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ORIGINAL ARTICLE

GENETIC POLYMORPHISMS IN CYP2 GENE FAMILY IN BULGARIAN INDIVIDUALS AND THEIR CLINICAL IMPLICATIONS

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Abstract. *The cytochrome P450 superfamily consists of hemeproteins involved in the detoxication of different xenobiotics, including drugs. The CYP2 gene family is responsible for the metabolism of 80% of the drugs in clinical use. There are considerable interindividual and interethnic variabilities in the rate of drug metabolism as a result of genetic polymorphisms. The goal of our study was to determine the frequency of 10 genetic polymorphisms in CYP2 family genes to give light on the pharmacogenetic defects of the main CYPs, involved in drug metabolism, in Bulgarian individuals. We detected high allele frequency for CYP2D6*10 (0.27), CYP2D6*4 (0.22), and CYP2B6*9 (0.24), followed by CYP2C19*2 (0.14), CYP2C9*3 (0.11) and CYP2C9*2 (0.09). The genotype frequencies were also determined for all investigated variants. In total 47.2% of the analyzed individuals carried CYP2D6 genetic polymorphisms – 5.6% carried a single variant and 41.6% were found to have two or more such variants. Homozygotes for CYP2D6 variants were established among 14% of Bulgarian individuals. Determination of the prevailing pharmacogenetic polymorphisms of the CYPs, most responsible for drug metabolism, will lead to a lower risk of drug toxicity, increased drug efficacy, and drug dose optimization.*

Key words: *cytochrome P450, genetic polymorphisms, pharmacogenetics, drug safety*

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INTRODUCTION

The human cytochrome P450 superfamily is composed of heme-containing enzymes, responsible for the biotransformation of different xenobiotics, including drugs. Although CYP enzymes are expressed in different organs – kidneys, placenta, gonads, adrenal glands, etc. [1], they are most concentrated in the liver and intestines. CYPs are the main enzymes involved in drug detoxication. They perform the reactions of oxidation during phase I of drug metabolism, converting lipophilic compounds to water-soluble ones that can be easily excreted from the body. There are at least 57 functional genes and 58 pseudogenes, associated with CYPs, organized in 18 families and 44 sub-families, based on the amino acid sequence homology of the enzymes [2, 3]. Of all human CYPs, CYP1, 2, and 3

are involved in the metabolism of 80% of the drugs in clinical use [2-4]. CYP2D6 is highly polymorphic, which determines a considerable interindividual difference in drug response. The gene is located on the long arm of chromosome 22 (22q13.2) and is the most common mutant isoform [3]. The CYP2D6 enzyme is involved in the metabolism of nearly 25% of clinically prescribed drugs. Substrates for the enzyme include tricyclic antidepressants (clomipramine, imipramine, desipramine, nortriptyline), selective serotonin reuptake inhibitors (fluoxetine, paroxetine), certain neuroleptics (chlorpromazine, thioridazine, olanzapine, haloperidol), opioid analgesics (codeine, tramadol, methadone), antiarrhythmic drugs (propafenone, lidocaine, procainamide, mexiletine), anticancer drugs (cyclophosphamide), etc. The CYP2B6 gene is part of the CYP2 cluster (together with CYP2A) located on chromosome 19 (19q13.2) and is one of the most polymorphic genes in humans [11]. The CYP2B6 enzyme constitutes up to 10% of the functional monooxygenases in the liver and is involved in 10-12% of the clinically used drugs, including the antiretroviral drugs (efavirenz, nevirapine), antimalarial (artemisinin), anticancer (cyclophosphamide, ifosfamide), antidepressants (fluoxetine, sertraline), antiseizure drugs (phenytoin, mephenytoin), opioids (methadone) and others [12]. CYP2C19 is involved in the bioactivation of the antiplatelet drug clopidogrel. Clopidogrel is a purinergic receptor inhibitor, preventing platelet aggregation and reducing the risk of thrombosis. As a prodrug, clopidogrel must be activated in the liver by the CYP2C19 enzyme isoform. The carriers of two loss-of-function copies are considered as CYP2C19 poor metabolizers, and exhibit reduced antiplatelet effect of clopidogrel.

