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PREVALENCE OF POLYMORPHISMS IN WARFARIN METABOLISM-RELATED GENES AMONG THE KAZAKH POPULATION

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Abstract

Objective: The study aims to perform a comparative analysis of population frequencies of minor alleles of polymorphisms in the genes CYP2C9 *2 (rs1799853), *3 (rs1057910), *5 (rs28371686), and *6 (rs9332131); CYP2C19 (rs3814637), VKORC1 (rs9934438), CYP4F2 (rs2108622), GGCX (rs11676382), as well as GWAS-associated variants related to resistance to vitamin K antagonists in an ethnically homogeneous Kazakh population, and to assess the distribution and perform a comparative analysis of metabolic phenotypes ("metabolizer types") in comparison with previously studied global populations.

Materials and Methods: The research was based on genomic analysis data from 1,900 conditionally healthy individuals of Kazakh ethnicity, obtained within the framework of the 7th Framework Programme of the European Union under Grant Agreement No. 282540.

Results: A high frequency of the minor allele of the "Asian" variant rs11676382 in the GGCX gene was identified in the Kazakh population (14.4%) compared to European, East Asian, and South Asian groups. It may indicate a potentially more pronounced impact of this polymorphism on individual warfarin dosing requirements in individuals of Kazakh ethnicity.

In the studied Kazakh group, the identified phenotypes and frequencies of metabolizers for CYP2C9 *2 (rs1799853) and *3 (rs1057910) alleles were as follows: 1/1 (80.1%), 1/3 (13.0%), 3/3 (0.25%), 1/2 (6.0%), 2/3 (0.40%), and 2/2 (0.25%). Normal metabolizers (*2 and *3 alleles) comprised 80.1%, intermediate metabolizers - 19.0%, and slow metabolizers - 0.9%.

For CYP2C9 *5 (rs28371686) and *6 (rs9332131) alleles, the phenotypes and metabolizer frequencies were: 1/1 (90.0%), 1/6 (6.7%), 1/5 (2.9%), 5/6 (0.3%), and 5/5 (0.1%). Normal metabolizers for *5 and *6 alleles accounted for 90.0%, intermediate - 9.6%, and slow - 0.4%.

Conclusion. The results provide additional pharmacogenetic database information for Central Asia, facilitating a better understanding of warfarin pharmacokinetics and pharmacodynamics for individualized warfarin dosing in patients undergoing heart surgery in Kazakhstan.

Keywords: *Population frequencies, gene polymorphisms, metabolizers, minor allele, warfarin pharmacogenetics.*

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Резюме

РАСПРОСТРАНЕННОСТЬ ПОЛИМОРФИЗМОВ ГЕНОВ, СВЯЗАННЫХ С МЕТАБОЛИЗМОМ ВАРФАРИНА, В КАЗАХСКОЙ ПОПУЛЯЦИИ

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Введение. В настоящее время приоритетным направлением персонализированной медицины является фармакогенетическое тестирование, в том числе определение типа метаболизаторов лекарственных препаратов.

Цель исследования: Определить удельный вес «типов метаболизаторов» в казахской популяции и провести сравнительный анализ популяционных частот минорных аллелей полиморфизмов генов CYP2C9*2 (rs1799853), *3 (rs1057910), *5 (rs28371686) и *6 (rs9332131); CYP2C19 (rs3814637), VKORC1 (rs9934438), CYP4F2 (rs2108622), GGCX (rs11676382), GWAS ассоциированных с резистентностью к антикоагулянтам группы антагонистов витамина К, в этнически однородной популяции казахов с ранее изученными популяциями мира.

Материалы и методы. В данном исследовании использована геномная база данных 1900 условно здоровых казахов, полученная в рамках выполнения проекта «Генетические исследования преэклампсии в популяциях Центральной Азии и Европы» (InterPregGen).

Результаты. В исследуемой группе казахов определены фенотипы и частоты метаболизаторов по аллелям *2 (rs1799853) и *3 (*rs1057910) *гена CYP2C9* - 1/1, 1/3, 3/3, 1/2, 2/3, 2/2 которые составили: 80,1%, 13,0%, 0,25%, 6,0%, 0,40%, 0,25%, соответственно. Нормальные метаболизаторы по аллелям *2 и *3 имеют частоту 80,1%, промежуточные – 19,0% и медленные – 0,9%.

Определены фенотипы и частоты метаболизаторов аллелей *5 (rs28371686) и *6 (rs9332131) гена *CYP2C9* - 1/1, 1/6, 1/5, 5/6, 5/5 в популяционной выборке казахов составили: 90,0%, 6,7%, 2,9%, 0,3%, 0,1%, соответственно. Частоты нормальных метаболизаторов по аллелям *5, и *6 составили 90,0%, промежуточных - 9,6% и медленных - 0,4%.

Сравнительный анализ популяционных частот изученных полиморфизмов генов показал их промежуточное положение по сравнению с изученными Европейскими, Восточно Азиатскими и Южно Азиатскими популяциями.

