ORIGINAL ARTICLE

CONTENTS

The structure of the Poltava region population, determined by the polymorphisms rs3745274 and rs1799971 significant in the kinetics of anaesthetics

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ABSTRACT

Aim: To determine the population structure of the Poltava region by the significant SNPs rs3745274 and rs1799971 of the CYP2B6 and OPRM1 genes in the kinetics of anesthetics.

Materials and Methods: The study involved 106 people: 51 patients with oncological pathology of the gastrointestinal tract and 55 people in the control group. Genotyping of SNPs rs3745274 and rs1799971 in the CYP2B6 and OPRM1 genes was performed by the polymerase chain reaction method with determination of the length of restriction fragments. Statistical analysis of the data was performed using the GenAlEx population genetic analysis package.

Results: The frequencies of allelic variants and genotypes of the CYP2B6 (c.516G>T) and OPRM1 (c.118A>G) genes are close to the corresponding indicators in the Ukrainian and other European populations. The statistically significant difference in expected genotype frequencies ($p \leq 0.05$) between the patient and control groups for the SNPs of the CYP2B6 gene (c.516G>T) is obviously related to the clinical features of the patient sample.

Conclusions: The identified genetic polymorphism of the population of the Poltava region for the CYP2B6 (c.516G>T) and OPRM1 (c.118A>G) genes may be a pharmacogenetic basis for personalized anesthetics.

KEYWORDS: oncology, personalized anesthetics, single nucleotide polymorphisms, CYP2B6 (c.516G>T), OPRM1 (c.118A>G)

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INTRODUCTION

One of the major challenges in effective pharmacotherapy for pain management is the selection of the drug that best matches the patient's genetic makeup. Genetic variations in clinically significant polymorphisms in the cytochrome p450 2D6 (CYP2D6) and opioid receptor μ1 (OPRM1) genes are relevant to opioid drugs used to treat pain and can be used to predict and support clinical decision-making. Patients can be divided into 3 broad risk categories for opioid side effects and dependence. High-risk patients with dysfunction of CYP2D6 or OPRM1 represent approximately 14% of the population and are best treated with non-opioid drugs. Intermediate-risk patients with reduced CYP2D6 or OPRM1 activity represent approximately 48% of the population and can be treated with dose monitoring. Low-risk patients with functional CYP2D6 and OPRM1 activity constitute approximately 38% of the population and should receive opioid therapy [1].

Cytochrome CYP2B6 is a drug-metabolizing P450 enzyme in the human liver. Expression is highly variable both between and within individuals, due to non-genetic factors, genetic polymorphisms, inducibility, and irreversible inhibition by many compounds. Drugs primarily metabolized by CYP2B6 include artemisinin, bupropion, cyclophosphamide, efavirenz, ketamine, and methadone. *CYP2B6* is one of the most polymorphic *CYP* genes in humans, and its variants have been shown to affect transcriptional regulation, splicing, mRNA and protein expression, and catalytic activity. The most common functionally deficient allele is *CYP2B6*6*, which occurs at a frequency ranging from 15 to over 60% in different populations. The allele results in reduced expression in the liver due to aberrant splicing. Substitutions in the nucleotide sequence of the *CYP2B6*6* allele (516G>T and 785A>G), leading to two amino acid changes, glycine/histidine and lysine/arginine (Q172H and K262R) [2].

A study by Noritaka Ariyoshi et al. (2011) determined that two amino acid substitutions in CYP2B6.6 exhibit completely opposite patterns, suggesting that Q172H has the opposite effect on the metabolic activity of CYP2B6 that is affected by K262R. This study provided the first evidence that the amino acid substitution Q172H can reverse the direction of the effect caused by the K262R substitution in the CYP2B6 polypeptide on the metabolism of certain drugs [3]. A. Mikstacki et al. (2017) studied nucleotide substitutions in the *CYP2B6* (c.516G>T), *UGT1A9* (c.98T>C) and *CYP2C9* (c.1075A>C) genes and found that only the c.516G>T (rs3745274) polymorphism in the *CYP2B6* gene and body mass index affect the rate of propofol metabolism and may play an important role in optimizing propofol anesthesia [4].