Evidence is constantly accumulating for their clinical significance in terms of drug toxicity, efficacy, and dose determination. There is considerable variability in CYPs'activity among individuals and populations. The main types of genetic variations in CYP genes that were determined are loss-of-function and gain-of-function variants [3, 7]. Loss-of-function variants predispose to a high risk of adverse drug reactions, due to reduced elimination and enhanced plasma concentrations [8]. The gain-of-function variants increase the rate of drug elimination, resulting in subtherapeutic plasma concentration and inefficient drug response. Loss- and gain-of-function variants are a result of multiallelic polymorphisms. These polymorphisms depend highly on ethnicity and lead to various pharmacogenetic phenotypes, classified as poor, intermediate, extensive, and ultra-rapid metabolizers [3, 9].

AIM OF THE STUDY

The goal of our study was to determine the frequency of genetic polymorphisms in CYP2 family genes to give light on the pharmacogenetic defects of main CYPs, involved in drug metabolism, in Bulgarian individuals. Determination of the allele and genotype frequencies in the population will lead to significant improvements in pharmacotherapy.

MATERIALS AND METHODS

We collected data from 200 unselected Bulgarian patients and attended the laboratory for genomic diagnostics. An informed consent form was signed by all patients before testing. The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects. DNA was isolated from peripheral venous blood, using CHEMAGEN® Magnetic Separation Station (PerkinElmer) following the manufacturer's instructions. The concentration of the genomic DNA was determined with the Qubit dsDNA BR Assay Kit on the Qubit 2.0 fluorimeter. DNA samples of index patients were processed for targeted sequencing. TruSight One panel by Illumina, which includes 4127 genes associated with hereditary diseases, was used for library preparation. Accurate concentrations of the dilutions were calculated followed by denaturation and dilution of libraries according to MiSeq System Denature and Dilute Libraries Guide. Samples were loaded for sequencing by use of a cartridge as described in MiSeq System User Guide (part # 150276) and sequencing was performed on a MiSeq System using the MiSeq Reagent Kit v3. Data aligned to the Human reference sequence – Genome Reference Consortium Human Build 37 (GRCh37/hg19) led to a list of variants that in terms of filtering was annotated by the VariantStudio Software.

We extracted the data for genetic polymorphisms in twenty-two genes belonging to CYP 1, 2, and 3 families. The examined CYP allele variants are presented in Table 1.

RESULTS

Allele and genotype frequencies of the studied polymorphisms

We determined allele and genotype frequencies for all studied genetic polymorphisms among Bulgarian individuals – Table 2. The minor allele frequencies (MAF) were comparable with those in the European population.

The highest allele frequency of drug response-associated polymorphisms was identified in the CYP2D6 gene – CYP2D6*10 (0.27) and CYP2D6*4 (0.22), encoding enzymes with reduced activity. We estab-

lished 38.8% heterozygotes and 2.25% homozygotes for CYP2D6*4 and 30.3% heterozygotes and 11.8% homozygotes for CYP2D6*10 among Bulgarian individuals – Figure 1. For CYP2D6*3 we found very low allele frequency (0.008) and only 1.7% heterozygotes among investigated Bulgarians.

