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Prevalence of *AOX1* and *CYP1A2* gene polymorphisms associated with response to favipiravir therapy in novel coronavirus infection COVID-19 among ethnic groups of the North Caucasus

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Drug sensitivity to, in particular to favipiravir, may vary among representatives of different ethnic groups. Studies have previously shown that carrying certain variants of the *AOX1* and *CYP1A2* genes may be associated with an increased incidence of adverse reactions with patients having COVID-19 and taking favipiravir. This work is devoted to studying the prevalence of mutant variants rs55754655 and rs10931910 of the *AOX1* gene and rs762551 of the *CYP1A2* gene in various ethnic groups of the North Caucasus.

The aim. To characterize the distribution structure of *AOX1* (rs55754655 and rs10931910) and *CYP1A2* (rs762551) variants among the peoples of the North Caucasus (Ossetians, Balkars, Kabardians, Avars, Dargins, Laks, Kumyks and Lezgins).

Materials and methods. The frequency of distribution of *AOX1* and *CYP1A2* gene variants was studied among 897 conditionally healthy volunteers (362 men — 40.4% and 535 women — 59.6%; average age — 34.6±6.3%), from 8 ethnic groups of the North Caucasus: Ossetians, Balkars, Kabardians, Avars, Dargins, Laks, Kumyks and Lezgins (n=100 for each), as well as 97 Russians (reference group).

Results. As a result of the analysis, a significant difference was found in the allele frequencies for the rs10931910 *AOX1* genetic polymorphism between Balkars and Russians (p <0.05), Laks and Russians (p <0.05), and especially between Dargins and Russians (p <0.0001). No statistically significant differences in the allele frequencies of the *CYP1A2* gene were found in the comparative analysis of ethnic groups with the comparison group.

Conclusion. Significant differences were revealed in the frequency of *AOX1* polymorphisms (rs10931910, rs55754655) in the peoples of the North Caucasus relative to the Russian population. The largest deviations were recorded in Dargins: a decrease in the frequency of the minor allele rs10931910 to 28.5% (p <0.0001) and rs55754655 to 3.0% (p=0.0105). The results may be useful for optimizing therapy with medicines that are *AOX1* substrates, which include favipiravir, used to treat patients with COVID-19.

Keywords: favipiravir; COVID-19; ethnic groups; *AOX1*; *CYP1A2*

Abbreviations: AR — adverse reaction; AOX — aldehyde oxidase; ALT — alanine aminotransferase; AST — aspartate aminotransferase; PCR — polymerase chain reaction; dNTP — deoxynucleotides; TPMT — thiopurine methyltransferase.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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Распространённость полиморфизмов генов *AOX1* и *CYP1A2*, ассоциированных с ответом на терапию фавипиравиром при новой коронавирусной инфекции COVID-19, среди этнических групп Северного Кавказа

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Чувствительность к лекарственным препаратам, в частности к фавипиравиру, может варьировать у представителей разных этнических групп. В исследованиях ранее показано, что носительство некоторых вариантов генов *AOX1* и *CYP1A2* может ассоциироваться с повышенной частотой нежелательных реакций на фоне приёма фавипиравира у пациентов с COVID-19. Данная работа посвящена изучению распространённости мутантных вариантов rs55754655 и rs10931910 гена *AOX1* и rs762551 гена *CYP1A2* в различных этнических группах Северного Кавказа.

Цель. Охарактеризовать структуру распределения вариантов *AOX1* (rs55754655 и rs10931910) и *CYP1A2* (rs762551) среди народов Северного Кавказа (осетин, балкарцев, кабардинцев, аварцев, даргинцев, лакцев, кумыков и лезгинов).

Материалы и методы. Изучена частота распределения вариантов генов *AOX1* и *CYP1A2* среди 897 условно здоровых добровольцев (362 мужчин — 40,4% и 535 женщин — 59,6%; средний возраст — 34,6±6,3%), из 8 этнических групп Северного Кавказа: осетины, балкарцы, кабардинцы, аварцы, даргинцы, лакцы, кумыки и лезгины (n=100 для каждой), а также 97 русских (группа сравнения).

Результаты. В результате анализа было обнаружено достоверное различие в частотах аллелей по генетическому полиморфизму rs10931910 *AOX1* между балкарцами и русскими (p <0,05), лакцами и русскими (p <0,05) и в особенности между даргинцами и русскими (p <0,0001). Статистически значимых различий в частотах аллелей гена *CYP1A2* при сравнительном анализе этногрупп с группой сравнения обнаружено не было.

Заключение. Выявлены значимые различия в частоте полиморфизмов *AOX1* (rs10931910, rs55754655) у народов Северного Кавказа относительно русской популяции. Наибольшие отклонения зафиксированы у даргинцев: снижение частоты минорного аллеля rs10931910 до 28,5% (p <0,0001) и rs55754655 до 3,0% (p=0,0105). Результаты могут быть полезны для оптимизации терапии препаратами, являющимися субстратами *AOX1*, в число которых входит фавипиравир, применяемый для лечения пациентов с COVID-19.

Ключевые слова: фавипиравир; COVID-19; этнические группы; *AOX1*; *CYP1A2*

Список сокращений: НР — нежелательная реакция; АОХ — альдегидоксидаза; АЛТ — аланинаминотрансфераза; АСТ — аспартатаминотрансфераза; ПЦР — полимеразная цепная реакция; дНТФ — дезоксинуклеотиды; ТРМТ — тиопуринметилтрансфераза.

