[15] Wiggans, G. R. (1997). NCDHIP participation as of January 1, 1997. Fact Sheet K-1. Extension Servise, US Department of Agriculture. Washington DC, 32–35.

[16] Zhebrovsky, L. S. et. al (2005). The state of the gene pool of dairy cattle in Russia. Bulletin of the RASHN, 5, 78–79.

[17] Van Tassel, C. P. (1997). Changes in USDA-DHIA genetic evaluations (August 1997). AIPL. Res. Rpt., 9 (8-97).

[18] Hoffman, K. (2002). We must widen our genetic focus. Hoard's Dai-ryman, 25, 244.

[19] Kuznetsov, V. M. (2002). Holsteinisstion of Kholmogorsky cattle in the Kirov region. Zootechnia, 2, 8–10.

[20] Cassel, B. (2002). What longevity traits should you select? Hoard's Dairyman, 25, 244.

POLYMORPHISMS OF DRUG-METABOLIZING ENZYMES CYP1A2, CYP2D6, GST, NAT2 AND TRANSPORTER MDR1 IN POPULATION OF BELARUS: COMPARISON WITH SELECTED EUROPEAN AND ASIAN POPULATIONS

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Abstract

Drug therapeutic efficiency and development of unfavorable pharmacologic responses as well as the disease predisposition are caused first of all by patient's genetic features. Genetic variations in genes encoding drug-metabolizing enzymes and transporter proteins are essential to understand the ethnic differences in disease occurrence, development, prognosis, therapeutic response and toxicity of drugs. For that reason, it is necessary to establish the normative frequency distribution of genotypes and alleles of these

genes in a particular population. Data on frequency of pharmacogenetic polymorphisms in the of Belarus population are limited. The goal of our investigation was to analyze the frequency distribution of genotypes and alleles of genes encoding drug-metabolizing enzymes (CYP1A2, CYP2D6 – I phase; GSTs, NAT2 – II phase) and transporter protein MDR1 in the population of Belarus and comparisons with other ethnic populations. Our results indicate that clinically important genes are genetically highly variable and differ considerably between populations. Differences in allele frequencies across continents should be considered when designing clinical trials of new drugs continents should be considered when designing clinical trials of new drugs.

Keywords: drug-metabolizing enzymes, polymorphism, pharmacogenetic.

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1. Introduction

One of the important problems of drug therapy is variability of patients' responses to the drug used. Heterogeneity of organism reactions is also observed when taking vitamins and other bracing products used for correcting a functional state of a healthy human, improving physical efficiency and for recovering organism after endured diseases. As a result of applying the same pharmacologic preparation, the absence of a therapeutic effect is observed in same people and various complications (from slight fatigue to serious health disorders) emerge in others. At present many causes, which underlie interindividual differences in a pharmacologic response (sex, age, weight, pattern of a disease course, concomitant pathology, etc.), are known [1]. However, genetic distinctions of a patient are the most important stable factor determining kinetics of metabolic transformations of drugs in organism and heterogeneity of individual's reaction to a drug [2, 3]. Such distinctions are realized via polymorphic sites of protein genes involved in drug pharmacokinetics and pharmacodynamics. According to an original conception of pharmacologic metrology of academician L. A. Piruzian, an individual human response to drug application is determined by a "starting state" of enzyme systems of chemical compound (xenobiotics) metabolism [4]. Genetic polymorphism of xenobiotic biotransformation enzymes results in differences in their activity from several times to scores of times and hundred times. At present regular search for and identification of functionally important polymorphisms of drug metabolism genes are under way for conducting pharmacogenetic testing (PT) since it is considered, at a given moment, one of the most important technologies in personalized medicine [5]. The PT results will allow a physician to select a drug and conditions of its dosage individually for every patient providing maximum efficiency and safety of drug therapy.

However, it should be taken into consideration that the occurrence frequency of allelic variants in drug metabolism genes varies greatly in different ethnic groups particularly belonging to diverse races (from 0 to 50 %) [6–8]. That's why it is necessary to determine frequencies of allelic variants in the given genes in a particular population as far as it is obvious that PT introduction for certain genes will be advantageous only in that case when allelic variants of this genes occur often enough in the population (above 1 %).

2. Aim

The goal of our investigation was to analyze the frequency distribution of genotypes and alleles of genes encoding drug-metabolizing enzymes (CYP1A2, CYP2D6 – I phase; GSTs, NAT2 – II phase) and transporter protein MDR1 in the population of Belarus and comparisons with other ethnic populations.