Table 1. Characteristics of the studied allele variant

Allele	Annotation	Variant type	Functional consequence
CYP2D6 - metabolism of dextromethorphan, sparteine, metoprolol, nortriptyline and many other antidepressants and codeine			
CYP2D6*3	rs35742686	Frameshift	Inactive
CYP2D6*4	rs3892097	Splicing defect	Homozygotes are poor metabolizers
CYP2D6*10	rs1065852	Missense (Pro34Ser)	Homozygotes are poor metabolizers
CYP2C9 – warfarin, piroxicam, lesinurad, phenytoin, flurbiprofen response			
CYP2C9*2	rs1799853	Missense (Cys144Arg)	Reduced metabolism
CYP2C9*3	rs1057910	Missense (Ile359Leu)	Reduced metabolism
CYP2C8 – acute gastrointestinal bleeding during the use of NSAIDs			
CYP2C8*3	rs10509681	Missense (Lys329Arg)	Increased toxicity
CYP2C19 – mephenytoin, proguanil, clopidogrel, amitriptyline, citalopram, clomipramine response			
CYP2C19*2	rs4244285	Splice acceptor activation (p.Pro227=)	Poor metabolizers
CYP2C19*4	rs28399504	Missense (Met1Val)	Poor metabolizers
CYP2B6 – nevirapine, efavirenz, methadone response			
CYP2B6*9	rs3745274	Missense (Gln172His)	Increased toxicity
CYP2A6 – warfarin, nicotine response			
CYP2A6*2	rs1801272	Missense (Leu160His)	Reduced metabolism

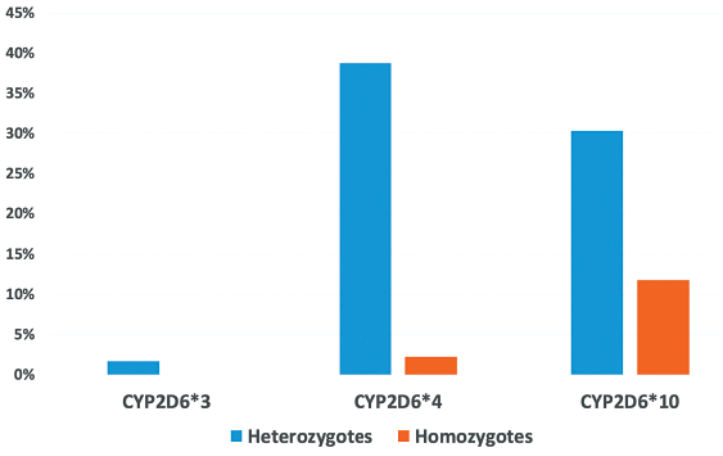

Fig. 1. Incidence of CYP2D6 functional polymorphisms' genotype in Bulgarian population

Table 2. Genotype and allele frequency for the studied variants

Allele	% of heterozygotes	% of homozygotes	MAF (BG)	MAF (EU)
CYP2D6*3	1.68%	0	0.008	0.02
CYP2D6*4	38.76%	2.25%	0.22	0.22
CYP2D6*10	30.34%	11.80%	0.27	0.24
CYP2C9*2	16.29%	1.12%	0.093	0.13
CYP2C9*3	18.54%	1.68%	0.11	0.068
CYP2C8*3	15.73%	1.12%	0.09	0.11
CYP2C19*2	25.28%	1.68%	0.14	0.15
CYP2C19*4	0.56%	0.00%	0.003	0.003
CYP2B6*9	35.40%	6.74%	0.24	0.24
CYP2A6*2	6.18%	0.56%	0.04	0.025

The two CYP2C9 polymorphisms - CYP2C9*2 and CYP2C9*3, have an allele frequency of 0.09 and 0.11, respectively. We detected 16.3% heterozygotes and 1.12% homozygotes for CYP2C9*2 and 18.5% heterozygotes and 1.7% homozygotes for CYP2C9*3 – Figure 2. Similar allele (0.09) and genotype frequencies (15.7% heterozygotes and 1.12% homozygotes) were established for CYP2C8*3 – Figure 3.

The highly prevalent were the genetic polymorphisms CYP2B6*9 and CYP2C19*2 with allele frequencies 0.24 and 0.14, respectively. The heterozygotes were 35.4% for CYP2B6*9 and 25.3% for CYP2C19*2, and homozygotes – 6.7% and 1.7%, respectively. Very low was the allele frequency for CYP2C19*4 (0.003) with 0.6% heterozygotes – Figure 4.

CYP2A6*2 has an allele frequency of 0.04 with 6.2% heterozygotes and 0.6% homozygotes among Bulgarian individuals – Figure 3.