INTRODUCTION

The COVID-19 pandemic has posed a significant challenge to healthcare systems worldwide. The rapid identification and determination of drug treatment options were crucial in combating the outbreak in 2020–2021. It was found out that the genome structure of SARS-CoV-2 was 75–80% identical to the genome sequence of SARS-CoV [1]. This result led to the development of etiotropic therapy regimens using favipiravir, which was indicated for the treatment of SARS and MERS infections. However, the widespread use of favipiravir revealed that this medicine is characterized by the development of a range of adverse reactions (ARs), including elevated liver enzymes (AST / ALT), leukopenia, hyperuricemia, and gastrointestinal disorders [2]. A recent meta-analysis of 25 clinical trials evaluating the use of favipiravir for the treatment of COVID-19 showed that its use is associated with an increased incidence of ARs (OR = 1.27, 95% CI 1.05–1.54; 18 RCTs, 4 699 participants) [2].

Over the past two decades, the field of pharmacogenetics has greatly developed, focusing on the study of the contribution of a patient's genetic profile to the pharmacological effect of the pharmacotherapy they receive. In the context of the development of ARs, the search for possible associations of genetic markers with the safety of the medicine is of interest. Favipiravir is metabolized primarily by aldehyde oxidase 1 (AOX1) to form the inactive metabolite T705M1 and, to a lesser extent, by xanthine oxidase [3]. Possible associations of mutations in the *AOX1* gene with the safety of favipiravir in patients with COVID-19 are currently poorly understood; nevertheless, the use of the "gene-candidate" approach suggests this connection. In addition, *in silico*, using the PASS 2022 program, it was predicted that favipiravir is also a substrate of *CYP1A2* [4].

In our earlier study, which included patients with COVID-19 who received favipiravir in the hospital, we were able to find associations between carrying the rs55754655 and rs10931910 variants of the *AOX1* gene and the rs762551 variant of the *CYP1A2* gene with an increase in the level of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and leukocytes [5]. There is also data on the effect of the rs55754655 polymorphism of the *AOX1* gene on the metabolism of purine compounds, in particular azathioprine [6]. Thus, it can be assumed that in the presence of concomitant diseases requiring the use of medicines that are substrates of *AOX1*, genotyping of the latter will allow timely prescription of adequate therapy and prevention of possible complications. Studies on the dependence between variants of the cytochrome *CYP1A2* gene and the response to drugs metabolized by CYP1A2 are extremely limited. Thus, in a sample of 60 patients, it was shown that the genetic polymorphisms rs2069514 and rs762551 in the *CYP1A2* gene have a statistically significant prognostic value in relation to the severity of COVID-19 [7].

In the works of a number of authors, it was shown that in Russia the frequency of significant pharmacogenetic markers varies between populations and ethnic groups [8–10]. The level of genetic heterogeneity of the populations of Russia, for example, for cytochrome genes, is relatively low, but is closely related to the geographical location of residence of these peoples. Particular attention should be paid to the North Caucasus, which is the most ethnically diverse region and is an ideal object for studying differences in the distribution of genetic variations in ethnic groups [11]. Determining the nature of the carriage of pharmacogenetic markers among local populations remains an important task in the context of the transition to personalized medicine. Knowledge of the structure of the distribution of markers can help identify areas and regions where the introduction of testing will be most priority and justified from the point of view of the healthcare system. This also avoids unnecessary and unjustified prescribing of testing for all patients without the need.

THE AIM. In connection with the above information, the aim of this study was to characterize the structure of the distribution of *AOX1* (rs55754655 and rs10931910) and *CYP1A2* (rs762551) variants among the peoples of the North Caucasus (Ossetians, Balkars, Kabardins, Avars, Dargins, Laks, Kumyks and Lezgins) to predict the response to substrates of these enzymes, including favipiravir.

MATERIALS AND METHODS

Study design

A cross-sectional retrospective genetic epidemiology study was conducted on conditionally healthy volunteers to determine the population frequency of polymorphisms of the *AOX1* and *CYP1A2* genes, affecting the metabolism and safety of favipiravir according to literature data [3, 5, 12].

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The study involved 897 conditionally healthy volunteers — men (*n* = 362) and women (*n* = 535) from 9 ethnic groups: 100 participants from the Ossetian, Balkar, Kabardin, Avar, Dargin, Lak, Kumyk and Lezgin ethnic groups (North Caucasus) and 97 Russians.

Eligibility criteria

Inclusion criteria: age ≥18 years, ethnicity was determined by self-identification of participants and their parents. There is a high correlation between the self-identification used method and the determination of microsatellite markers of ethnicity as shown in a previous study [13].

Exclusion criteria: the study did not include descendants of mixed marriages; refusal to participate in the study.

Study conditions

The collection of biomaterials was carried out on the bases of the Lak Central District Hospital, the Clinical Hospital of the Ossetian State Medical Academy and the Republican Clinical Hospital.

Study duration

Biomaterial for analysis was obtained from the bioresource collection of the Russian Medical Academy of Continuing Professional Education, formed in the period from 2015 to 2021. Laboratory genotyping and statistical data processing were carried out in 2024. Thus, the work is a retrospective analysis of the prevalence of alleles in selected samples.

Genotyping

Genotyping was performed by real-time polymerase chain reaction (PCR). DNA was extracted from 100 µl of venous blood collected in tubes with ethylenediaminetetraacetate (VACUETTE, Greiner Bio-One, Austria). DNA was extracted using "DNA-Extran-1" kits (CJSC "Syntol", Russia) and MagnoPrime UNI (LLC "NextBio", Russia) according to the manufacturer's instructions.