3. Materials and methods

The study population consisted of 538 persons without oncopathology (282 men and 256 women). All participants were Caucasian from Belarus. Written informed consent was obtained from all individuals before enrolment in the study.

As for the age of the examined persons, the sample was divided into two groups: "under 50 years" – 322 persons and "above 50 years" – 216 persons; smoking status was known in 302 persons (109 smokers and 193 non-smokers).

DNA was isolated from peripheral blood lymphocytes by phenol-chloroform extraction.

We genotyped 9 SNPs in six genes involved in the hormone metabolism *CYP2D6* (rs3892097), CYP1A2 (rs762551), GSTT1 (deletion), GSTM1 (deletion), GSTP1 (rs1695), NAT2 (rs1799929, rs1799930, rs1799931) and *MDR1* (rs1045642). Characteristics of the polymorphisms are listed in **Table 1**.

Table 1
Characteristic of the polymorphisms genotyped in this study

Gene symbol	rs no	Nucleotide substitution	SNP function[a]	Protein effect	Location[b]	MAF[c]
CYP1A2	rs762551	C734A	intron variant	–	15:74749576	0.37
CYP2D6	rs3892097	1846G>A		splicing defect	22:42128945	0,17
GSTT1	–	ins/del	deletion	deleted	22q11.23	–
GSTM1	–	ins/del	deletion	deleted	1p13.3	–
GSTP1	rs1695	A313G	missense	I105V	11:67585218	0,35
NAT2	rs1799929	481C>T	synonymous	L161L	8:18400484	0,26
NAT2	rs1799930	590G>A	missense	R197Q	8:18400593	0,26
NAT2	rs1799931	857G>A	missense	G286E	8:18400860	0.08
MDR1	rs1045642	3435C>T	synonymous	I1145I	7:87509329	

Note: a – According to the Single Nucleotide Polymorphism database (dbSNP); b – Based on UCSC Human Genome Browser, human reference sequence (GRCh38); c – MAF, minor allele frequency, according to dbSNP

Genotyping for *CYP1A2, CYP2D6, GSTP1, NAT2* and *MDR1* genes was performed using a polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP) assay. Following amplification, PCR products were digested with ApaI (rs762551), MvaI (rs3892097), Alw26I (rs1695), KpnI (rs1799929), TaqI (rs1799930), BamHI (rs1799931), MboI (rs1045642) (Fermentas, Lithuania). The GSTT1 and GSTM1 gene polymorphisms were examined using multiplex PCR out according to the technique described earlier [9].

The Hardy-Weinberg equilibrium for SNPs was tested with the Pearson's $\chi 2$ test. The analysis comparing genetic and allelic frequencies among ethnic groups was performed using $\chi 2$ tests. An odds ratio (OR) with a 95 % confidence interval (CI) was applied to assess the genetic associations by sex, age, smoking status. All statistical analyses were two-sided, and $P<0.05$ was considered as statistically significant. Statistical analysis of the material was carried out using SNPStats program (http://bioinfo.iconcologia.net/SNPstats_web) and Statistica 6.0.

4. Results

Genotype distributions of the polymorphisms were in the Hardy-Weinberg equilibrium, only for rs762551 HWE p-values was < 0,05.

Table 2 presents the data on distribution of alleles and genotypes rs762551 polymorphism of *CYP1A2* gene depending on sex, age and smoking status in the population of Belarus. On the population studied, the genotype CC occurs in 6,5 %, CA – 48,8 % and AA – 44,7 %. Analysis of the relationship between the frequency *CYP1A2* genotype and allele distribution and sex, age and smoking status has not revealed any significant difference.

Table 3 presents distribution of *CYP1A2* genotype and allele frequencies in various populations. The frequency of the mutant allele *A* in Belarus did not differ from that in the European and was significantly higher than in the Japanese population.

Table 2
Distribution of CYP1A2 genotype and allele frequencies in the population of Belarus

Group	Genotype						Allele			
	AA		CA		CC		A		C	
	n	%	n	%	n	%	n	%	n	%
In all	240	44,7	262	48,8	35	6,5	742	69,0	332	31,0
Men	114	40,4	147	52,1	21	7,5	375	66,0	189	34,0
Women	126	49.4	115	45,1	35	5.5	367	72,0	143	28,0
Under 50 years	144	44,9	152	47,4	25	7,8	440	69,0	202	31,0
Above 50 years	96	44,4	110	50,9	10	4,6	302	70,0	130	30,0
Smokers	53	48,6	50	45,9	6	5,5	156	72,0	62	28,0
Non-smokers	87	45.1	94	48,7	12	6,2	268	69,0	118	31,0

