



## ORIGINAL ARTICLE

# CYP2C9, CYP2C19 and CYP2D6 gene profiles and gene susceptibility to drug response and toxicity in Turkish population



Merve Arici, Gül Özhan \*

Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Beyazit, 34116 Istanbul, Turkey

Received 26 June 2016; accepted 9 September 2016

Available online 17 September 2016

## KEYWORDS

Genetic polymorphism;  
Turkish population;  
CYP2C9;  
CYP2C19;  
CYP2D6;  
Cytochrome P450

**Abstract** Pharmacogenetics is a vast field covering drug discovery research, the genetic basis of pharmacokinetics and dynamics, genetic testing and clinical management in diseases. Pharmacogenetic approach usually focuses on variations of drug transporters, drug targets, drug metabolizing enzymes and other biomarker genes. Cytochrome P450 (CYP) enzymes, an essential source of variability in drug-response, play role in not only phase I-dependent metabolism of xenobiotics but also metabolism of endogenous compounds such as steroids, vitamins and fatty acids. CYP2C9, CYP2C19 and CYP2D6 enzymes being highly polymorphic are responsible for metabolism of a variety of drug groups. In the study, it was determined the genotype and allele frequency of *CYP2C9\*2*, *CYP2C19\*3*, *CYP2C19\*2*, *CYP2C19\*3*, *CYP2C19\*17*, *CYP2D6\*9* and *CYP2D6\*41*, very common and functional single-nucleotide polymorphisms (SNPs), in healthy volunteers. The genotype distributions were consistent with the Hardy-Weinberg equilibrium in the population ( $p > 0.05$ ). It is believed that the determination of polymorphisms in the enzymes may be beneficial in order to prevention or reduction in adverse effects and death. The recessive allele frequencies of *CYP2C9\*2*, *CYP2C19\*3*, *CYP2C19\*2*, *CYP2C19\*3*, *CYP2C19\*17*, *CYP2D6\*9* and *CYP2D6\*41* were 11, 13, 12, 13, 25, 4 and 15%, respectively. According to the obtained results, the carriers of *CYP2D6\*9* variant allele should be received higher doses of the drugs metabolizing with this enzyme in Turkish population, while the carriers of other variant alleles do not generally have any requirement of dose regimen.

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\* Corresponding author. Fax: +90 2124400252.

E-mail address: [gulozhan@istanbul.edu.tr](mailto:gulozhan@istanbul.edu.tr) (G. Özhan).

Peer review under responsibility of King Saud University.



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## 1. Introduction

CYP enzymes are responsible for phase I metabolism over 90% of drugs and naturally occurring xenobiotics and endogenous substrates. To date, fifty-seven *CYP* genes, which involve three families (*CYP1*, *CYP2* and *CYP3*) contributing to the oxidative metabolism of various compounds, have been

detected (Shastry, 2006). CYP2C subfamily has at least four isoforms (CYP2C8, CYP2C9, CYP2C18 and CYP2C19) located on chromosome 10 (Scordo et al., 2004).

CYP2C9, which is greatly polymorphic and the most abundant isoform of CYP2C, metabolizes a variety of drug groups including anticoagulants, anticonvulsants, and non-steroidal anti-inflammatory agents (Sosa-Macías et al., 2010). More than thirty *CYP2C9* variants and sub-variants have been identified. *CYP2C9\*2* and *CYP2C9\*3*, the most common variants, have effect in decreasing enzyme activity (Alessandrini et al., 2013).

CYP2C19 is responsible for the metabolism of more than 25 clinically important drug groups including a lot of psychotropics, proton pump inhibitors and anticonvulsants. Also, it contributes to the clearance of *S*-mephenytoin, diazepam, omeprazole, proguanil and *R*-warfarin (Scordo et al., 2004; Rosemary and Adithan, 2007). There are more than 30 *CYP2C19* allelic variants. The most common variants are *CYP2C19\*2* and *CYP2C19\*3*, which reduce enzyme function. Recently, another variant, *CYP2C19\*17*, awakens researchers' interest and is associated with increased enzyme function (Alessandrini et al., 2013).