The presence of genetic polymorphisms was detected using reagent kits containing allele-specific TaqMan® probes (Applied Biosystems, USA; TestGen LLC, Russia) on Real-Time CFX96 Touch amplifiers (Bio-Rad Laboratories Inc., USA). PCR was performed in a reaction volume of 10 µl containing genomic DNA — 15 ng, oligonucleotide primers — 0.5 pM, 10X PCR buffer — 1 µl, deoxynucleotides (dNTP) — 250 µM, magnesium chloride — 3 mM and DNA polymerase — 0.25 U. The amplification program included pre-incubation at 95°C for 3 min, then for 50 cycles denaturation at 95°C — 10 s and annealing at 60°C — 30 s. The analysis is based on the detection of a fluorescent signal after each amplification cycle. Genotypes were determined by fluorescence growth curves in the FAM and VIC channels.

Ethics approval

The study was approved by the Ethics Committee of the Russian Medical Academy of Continuous Professional Education (Protocol No. 15 dated October 16, 2021). At the stage of collection of biomaterials, the study was approved by the Local Ethics Committee of the Republican Clinical Hospital (Protocol No. 2 dated September 05, 2016); of the Lak Central District Hospital (Protocol No. 12 dated September 22, 2015); by the Ethics Committee of the North Ossetian State Medical Academy (Protocol No. 11-3 dated November 16, 2016). The study was conducted in accordance with the legislation of the Russian Federation and International Regulatory Documents (Helsinki Declaration of the World Medical Association, 2013; National Standard of the Russian Federation GOST R 52379-2005).

All participants gave their voluntary informed consent to participate in the study and to the collection and storage of genetic material. According to the terms of informed consent, all study results can be analyzed and published in the relevant scientific journal without disclosing personal information.

Statistical analysis

The number of samples (100 people per ethnic group) was determined basically on the practice of genetic studies of isolated populations [11, 14].

The Pearson χ^2 criterion ($p < 0.05$) for each gene according to the Hardy-Weinberg law was used to carry out the assessment of the correspondence of the independent distribution of alleles.

The distribution of *AOX1* (rs55754655 and rs10931910) and *CYP1A2* (rs762551) alleles within the Russian ethnic group was used as a reference group.

Russians (*n* = 97), representing the largest ethnic group in Russia, were selected as the reference group. This allows: interpreting the results in the context of All-Russian clinical guidelines; comparing data with previous pharmacogenetic studies [8, 10, 15]; assessing the specificity of the North Caucasian populations relative to the dominant demographic group of the country.

Intergroup comparisons of allele frequencies were performed using the χ^2 criterion (with Yates› correction for small expected frequencies (n = 5–10; $p < 0,05$). The normal distribution was not analyzed, since working with categorical data does not require parametric tests. The results were evaluated in the GraphPad InStat program (GraphPad Software Inc., USA).

RESULTS

The results of genotyping of subjects by genotype frequency and carriage of variants of the studied markers are presented in tables 1–3.

In most cases, the distribution of *AOX1* and *CYP1A2* genotypes corresponded to the Hardy-Weinberg equilibrium law. Exceptions were *AOX1* rs10931910 T>C (p = 0.0188; Table 1) and *CYP1A2*F1* rs762551 A>C (p = 0.0132; Table 3) in Kabardins, where an excessive number of heterozygous alleles were represented, and *AOX1* rs55754655 T>C in Dargins (p = 0.0018). On the one hand, the Hardy-Weinberg law describes the equilibrium of allele frequencies in a population, but in real conditions there can be disruptive factors. On the other hand, it is necessary to take into account the relatively rare prevalence of the rs55754655 allele in Dargins in comparison with other ethnic groups, statistical errors may occur that require an increase of the number of samples of the Dargin ethnic group for further studies of this genetic polymorphism.

In the context of our study, the results of the analysis revealed significant differences in allele frequencies for rs10931910 of the *AOX1* gene between Balkars and Russians, Dargins and Russians, and Laks and Russians; with respect to rs55754655 of the *AOX1* gene — between Dargins and Russians (Table 4).

No statistically significant differences in the allele frequencies of the *CYP1A2* gene were found in the comparative analysis of ethnic groups.

Despite the relatively small number of samples in each of the comparison groups, there is a noticeable uneven distribution of the allele frequency in the ethnic groups. Thus, the highest occurrence of the minor variant rs10931910 of the *AOX1* gene was 48.5% in Avars and Russians, and the lowest was 28.5% in Dargins. A similar distribution is observed for the rs55754655 alleles of the same gene: the lowest in Dargins (3%), the highest in Ossetians (11.5%), and slightly lower in Russians (9.8%). However, this was not typical for another gene: the highest and lowest percentage of polymorphic allele occurrence was in the Lezgin and Ossetian ethnic groups, 42.5% and 26.5%, respectively.

According to the Ensembl 2024 database [16], the frequency of the C allele rs10931910 of the *AOX1* gene is 43.5%, which is the lowest among all major ethnic groups; for them, this allele is the major one. In our studied samples, the proportion of the minor allele also did not reach 50%. The frequency of the allele variant C rs55754655 of the *AOX1* gene in the European population, on the contrary, is more common than in most others and amounts to 12%. In our samples, the frequencies of this allele are lower than the population average. The minor allele A rs762551 of the *CYP1A2*F1* gene in the large population has a frequency of 32%. The allele frequency of this allele among the ethnic groups of the North Caucasus was higher than 32%, with the exception of Ossetians, Balkars, and Avars.