Combined carriership of different drug response variants of CYP2D6

The simultaneous carriership of two CYP2D6 variants (Inactive + Decreased) was determined. In total 47.2% of the analyzed individuals carried CYP2D6 genetic polymorphisms. We detected a considerably higher frequency of combined carriership (41.6% – 41% for two variants and 0.6% for three variants) compared to a single one (1.7% for each CYP2D6 variant) – Table 3, Figure 5.

DISCUSSION

CYP2 is the largest family of all human CYPs, with CYP2D6, CYP2C9, CYP2C19, and CYP2B6 contributing to drug metabolism the most. Our research showed that 47.2% of the analyzed individuals carried CYP2D6 genetic polymorphisms. There is only one Bulgarian study on the frequency of these poly-

Table 3. Single and combined carriership of CYP2D6 variants

CYP2D6 variant (s)	Number of individuals (%)
Only 1 CYP2D6 variant	10 (5.6%)
rs35742686 Inactive	3 (1.7%)
rs3892097 Inactive	2 (1.1%)
rs5030655 Inactive	2 (1.1%)
rs1065852 Decreased	3 (1.7%)
2 CYP2D6 variants	73 (41%)
rs3892097+ rs1065852 Inactive+Decreased	72 (40.4%)
rs5030655+ s1065852 Inactive+Decreased	1 (0.6%)
3 CYP2D6 variants	1 (0.6%)
rs35742686+rs3892097+ rs1065852	1 (0.6%)

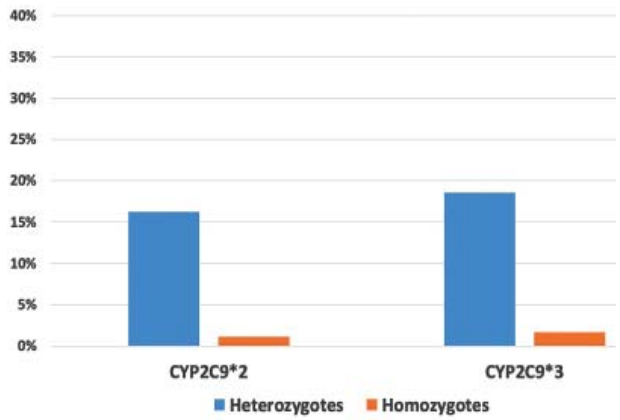

Fig. 2. Incidence of CYP2C9 polymorphisms' genotypes in Bulgarian population

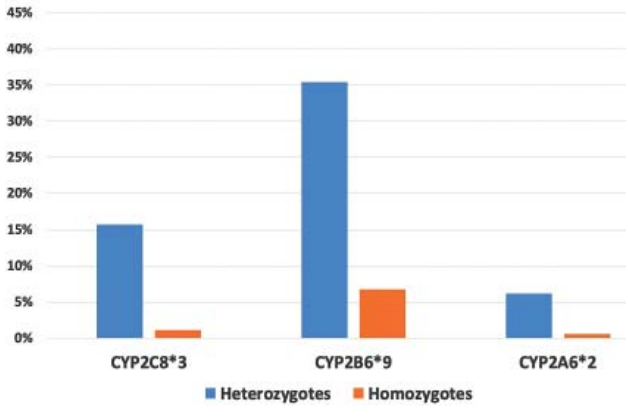

Fig. 3. CYP2C8, CYP2B6, and CYP2A6 polymorphisms' genotypes in Bulgarian population