CYP2D6 is responsible for hydroxylation or demethylation of approximately 25% of clinically important drugs such as antiarrhythmic, psychiatric, antihistaminic and antidepressant (Gardiner and Begg, 2006; Zanger et al., 2004). Also, it is known that CYP2D6 plays important role in the metabolism of the analgesic codeine (Crews et al., 2012). It was identified over one hundred variant alleles of CYP2D6. While some alleles of those cause normal or increased activity in enzyme function (\*1, \*2 and \*35), some lead to decreased activity (\*9, \*10, \*17, \*29, and \*41) or the absence of enzyme function (\*3, \*4, \*5, and \*6) (Broly and Meyer, 1993; Gaedigk et al., 1991; Gaedigk et al., 2003; Sakuyama et al., 2008).

In the present study, it was aimed that the results may provide a helpful support in the optimization of pharmacological therapies in Turkish population by determining their *CYP2C9*, *CYP2C19* and *CYP2D6* genotype profiles.

## 2. Material and methods

Genomic DNA was extracted from whole blood samples of unrelated 160 Turkish healthy volunteers (88 females and 72 males, aged 20–65 years) by High Pure PCR Template Preparation Kit (Roche, Germany) according to the manufacturer's protocol. Genotyping of *CYP2C9\*2* (rs1799853, 430C > T), *CYP2C9\*3* (rs1057910, 1075A > C), *CYP2C19\*2* (rs4244285, 681G > A), *CYP2C19\*3* (rs4986893, 636G > A), and *CYP2C19\*17* (rs12248560, 806C > T) variants was performed by polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) methods. The temperature was controlled by a programmable heat block (Gene Amp PCR System 9700; Applied Biosystems, Carlsbad, CA, USA). Restriction enzymes were obtained from New England Biolabs (Hitchin, UK) and Fermentas (Vilnius, Lithuania). The other information about the genetic variants studied is given in Table 1.

Genotyping of *CYP2D6\*9* (rs5030656, 2615\_2617delAAG) and *CYP2D6\*41* (rs28371725, 2988G > A) variants was performed on Roche Light Cycler 480 Real-Time PCR platform. Required DNA purification ensured by using High Pure PCR Product Purification Kit and single nucleotide polymorphism

(SNP) analysis was performed by using LightCycler FastStart DNA Master HybProbe and custom designed LightSNiP assay probe (Roche, Germany). All participants provided informed consent and studies were approved by the ethics committee of Istanbul University (2014/1546).

The Hardy-Weinberg equilibrium analysis was performed to compare the observed and expected genotype frequencies of subjects by using the chi-square ( $\chi^2$ ) test. Differences in the *CYP2C9\*2*, *CYP2C19\*3*, *CYP2C19\*2*, *CYP2C19\*3*, *CYP2C19\*17*, *CYP2D6\*9* and *CYP2D6\*41* genetic variants between Turkish and other ethnic populations were also assessed by  $\chi^2$  test. A *p* value below 0.05 was considered statistically significant throughout the population comparisons. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (Version 17, Chicago, USA).

## 3. Result and discussion

In the present study, it was determined the genotype and allele frequencies of *CYP2C9*, *CYP2C19* and *CYP2D6* genes in Turkish population. There were no *CYP2C19\*3* homozygous variant type (A) and *CYP2D6\*9* homozygous wild type (–) (Table 2). There are a lot of publications about *CYP2C9*, *CYP2C19* and *CYP2D6* enzyme activities and the relationship between the gene variants and drug-response. However, there are few data on evaluation of genetic profile in Turkish population.

In the present study, it was determined the frequencies of *CYP2C9\*2* (C) and *CYP2C9\*3* (C) variant alleles were 11 and 13%, respectively. According to the previous studies, the frequency of *CYP2C9\*2* (C) was 10, 7, and 28% in European, Caucasian, and Japan, respectively. In Chinese population, *CYP2C9\*2* (C) was not observed. The frequencies of *CYP2C9\*3* (C) were 6, 5.8, 7, 4, and 2.7% in Asian, European, Caucasian, Chinese and Japan, respectively (www.hapmap.org; Allabi et al., 2003; Kimura et al., 1998; Ota et al., 2015; Sugimoto et al., 2007). Bűdi et al. (2015) suggested that it could improve the safety of antiepileptic therapies in vulnerable pediatric patients and prevent patients from misdosing when genotyping *CYP2C9\*2* and *CYP2C9\*3*. Similarly, Kawai et al. (2014) investigated whether there were any associations with some genetic variants and adverse drug reactions as receiving warfarin therapy which has narrow therapeutic index and is commonly used as anticoagulant. According to the results, the patients who carried *CYP2C9\*3* variant allele and received warfarin for 30 or more day might have 2-fold risk of major bleeding. In another study, it has been reported the carriers having *CYP2C9\*2* and *CYP2C9\*3* had 10-fold lower *S*-warfarin clearance in contrary to *CYP2C9\*11* and *CYP2C9\*33* (Scordo et al., 2002). Higashi et al. (2002) indicated that there was a significant association with the increasing risk of over-anticoagulation and bleeding events in the carriers having *CYP2C9\*2* and *CYP2C9\*3*, and genotyping of *CYP2C9* variants could provide developing dosing protocols rightly and reducing adverse effects in patients being treated warfarin.