DISCUSSION

A comparison of the frequency of occurrence of the studied allele variants in groups was carried out. The peoples of the North Caucasus differ in a more compact area of residence compared to the Russian ethnic group, which lives relatively evenly throughout Russia. The North Caucasus is an excellent example of a region where the distribution of genes can be significantly influenced by the geographical factor; the mountainous isolated nature of settlement determines the genetic structure of the population [15]. Thus, 26 of the 50 autochthonous peoples of the North Caucasus live in the Caspian Sea region. Our study included 5 peoples of the Republic of Dagestan: Avars, Dargins, Laks, Kumyks, and Lezgins. The next ethnic group included in our study is the Ossetians, an Iranian-speaking people living on the northern and southern slopes of the Greater Caucasus Range. Kabardians, a people belonging to the Abkhaz-Adyghe language group, make up the majority of the population of the Kabardino-Balkarian Republic. The second largest ethnic group in the republic is the Balkars, a Turkic-speaking people of the Altai language family. The selection of these populations was due to the criterion that genetic isolation can also be influenced by religious disunity and the absence of a common language (lingua franca) among the Caucasian peoples. Earlier studies have shown that the distribution of pharmacologically significant genetic markers is consistent with this feature of populations living in the North Caucasus; ethnic groups differ significantly with respect to the distribution of pharmacogenetic markers [15, 17].

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Table 1 – Assessment of the correspondence of *AOX1* rs10931910 T>C genotypes according to the Hardy-Weinberg law

Ethnic group (*n*)	Gender (*n*)	Age (M ± SD)	Frequency	Genotype			Minor allele frequency, %	Correspondence to Hardy-Weinberg distribution	
				TT	TC	CC		χ^2	*p*
Russians (*n* = 97)	Male (17) Female (80)	43 ± 12	observed	24	52	21	48.45%	0.5196	0.4710
			expected	25.8	48.5	22.8			
			%	24.7%	53.6%	21.6%			
Ossetians (*n* = 100)	Male (27) Female (73)	33 ± 11	observed	35	42	23	44.00%	2.1823	0.1396
			expected	31.4	49.3	19.4			
			%	35.0%	42.0%	23.0%			
Balkars (*n* = 100)	Male (41) Female (49)	46 ± 19	observed	34	56	10	38.00%	3.5515	0.0595
			expected	38.4	47.1	14.4			
			%	34.0%	56.0%	10.0%			
Kabardins (*n* = 100)	Male (38) Female (62)	47 ± 18	observed	25	61	14	44.50%	5.5198	**0.0188**
			expected	30.8	49.4	19.8			
			%	25.0%	61.0%	14.0%			
Avars (*n* = 100)	Male (79) Female (21)	24 ± 9	observed	27	50	23	48.00%	0.0003	0.9872
			expected	27.0	49.9	23.0			
			%	27.0%	50.0%	23.0%			
Dargins (*n* = 100)	Male (63) Female (37)	31 ± 15	observed	51	41	8	28.50%	0.0036	0.9521
			expected	51.1	40.8	8.1			
			%	51.0%	41.0%	8.0%			
Laks (*n* = 100)	Male (53) Female (47)	29 ± 9	observed	41	43	17	38.12%	0.9613	0.3269
			expected	38.7	47.6	14.7			
			%	40.6%	42.6%	16.8%			
Kumyks (*n* = 100)	Male (20) Female (80)	34 ± 11	observed	37	41	22	42.50%	2.5961	0.1071
			expected	33.1	48.9	18.1			
			%	37.0%	41.0%	22.0%			
Lezgins (*n* = 100)	Male (24) Female (76)	35 ± 10	observed	37	53	20	42.27%	0.0180	0.8933
			expected	36.7	53.7	19.7			
			%	33.6%	48.2%	18.2%			

Table 2 – Assessment of the correspondence of *AOX1* rs55754655 T>C genotypes according to the Hardy-Weinberg law

Ethnic group (*n*)	Gender (*n*)	Age (M ± SD)	Frequency	Genotype			Minor allele frequency, %	Correspondence to Hardy-Weinberg distribution	
				TT	TC	CC		χ^2	*p*
Russians (*n* = 97)	Male (17) Female (80)	43 ± 12	observed	80	15	2	9.79%	1.5111	0.2190
			expected	78.9	17.1	0.9			
			%	82.5%	15.5%	2.1%			
Ossetians (*n* = 100)	Male (27) Female (73)	33 ± 11	observed	78	21	1	11.50%	0.1004	0.7513
			expected	78.3	20.4	1.3			
			%	78.0%	21.0%	1.0%			
Balkars (*n* = 100)	Male (41) Female (49)	46 ± 19	observed	86	14	0	7.00%	0.5665	0.4516
			expected	86.5	13.0	0.5			
			%	86.0%	14.0%	0.0%			
Kabardins (*n* = 100)	Male (38) Female (62)	47 ± 18	observed	83	17	0	8.50%	0.8630	0.3529
			expected	83.7	15.6	0.7			
			%	83.0%	17.0%	0.0%			
Avars (*n* = 100)	Male (79) Female (21)	24 ± 9	observed	86	14	0	7.00%	0.5665	0.4516
			expected	86.5	13.0	0.5			
			%	86.0%	14.0%	0.0%			
Dargins (*n* = 100)	Male (63) Female (37)	31 ± 15	observed	95	4	1	3.00%	9.7791	**0.0018**
			expected	94.1	5.8	0.1			
			%	95.0%	4.0%	1.0%			
Laks (*n* = 100)	Male (53) Female (47)	29 ± 9	observed	91	9	0	4.50%	0.2220	0.6375
			expected	91.2	8.6	0.2			
			%	91.0%	9.0%	0.0%			
Kumyks (*n* = 100)	Male (20) Female (80)	34 ± 11	observed	89	10	1	6.00%	1.2877	0.2565
			expected	88.4	11.3	0.4			
			%	89.0%	10.0%	1.0%			
Lezgins (*n* = 100)	Male (24) Female (76)	35 ± 10	observed	88	12	0	6.00%	0.4074	0.5233
			expected	88.4	11.3	0.4			
			%	88.0%	12.0%	0.0%			