Выводы. Полученные результаты по популяционным частотам изученных полиморфизмов генов у казахов являются дополнительной информацией для фармакогенетических баз данных по Центральной Азии и будут использованы для понимания фармакогенетики варфарина при дифференцированном подходе к назначению дозы варфарина пациентам с оперированным сердцем в Казахстане.

Ключевые слова: *метаболизаторы, популяционные частоты, минорный аллель, фармакогенетика варфарина.*

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Түйіндеме

ҚАЗАҚ ПОПУЛЯЦИЯСЫНДА ВАРФАРИН АЛМАСУЫМЕН БАЙЛАНЫСТЫ ГЕНДІК ПОЛИМОРФИЗМДЕРДІҢ ТАРАЛУЫ

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Кіріспе. Қазіргі уақытта дербестендірілген медицинаның басым бағыты — дәрілік заттардың метаболизатор түрін анықтауды қоса алғанда, фармакогенетикалық тестілеу болып табылады.

Зерттеу мақсаты: Қазақ популяциясындағы «метаболизатор түрлерінің» үлестік салмағын анықтап, CYP2C9*2 (rs1799853), *3 (rs1057910), *5 (rs28371686), *6 (rs9332131); CYP2C19 (rs3814637), VKORC1 (rs9934438), CYP4F2 (rs2108622), GGCX (rs11676382) гендер полиморфизмдерінің, сондай-ақ К витаминінің антагонистері тобына жататын антикоагулянттарға төзімділікпен байланысты GWAS маркерлерінің аз жиілікті аллельдерінің популяциялық жиіліктерін бұрын зерттелген әлем популяцияларымен салыстыра отырып талдау жүргізу.

Материалдар мен әдістері. Бұл зерттеуде Орталық Азия мен Еуропа популяцияларында преэклампсияны генетикалық зерттеу жобасы (InterPregGen) аясында алынған 1900 шартты түрде сау қазақтың геномдық деректер базасы пайдаланылды.

Нәтижелер. Зерттелген қазақ тобы арасында CYP2C9 генінің *2 (rs1799853) және *3 (rs1057910) аллельдері бойынша келесі фенотиптер мен жиіліктер анықталды: 1/1 – 80,1%, 1/3 – 13,0%, 3/3 – 0,25%, 1/2 – 6,0%, 2/3 – 0,40%, 2/2 – 0,25%. *2 және *3 аллельдері бойынша қалыпты метаболизаторлардың жиілігі – 80,1%, аралық – 19,0%, баяу – 0,9%.

Сондай-ақ CYP2C9 генінің *5 (rs28371686) және *6 (rs9332131) аллельдері бойынша фенотиптер мен жиіліктер анықталды: 1/1 – 90,0%, 1/6 – 6,7%, 1/5 – 2,9%, 5/6 – 0,3%, 5/5 – 0,1%. *5 және *6 аллельдері бойынша қалыпты метаболизаторлар – 90,0%, аралық – 9,6%, баяу – 0,4%.

Зерттелген ген полиморфизмдерінің популяциялық жиіліктерін салыстырмалы талдау олардың Еуропа, Шығыс Азия және Оңтүстік Азия популяцияларымен салыстырғанда аралық позицияда екенін көрсетті.

Қорытындылар. Қазақ популяциясында зерттелген ген полиморфизмдерінің жиіліктері бойынша алынған нәтижелер Орталық Азияға арналған фармакогенетикалық деректер базасына қосымша ақпарат болып табылады және Қазақстанда жүрекке ота жасалған пациенттерге варфариннің дозасын даралап тағайындау кезінде варфариннің фармакогенетикасын түсіну үшін қолданылатын болады.

Түйінді сөздер: *метаболизаторлар, популяциялық жиіліктер, минорлы аллель, варфариннің фармакогенетикасы.*

Дәйексөз үшін:

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Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide and remain a significant public health concern both in Kazakhstan and globally. In most developed European countries, the mortality rate from CVD reaches up to 40% [30]. Currently, around two million people in Kazakhstan are registered as suffering from CVD, which accounts for 12% of the economically active population. The incidence rate of diagnosed circulatory system diseases is 3856.4 per 100,000 population [1].

Patients with CVD with a history of heart valve replacement surgery, cardiac arrhythmias, or venous thromboembolic complications are forced to take long-term anticoagulant therapy to prevent potential complications. Warfarin is the primary oral anticoagulant used in the Republic of Kazakhstan, and it is included in the Kazakhstan National Drug Formulary (Anatomical Therapeutic Chemical Classification B01AA03, 2023).

Modern approaches in personalized medicine aim to improve the effectiveness of long-term anticoagulant therapy through pharmacogenetic testing. The main goal is to identify genetic markers that determine warfarin metabolism in each patient, thereby optimizing individualized treatment and minimizing the risk of side effects. However, significant challenges arise when attempting to adapt existing international personalized medicine protocols to the Kazakhstani population due to genetic differences among ethnic groups. Genetic predisposition to warfarin metabolism can vary from 0% to 50%, depending on ethnicity. It highlights the need for dedicated scientific research that takes into account the genetic characteristics of specific ethnic groups in order to achieve optimal treatment outcomes [2,3,4,6,9,28,34].