In the present study, the allele frequencies of *CYP2C9\*2* (C), *CYP2C19\*3*(A) and *CYP2C19\*17*(T) were 12, 13, and 25%, respectively. The frequencies of *CYP2C19\*2* were 15, 17, and 29% in European, Caucasian and Japan, respectively,

**Table 1** The conditions about studied genes in the present study.

SNPs	Primer sequences	Annealing temperature	Restriction enzyme	Digestion products (bp)
<i>CYP2C9</i> *2 (rs1799853)	F: 5'gTATTTTggCCTgAAACCCATA 3' R: 5' ACCCTTggTTTTCTCAACTC 3'	60.6 °C	<i>AvaII</i>	Wild (CC): 454 Mutant (TT): 57, 397
<i>CYP2C9</i> *3 (rs1057910)	F: 5' TgCACgAggTCCAgAgATgC 3' R: 5' gATACTATgAATTTggggACTTC 3'	59 °C	<i>NsiI</i>	W (AA): 168 M (CC): 50, 118
<i>CYP2C19</i> *2 (rs4244285)	F: 5' AATTACAACCgAgCTTggC 3' R: 5' TATCACTTCCATAAAAgCAAg 3'	57.9 °C	<i>SmaI</i>	W (GG): 168 M (AA): 50, 118
<i>CYP2C19</i> *3 (rs4986893)	F: 5' CATTTAgCTTCACCCTgTg 3' R: 5' gggCTTggTCAATATAgAAT 3'	50.6 °C	<i>BsaJI</i>	W (GG): 251 M (AA): 33, 94, 124
<i>CYP2C19</i> *17 (rs12248560)	F: 5' gTgAAgCCTgTTTTATgAA 3' R: 5' gTggCgCATTATCTCTTA 3'	57.2 °C	<i>SfaNI</i>	W (CC): 165 M (TT): 20, 145

bp: base pair.

**Table 2** Genotype frequencies of investigated genes in the present study ( $n = 160$ ).

SNPs	Genotype	Genotype frequency $n$ (%)	Allele frequency
<i>CYP2C9</i> *2 (rs1799853)	C/C	127 (79.36)	C: 0.89
	C/T	31 (19.38)	T: 0.11
	T/T	2 (1.25)	
<i>CYP2C9</i> *3 (rs1057910)	A/A	114 (80.28)	A: 0.87
	A/C	18 (12.67)	C: 0.13
	C/C	10 (7.04)	
<i>CYP2C19</i> *2 (rs4244285)	G/G	95 (65.52)	G: 0.88
	G/A	34 (23.45)	A: 0.12
	A/A	16 (11.03)	
<i>CYP2C19</i> *3 (rs4986893)	C/C	118 (74.68)	A: 0.13
	C/A	40 (25.32)	C: 0.87
	A/A	0 (0)	
<i>CYP2C19</i> *17 (rs12248560)	C/C	98 (64.47)	C: 0.75
	C/T	33 (21.71)	T: 0.25
	T/T	21 (13.81)	
<i>CYP2D6</i> *9 (rs5030656)	AAG/AAG	159 (99.38)	AAG: 0.96
	(-)/AAG	1 (0.63)	(-): 0.04
	(-)/(-)	0 (0)	
<i>CYP2D6</i> *41 (rs28371725)	G/G	112 (73.68)	G: 0.85
	G/A	35 (23.03)	A: 0.15
	A/A	5 (3.29)	