Table 3 – Assessment of the correspondence of *CYP1A2*F1* rs762551 A>C genotypes according to the Hardy-Weinberg law

Ethnic group (*n*)	Gender (*n*)	Age (M ± SD)	Frequency	Genotype			Minor allele frequency, %	Correspondence to Hardy-Weinberg distribution	
				AA	AC	CC		χ^2	*p*
Russians (*n* = 97)	Male (17) Female (80)	43 ± 12	observed	41	44	12	35.05%	0.0014	0.9707
			expected	40.9	44.2	11.9			
			%	42.3%	45.4%	12.4%			
Ossetians (*n* = 100)	Male (27) Female (73)	33 ± 11	observed	51	45	4	26.50%	2.4081	0.1207
			expected	54.0	39.0	7.0			
			%	51.0%	45.0%	4.0%			
Balkars (*n* = 100)	Male (41) Female (49)	46 ± 19	observed	52	39	9	28.50%	0.1854	0.6667
			expected	51.1	40.8	8.1			
			%	52.0%	39.0%	9.0%			
Kabardins (*n* = 100)	Male (38) Female (62)	47 ± 18	observed	38	56	6	34.00%	6.1391	**0.0132**
			expected	43.6	44.9	11.6			
			%	38.0%	56.0%	6.0%			
Avars (*n* = 100)	Male (79) Female (21)	24 ± 9	observed	47	44	9	31.00%	0.0813	0.7755
			expected	47.6	42.8	9.6			
			%	47.0%	44.0%	9.0%			
Dargins (*n* = 100)	Male (63) Female (37)	31 ± 15	observed	40	44	16	38.00%	0.4384	0.5079
			expected	38.4	47.1	14.4			
			%	40.0%	44.0%	16.0%			
Laks (*n* = 100)	Male (53) Female (47)	29 ± 9	observed	38	42	20	41.00%	1.7390	0.1873
			expected	34.8	48.4	16.8			
			%	38.0%	42.0%	20.0%			
Kumyks (*n* = 100)	Male (20) Female (80)	34 ± 11	observed	37	48	15	39.00%	0.0078	0.9297
			expected	37.2	47.6	15.2			
			%	37.0%	48.0%	15.0%			
Lezgins (*n* = 100)	Male (24) Female (76)	35 ± 10	observed	35	45	20	42.50%	0.6286	0.4279
			expected	33.1	48.9	18.1			
			%	35.0%	45.0%	20.0%			

Table 4 – Allele frequency of AOX1 (rs55754655 and rs10931910) and CYP1A2 (rs762551) genetic markers among various ethnic groups of the North Caucasus compared to the Russian population

Ethnic groups (*n*)	*AOX1* rs10931910 T>C			*AOX1* rs55754655 T>C			*CYP1A2*F1* rs762551 A>C		
	Minor allele frequency, *n* (%)	χ^2	*p*	Minor allele frequency, *n* (%)	χ^2	*p*	Minor allele frequency, *n* (%)	χ^2	*p*
Russians (*n* = 97)	94 (48.5%)	–	–	19 (9.8%)	–	–	68 (35.1%)	–	–
Ossetians (*n* = 100)	88 (44.0%)	0.786	0.3754	23 (11.5%)	0.301	0.5832	53 (26.5%)	3.384	0.0658
Balkars (*n* = 100)	76 (38.0%)	4.387	**0.0362**	14 (7.0%)	1.002	0.3169	57 (28.5%)	1.951	0.1624
Kabardins (*n* = 100)	89 (44.5%)	0.619	0.4315	17 (8.5%)	0.199	0.6559	68 (34%)	0.048	0.8263
Avars (*n* = 100)	96 (48.0%)	0.008	0.9282	14 (7.0%)	1.002	0.3169	62 (31.0%)	0.731	0.3925
Dargins (*n* = 100)	57 (28.5%)	16.588	**<0.0001**	6 (3.0%)	6.548	**0.0105**	76 (38.0%)	0.369	0.5435
Laks (*n* = 100)	77 (38.5%)	3.972	**0.0463**	9 (4.5%)	3.417	0.0645	82 (41.0%)	1.478	0.2241
Kumyks (*n* = 100)	85 (42.5%)	1.408	0.2354	12 (6.0%)	1.955	0.162	78 (38.0%)	0.658	0.4172
Lezgins (*n* = 100)	83 (41.5%)	1.924	0.1654	12 (6.0%)	1.955	0.162	85 (42.5%)	2.3	0.1294

Information of the distribution of clinically significant markers among ethnic groups of the population makes it possible to identify regions with increased sensitivity to certain drugs. From a practical point of view, the study of the carriage of polymorphic alleles of genes involved in the biotransformation and effects of drugs in various populations is relevant from the perspective of optimizing pharmacogenetic studies and introducing such testing into routine practice in individual regions.