Central Asian populations are underrepresented in the scientific literature regarding the frequency of gene polymorphisms associated with warfarin pharmacogenetics. Several pharmacogenetic studies of the Kazakh population are known. For example, in the study by Zholdybayeva E. et al. (2014), allele frequencies of several polymorphisms in the Kazakh population were presented, along with promising directions for pharmacogenomic research in Kazakhstan [33]. In the study by Iskakova A. et al. (2016), gene polymorphisms affecting the metabolism of drugs concerning several multifactorial diseases (cardiovascular diseases, diabetes) in Kazakhs were investigated [12].

This study aims to determine the distribution of types of metabolizers in the Kazakh population and conduct a comparative analysis of the frequencies of minor alleles of polymorphisms of the CYP2C9 genes (* 2,* 3,* 5,* 6), CYP2C19, VKORC1, CYP4F2, and GGCX, which GWAS are associated with resistance to anticoagulants (vitamin K antagonists) compared with previously studied populations worldwide.

Materials and methods. The scientific research on warfarin pharmacogenetics in the Kazakh population was approved by the Local Ethics Committee of the "National Scientific Center of Surgery named after A.N. Syzganov" (Protocol No. 3 dated August 25, 2023).

Type of study: fundamental research.

The study used the genomic database of a control group of 1,900 conditionally healthy Kazakhs. The inclusion criteria for the control group were Kazakh ethnicity, reproductive age, and the ability to conceive. All participants provided informed consent and understood the study's purpose.

The genomic database was obtained through the InterPregGen project, with molecular genetic studies conducted at the Decode Genetics Center (Iceland) using IlluminaOmniChip 2.5 arrays. Quality control measures included the exclusion of SNPs based on statistical analysis of minor allele frequency (MAF < 0.05). Quality control measures excluded SNPs based on statistical analysis of minor allele frequency (MAF < 0.05). The PLINK software performed allele frequency statistics and non-parametric χ^2 (chi-square) tests.[21].

Results

The most well-known clinically significant biomarkers for drug dosing are genes encoding cytochrome P450 enzymes (CYP450). Polymorphisms in the CYP450 family (particularly CYP2C9 and CYP2C19) are highly polymorphic, exhibit ethnographic variation, and display specific patterns of metabolizer phenotypes. Other important genetic determinants of warfarin dosage include polymorphisms in the VKORC1, CYP4F2, and GGCX genes [6,9, 10, 32, 34].

Table 1 presents the genetic characteristics of the gene polymorphisms, including the SNP identifier, reference number, chromosomal location, actual base pair position, and the full gene name.

The metabolic capacity of the enzyme systems encoded by the examined gene polymorphisms varies between individuals and ethnic groups. These interindividual and interethnic differences affect drug metabolism processes within the population. As a result, the metabolic conversion and drug elimination rates can range from extremely slow to ultra-rapid among different individuals. Through the screening of genetic variants, it is possible to characterize an individual's drug metabolism phenotype [9,23,34,35].

Table 1.

Genetic characteristics of significant gene polymorphisms associated with sensitivity to warfarin.

N	Gene		Chromosome	rs	Position	A1	A2
1	CYP2C9*2	Cytochrome P450 Family 2 Subfamily C Member 9	10q23.33	rs1799853	94942290	C	T
2	CYP2C9*3			rs1057910	94981296	A	C
3	CYP2C9*5			rs28371686	94981301	C	G
4	CYP2C9*6			rs9332131	94949282	A	del
5	CYP2C19	Cytochrome P450 Family 2 Subfamily C Member 19	10q23.33	rs3814637	94761288	C	T
6	VKORC1 (-1639G>A)	Vitamin K Epoxide Reductase Complex Subunit 1	16p11.2	rs9923231	31096368	C	T
7	CYP4F2	Cytochrome P450 Family 4 Subfamily F Member 2	19p13.12	rs2108622	15879621	C	T
8	GGCX	Gamma-Glutamyl Carboxylase	2p11.2	rs11676382	85550510	C	G
Note: A1 – wild-type allele, A2 – minor allele							

The main metabolizer phenotypes are distinguished for several drugs, including warfarin. Normal or fast metabolizers (NM/FM) are defined by the presence of two functional alleles of gene polymorphisms. Carriers of one normal and one non-functional minor allele are classified as intermediate metabolizers (IM), while individuals with two non-functional alleles are considered slow metabolizers (SM). People with duplicated copies of normal alleles in their haplotype are categorized as ultra-rapid metabolizers (UM) [8,9].