Table 3
Genotype and allele frequencies (%) of rs762551 polymorphism CYP1A2 gene in some populations

Country	In all, n	Genotype			Allele		p-value[a]
		AA	CA	CC	A	C	
Belarus	537	44,7	48,8	6,5	70,0	30,0	–
Germany [13]	722	41,9	40,9	7,2	72,4	27,6	0,07
Japan [14]	403	40,4	46,2	13,4	63,5	36,5	**<0,05**
USA [15]	333	49,0	41,0	10,0	69,5	30,5	0,85

Note: a – p-value for comparison between the population of Belarus and selected populations

The frequency of the genotype *AA* rs3892097, determining complete absence of the *CYP2D6* enzyme activity, was 6,7 % in the population of Belarus (**Table 4**). The genotype GA occurred in 35,5 % of the examined persons and 57,8 % were the carriers of the genotype GG. Analysis of the relationship between genotype and allele frequency distributions of rs3892097 polymorphism and sex and smoking status has not revealed any significant difference. There was a difference in the allelic and genotypic distribution between the group of persons under 50 years of age and persons above 50 years. The frequency of GG genotype rs3892097 in persons above 50 years was significantly higher and the combined AG+AA genotype frequency was lower than in persons under 50 years. OR for dominant model GG vs GA+AA was 0,62 CI95 %:0,43–0,91; p=0,012, p log-additive=0,026.

Table 4
Genotype and allele frequencies of rs3892097 polymorphism in the population of Belarus

Group	Genotype						Allele			
	GG		GA		AA		G		A	
	n	%	n	%	n	%	n	%	n	%
In all	311	57,8	191	35,5	36	6,7	813	76,0	263	24
Men	165	58,5	98	34,8	19	6,7	428	76,0	136	24,0
Women	146	57,1	93	36,3	17	6,6	385	75,0	127	25,0
Under 50 years[a]	172	64,3	127	39,4	23	7,1	471	73,0	173	27,0
Above 50 years	139	53,4	64	29,6	13	6,1	342	79,0	90	21,0
Smokers	67	61,5	34	31,2	8	7,3	168	77,0	50	23,0
Non-smokers	127	65,8	56	29,0	10	5,2	310	80,0	76	20,0

Note: a – significant difference between the group of persons under 50 years of age and persons above 50 years

The data on *GSTs*-gene genotyping in the population of Belarus are given in **Table 5**. The frequency of the "null genotype" for genes *GSTT1* and *GSTM1* was 14,9 % and 43,7 % respectively, that is consistent with the occurrence frequency of these genotypes in the Europeoids. No significant differences were revealed in the occurrence frequency of null-genotyping depending on age, sex and smoking status.

Table 5
Distribution of GSTs genotype and allele frequencies in the population of Belarus

Genotype	In all		Sex				Age				Smoking status			
			men		women		<50		>50		smokers		Non-smokers	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
*GSTM1 (*present)	303	56,3	165	58,5	138	53,9	171	53,1	132	61,1	66	60,5	106	54,9
GSTM1 (null)	235	43,7	117	41,5	118	46,1	151	46,9	84	38,9	43	39,5	87	45,1
GSTT1 (present)	458	85,1	238	84,4	220	85,9	276	85,7	182	84,3	95	87,2	161	83,4
GSTT1 (null)	80	14,9	44	15,6	36	14,1	46	14,3	34	15,7	14	12,8	32	16,6
GSTP1														
AA	258	48,0	134	47,5	124	48,4	149	46,3	109	50,5	45	41,3	94	48,7
GA	242	45,0	124	44,0	118	46,1	150	46,6	92	42,6	54	49,5	89	46,1
GG	38	7,0	24	8,5	14	5,5	23	7,1	15	6,9	10	9,2	10	5,2
Allele A	758	70,0	392	70,0	366	71,0	448	70,0	310	71,8	144	66,0	277	71,8
Allele G	318	30,0	172	30,0	146	29,0	196	30,0	122	28,2	74	34,0	109	28,2

Analysis of rs1695 polymorphism in the population of Belarus has shown that distribution of genotype frequencies was as follows: the genotype AA – 48,0 %; the genotype GA – 45,0 % and the genotype GG – 7,0 %. No significant differences were also revealed for distribution of *GSTP1* genotypes depending on age, sex and smoking status. On the studied group, the frequency of the mutant allele was comparable with frequencies in representatives of the European population and was lower than in the Afro-Americans and higher than in the Chinese population (**Table 6**).