Cytochrome P450 (CYP) is a superfamily of monooxygenases containing heme as a cofactor and found in all cells and tissues of mammals, with the exception of mature erythrocytes and skeletal muscle tissue cells [18]. CYPs are most studied as enzymes that metabolize drugs. For *CYP1A2*, the substrate of

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which, according to in silico modeling, is favipiravir, some relationships have been identified between variants of the enzyme gene and changes in the drug response to clozapine, paroxetine, opioids, and escitalopram [19]. The frequency of ARs to drugs is higher in carriers of alleles that reduce the activity of the enzyme, which leads to a decrease in metabolism and its elimination from the body, which causes the manifestation of toxic effects. In the context of our study, we did not find that the frequency of the rs762551 allele of the *CYP1A2* gene differs in the studied groups. Thus, it can be assumed that the population of the North Caucasus region does not stand out for increased sensitivity to favipiravir. However, further study of the contribution of *CYP1A2* and its variants to changes in the metabolism and effects of the medicine is necessary.

Aldehyde oxidase (AOX) is a molybdenum-containing flavoenzyme involved in phase I of medicine metabolism [20]. Four isoforms of AOX have been identified in mammals, but only *AOX1* is the functional gene among them [21]. The *AOX1* protein is localized in the cytoplasm and is mainly represented as monomers and homodimers. Its function is to catalyze the oxidation of many different aldehydes and heterocyclic medicine molecules containing nitrogen atoms, such as azathioprine, famciclovir, and methotrexate [22, 23], as well as to catalyze the reduction of nitrogenous aromatic compounds, such as nitrazepam and dantrolene [12, 24]. The results of several studies indicate the clinical significance of interactions between medicine molecules that are substrates of *AOX1*, for example, between methotrexate and favipiravir in a patient with osteosarcoma [25]. Given this, inhibition of *AOX1* may be an effective approach that blocks the metabolism of methotrexate and thereby increases its effectiveness [26]. Thus, it is necessary to take into account the enzymatic activity of *AOX1* when, with the use of standard doses of medicines that are substrates of *AOX1*, the patient does not observe an adequate response to therapy. In our study, on a sample including 100 volunteers from various ethnic groups of the North Caucasus, data were obtained on the heterogeneity of the distribution of polymorphisms rs10931910 and rs55754655 of the *AOX1* gene. The greatest differences from the Russian population among the peoples of the North Caucasus were demonstrated by variants of the *AOX1* gene. Thus, in addition to the lower prevalence of the C allele in the rs55754655 polymorphism in Dargins (3% compared to 9.8% in Russians, $p = 0.0105$), there is also a decrease in the frequency of the risk allele C in rs10931910 T>C compared to the Russian population (48.5%), Balkars (38%), Laks (38.5%) and Dargins (28.5%; $p < 0.0001$). These observations probably indicate the degeneration of risk alleles in the *AOX1* gene in certain populations of the North Caucasus.

To date, there are data from isolated studies that have shown an association between individual polymorphisms of the *AOX1* gene and the response to therapy with azathioprine [27], allopurinol [28], and the antitumor medicine XK469 [29]. Thus, in the presence of the rs55754655 T>C mutation in combination with an increased level of thiopurine methyltransferase (TPMT), only 33% of patients demonstrated a normal response to azathioprine therapy. Conversely, when both of these factors were favorable (T allele in rs55754655 in combination with a normal TPMT level), a normal response to azathioprine therapy was observed in 86% of cases [27]. Genetic polymorphisms rs11678615 C>T, rs3731722 A>G, and rs75995567 T>C, in turn, led to the need to increase the dose of allopurinol to 300 mg/day or more [28]. Finally, the rs10931910 T>C mutation led to a 41% slowdown in the elimination of the antitumor drug XK469 from the body in the case of the TC heterozygote and 67% in the case of the CC homozygote during therapy for solid tumors [29].

The official instructions for the medical use of favipiravir[1], available on the website of the Russia State Registry of Medicines, indicate the medicine interaction of favipiravir with pyrazinamide, repaglinide, theophylline, famciclovir, sulindac, and it is the interaction with the latter two drugs that is associated with the inhibition of AOX by favipiravir.

Thus, further study of the clinical significance of *AOX1* gene polymorphisms is necessary when prescribing medicines whose biotransformation is associated with the *AOX1* enzyme, as well as medicine interactions at the *AOX1* level, including favipiravir, which is especially important for patients with concomitant diseases in which other *AOX1* substrate drugs may be prescribed. Genotyping of the polymorphisms we studied may in the future become one of the important ways to improve the effectiveness and safety of therapy for patients with COVID-19.

Limitations of the study

The main study limitations are the lack of a preliminary sample size calculation. Although the size of the groups ($n = 100$ for the ethnic groups of the Caucasus, $n = 97$ for Russians) corresponds to the standards of population studies [11, 13, 15] and provides acceptable accuracy for allele frequencies >5% (error ≤7%), for rare variants (for example, rs55754655 with a frequency of 3% in Dargins), the estimation error reaches 3.4% (95% CI: 0.6–8.5%), which may affect the reliability of the identified intergroup differences.