In recent years, studies on the genetic basis of adverse drug reactions, therapy effectiveness, and dosage variations have increased [19,35]. Therefore, data on the variability of gene polymorphisms associated with sensitivity to anticoagulants from the vitamin K antagonist group are of great importance for optimizing genotyping in the pharmacotherapy of medications for each ethnic group within a specific population.

The allele and genotype distribution frequencies of significant gene polymorphisms were analyzed in the Kazakh population to determine the metabolic phenotype and population-specific frequencies of gene polymorphisms and to perform a comparative analysis with other global populations: CYP2C9*2 (rs1799853), *3 (rs1057910), *5 (rs28371686), *6 (rs9332131); CYP2C19 (rs3814637), VKORC1 (rs9934438), CYP4F2 (rs2108622), GGCX (rs11676382), based on GWAS data associated with sensitivity to anticoagulants from the vitamin K antagonist group.

Ethnicity is an important factor determining both warfarin's sensitivity and maintenance dose. It has been observed that Asians are highly sensitive, whereas African Americans are less sensitive. According to previous publications, the variability in the warfarin dosage from 2% to 40% depends on the genotypes that affect its metabolism. In populations from Iran, European countries, and the Americas, the CYP2C9*2/*3 variants have shown the greatest influence on CYP2C9 enzyme activity [3,5,13,23,28].

Razavi F. et al. (2017) describe SNPs determining CYP2C9 activity (allele *2 rs1799853 and allele *3 rs1057910). Data from 120 individuals of the Iranian population are presented regarding the frequency of CYP2C9 metabolic phenotypes 1/1, 1/2, 2/2, 3/1, 3/2, and 3/3, which were 64.1%, 15.8%, 0%, 17.5%, 2.5%, and 0%, respectively [23].

If an individual is homozygous for the wild-type alleles *2 and *3 of the CYP2C9 gene, the normal genotype CYP2C9 1/1 is defined. The combination of homozygous wild-type *3 and heterozygous *2 corresponds to the CYP2C9 1/2 genotype. The CYP2C9 2/2 genotype is defined by the presence of homozygous wild-type *3 and homozygous minor allele *2. Individuals who are homozygous for the wild-type *2 allele and heterozygous for *3 have the CYP2C9 1/3 genotype. Heterozygosity for both *2 and *3 alleles defines the CYP2C9 2/3 genotype. The CYP2C9 3/3 genotype is defined by homozygosity for the frequent allele *2 and homozygosity for the rare allele *3 [23].

As shown in Table 2, the frequencies of metabolizer phenotypes based on the two CYP2C9 alleles (*2, *3) for the Kazakh ethnic group were determined as follows: 1/1 – 80.1%, 1/3 – 13.0%, 3/3 – 0.25%, 1/2 – 6.0%, 2/3 – 0.40%, and 2/2 – 0.25%. Normal metabolizers accounted for 80.1%, intermediate metabolizers - 19.0%, and poor metabolizers - 0.9%.

The frequencies of metabolizer phenotypes based on two other CYP2C9 alleles (*5, *6) — 1/1, 1/6, 1/5, 5/6, and 5/5 - were 90.0%, 6.7%, 2.9%, 0.3%, and 0.1%, respectively, as shown in Table 2. The frequency of normal metabolizers was 90.0%, intermediate metabolizers – 9.6%, and poor metabolizers – 0.4%.

Globally, the prevalence of drug metabolizer types via CYP2C9 varies. In Southern Europe, the frequency of CYP2C9 metabolites ranges from 3-4%. The east coast of the Mediterranean Sea, Asia, and Africa show less than 1% poor metabolizers, except for the United Arab Emirates (UAE), where the incidence of CYP2C9 *3 and *5 is 11.1%. Intermediate metabolizers of CYP2C9 are most common in the UAE (48.7%), Croatia (41.2%), and Iran (40.3%) [35]. Most studies have shown that carriers of the “slow” allelic variants *2 and *3 of the CYP2C9 gene exhibit reduced rates of warfarin biotransformation and higher plasma concentrations of the drug. As a result, warfarin remains in circulation longer, and lower doses are required to achieve the desired anticoagulant effect [4,8,10,27].

Table 3 presents a comparative analysis of minor allele frequencies of gene polymorphisms associated with sensitivity to vitamin K antagonists in the Kazakh population based on GWAS data, compared with previously studied populations worldwide.

Table 2.

Frequencies of CYP2C9 metabolic phenotypes based on *2 and *3, *5 and *6 polymorphisms in the Kazakh population control group.