Table 6
Genotype and allele frequencies (%) of rs1695 polymorphism in different ethnic groups

Population	In all, n	Genotype			Allele		p-value[a]
		AA	GA	GG	A	G	
Belarus population	538	48,0	45,0	7,0	70,0	30,0	
The Europeoids [16]	287	42,0	51,0	7,0	67,0	33,0	0,76
The Afro-Americans [17]	120	31,0	53,0	16,0	58,0	42,0	<0,05
The Chinese [18]	1211	67,0	30,0	3,0	82,0	18,0	<0,05

Note: a – p-value for comparison between the population of Belarus and selected populations

We have carried out *NAT2* genotyping for three polymorphic sites: rs1799929, rs1799930 and rs1799931. The frequency of homozygous mutation (TT) in the position C481T (rs1799929) was 19,7 % in the studied group, homozygous substitution (AA) in the position G590A (rs1799930) occurred in 8,0 %. It should be noted that no individuals with the genotype *AA* were detected during studying rs1799931 polymorphism. Analysis of the relationship between the frequency *NAT2* genotype and allele distribution and sex and age has not revealed any significant difference. Significant differences were found in the distribution of polymorphic variants of rs1799929 and rs1799930 polymorphisms between smokers and nonsmokers (**Table 7**). The results of our study showed an association between the carriers of CC genotype rs1799929 polymorphism and GG genotype rs1799930 polymorphism (dominant model) and cigarette smoking (p-value=0,019 and 0,022 respectively).

Table 7
Genotype frequencies of rs1799929 and rs1799930 polymorphisms in smokers and nonsmokers

Genotype	Nonsmokers	Smoker	OR (95 % CI)	P-value
		rs1799929		
CC	37 (19,2 %)	34 (31,2 %)	1,00	0,019
CT+TT	156 (80,8 %)	75 (68,8 %)	0,52 (0,30–0,90)	
Log-additive	–	–	0,73 (0,51–1,05)	0,088
		rs1799930		
GG	73 (37.8 %)	56 (51.4 %)	1,00	0,022
GA+AA	120 (62.2 %)	53 (48.6 %)	0,58 (0.36–0.93)	
Log-additive			0,69 (0,47–1,03)	0,065

The examined individuals were divided into "fast" and "slow" acetylators according to accepted approaches [19]. The holders of three dominant alleles in the homozygous state (481CC, 590GG и 857GG) as well as those in whom only one of the three studied genotypes was in the heterozygous state (481CT, 590GG, 857GG; 481CC, 590GA, 857GG и 481CC, 590GG, 857GA) were attributed to "fast" acetylators. All the rest of the genotype combinations formed the group of "slow" acetylators. The frequency of "fast" acetylators was 38,5 % in the population of Belarus and that of "slow" acetylators – 61,5 % (**Table 8).** The observed ratio of "fast" and "slow" acetylators differed significantly from distribution of acetylators in the populations of Germany and Italy.

Table 8
The frequency (%) of "fast" and "slow" acetylators in various populations

Country	"Fast" acetylators	"Slow" acetylators	p-value[a]
Belarus	38,5	61,5	
Germany [20]	43,2	56,8	<0,05
Italy [21]	48,2	51,8	<0,05
Sweden [22]	40,5	59,5	0.07
USA [23]	37,9	62,1	0,42

Note: a – p-value for comparison between the population of Belarus and selected populations

Distribution of the *MDR1* genotype in the population of Belarus (**Table 9**) was as follows: CC – 21,4 %, CT – 51,7 %, TT – 26,9 %.

Table 9
Genotype and allele frequencies of rs1045642 polymorphism in the population of Belarus

Groups	Genotype						Allele			
	CC		CT		TT		C		T	
	n	%	n	%	n	%	n	%	N	%
In all	115	21,4	278	51,7	145	26,9	508	47,0	568	53,0
Men	66	23,4	144	51,1	72	25,5	276	49,0	288	51,0
Women	49	19,1	134	52,3	73	28,5	232	45,0	280	55,0
Under 45 years	70	21,7	162	50,3	90	27,9	302	47,0	342	53,0
Above 45 years	45	20,8	116	53,7	55	25,5	206	48,0	226	52,0
Smokers	26	23,9	51	46,8	32	29,4	103	47,0	115	53,0
Nonsmokers	41	21,2	101	52,3	51	26,4	183	47,0	203	53,0

No significant differences in age, sex and smoking status were revealed for distribution of MDR1 genotypes.

5. Discussion

Nowadays polymorphism of genes encoding enzymes of drug metabolism I phase, in particular isoenzymes of cytochrome P-450 (CYP2D6, CYP1A2*)* is actively studied [7, 10, 11].