CONCLUSION

As a result of the study, the population frequency of clinically significant polymorphisms of the *AOX1* (rs55754655, rs10931910) and *CYP1A2* (rs762551)

[1] Favipiravir. Russia State Registry of Medicines. Available from: https://grls.rosminzdrav.ru/GRLS.px?RegNumber=&MnnR=фавипиравир&lf=&TradeNmR=&OwnerName=&MnfOrg=&MnfOrgCountry=&isfs=0&regtype=1%2c6&pageSize=10&token=aa088037-2cb7-4cb6-94aa-b1f-60b5e5ba5&order=Registered&orderType=desc&pageNum=1

genes in ethnic groups of the North Caucasus was characterized. Statistically significant differences were established in the distribution of *AOX1* alleles between the Russian reference group and the indigenous peoples of the region: lower frequencies of the minor allele rs10931910 in Balkars (38.0 *vs* 48.5%, $p = 0.036$), Laks (38.5 *vs* 48.5%, $p = 0.046$) and Dargins (28.5 *vs* 48.5%, $p < 0.0001$); rare occurrence of the risk allele rs55754655 was noted in Dargins (3.0 *vs* 9.8%, $p = 0.0105$).

The presented data create the basis for personalized prescription of *AOX1* substrates, including favipiravir, in the North Caucasus region. Carriage of the identified variants is associated with a change in medicine metabolism and the risk of ARs (hepatotoxicity, leukopenia). At the same time, the clinical significance of these polymorphisms requires further verification in prospective studies involving patients receiving therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Arvo T. Leinsoo — writing the text of the article, performing the laboratory part of the research; Natalia P. Denisenko, Sherzod P. Abdullaev — critical evaluation of the results and the text of the article; Svetlana N. Tuchkova — statistical analysis of the results; Alexander V. Kryukov, Suleiman N. Mammaev, Zhannet A. Sozaeva, Mariam S.-Kh. Sozaeva, Kristina A. Akmalova, Laura Z. Bolieva — selection of study participants, collection of biological material; Alina I. Dobroselskaya — performing the laboratory part of the research; Maxim L. Maximov, Karin B. Mirzaev, Dmitry A. Sychev — scientific consulting. All the authors have made an equivalent and equivalent contribution to the preparation of the publication. All authors confirm their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the research, and preparation of the article, read and approved the final version before publication).

REFERENCES

1. Ghasemnejad-Berenji M, Pashapour S. Favipiravir and COVID-19: A Simplified Summary. Drug Res (Stuttg). 2021;71(3):166–70. DOI: 10.1055/a-1296-7935
2. Korula P, Alexander H, John JS, Kirubakaran R, Singh B, Tharyan P, Rupali P. Favipiravir for treating COVID-19. Cochrane Database Syst Rev. 2024;2(2):CD015219. DOI: 10.1002/14651858.CD015219.pub2
3. Madelain V, Nguyen TH, Olivo A, de Lamballerie X, Guedj J, Taburet AM, Mentré F. Ebola Virus Infection: Review of the Pharmacokinetic and Pharmacodynamic Properties of Drugs Considered for Testing in Human Efficacy Trials. Clin Pharmacokinet. 2016;55(8):907–23. DOI: 10.1007/s40262-015-0364-1
4. Filimonov DA, Lagunin AA, Gloriozova TA, Rudik AV, Druzhilovskii DS, Pogodin PV. Prediction of the biological activity spectra of organic compounds using the pass online web resource. Chem Heterocycl Compd. 2014;50(3):444–57. DOI: 10.1007/S10593-014-1496-1/METRICS
5. Temirbulatov II, Kryukov AV, Mirzaev KB, Denisenko NP, Abdullaev SP, Petrova AV, Tkach EP, Shipacheva AV, Sychev DA. Pharmacogenetic Markers of Favipiravir Safety in COVID-19 Treatment. Antibiotics and Chemotherapy. 2023;68(5–6):55–61. DOI: 10.37489/0235-2990-2023-68-5-6-55-61-61
6. Kurzawski M, Dziewanowski K, Safranow K, Drozdzik M. Polymorphism of genes involved in purine metabolism (*XDH, AOX1, MOCOS*) in kidney transplant recipients receiving azathioprine. Ther Drug Monit. 2012;34(3):266–74. DOI: 10.1097/FTD.0b013e31824aa681
7. Bozkurt I, Gözler T, Yüksel I, Ulucan K, Tarhan KN. Prognostic Value of *CYP1A2* (rs2069514 and rs762551) Polymorphisms in COVID-19 Patients. Balkan J Med Genet. 2023;26(1):35–42. DOI: 10.2478/bjmg-2023-0005
8. Romodanovsky DP, Khapaev BA, Ignatiev IV, Kukes VG, Karkishchenko VN. Frequencies of "slow" allelic variants of genes encoding cytochrome P450 isoenzymes *CYP2D6, CYP2C19, CYP2C9* in Karachays and Circassians. Biomedicine. 2010;1(2):33–7. EDN: NTVJLV. Russian
9. Baturin VA, Tsarukyan AA, Kolodijchuk EV. Study of *CYP2C9* gene polymorphism in ethnic groups of the population of Stavropol region. Medical News of North Caucasus. 2014;9(1):45–8. DOI: 10.14300/mnnc.2014.09013
10. Mirzaev KB, Fedorinov DS, Ivashchenko DV, Sychev DA. ADME pharmacogenetics: future outlook for Russia. Pharmacogenomics. 2019;20(11):847–65. DOI: 10.2217/pgs-2019-0013
11. Abdullaev SP, Denisenko NP, Mirzaev KB, Shuev GN, Sozaeva ZA, Kachanova AA, Mammaev SN, Kasaeva EA, Gafurov DM, Grishina EA, Sychev DA. *CYP2C8, PTGS-1, 2* gene polymorphisms prevalence associated with sensitivity to non-steroidal anti-inflammatory drugs among North Caucasus ethnic groups.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-420-430