Gene	Polymorphisms, Genotypes		Frequency		Metabolic Phenotype	
	*2	*3	в %	n		
	CC	AA	80,09	1593	1/1	NM
	CC	CA	12,97	258	1/3	IM
	CC	CC	0,25	5	3/3	PM
	TC	AA	6,03	120	1/2	IM
	TC	CA	0,40	8	2/3	PM
	TT	AA	0,25	5	2/2	PM
			Всего	N=1989		
CYP2C9	*5	*6	в %	n	Метаболический фенотип	
	CC	AA	90,04	1790	1/1	NM
	CC	delA	6,69	133	1/6	IM
	GC	AA	2,87	57	1/5	IM
	GC	delA	0,15	3	5/6	PM
	GG	AA	0,10	2	5/5	PM
	GG	delA	0,05	1	5/6	PM
	GG	deldel	0,10	2	5/6	PM
			Всего	N=1988		

Note: NM – normal metabolizer; IM – intermediate metabolizer; PM – poor metabolizer

The superfamily of proteins known as cytochrome P450 (CYP) enzymes is involved in synthesizing and metabolizing various endogenous and exogenous cellular components. The CYP2C9 gene (Cytochrome P450 Family 2 Subfamily C Member 9) encodes an isoform of the endoplasmic reticulum enzyme that is involved in the metabolism of steroid hormones and fatty acids and plays a key role in the breakdown of the drug warfarin.

It has been reported that CYP2C9 *2 reduces warfarin metabolism by 30%, and the CYP2C9 *3 allele reduces it by 90% [17]. It has been established that carriers of the *2 or *3 alleles metabolize warfarin more slowly, leading to a prolonged drug elimination from the bloodstream. As a result, lower doses are required to achieve adequate anticoagulant effects and prevent complications. [2,8,9]. Thus, patients carrying one or two copies of the *2 or *3 allele are at a higher risk of bleeding during initiation of warfarin therapy at standard doses [2,8,9,10,27,11,17].

Several CYP2C9 alleles (*6, *15, *25, and *35) are associated with a complete loss of hydroxylation activity, whereas most other variants (*2, *3, *5, *11) are associated with reduced enzymatic activity [6,8].

Scientific studies conducted in 70 populations worldwide have demonstrated that the CYP2C9*2 allele is more commonly found in European populations, with an average frequency of 14%, including 15.0% in France, the Middle East (Iran – 18.1%), Brazil (10.7%), Croatia (16.5%), and Lebanon (15.4%). Intermediate frequencies are observed in Mexico (3.7%) and Peru (3.8%). In comparison, the lowest frequencies are found in Africans (0.46%), except North Africa (about 12%), as well as in Asians (0.56%), Ecuador (0.5%), and Native Americans (1.25%). The CYP2C9*2 allele is not found in East Asian populations; low frequencies (approximately 5%) were registered in South Asian populations. [35].

Populations of the Middle East and Europe have a high frequency of the allele *3 of CYP2C9 (average 7.8%), including Spain (10.1%) and Turkey (9.8%). Frequencies in South America have also been reported: Uruguay (7.6%), Colombia (6.8%), and Brazil (6.0%). As opposed to the *2 allele, the *3 allele is prevalent in South Asia, with frequencies of 9.9% in Pakistan, 11.6% in Bangladesh, and up to 13.1% in India. A very high frequency of the *3 allele has been identified in the United Arab Emirates (21.3%) and among Indigenous Malaysians (36.0%) [6,8,35]. The combination of *2 and *3 variants within a single genotype is rare (<2%) and occurs more often in individuals of African or Asian descent [35].

According to the literature, the CYP2C9 *5 and *6 alleles are rare, and their ethnographic distribution is poorly studied. However, they have been detected in the United Arab Emirates (7.8%) and Sudan (2%). CYP2C9 *5 occurs among African Americans at a frequency of 1.56%, while CYP2C9 *6 is more common among Black Africans, with a frequency of 2.70% [35].

Table 3 shows that the frequency of the minor T allele of the CYP2C9*2 polymorphism (rs1799853) in the Kazakh ethnic sample is 3.5%, which is significantly higher ($p < 0.05$) compared to the corresponding frequency in East Asian populations (e.g., 0.5% in China; virtually absent in Japan and Vietnam), but significantly lower than the population frequency in Europe (England – 8.8%, Spain – 14.0%, Italy – 15.4%) ($p<0.001$). No statistically significant differences were found compared to previously studied South Asian populations (Bangladesh – 1.7%, India – 4.9%, Pakistan – 5.2%) ($p>0.05$).

The minor C allele frequency of CYP2C9 *3 (rs1057910) in Kazakhs was 6.9%, which is comparable to its frequency in European populations (England – 7.1%, Spain and Italy – 8.4%) and in some Asian populations (China – 4.8%, Vietnam – 3.5%, Pakistan – 9.9%) ($p>0.05$). However, it was significantly higher than the corresponding frequency in specific Southeast Asian populations (Bangladesh – 1.2%, India – 1.3%, Japan – 1.9%) ($p<0.05$).

For the CYP2C9 *5 (rs28371686) and CYP2C96* (rs9332131) alleles, the minor allele frequency in the Kazakh ethnic group was 1.8% and 3.6%, respectively. For the population samples from Europe, South Asia, and East Asia presented in Table 3, the corresponding frequencies were 0, indicating their infrequent occurrence in those populations.

Table 3.