The CYP1A2 enzyme, a member of the cytochrome P450 superfamily of proteins is a key component of monooxygenases. CYP1A2 catalyzes the metabolic activation of a variety of aryl- and heterocyclic amines such as 2-aminoanthracene and 2-acetylaminofluoren. Above 40 genetic polymorphisms of the CYP1A2 enzyme were indentified but few of them have been reported to affect the activity of CYP1A2 [12]. The CYP1A2*1F polymorphism (rs762551, –163C<A) in the first intron *CYP1A2* gene is one of the most common studied variants. For this polymorphism was shown association with the enzyme activity: the allele *A* determines higher activity of the CYP1A2 enzyme and the allele C – low activity.

CYP2D6 is an important polymorphic phase- I drug-metabolism enzyme and plays an important role in the metabolism of a variety of drugs and environmental compounds. *CYP2D6* is involved in metabolism of more than 20 % drugs (for instance, debrisoquine, antidepressants, beta-blockers et al [5, 7, 10, 24]. The CYP2D6 gene located at chromosome 22q 13.2 is one of the most polymorphic CYP450 genes. At present above 70 alleles of this gene are known, although multiple allele identified no function [25]. CYP2D6*3, CYP2D6*4, CYP2D6*5, and CYP2D6*6 are reported to be associated with enzymatic activity and varies from complete absence ("poor" metabolizer) to ultra-fast metabolism ("fast" metabolizer). However, it was shown that 75 % of "poor" metabolizers were carriers of *CYP2D6*4* (rs3892097,1846G>A) polymorphism [24].

The frequency of AA genotype rs3892097, determining complete absence of the enzyme activity, varied greatly in different ethnic groups: in the Europeans – 5–10 %, the Afro-Americans – 1,8 %, the Chinese – 1 % [7, 11, 26,2 7]. The frequency of the mutant allele *A* (24,0 %) and AA genotype (6,7 %) of rs3892097 in Belarus did not differ from that in the European populations.

Glutathione-S-transferase (GST) and N-acetyltransferase (NAT) are key enzymes of the second phase in biotransformation. Out of these enzymes glutathione transferases of μ class (GSTM1), θ class (GSTT1) and π class (GSTP1) are the most studied.

GSTM1 and *GSTT1* polymorphisms are caused by the presence of extensive deletion in the coding region ("null genotype"). It is important to note that about 50 % of the Europeans have homozygous deletion of *GSTM1* gene and 10–20 % – homozygous deletion of *GSTT1* gene [28]. Synthesis of the corresponding protein product does not occur at the given mutations. The presence of the "null genotype", even if for one of these genes (*GSTM1* or *GSTT1*), is related to an increase in risk of multifactorial disease development. In recent years the data on association of *GSTM1* and *GSTT1* with development of unfavorable reactions after chemotherapy came to light [28].

The enzyme glutathione S-transferase of π class (GSTP1) is involved in metabolism of wide spectrum xenobiotics including drugs. The rs1695 polymorphism in the 5th exon of *GSTP1* gene, manifesting itself in substitution of isoleucine 105 by valine (Ile105Val), is associated with development of drug resistance in oncologic disease treatment. Watson et al. showed that allele G (Ile/Val and Val/Val) were characterized by a reduced conjugation activity of the enzyme as compared to individuals with the genotype AA (Ile/Ile) [16].

N-acetyltransferase 2 (NAT2) is a major enzyme of acetylating xenobiotics with the primary aromatic and hydrazine structure. NAT2 metabolizes and detoxifies xenobiotics such as caffeine, tobacco smoke, pesticides, and drugs [29, 30] Metabolic acetylation polymorphism, which manifests itself by the presence of "fast" and "slow" acetylators in the population of phenotypes, is known. Thirteen point mutations, in the coding region *NAT2,* which form 36 alleles in different combinations is its bases [31]. Pronounced ethnic differences are a distinction of *NAT2* polymorphism. Among populations of Europe and North America, 40–70 % are "slow" acetylators whereas among populations of the Pacific shore of Asia (the Japanese, the Chinese, Koreans) only 10–30 % of representatives are "slow" acetylators [19, 31]. Individual and ethnic differences in the acetylation rate exert an effect on development of unfavorable reactions when taking some drugs.

Our study showed an association between the carriers of CC genotype rs1799929 polymorphism and GG genotype rs1799930 polymorphism and cigarette smoking. It is possible that the

carrier of CC genotype rs1799929 and GG genotype rs1799930 (“fast” acetylator status) reduces a detrimental effect of smoking.