Terapevticheskii arkhiv. 2021;93(11):1334–9. DOI: 10.26442/00403660.2021.11.201220

12. Demir E, Sütcüoğlu O, Demir B, Ünsal O, Yazıcı O. A possible interaction between favipiravir and methotrexate: Drug-induced hepatotoxicity in a patient with osteosarcoma. J Oncol Pharm Pract. 2022;28(2):445–8. DOI: 10.1177/10781552211031304
13. Tang H, Quertermous T, Rodriguez B, Kardia SL, Zhu X, Brown A, Pankow JS, Province MA, Hunt SC, Boerwinkle E, Schork NJ, Risch NJ. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. Am J Hum Genet. 2005;76(2):268–75. DOI: 10.1086/427888
14. Yunusbayev B, Kutuev I, Khusainova R, Guseinov G, Khusnutdinova E. Genetic structure of Dagestan populations: a study of 11 Alu insertion polymorphisms. Hum Biol. 2006;78(4):465–76. DOI: 10.1353/hub.2006.0059
15. Balanovska EV, Abdulaev SP, Gorin IO, Belov RO, Mukatdarova EA, Pylev VY. Gene geography of pharmacogenetically significant *CYP2C19* cytochrome superfamily DNA markers in the populations of Russia and neighboring countries. Bulletin of RSMU. 2023;(5):26–40. DOI: 10.24075/brsmu.2023.039
16. Harrison PW, Amode MR, Austine-Orimoloye O, et al. Ensembl 2024. Nucleic Acids Res. 2024;52(D1):D891–D899. DOI: 10.1093/nar/gkad1049
17. Balanovska EV, Petrushenko VS, Koshel SM, Pocheshkhova EA, Chernevskiy DK, Mirzaev KB, Abdullaev SP, Balanovsky OP. Cartographic atlas of frequency variation for 45 pharmacogenetic markers in populations of Russia and its neighbor states. Bulletin of RSMU. 2020;(6):38–50. DOI: 10.24075/brsmu.2020.080
18. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;323(18):1824–36. DOI: 10.1001/jama.2020.6019
19. Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, Whaley R, Klein TE. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. Clin Pharmacol Ther. 2021;110(3):563–72. DOI: 10.1002/cpt.2350
20. Ueda H, Narumi K, Furugen A, Saito Y, Kobayashi M. Thers35217482 (T755I) single-nucleotide polymorphism in aldehyde oxidase-1 attenuatesproteindimer formation and reduces the rates of phthalazine metabolism. Drug Metab Dispos. 2022:DMD-AR-2022-000902. DOI: 10.1124/dmd.122.000902
21. Garattini E, Fratelli M, Terao M. Mammalian aldehyde oxidases: genetics, evolution and biochemistry. Cell Mol Life Sci. 2008;65(7–8):1019–48. DOI: 10.1007/s00018-007-7398-y
22. Obach RS, Huynh P, Allen MC, Beedham C. Human liver aldehyde oxidase: inhibition by 239 drugs. J Clin Pharmacol. 2004;44(1):7–19. DOI: 10.1177/0091270003260336
23. Kitamura S, Sugihara K, Ohta S. Drug-metabolizing ability of molybdenum hydroxylases. Drug Metab Pharmacokinet. 2006;21(2):83–98. DOI: 10.2133/dmpk.21.83
24. Konishi K, Fukami T, Gotoh S, Nakajima M. Identification of enzymes responsible for nitrazepam metabolism and toxicity in human. Biochem Pharmacol. 2017;140:150–60. DOI: 10.1016/j.bcp.2017.06.114
25. Amano T, Fukami T, Ogiso T, Hirose D, Jones JP, Taniguchi T, Nakajima M. Identification of enzymes responsible for dantrolene metabolism in the human liver: A clue to uncover the cause of liver injury. Biochem Pharmacol. 2018;151:69–78. DOI: 10.1016/j.bcp.2018.03.002
26. Morgan SL, Baggott JE. The importance of inhibition of a catabolic pathway of methotrexate metabolism in its efficacy for rheumatoid arthritis. Med Hypotheses. 2019;122:10–5. DOI: 10.1016/j.mehy.2018.10.002
27. Smith MA, Marinaki AM, Arenas M, Shobowale-Bakre M, Lewis CM, Ansari A, Duley J, Sanderson JD. Novel pharmacogenetic markers for treatment outcome in azathioprine-treated inflammatory bowel disease. Aliment Pharmacol Ther. 2009;30(4):375–84. DOI: 10.1111/j.1365-2036.2009.04057.x
28. Carroll MB, Smith DM, Shaak TL. Genomic sequencing of uric acid metabolizing and clearing genes in relationship to xanthine oxidase inhibitor dose. Rheumatol Int. 2017;37(3):445–53. DOI: 10.1007/s00296-016-3592-2
29. Ramírez J, Kim TW, Liu W, Myers JL, Mirkov S, Owzar K, Watson D, Mulkey F, Gamazon ER, Stock W, Undevia S, Innocenti F, Ratain MJ. A pharmacogenetic study of aldehyde oxidase I in patients treated with XK469. Pharmacogenet Genomics. 2014;24(2):129–32. DOI: 10.1097/FPC.0000000000000023

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