The μ1 opioid receptor (OPRM1) is key to analgesia. It is localized primarily in the brain and is responsible for the major positive effects of opioids. The *OPRM1* gene, which encodes this receptor, has a number of single-nucleotide polymorphisms. The most functional polymorphism, c.118G>A (rs1799971), in this gene is associated with altered receptor binding and subsequent signaling, potentially affecting both the efficacy and tolerability of opioid therapy [5]. Studies by L. Wang et al. (2019) showed that carriers of the A allele, the c.118G>A polymorphism of the *OPRM1* gene (rs1799971), affect the dose of opioid analgesics [6]. A meta-analysis of a large number of publications confirmed that carriers of the *G* allele (*AG*+*GG*) of the single nucleotide polymorphism c.118G>A of the *OPRM1* gene (rs1799971) require greater opioid analgesia for the treatment of cancer pain. It has also been shown that this polymorphism can help predict people's response to analgesia and achieve satisfactory pain control in oncological pathologies [7].

DNA analysis of 97 individuals from major regions of Ukraine using genome-wide association studies (GWAS) T.K. Oleksyk et al. (2021) conducted a search of genomic data for genomic variation. The results obtained showed that the genetic diversity of the Ukrainian population is uniquely shaped by evolutionary and demographic factors and cannot be ignored in future genetic and biomedical research [8]. Studies of the clinically significant SNP c.516G>T of the CYP2B6 gene in the Ukrainian population have already been conducted. However, the sample consisted mainly of residents of eastern Ukraine (Kharkiv, Luhansk, and Donetsk regions). [14].

AIM

To determine the population structure of the Poltava region by the significant SNPs rs3745274 and rs1799971 of the CYP2B6 and OPRM1 genes in the kinetics of anesthetics.

MATERIALS AND METHODS

The study included patients of the main group aged 42 to 78 years, living in Poltava and the Poltava region. Among them were 28 men and 23 women (n=51). The patients were examined by doctors of the Municipal Enterprise "Poltava Regional Clinical Oncological Dispensary of the Poltava Regional Council", where they were treated. These patients underwent abdominal surgery for oncological pathology of the gastrointestinal tract in compliance with the basic biotic provisions of the Council of Europe Convention on Human Rights and Biomedicine, the Declaration of Helsinki of the World Medical Association on the ethical principles of conducting scientific medical research involving human participants. All patients signed written informed consents in accordance with the Declaration of Helsinki. The control group consisted of 32 men and 23 women (n=55) aged 27-64 years. They did not have pronounced signs of metabolic syndrome, type 2 diabetes mellitus and cardiovascular diseases. The study participants' ethnicity was not considered, just their residence.

Peripheral venous blood was collected from the cubital vein in BD Vacutainer® K2EDTA tubes (Becton Dickinson, USA). DNA extraction from peripheral blood samples was performed using the QIAqube Connect automated nucleic acid extraction system (QIAGEN, Germany) using the DNeasy Blood&Tissue Kit (QIAGEN, Germany) according to the manufacturer's instructions. The quality and quantity of extracted DNA were assessed using a NanoPhotometer NP-80 spectrophotometer (IMPLEN, Germany), and the extracted DNA was stored at -80˚C until use.

Genotyping of single nucleotide polymorphisms of the CYP2B6 (c.516G>T) and OPRM1 (c.118A>G) genes was performed by polymerase chain reaction with restriction fragment length determination (PCR-RFLD) according to I. Soultati et al. (2023) [9].

Amplification of DNA fragments of CYP2B6 and OPRM1 genes was performed using the Multiplex PCR Kit according to the manufacturer's instructions (QIAGEN, Germany) in a CFX Opus 96 amplifier (Bio-Rad, USA). Primers were synthesized (Thermo Fisher Scientific, USA). The sequence of oligonucleotide primers and genotyping conditions in PCR–RFLP of *CYP2B6* (c.516G>T) and *OPRM1* (c.118A>G) gene polymorphisms are given in (Table 1).