In recent years the influence of P-glycoprotein, encoded by *MDR1* gene, on drug pharmokinetics was studied. P-glycoprotein is involved in elimination of a lot of drugs into extracellular space [6, 32]. The level of enzyme expression causes drug concentration in cell: the higher is expression of an active transporter, the faster substrate or its metabolites are removed from cell and the quicker their concentration is reduced. The rs1045642 polymorphism (3435C<T) was revealed to be associated with the level of P-glicoprotein expression: CC-homozygotes are characterized with a high level of P-glicoprotein expression, TT-homozygotes – with a low level and heterozygotes CT – with an intermediate level [33]. The frequency of *C3435T* substitution differed greatly among ethnics groups: the frequency of the TT genotype in the European populations – 17–28 % [34–36], in the Iranians – 19 % [37], in the Japanese – 12 % [38], in the Afro-Americans – 1 % [35]. The genotype frequency of rs1045642 in Belarus corresponded to that in the European population and was significantly higher than in the Japanese and in the Afro-Americans.

No significant differences in sex were revealed for distribution of *MDR1* genotypes. However, it is known from the literature data that *P*-glycoprotein expression was higher by a factor of 2,4 in men than in women. Therefore pharmacogenetic investigations on metabolism of drugs, being *P*-glycoprotein substrate, should be performed taking into account sex differences [39, 40]. Application of such an approach allows differentiated prescription of drug therapeutic dose for men and women.

6. Conclusion

Study on genetic polymorphism of biotransformation enzymes involved in drug metabolism was first carried out in the population of Belarus. Our results indicate that clinically important genes are genetically highly variable and differ considerably between populations. These investigations can underlie an individual genetic passport which enables correction of treatment (drug selection and conditions of its dosage) in view of individual features of patients that will make pharmacotherapy more effective and safe. It should be emphasized that a genetic component of drug efficiency and/or toxicity can be determined before starting treatment.

References

[1] Franceschi, M., Scarcelli, C., Niro, V., Seripa, D., Pazienza, A. M., Pepe, G. et. al (2008). Prevalence, Clinical Features and Avoidability of Adverse Drug Reactions as Cause of Admission to??a??Geriatric Unit. Drug Safety, 31 (6), 545–556. doi: 10.2165/00002018-200831060-00009

[2] Lonetti, A., Fontana, M. C., Martinelli, G., Iacobucci, I. (2016). Single Nucleotide Polymorphisms as Genomic Markers for High-Throughput Pharmacogenomic Studies. Microarray Technology, 143–159. doi: 10.1007/978-1-4939-3136-1_11

[3] Chaudhary, R., Singh, B., Kumar, M., Gakhar, S. K., Saini, A. K., Parmar, V. S., Chhillar, A. K. (2015). Role of single nucleotide polymorphisms in pharmacogenomics and their association with human diseases. Drug Metabolism Reviews, 47(3), 281–290. doi: 10.3109/03602532.2015.1047027

[4] Piruzyan, L. A. (2004). Human metabolic passport – the basis of a new strategy in pharmacology. Vesti. RAN, 74, 610–618.

[5] Ma, Q., Lu, A. Y. H. (2011). Pharmacogenetics, Pharmacogenomics, and Individualized Medicine. Pharmacological Reviews, 63 (2), 437–459. doi: 10.1124/pr.110.003533

[6] Ono, C., Kikkawa, H., Suzuki, A., Suzuki, M., Yamamoto, Y., Ichikawa, K. et. al (2013). Clinical impact of genetic variants of drug transporters in different ethnic groups within and across regions. Pharmacogenomics, 14(14), 1745–1764. doi: 10.2217/pgs.13.171

[7] Daly, A. K. (2015). Pharmacogenetics of drug metabolizing enzymes in the United Kingdom population: review of current knowledge and comparison with selected European populations. Drug Metabolism and Personalized Therapy, 30 (3). doi: 10.1515/dmdi-2014-0034

[8] Ramamoorthy, A., Pacanowski, M., Bull, J., Zhang, L. (2015). Racial/ethnic differences in drug disposition and response: Review of recently approved drugs. Clinical Pharmacology & Therapeutics, 97 (3), 263–273. doi: 10.1002/cpt.61

[9] Chakova, N. N., Mikhalenko, E. P., Polonetskaya, S. N., Chebotareva, N. V., Demidchik, Y. E., Zhilko, A. A. et. al (2009). GST polymorphism and cytogenetic changes in lung tissues of lung cancer patients. Cytology and Genetics, 43 (1), 38–41. doi: 10.3103/s0095452709010071