Comparative analysis of population frequencies of minor alleles of gene polymorphisms associated with warfarin sensitivity in Kazakhs and global populations.

Population	N	MAF	χ2	p
CYP2C9*2 (rs1799853)				
Kazakhs	1995	0,03534	3849	141
Europe:				
England**	91	0,088	13,284*	<0,001
Spain**	107	0,14	57,220*	<0,001
Italy**	107	0,154	72,330*	<0,001
East Asia:				
China**	105	0,005	5,710*	0,017
Japan**	104	0	7,606*	0,006
Vietnam**	99	0	7,241*	0,008
South Asia:				
Bangladesh**	86	0,017	1,581	0,209
India**	103	0,049	0,985	0,322
Pakistan**	96	0,052	1,476	0,225
CYP2C9*3 (rs1057910)				
Kazakhs	1996	0,06914	3709	283
Europe:				
England**	91	0,071	0,001	0,978
Spain**	107	0,084	0,534	0,465
Italy**	107	0,084	0,534	0,465
East Asia:				
China**	105	0,048	1,666	0,197
Japan**	104	0,019	8,288*	0,004
Vietnam**	99	0,035	3,698	0,055
South Asia:				
Bangladesh**	86	0,116	5,034*	0,025
India**	103	0,131	10,372*	0,002
Pakistan**	96	0,099	2,155	0,143
CYP2C9*5 (rs28371686)				
Kazakhs	1991	0,01808	3910	72
Europe:				
England**	91	0	3,349	0,068
Spain**	107	0	3,937*	0,048
Italy**	107	0	3,937*	0,048
East Asia:				
China**	105	0	3,863*	0,050
Japan**	104	0	3,827	0,051
Vietnam**	99	0	3,643	0,057
South Asia:				
Bangladesh**	86	0	3,165	0,076
India**	103	0	3,790	0,052
Pakistan**	96	0	3,533	0,061
CYP2C9*6 (rs9332131)				
Kazakhs	1995	0,03609	3846	144
Europe:				
England**	91	0	0,662	0,416
Spain**	107	0	0,779	0,378
Italy**	107	0	0,779	0,378
East Asia:				
China**	105	0	0,764	0,382
Japan**	104	0	0,757	0,385
Vietnam**	99	0	0,721	0,396
South Asia:				
Bangladesh**	86	0	0,626	0,429
India**	103	0	0,750	0,387
Pakistan**	96	0	0,699	0,404

Continuation of Table 3.

CYP2C19 (rs3814637)				
Kazakhs	1984	0,04637	3784	184
Europe:				
England**	91	0,066	1,480	0,224
Spain**	107	0,079	4,853*	0,028
Italy**	107	0,084	6,292*	0,013
East Asia:				
China**	105	0,09	8,393*	0,004
Japan**	104	0,12	22,654*	<0,001
Vietnam**	99	0,076	3,580	0,059
South Asia:				
Bangladesh**	86	0,14	29,986*	<0,001
India**	103	0,136	32,575*	<0,001
Pakistan**	96	0,12	20,879*	<0,001
VKORC1 (rs9923231)				
Kazakhs	1988	0,288	2831	1145
Europe:				
England**	91	0,357	4,035*	0,045
Spain**	107	0,36	5,072*	0,025
Italy**	107	0,477	34,575*	<0,001
East Asia:				
China**	105	0,89	333,748*	<0,001
Japan**	104	0,9	345,342*	<0,001
Vietnam**	99	0,843	269,998*	<0,001
South Asia:				
Bangladesh**	86	0,157	13,957*	<0,001
India**	103	0,175	12,389*	<0,001
Pakistan**	96	0,198	7,308*	0,007
CYP4F2 (rs2108622)				
Kazakhs	1992	0,3303	2668	1316
Europe:				
England**	91	0,286	1,570	0,211
Spain**	107	0,355	0,564	0,453
Italy**	107	0,336	0,034	0,853
East Asia:				
China**	105	0,2	15,474*	<0,001
Japan**	104	0,231	8,925*	0,003
Vietnam**	99	0,222	10,044*	0,002
South Asia:				
Bangladesh**	86	0,413	5,043*	0,025
India**	103	0,437	9,978*	0,002
Pakistan**	96	0,391	2,999	0,084
GGCX (rs11676382)				
Kazakhs	1991	0,1444	3407	575
Europe:				
England**	91	0,159	0,313	0,576
Spain**	107	0,093	4,331*	0,038
Italy**	107	0,042	17,755*	<0,001
East Asia:				
China**	105	0	35,145*	<0,001
Japan**	104	0	34,813*	<0,001
Vietnam**	99	0	33,151*	<0,001
South Asia:				
Bangladesh**	86	0,023	20,172*	<0,001
India**	103	0,01	29,912*	<0,001
Pakistan**	96	0,021	23,409*	<0,001

*Note: N – number of DNA samples; MAF – minor allele frequency; χ^2 – Chi-square test; P – statistical significance; * – statistically significant differences (p<0.05); ** – https://asia.ensembl.org/Homo_sapiens/Info/Index; Fiona Cunningham and others, Ensembl 2022,* Nucleic Acids Research*, Volume 50, Issue D1, 7 January 2022, Pages D988–D995, https://doi.org/10.1093/nar/gkab1049*

The CYP2C19 gene (Cytochrome P450 Family 2 Subfamily C Member 19) from the cytochrome P450 family encodes a monooxygenase enzyme that catalyzes many reactions involved in drug metabolism and the synthesis of cholesterol, steroids, and other lipids [29].