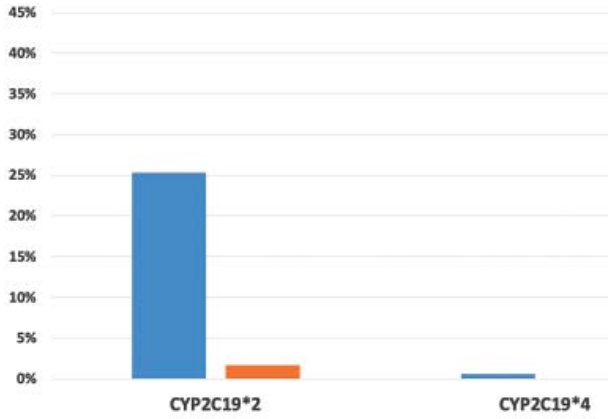

Fig. 4. CYP2C19 polymorphisms' genotypes in Bulgarian population

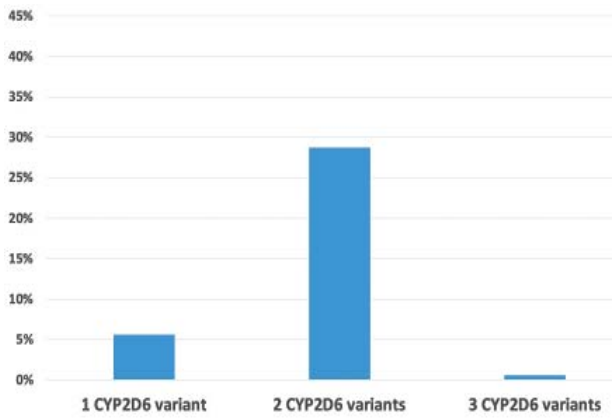

Fig. 5. Incidence of single, double, and triple carriership of CYP2D6 variants

morphisms, but among patients with psychiatric disorders [10] and they found 48.6% frequency of CYP2D6 polymorphisms among these patients. Our results showed that the most frequent drug response variants are the polymorphisms in CYP2D6 – CYP2D6*4 and CYP2D6*10. According to the existing data, CYP2D6*10 is the most common non-functional allele variant in the world population and is identified with the highest frequency in the Asian population (allele frequency more than 50%), followed by Chinese (50.7%) and Japanese (23-43%) cohorts [11, 12]. This allele variant in all its variations is rarer identified in the European population (24%), as well as in our Bulgarian cohort (27%) and it predisposes to supratherapeutic plasma levels and increased risk of drug toxicity. The CYP2D6*10 enzyme is unstable with reduced metabolic activity (60% of normal) and decreased affinity for its substrates. CYP2D6*4 is the second most common CYP2D6 allele variant established among Bulgarian individuals (22%), which coincides with the Caucasian population. In the Caucasian population, the CYP2D6*4 is the most common non-functional allele variant (20% of the population), established in 75%-90% of all poor metabolizers [12, 13]. In the Spanish and Turkish populations, this allele variant is established at a lower rate of 11-12%. CYP2D6*4 is rarely identified in Chinese and Japanese cohorts – less than 1% [13]. In the Asian population, the CYP2D6*4 is established in only 1-2% of the poor metabolizers. Homozygote carriers of both CYP2D6 variants were detected in 11.8% and 2.2%, respectively – that means 14% of Bulgarian individuals are poor metabolizers due to homozygosity of these genetic polymorphisms. The double carriership of non-functional CYP2D6 allele variants was established with high frequency in the Bulgarian population (41%), as it is worth investigating if these variants exist at cis- or trans-position in the same individual. Their compound heterozygosity additionally will increase the frequency of poor metabolizers in the Bulgarian population.

We found a 24% allele frequency of CYP2B6*9, as heterozygotes were 35% of the individuals, and 6.74% – were homozygotes. CYP2B6*9 encodes an enzyme with reduced activity. It is established with different frequencies amongst the ethnic groups. A relatively high frequency of the allele is observed in the German, British, and Swiss populations, 28%, 28%, and 26%, respectively. It is established in more than 40% of the populations of South India and Indonesia (Timorian), but less than 5% of the Asian population. The CYP2B6 enzyme is involved in the metabolism of many clinically used drugs, including the non-nucleoside reverse transcriptase inhibitors – efavirenz and nevirapine. Efavirenz and nevirapine are applied as first-line treatment for human immunodeficiency virus (HIV) –infected patients [14]. Considerable interindividual variability in the plasma concentrations of both drugs was determined. Efavirenz and nevirapine are metabolized by the CYP2B6 enzyme in the liver. The carriership of loss-of-function CYP2B6 gene variants is associated with a higher risk of Steven-Johnson syndrome and toxic epidermal necrolysis. Longer and massive exposure to these drugs, observed in poor metabolizers, could cause significant immune reactions, resulting in severe adverse effects [15]. CYP2B6 is the major enzyme responsible for the bioactivation of cyclophosphamide, converting it to 4-hydroxy-cyclophosphamide. Cyclophosphamide is an alkylating anticancer prodrug, which requires enzymatic activation in the liver. Carriers of CYP2B6*9 are considered to have worse pharmacotherapeutic outcomes from treatment with cyclophosphamide [16]. Determination of the CYP2B6 genotype of these