[10] Samer, C. F., Lorenzini, K. I., Rollason, V., Daali, Y., Desmeules, J. A. (2013). Applications of CYP450 Testing in the Clinical Setting. Molecular Diagnosis & Therapy, 17 (3), 165–184. doi: 10.1007/s40291-013-0028-5

[11] Ota, T., Kamada, Y., Hayashida, M., Iwao-Koizumi, K., Murata, S., Kinoshita, K. (2015). Combination Analysis in Genetic Polymorphisms of Drug-Metabolizing Enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A5 in the Japanese Population. International Journal of Medical Sciences, 12 (1), 78–82. doi: 10.7150/ijms.10263

[12] Zhou, S.-F., Yang, L.-P., Zhou, Z.-W., Liu, Y.-H., Chan, E. (2009). Insights into the Substrate Specificity, Inhibitors, Regulation, and Polymorphisms and the Clinical Impact of Human Cytochrome P450 1A2. The AAPS Journa, 11 (3), 481–494. doi: 10.1208/s12248-009-9127-yy.

[13] Sainz, J., Rudolph, A., Hein, R., Hoffmeister, M., Buch, S., von Schonfels, W. et. al (2011). Association of genetic polymorphisms in ESR2, HSD17B1, ABCB1, and SHBG genes with colorectal cancer risk. Endocrine Related Cancer, 18 (2), 265–276. doi: 10.1530/erc-10-0264

[14] Shimada, N., Iwasaki, M., Kasuga, Y., Yokoyama, S., Onuma, H., Nishimura, H. et. al (2009). Genetic polymorphisms in estrogen metabolism and breast cancer risk in case–control studies in Japanese, Japanese Brazilians and non-Japanese Brazilians. Journal of Human Genetics, 54 (4), 209–215. doi: 10.1038/jhg.2009.13

[15] Li, D. (2005). Polymorphisms of cytochrome P4501A2 and N-acetyltransferase genes, smoking, and risk of pancreatic cancer. Carcinogenesis, 27 (1), 103–111. doi: 10.1093/carcin/bgi171

[16] Watson, M. (1998). Human glutathione S-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution. Carcinogenesis, 19 (2), 275–280. doi: 10.1093/carcin/19.2.275

[17] Cote, M. L., Wenzlaff, A. S., Bock, C. H., Land, S. J., Santer, S. K., Schwartz, D. R., Schwartz, A. G. (2007). Combinations of cytochrome P-450 genotypes and risk of early-onset lung cancer in Caucasians and African Americans: A population-based study. Lung Cancer, 55 (3), 255–262. doi: 10.1016/j.lungcan.2006.11.002

[18] Egan, K. M. (2004). Genetic Polymorphisms in GSTM1, GSTP1, and GSTT1 and the Risk for Breast Cancer: Results from the Shanghai Breast Cancer Study and Meta-Analysis. Cancer Epidemiology Biomarkers & Prevention, 13 (2), 197–204. doi: 10.1158/1055-9965.epi-03-0294

[19] Hein, D. W., Grant, D. M., Sim, E. (2000). Update on consensus arylamine N-acetyltransferase gene nomenclature. Pharmacogenetics, 10 (4), 291–292. doi: 10.1097/00008571-200006000-00002

[20] Wikman, H., Thiel, S., Jäger, B., Schmezer, P., Spiegelhalder, B., Edler, L., Dienemann, H., Kayser, K., Schulz, V., Drings, P., Bartsch, H., Risch, A. (2001). Relevance of N-acetyltransferase 1 and 2 (NAT1, NAT2) genetic polymorphisms in non-small cell lung cancer susceptibility. Pharmacogenetics, 11 (2), 157–168. doi: 10.1097/00008571-200103000-00006

[21] Boccia, S., Sayed-Tabatabaei, F. A., Persiani, R., Gianfagna, F., Rausei, S., Arzani, D. et. al (2007). Polymorphisms in metabolic genes, their combination and interaction with tobacco smoke and alcohol consumption and risk of gastric cancer: a case-control study in an Italian population. BMC Cancer, 7 (1), 206. doi: 10.1186/1471-2407-7-206

[22] Hou, S. M., Fält, S., Yang, K., Nyberg, F., Pershagen, G., Hemminki, K., Lambert, B. (2001). Differential interactions between GSTM1 and NAT2 genotypes on aromatic DNA adduct level and HPRT mutant frequency in lung cancer patients and population controls. Cancer Epidemiol Biomarkers Prev., 10 (2), 133–140.

[23] McGrath, M., Michaud, D., De Vivo, I. (2006). Polymorphisms in GSTT1, GSTM1, NAT1 and NAT2 genes and bladder cancer risk in men and women. BMC Cancer, 6 (6), 239.

