2C9*3* carriers increases: 1.78 for any NSAID, and 2.33 for NSAIDs that are substrates of *CYP2C8* or *CYP2C9*. For *CYP2C8*3* the OR of GIB was 1.91 in patients treated with any NSAID, and 3.40 with NSAIDs of *CYP2C8* or *CYP2C9* substrates. The authors emphasized the need for further association studies, especially for *CYP2C8*3*. Thus, the summarized results show that all three polymorphisms (*CYP2C8*3, CYP2C9*2* and *CYP2C9*3*) are associated with a decreased metabolism of NSAID, prolonging their half-life and may be considered as determinants of risk of GIB [2].

In the present study, no regional peculiarities of *CYP2C8*3* marker distribution were detected. The frequency of the allelic variant rs10509681 of the *CYP2C8* gene ranged from 6.6% in Russians to 12.5% in Balkars, but with Bonferroni correction, the differences did not reach statistical significance. The frequency of the second marker rs11572080 of the *CYP2C8* gene ranged from 6.9% in Ossetians to 11.4% in Balkars, and had no statistically significant differences. Analysis of the co-occurrence of allelic variants of *CYP2C8* and *CYP2C9* genes shows that the phenotypes of normal metabolizers, characterized by a usual average drug metabolic rate, predominate in the Caucasian ethnic groups. It is worth noting that the occurrence of both variants within one ethnic group was comparable:12.5% and 11.4% in Balkars, 10.6% and 10.6% in Kabardins, 7.5% and 6.9% in Ossetians, and 6.6% and 7.0% in Russians, respectively. Once again, this clearly demonstrates a significant influence of ethnicity, if we take into account the overall distribution of the gene in the whole population of the country.

NSAIDs inhibit cyclooxygenase (COX) 1 and 2 activity, which results in inhibiting the metabolism of arachidonic acid to prostaglandins. The activity and affinity of COX1 and COX2 is determined by the expression of the *PTGS1* and *PTGS2* genes, genetic rearrangements in which may alter the analgesic effect of a particular NSAID. For example, a cohort study by C.G. St Germaine et al. [30] showed an association of two polymorphisms of *PTGS1* gene, rs10306135 and rs12353214, with the risk of cardiotoxicity (acute coronary syndrome) while taking NSAIDs: OR – 6.94 (p=0.016) and 7.11 (p=0.033), respectively. Another study evaluated the association between *PTGS1* haplotype *A-842G/C50T* (rs10306114/rs3842787) carriage and the occurrence of ulcerative GIB, but found no statistically significant association [31]. The *A-842G/C50T* haplotype combination was not associated with the development of aspirin resistance either [32]. A.A. Kornilova et al. [33] in an observational RCT evaluated aspirin resistance in patients with cerebrovascular disease depending on the carriage of variants *A-842G* (rs 10306114), *C50T* (rs3842787) and *A1676G* (rs1330344) of the *PTGS1* gene. *A-842G* carriage was found to be more frequently associated with aspirin insensitivity. As we see, the question of the association of *PTGS1* gene variants with resistance to NSAIDs and gastrotoxicity remains open.

Our data show that rs10306135 and rs12353214 variants of *PTGS1* gene are distributed extremely irregularly even in one ethnic group. The frequency of rs10306135 carriage varies from 1.1% in the Balkars to 10.6% in the Ossetians. The second marker (rs12353214) is distributed more evenly among the Caucasian peoples, where it occurs in about 10% of cases, whereas among Russians it occurs in 19% of cases.

The group of selective NSAIDs is characterized by selective inhibition of COX2 predominantly. The *-765G>C* (rs20417) polymorphism variant of the *PTGS2* gene determines a decrease in COX2 expression and its affinity for selective COX2 inhibitors. One study evaluated the analgesic ability of rofecoxib and ibuprofen after minor tooth extraction surgery depending on the carriage of the *-765G>C* (rs20417) polymorphism. In wild-type *GG* homozygotes, administration of rofecoxib resulted in a more marked reduction in pain intensity on the visual analogue scale (7.2±2.5 mm; p=0.008) than the use of ibuprofen (31.3±6.7 mm). The opposite pattern was observed in *GC* and *CC* genotype carriers: the analgesic effect was more pronounced in the ibuprofen group (7±1.9 mm; p=0.002) than in the rofecoxib group (37±6.8 mm) [34]. The variability in PTGS2 expression encoded by this polymorphism may lead to less potent effects of selective COX2 inhibitors and NSAIDs in general.

The frequency of carriage of the rs20417 allele variant associated with decreased PTGS2 expression, according to the 1000 Genomes Project, is, on average, 15.11% in European population. We see that in Russia, this level is much lower: from 0.4% in Russians to 5.0% in Balkars. However, at this stage, we cannot assume a possible difference of clinical effect between some ethnic groups

in the presence of the rs20417 PTGS2 gene. At the same time, the ethnic factor should not be neglected.

**Conclusion.** Thus, according to our data, the distribution of *CYP2C8*3* allelic variants (rs10509681 and rs11572080) among Balkars and Kabardins generally corresponds to their frequency in Europeans (about 11.5%) and to a lesser extent in Ossetians and Russians (about 7%), which is typical for Asian and African peoples [35]. The general pattern for both single-nucleotide polymorphisms is preserved. A different picture can be observed in the distribution of *PTGS1* and *PTGS2* gene variants: in European populations, the prevalence of rs10306135, rs12353214 and rs20417 variants is 14.86%; 10.54% and 15.75%, respectively [35]. At the same time, the Russian groups are distinguished by a significant variability of frequencies without a general trend. The present study showed that among the three analyzed ethnic groups of the North Caucasus, a combination of *CYP2C9* and *CYP2C8* genes, indicating normal enzyme activity, was detected in 75% of cases. The remaining allele combinations were found in 1–12% of cases and encoded enzymes with intermediate metabolizing activity.

These findings can be used to develop a more rational approach to prescribing NSAIDs (*CYP2C8* substrates and *PGTS1* and *PGTS2* targets) that takes into account genetic characteristics of ethnic groups, and can also be a stimulus for further study of the relationship between variability in drug response and distribution of pharmacogenetic markers. These data will be useful in the development and implementation of therapeutic guidelines, pharmacogenetic formularies, and adaptation and extrapolation of the results of RCTs conducted on larger (non-local) populations.

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**Conflict of Interest Statement**

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