Alleles were identified based on the sizes of restriction fragments. Restriction analysis of the amplified DNA fragments was conducted according to the manufacturer's instructions (Thermo Scientific, USA). The resulting frag-

Table 1. Sequence of oligonucleotide primers and genotyping conditions in PCR-RFLP of polymorphisms of the *CYP2B6* (c.516G>T) and *OPRM1* (c.118A>G) genes

Polymorphisms	Primers	Restriction enzyme	Alleles (bp)
CYP2B6 c.516G>T, rs3745274	F: GGTCTGCCCATCTATAAAC R: CTGATTCTTCACATGTCTGCG	BseNI	516G: 268; 241; 17 516T: 509; 17
OPRM1 c.118A>G, rs1799971	F: GGTCAACTTGTCCCACTTAGATCGC R: AATCACATACATGACCAGGAAGTTT	Bsh1236I	118A: 193 118G: 169; 24

Source: compiled by the authors of this study

Table 2. Results of genotyping of healthy men and women of the Poltava population for polymorphisms of the *CYP2B6* (c.516G>T) and *OPRM1* (c.118A>G) genes

Polymorphisms	Alleles	Sex	N	Expected genotype frequency			χ2	p
				MM	*Mm*	*mm*		
CYP2B6, (c.516G>T), rs3745274	*516G*	Women	23	0.546	0.386	0.068	2.865	0.091
	516T	Men	32	0.610	0.342	0.048	2.509	0.113
OPRM1, (c.118A>G), rs1799971	*118A*	Women	23	0.756	0.227	0.017	0.518	0.472
	118G	Men	32	0.739	0.242	0.020	0.857	0.355

Notes. N – sample size, M – major allele, m – minor allele, MM – homozygous for the major allele, Mm – heterozygous, mm – homozygous for the minor allele, p – probability level

Source: compiled by the authors of this study

Table 3. Results of genotyping of patients and control groups of the Poltava population for polymorphisms of the *CYP2B6* (c.516G>T) and *OPRM1* (c.118A>G) genes

Polymorphisms	Alleles	Groups	N	H_e (%)			χ2	p
				MM	*Mm*	*mm*		
CYP2B6, (c.516G>T), rs3745274	*516G*	Patients	51	26.123 (51)	20.755 (41)	4.123 (6)	4.618	0.032*
	516T	Control	55	32.073 (58)	19.855 (36)	3.073 (6)	5.269	0.022*
OPRM1, (c.118A>G), rs1799971	*118A*	Patients	51	38.828 (76)	11.343 (22)	0.828 (2)	1.088	0.297
	118G	Control	55	41.023 (75)	12.955 (24)	1.023 (2)	1.371	0.242

Notes: *N* – sample size, H_e – expected genotype frequency, *MM* – homozygous for the major allele, *Mm* – heterozygous, *mm* – homozygous for the minor allele; *p* – probability level, * - p≤0.05, according to Fisher's exact test

Source: compiled by the authors of this study

ments were separated by size using electrophoresis in a 3% agarose gel (Agarose SFR™, Amresco, USA) in TAE buffer (Thermo Fisher Scientific, USA), with the inclusion of ethidium bromide for staining. Visualization of the fragments was performed using the GelDoc Go Gel Imaging System (Bio-Rad, USA). To assess the accuracy of genotyping, both negative and positive DNA controls were utilized. Statistical analysis of the data was carried out using the GenAlEx population genetic analysis software [10].

RESULTS

The expected genotype frequencies for the studied *CYP2B6* gene polymorphism in women were (0.546, 0.386, 0.068) in men (0.610, 0.342, 0.048). For the *OPRM1* gene polymorphism, the expected genotype frequencies for women and men were (0.756, 0.227, 0.017) and (0.739, 0.242, 0.020), respectively (Table 2). Analysis of the genotyping results of healthy men and women of the Poltava population - the control group, for the *CYP2B6* (c.516G>T) and *OPRM1* (c.118A>G) gene polymorphisms did not reveal statistically significant gender differences in genotype frequencies. This allowed combining the data of men and women into one group.