[24] Ingelman-Sundberg, M., Sim, S. C., Gomez, A., Rodriguez-Antona, C. (2007). Influence of cytochrome P450 polymorphisms on drug therapies: Pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacology & Therapeutics, 116 (3), 496–526. doi: 10.1016/j.pharmthera.2007.09.004

[25] CYP2D6 allele nomenclature. Available at: http://www.cypalleles.ki.se/cyp2d6.htm

[26] McGraw, J., Waller, D. (2012). Cytochrome P450 variations in different ethnic populations. Expert Opinion on Drug Metabolism & Toxicology, 8 (3), 371–382. doi: 10.1517/17425255.2012.657626

[27] Bradford, L. D. (2002). CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics, 3 (2), 229–243. doi: 10.1517/14622416.3.2.229

[28] Ginsberg, G., Smolenski, S., Hattis, D., Guyton, K. Z., Johns, D. O., Sonawane, B. (2009). Genetic Polymorphism in Glutathione Transferases (GST): Population Distribution of GSTM1, T1, and P1 Conjugating Activity. Journal of Toxicology and Environmental Health, Part B, 12 (5-6), 389–439. doi: 10.1080/10937400903158375

[29] Makarova, S. (2008). Human N-Acetyltransferases and Drug-Induced Hepatotoxicity. Current Drug Metabolism, 9 (6), 538–545. doi: 10.2174/138920008784892047

[30] Moslehi, R., Chatterjee, N., Church, T. R., Chen, J., Yeager, M., Weissfeld, J. et. al(2006). Cigarette smoking, N -acetyltransferase genes and the risk of advanced colorectal adenoma. Pharmacogenomics, 7 (6), 819–829. doi: 10.2217/14622416.7.6.819

[31] Walraven, J., Zang, Y., Trent, J., Hein, D. (2008). Structure/Function Evaluations of Single Nucleotide Polymorphisms in Human N-Acetyltransferase 2. Current Drug Metabolism, 9 (6), 471–486. doi: 10.2174/138920008784892065

[32] Stieger, B., Meier, P. J. (2011). Pharmacogenetics of drug transporters in the enterohepatic circulation. Pharmacogenomics, 12 (5), 611–631. doi: 10.2217/pgs.11.53

[33] Sakaeda, T., Nakamura, T., Okumura, K. (2003). Pharmacogenetics of MDR1 and its impact on the pharmacokinetics and pharmacodynamics of drugs. Pharmacogenomics, 4 (4), 397–410. doi: 10.1517/phgs.4.4.397.22747

[34] Brambila-Tapia, A. J. (2013). MDR1 (ABCB1) polymorphisms: functional effects and clinical implications. Rev. Invest. Clin., 65 (5),445–454.

[35] Ameyaw, M.-M., Regateiro, F., Li, T., Liu, X., Tariq, M., Mobarek, A. et. al (2001). MDR1 pharmacogenetics: frequency of the C3435T mutation in exon 26 is significantly influenced by ethnicity. Pharmacogenetics, 11 (3), 217–221. doi: 10.1097/00008571-200104000-00005

[36] Jamroziak, K., Balcerczak, E., Młynarski, W., Mirowski, M., Robak, T. (2002). Distribution of allelic variants of functional C3435T polymorphism of drug transporter MDR1 gene in a sample of Polish population. Pol. J. Pharmacol., 54 (5), 495–500.

[37] Saidijam, M., Mahjub, H., Shabab, N., Yadegarazari, R. (2015). Simultaneous analysis of multidrug resistance 1(MDR1) C3435T, G2677T/A, and C1236T genotypes in Hamadan City population, West of Iran. Iran Biomed J., 19 (1), 57–62. doi: 10.6091/ibj.1381.2014

[38] Sakaeda, T., Nakamura, T., Horinouchi, M., Kakumoto, M., Ohmoto, N., Sakai, T. et. al (2001). MDR1 genotype-related pharmacokinetics of digoxin after single oral administration in healthy Japanese subjects. Pharmaceutical Research, 18 (10), 1400–1404. doi: 10.1023/a:1012244520615

[39] Franke, R., Gardner, E., Sparreboom, A. (2010). Pharmacogenetics of Drug Transporters. Current Pharmaceutical Design, 16 (2), 220–230. doi: 10.2174/138161210790112683

[40] Gao, B., Yang, F. M., Yu, Z. T., Li, R., Xie, F., Chen, J. et. al (2015). Relationship between the expression of MDR1 in hepatocellular cancer and its biological behaviors. Int J Clin Exp Pathol., 8 (6), 6995–7001.