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ORIGINAL ARTICLE

CYP2C9, CYPC19 and CYP2D6 gene profiles and gene susceptibility to drug response and toxicity in Turkish population

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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.

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

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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 manufacture'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 (χ^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 χ^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,