whereas the distribution of *CYP2C19*\*3 was 11% in Japan. Germany, American, and Caucasian did not have *CYP2C19*\*3 variants. Moreover, the values for *CYP2C19*\*17 were 18, 3, and 1 in Caucasian, Chinese and Japan (Allabi et al., 2003; Ota et al., 2015; Sugimoto et al., 2007; Hamdy et al., 2002; Saber et al., 2014; Santos et al., 2011; Zhou et al., 2009). Kubica et al. (2011) reported *CYP2C19*\*2 had an association about excess of ischemic events such as myocardial infarction and stent thrombosis while *CYP2C19*\*17 variant allele undertakes a critical role for bleeding. In a study, *CYP2C19*\*17 enzyme and its effects were investigated in clopidogrel-treated patients with coronary stent placement. It was observed that the carriers *CYP2C19*\*17 heterozygous and homozygous variant alleles had the lowest (ADP)-induced platelet aggregation values ( $AU_{min}$  (area under the curve of arbitrary units): 186) and the highest risk of bleeding events. In

particular, the risk of bleeding events was approximately 4-fold more in the carriers homozygous *CYP2C19*\*17 allelic variant (Sibbing et al., 2010). Moreover, the presence of *CYP2C19*\*17 variant allele in a large cohort of Caucasian subjects was associated with the endoscopically peptide ulcer diseases (Musumba et al., 2013). Mega et al. (2009) showed that the plasma concentration of the active metabolites of clopidogrel and the maximal platelet aggregation decreased in the ratio of 32.4% and 9%, respectively, in the carriers who had at least one *CYP2C19* variant contrary to non-carriers. According to this study, *CYP2C19*\*2 genetic variant was associated with higher rate of stent thrombosis. Similarly, the risk of stent thrombosis was an importantly higher in the carriers having at least one *CYP2C19*\*2 variant allele on the contrary to *CYP2C19*\*2 wild type homozygous patients with received clopidogrel. Moreover, *CYP2C19*\*2 variant allele carriers

had ~3-fold higher risk of bleeding (Sibbing et al., 2009). It has been suggested an association between *CYP2C19* genotype and an increased risk of cardiovascular events in Japanese patients receiving rabeprazole, a proton pump inhibitor (Hokimoto et al., 2014).

According to the study about risperidone being an atypical antipsychotic drug for treatment of schizophrenia, it was found higher risperidone C<sub>max</sub> ( $9.66 \pm 2.24$  ng/ml), higher AUC<sub>0-t</sub> (area under the curve) ( $161.43 \pm 39.31$  ng/ml h) and lower clearance in poor *CYP2D6* metabolizers. Moreover, it was detected a relationship between adverse effects (such as headache, neurological, psychiatric) and some *CYP2C9* and *CYP2C19* variants (Cabaleiro et al., 2014). On the other hand, there was no association between the metabolism of olanzapine, an atypical antipsychotic, and *CYP2D6* polymorphism (Hägg et al., 2001). Noetzi et al. (2014) investigated the relationship between some genetic variants and donepezil, and is commonly used acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. They observed a significant association with functional alleles of *CYP2D6* and donepezil clearance. While its clearance was 32% slower in poor metabolizer, donepezil elimination was 67% faster in ultra-rapid metabolizers. In our population, it was determined the distributions of *CYP2D6\*9* (AAG) and *CYP2D6\*41(A)* are 96 and 15%, respectively. While the distribution of *CYP2D6\*9* was 97 and 100% in European and Asian, respectively, the value of *CYP2D6\*41* was 8 and 4% in Caucasian and China, respectively (www.hapmap.org., Zhou et al., 2009; Gaedigk and Coetsee, 2008). Seven et al. (2014) pointed out that *CYP2C9\*3* variant allele played an important role as preventing in which drug resistance is developed for epilepsy patients. Also, it was shown that *CYP2C9*, *CYP2C19* and *CYP2D6* SNPs could affect the response to antiepileptic drugs.

In conclusion, this study will contribute to represent their genetic profile in terms of important drug-metabolizing enzymes because there was only one study about the genetic profiles of *CYP2C9*, *CYP2C19* and *CYP2D6* in Turkish population. The determination of polymorphisms in mentioned enzymes might provide advantage for dose adjustment of a lot of drugs in order to prevent and reduce adverse effects and even death.

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