A meta-analysis involving 1,393 patients showed that carriage of the minor allele rs3814637 of the CYP2C19 polymorphism is associated with a significant 18% reduction in warfarin dose requirement in patients with the T allele (rs3814637) and TT and CT genotypes, compared to patients with the CC genotype [29]. However, opposite findings have also been reported. An evaluation of warfarin therapy in 492 patients found that CYP2C19 polymorphisms were not associated with the need to adjust warfarin dosage [15].

Population frequencies of the CYP2C19 gene exhibit ethnic stratification and range from 15% to 25% among Chinese, Japanese, Koreans, and Indians and from 3% to 5% among White Europeans. Association studies on allele carriage and response to warfarin dosing have shown conflicting results [15]. As shown in Table 3, the frequency of the minor T allele of the CYP2C19 rs3814637 polymorphism was 4.6% in Kazakhs residing in Central Asia. This frequency is significantly lower ($p < 0.001$) compared to the corresponding frequencies in Europe (Spain – 7.9%, Italy – 8.4%), East Asia (China – 9.0%, Japan – 12.7%), and South Asia (Bangladesh – 14.0%, India – 13.6%, Pakistan – 12.0%). However, it did not differ significantly ($p>0.05$) from the frequencies observed in European (England – 6.6%) and East Asian (Vietnam – 7.6%) populations.

It is well known that the VKORC1 gene (Vitamin K Epoxide Reductase Complex Subunit 1) encodes one of the key enzymes involved in vitamin K metabolism, converting its inactive form (2,3-epoxide – vitamin K) into its active form (vitamin K – hydroquinone). VKORC1 gene polymorphisms are associated with increased sensitivity to warfarin anticoagulant therapy and lower required doses, indicating the need for dose adjustment. Pharmacogenetic dosing algorithms for warfarin commonly include testing for VKORC1 genotypes [25].

Many studies have shown that the frequency of the minor T allele of the VKORC1 polymorphism (c.-1639G>A) varies significantly across populations. In Europe, the frequency ranges from 37% to 47%, while in the Middle East it varies from 41% to 51%. East Asian populations exhibit much higher frequencies, ranging from 88% to 90%. In contrast, the prevalence of this allele is considerably lower in African populations, ranging from 13% to 15%, and is approximately 15% in South Asia [18,25,31]. In the Chinese population, carriage of the T/T genotype is observed in more than 83% of individuals [32], which is important to consider when determining warfarin dosage for patients in this population. It has also been shown that the rs9923231 polymorphism in the VKORC1 promoter reduces gene expression, thereby decreasing warfarin dose requirements and increasing sensitivity to the drug [13,25,32].

VKORC1 rs9923231 polymorphism in Kazakhs is 28.8%, which is significantly higher ($p < 0.001$) than in South Asian populations — 15.7% in Bangladesh, 17.5% in India, and 19.8% in Pakistan — and markedly lower than in East Asian populations — 89.0% in China, 90.0% in Japan, and 84.3% in Vietnam. These results highlight the diversity of the genetic landscape and the distribution of alleles in different geographical regions.

The enzyme CYP4F2 (Cytochrome P450 Family 4 Subfamily F Member 2) is involved in vitamin K metabolism by limiting its accumulation in the liver and catalyzing the production of hydroxylated vitamin K. This results in the need for higher doses of warfarin to achieve a therapeutic effect [7,22].

There are conflicting findings regarding the association between the CYP4F2 gene rs2108622 polymorphism and warfarin dose requirements. In Indian patients, only a weak association was found between genotype carriage and warfarin dose [22]. However, in Korean patients carrying the homozygous unfavorable TT genotype of CYP4F2, a significantly higher average warfarin dose was required compared to other genotypes (4.40 mg/day vs. 3.12 and 2.91 mg/day, respectively; $P=0.014$). As a result, genotyping of the CYP4F2 gene has been incorporated into pharmacogenetic warfarin dosing algorithms for Korean patients [7].

Table 3 presents the frequency of the minor T allele of the CYP4F2 rs2108622 polymorphism in the Kazakh population, which was 33.0%. This frequency is significantly lower ($p < 0.03$) compared to South Asian populations — Bangladesh (41.3%) and India (43.7%). In contrast, the frequency in Kazakhs is significantly higher ($p < 0.003$) than in East Asian populations — China (20.0%), Japan (23.1%), and Vietnam (22.2%). No statistically significant differences were found when comparisons were made ($p > 0.05$) with European populations — England (28.6%), Spain (35.5%), Italy (33.6%) — and the Pakistani population (39.1%) ($p>0.05$).