The expected genotype frequencies for the studied *CYP2B6* gene polymorphism in patients who underwent abdominal surgery for oncological pathology of the gastrointestinal tract were (*GG* = 26.123, *GT* = 20.755,

Table 4. Analysis of the distribution of allele frequencies, observed and expected heterozygosity and fixation index of patients and control groups of the Poltava population according to the studied polymorphisms of the *CYP2B6* (c.516G>T) and *OPRM1* (c.118A>G) genes

Polymorphisms	Groups	N	Alleles	Частота	H_o	H_e	F
CYP2B6, (c.516G>T), rs3745274	Patients Control	51	*516G*	0.716	0.529	0.407	0.301
			516T	0.284			
	Patients	55	*516G*	0.764	0.473	0.361	0.310
			516T	0.236			
OPRM1, (c.118A>G), rs1799971	Patients Control	51	*118A*	0.873	0.255	0.222	0.146
			118G	0.127			
	Patients	55	*118A*	0.864	0.273	0.236	0.158
			118G	0.136			

Notes: N – sample size, Ho – observed heterozygosity, He – expected heterozygosity, F – fixation index
Source: compiled by the authors of this study

TT = 4.123), Table 3. Among the control group sample, the expected genotype frequencies had the following values (*GG* = 32.073, *GT* = 19.855, *TT* = 3.073). A statistically significant difference in genotype frequencies (p≤0.05) was established between the patient and control groups (Table 3).

The expected genotype frequencies for the *OPRM1* gene single-nucleotide polymorphism (c.118A>G) in patients were (*AA* = 38.828, *AG* = 11.343, *GG* = 0.828). Among the control group sample, the expected genotype frequencies had the following values (*GG* = 41.023, *GT* = 12.955, *TT* = 1.023). Analysis of patients and control groups of the Poltava population by the polymorphism of the *OPRM1* gene (c.118A>G) by the expected genotype frequencies did not reveal statistically significant differences between the patient and control groups (Table 3).

The analysis of allele frequencies of the studied gene polymorphisms in a sample of patients who underwent abdominal surgery for oncological pathology of the gastrointestinal tract and in the control group is presented in Table 4. For the *CYP2B6* polymorphism in the patient and control groups, the *516G* allele was found with a higher frequency (p = 0.716 and p = 0.764). The frequencies of the minor allele *516T*, whose carriers are known to have a lower rate of anesthetic metabolism [4] were (q = 0.284 and q = 0.236) in the patient and control groups, respectively. Since there is an influence of the single nucleotide polymorphism of the *CYP2B6* gene (c.516G>T) on the risk of developing various oncological pathologies and a statistically significant difference in expected genotype frequencies (p≤0.05) was found between the patient and control groups, the population frequencies of the Poltava population were characterized by the control group (p = 0.764 and q = 0.236). The observed and the expected heterozygosity for the sample of patients who underwent abdominal surgery due to oncological conditions of the gastrointestinal tract, based on the *CYP2B6* gene polymorphism (c.516G>T), were found to be H_o = 0.529 and H_e = 0.407, as shown in (Table 4). In the control group, these values were slightly lower, with H_o = 0.473 and H_e = 0.361. There was no significant difference between the observed heterozygosity and the expected heterozygosity values. This corresponds to a slight genetic differentiation between the groups in the sample of patients relative to the control, the fixation index was (F = 0.301) and control relative to patients (F = 0.310).

According to the *OPRM1* gene polymorphism (c.118A>G), the actual and expected heterozygosity among the patient sample was H_o = 0.255 and $_{He}$ = 0.222, and for the control group H_o = 0.273 and H_e = 0.236. Significant genetic differentiation between the groups was also not found in the patient sample relative to the control (F = 0.146) and control relative to the patients (F = 0.158) (Table 4).