patients could improve their pharmacotherapeutic effects and anticancer therapy outcomes. Another metabolic pathway with clinical significance, associated with the CYP2B6 enzyme, is the biotransformation of methadone. CYP2B6 is the major enzyme involved in methadone metabolism and its activity determines the rate of drug's clearance and plasma concentration [17-20]. According to previous research data, there is a strong correlation between rs3745274 SNP of the gene CYP2B6 and opioid addiction. Some authors considered a higher rate of opioid addiction relapse in rs3745274 carriers. The CYP2B6*9 allele variant is also associated with fatalities caused by methadone application [6].

Another cytochrome enzyme associated with drug response is CYP2C19. Approximately 2% of Caucasians, 14% of Chinese, and 57% of Oceanians are CYP2C19-poor metabolizers. Our data (14% allele frequency) coincided with the allele frequency in the European population [21]. The therapeutic effect is reduced in intermediate metabolizers, as well. These individuals are carriers of one loss-of-function copy of the CYP2C19 gene, and one normal or gain-of-function allele variant. The frequency of intermediate metabolizers is relatively high in East Asia (45%), Central and South Asia (40%), Oceanians (36%), and 20-26% in American and European populations. The allele variants CYP2C19*2 and CYP2C19*4 encode non-functional enzymes. The results of our research revealed a lower frequency (25%) of CYP2C19*2 heterozygotes among Bulgarian individuals [22]. It is considered that 6-12% of the observed variability in the antiplatelet effect of clopidogrel is a result of the CYP2C19 polymorphism [23]. The allele variant CYP2C19*4 is established in less than 1% of the general population [21].

CYP2C9 is involved in the metabolism of acidic drugs including S-warfarin, phenytoin, and nonsteroidal anti-inflammatory drugs. The CYP2C9 gene is highly polymorphic with over 60 allele variants being identified. CYP2C9*2 is the most common mutant allele, encoding an enzyme with decreased activity and up to 40% reduction in S-warfarin biotransformation. CYP2C9*3 is caused by a missense mutation, encoding an enzyme with conformational changes and significantly reduced affinity for its substrates. This allele variant results in a considerable reduction in S-warfarin metabolism by up to 95% [24]. The results of our study revealed a frequency of these alleles (9% and 11%, respectively) in the Bulgarian population comparable to this one in Europe (13% and 7%) and higher than in Asian populations (< 5%). The CYP2C9*2 and *3 allele variants are frequent among the Caucasian population – 1% homozygotes and 22% heterozygotes, and 0.4% homozygotes and 15% heterozygotes for CYP2C9*2 and CYP2C9*3, respectively [24]. Warfarin is an anticoagulant that inhibits the vitamin K epoxide reductase complex and the carboxylation of factors II, VII, IX, and X as well as proteins C and S. The drug has a narrow therapeutic window requiring strict monitoring and precise dosing. Patients with reduced CYP2C9 enzyme activity are exposed to a higher risk of supratherapeutic anticoagulation and bleeding.

CONCLUSIONS

CYPs are the main enzymes responsible for drug biotransformation. Determining the most frequent polymorphisms of certain enzyme isoforms may help develop personalized medicine, and improve the individual approach towards the patients. Studying the most common pharmacogenetic defects of CYPs in the population will lead to a lower risk of drug toxicity, increased pharmacotherapeutic efficacy, and dose optimization, especially for drugs with narrow therapeutic windows.

Informed Consent Statement: *Informed consent was obtained from all subjects involved in the study.*

Disclosure Summary: *The authors have nothing to disclose.*

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