The GGCX gene (Gamma-Glutamyl Carboxylase) encodes the GGCX enzyme involved in the vitamin K cycle by synthesizing vitamin K-dependent proteins [17]. Scientific studies have shown that carriage of certain GGCX gene polymorphisms significantly impacts the adjustment of warfarin dosage [24,28].

A multicenter cross-sectional study involving 985 patients of European descent undergoing warfarin therapy included genotyping for the GGCX gene polymorphism (rs11676382). The study found that carriage of the minor G allele was associated with a significant 6.1% reduction in warfarin dose (95% CI: 0.6–11.4%) [14]. Similar results were obtained in a study of 186 European-American patients receiving warfarin. Carriage of GGCX rs11676382 genotypes was associated with lower warfarin doses, which was confirmed under a dominant genetic model [24].

However, in a study of 145 ethnically diverse patients, other researchers found no association between the G allele and therapeutic warfarin dose [20].

The minor G allele frequencies of the GGCX gene are either unreported or very low in East Asian populations. In South Asia, the allele frequencies range from 1% to 3% in Northern India. In European populations, the frequencies range from 4% to 16% [22,28].

The prevalence of the minor allele of the GGCX gene (rs11676382) in the ethnically homogeneous Kazakh population was measured at 14.4%, which is statistically significant ($p < 0.04$) compared to South Asian cohorts:

Bangladesh (2.3%), India (1.0%), and Pakistan (2.1%). Furthermore, this frequency is markedly higher than that observed in several European populations, with Spain at 9.3% and Italy at 4.2%. Notably, the allele frequency in Kazakhstan is comparable to that found in England, recorded at 15.9%. In stark contrast, East Asian populations, including samples from China, Japan, and Vietnam, exhibited a GGCX minor allele frequency of zero in the respective studies (N = 99–105), as summarized in Table 3.

Discussion

The study of allele frequency distributions of the analyzed gene polymorphisms in the Kazakh population revealed notable genetic diversity.

The frequency of the minor allele of the CYP2C19 gene (4.64%) in Kazakhs was significantly lower ($p < 0.05$) compared to the corresponding frequencies in European, East Asian, and South Asian populations. The frequency of the minor allele of the "Asian" polymorphism GGCX rs11676382 was significantly higher in Kazakhs (14.4%) compared to both European and other Asian populations ($p < 0.05$).

Analysis of genetic variability in the CYP2C9 gene showed that the frequency of the *2 allele in the Kazakh population is 3.53%, representing an intermediate level. It is significantly higher than in East Asian populations but significantly lower than in European samples ($p < 0.05$), and comparable to South Asian data.

The frequency of the *3 allele is 6.91%, placing the Kazakh population closer to European populations. However, it is significantly higher than in East Asian populations and lower than in South Asian populations ($p < 0.05$), again indicating an intermediate position.

The rare *5 (1.81%) and *6 (3.61%) alleles are considerably more prevalent in the Kazakh sample than in European, East Asian, and South Asian populations, where they are extremely rare or virtually absent.

A comparative analysis of the minor allele frequency of the CYP4F2 gene revealed a frequency of 33.0% in the Kazakh population. This value does not significantly differ from European samples ($p > 0.05$), but is significantly higher than in East Asian populations and lower than in South Asian populations ($p < 0.05$), again reflecting an intermediate genetic profile.

Regarding the minor allele rs9934438 of the VKORC1 gene, a frequency of 28.8% was observed in the Kazakh sample. This is significantly lower than in European and East Asian populations, but substantially higher than in South Asian populations ($p < 0.05$), further supporting the intermediate nature of the genetic profile in the Kazakh population.

The metabolic phenotypes of CYP2C9 were determined in the Kazakh population by examining the frequencies of functionally significant CYP2C9 alleles. This includes the standard *2 and *3 alleles, as well as the less common variant alleles *5 and *6, which reduce or eliminate enzyme activity.

The frequency of poor metabolizers among Kazakhs was 0.9% for *2 and *3 and 0.4% for *5 and *6, aligning with global data for Asian populations (<1%).

Intermediate metabolizers accounted for 19.0% for *2 and *3 and 9.6% for *5 and *6, while normal metabolizers made up 80.1% for *2 and *3 and 90.0% for *5 and *6.

Conclusions

The frequencies of metabolizer phenotypes in the Kazakh population, determined by polymorphisms in genes that encode enzymes involved in warfarin biotransformation and metabolism, are important for selecting the optimal dosage. Preventing the risk of both hemorrhagic and thrombotic adverse reactions during long-term anticoagulant therapy is essential.

The findings of this study will advance pharmacogenetics in Kazakhstan and provide a valuable resource for enhancing global data on allele and phenotype frequencies specific to the Kazakh ethnic group in Central Asia.

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