DISCUSSION

The statistically significant difference in expected genotype frequencies (p≤0.05) between the patient and control groups for the SNP of the *CYP2B6* gene (c.516G>T) is apparently related to the clinical characteristics of the patient sample. As noted above, this group consisted of patients with various oncological pathologies. Some publications have linked the SNP c.516G>T of the *CYP2B6* gene to an increased risk of cancer. Thus, X. Ma et.al. (2023) reported that the genotype frequencies of the c.516G>T polymorphism of the *CYP2B6* gene significantly (P<0.05) deviate from Hardy-Weinberg equilibrium in the patient ($\chi 2$ =4.618) and control ($\chi 2$ =4.758) groups and that the presence of the *516T* allele of the *CYP2B6* gene is associated with an increased risk of lung cancer [11]. Studies by C. Justenhoven et.al. (2014) have shown that the presence of the 516T allele of the CYP2B6 gene is associated with

an increased risk of breast cancer [12]. In turn, Z.H. Yuan et.al. (2011) associate the single-nucleotide polymorphism c.516G>T of the CYP2B6 gene with the risk of developing most forms of acute leukemia [13]. Thus, analyzing the already proven effect of the single nucleotide polymorphism of the CYP2B6 gene (c.516G>T) on the risk of developing various oncological pathologies, it is possible to explain the statistically significant difference in expected genotype frequencies ($p \leq 0.05$) between the patient and control groups.

The percentages of expected genotype frequencies of the Poltava population for the c.516G>T polymorphism of the CYP2B6 gene (GG - 58, GT - 36, TT - 6), Table 3, almost did not differ from the all-Ukrainian (GG - 56, GT - 37, TT - 6), obtained by O. Filiptsova et al. (2018) [14].

According to the SNP of the *OPRM1* gene (c.118A>G), no statistically significant differences were identified between the patient and control groups according to the expected genotype frequencies. The μ-opioid receptor, encoded by the *OPRM1* gene, plays a major role in opiate, alcohol, cocaine and nicotine addiction. Polymorphism in exon one of the *OPRM1* gene (c.118A>G) significantly alters the function of the receptor and the expression of this gene [15]. The results of a meta-analysis performed by Z. Yu et al. (2019) showed that carriers of the *G* allele (*AG*+*GG*) of the *OPRM1* gene polymorphism (c.118A>G) required higher doses of opioids for pain management than carriers of the homozygote *AA* ($P<0.001$). The meta-analysis shows that carriers of the *G* allele (*AG*+*GG*) of the *OPRM1* gene polymorphism (c.118A>G) require higher opioid analgesia for cancer pain management, and genotyping patients may help predict people's response to analgesia and achieve satisfactory cancer pain control [7]. We did not find any published results of studies of associations of the *OPRM1* gene polymorphism (c.118A>G) with increased cancer risk; therefore, the lack of differences in expected genotype frequencies between groups of patients with different oncological pathologies and controls is understandable.

The allele frequencies of the *CYP2B6* gene polymorphism (c.516G>T) in the sample of individuals from the control group – the Poltava population ($p = 0.76$ and $q = 0.24$) determined a significant similarity with the all-Ukrainian one ($p = 0.75$ and $q = 0.25$). [14]. Comparing the frequency of the *516T* allele in carriers known to have a lower rate of anesthetic metabolism, the Poltava population was similar to the Swedish ($q = 0.24$) and slightly different from the German and British ($q = 0.29$ and $q = 0.28$), respectively [16].

One of the most studied genetic variants associated with OPRM1 and opioid analgesic activity is the rs1799971 (p.118A>G) variant of the *OPRM1* gene. Strong evidence for this functional variant is provided in a meta-analysis, which found that the presence of the *GG* genotype was associated with reduced analgesic efficacy and the need for higher doses of opioids [17]. Since no statistically significant differences in expected genotype frequencies were identified between the patient and control groups, the frequencies of the *OPRM1* gene (c.118A>G) alleles of the Poltava population were considered as one group. Comparison of the total frequency of the *OPRM1* gene (c.118A>G) alleles of the Poltava population with other populations from the genotype and phenotype database of the National Centre for Biotechnology Information (NCBI) determined a complete coincidence with the European one ($p = 0.87$ and $q = 0.13$) [18].

CONCLUSIONS

The identified genetic polymorphism of the population of the Poltava region for the *CYP2B6* (c.516G>T) and *OPRM1* (c.118A>G) genes may be a pharmacogenetic basis for personalized anesthetics.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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