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Genetic polymorphism of *CYP2C8*4* in a healthy Turkish population

Zuhal Uckun Sahinogullari

Mersin University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Mersin, Turkey

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Abstract

Cytochrome P4502C8 (*CYP2C8*) is a significant member of CYP enzyme family and metabolizes about 20% of commonly prescribed drugs and endogenous compounds. Single nucleotide polymorphisms in *CYP2C8* gene may change *CYP2C8* enzyme activity and therefore may affect the adverse reactions and efficacy of drugs metabolized by this. The purpose of the current investigation was to detect the genotype and allele frequencies of *CYP2C8*4* in a healthy Turkish population and also to compare our findings with the other populations. *CYP2C8*4* polymorphism was analyzed by polymerase chain reaction-restriction fragment length method using DNA samples isolated from 109 healthy Turkish volunteers. The genotype frequencies were 95.4% for the homozygous wild-type, 4.6% for heterozygous and 0.0 % for homozygous variant. According to this, the frequencies of wild type and variant alleles were determined as 0.977 and 0.023, respectively. The genotype frequencies did not deviate from the Hardy-Weinberg equilibrium. Significant population differences were observed when the findings were compared with those of other populations. This is the first investigation to examine the frequencies of *CYP2C8*4* polymorphism in Turkish population. The determination of *CYP2C8*4* polymorphism may provide useful data about the pharmacokinetics, efficacy and/or toxicity of its substrates and predisposition to some diseases and may help to improve personalized therapy in the future and also contributes to epidemiological studies.

Keywords: *CYP2C8*, genetic polymorphism, drug metabolism, Turkish population

Introduction

Cytochrome P450 (CYP) predominantly found in liver is the main metabolizing enzymatic system in humans and are account for metabolism of exogenous compounds and some endogenous compounds [1]. There are 57 active CYP genes divided into 18 families in the human genome [2]. CYP1, CYP2 and CYP3 families are generally related to the metabolism of exogenous substances such as carcinogens, mutagens, many of the clinically used drugs [1].

CYP2C subfamily constitutes about 18-30% of all human CYPs [3] and is account for metabolism of approximately 20% of prescribed drugs and endogenous compounds [4]. The members of CYP2C8, CYP2C19, CYP2C18 and *CYP2C9* form CYP2C subfamily. CYP2C8 playing a main part in the metabolism of many drugs used in medicine comprises 7% of the total liver CYP content [5]. CYP2C8 is account for approximately 5% of currently prescribed drugs [4]. Some of drugs that are majorly metabolized by CYP2C8 enzyme are anticancer (paclitaxel), antidiabetics (repaglinide, rosiglitazone, pioglitazone), antiarrhythmics (amiodarone), antimalarials (amodiaquine, chloroquine) [3,6]. Besides, this enzyme plays an intermediate or minor role in the metabolism of some agents like tyrosine kinase inhibitors (imatinib), nonsteroidal anti-inflammatory drugs (diclofenac, ibuprofen), calcium channel blockers (verapamil), statins (simvastatin acid, fluvastatin), opioids (methadonem, orphine) [5]. CYP2C8 enzyme is predominantly found in liver and is also present in extrahepatic sites like kidney, duodenum, ovary, mammary gland, uterus, brain, adrenal gland, heart [6].

CYP2C8 enzyme is endoced by CYP2C8 gene that is located on chromosome 10q24 and spans 31 kb and consists of 9 exons [5]. Several single nucleotide polymorphisms (SNPs) have been determined in the CYP2C8 gene, which is polymorphic. The most examined SNPs are *CYP2C8*2*, **3* and **4* polymorphisms that may give rise to a decrease in enzyme activity [7]. *CYP2C8*4* polymorphism is known as CYP2C8 *C792G* (rs1058930)

***Coresponding Author:** Zuhal Uckun Sahinogullari, Mersin University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Mersin, Turkey E-mail: uckunzuhal@gmail.com

nucleotide change which lead to amino acid change Ile264Met in exon 5 [3]. The polymorphic enzyme resulting from the nucleotide change has 25% activity in comparison with the wild-type CYP2C8 enzyme [8]. The polymorphisms in CYP2C8 gene have been related with clinically related outcomes in drug pharmacokinetics, toxicity, and/or efficacy [9]. CYP2C8 allele frequencies may vary from population to population, thus leading to inter- and intra-population distinctions in drug response in respect of efficacy and/or possibility of adverse drug reactions [10].

Gene polymorphisms of CYPs is known to show significant differences in frequency among dissimilar racial and ethnic groups [11]. To our knownledge, there has been no study about *CYP2C8*4* polymorphism in Turkish population. The purpose of the investigation was to detect the allele and genotype frequencies of *CYP2C8*4* polymorphism in a healthy Turkish population and compare our findings with previously reported results.

Materials and Methods

Samples

The DNA samples isolated from the previous study (22/10/2015, protocol no: 2015/317) were included to the current study. The present study was also approved by the Ethics Committee of Mersin University (20/11/2019, protocol no: 2019/515). This investigation was performed on DNA samples of 109 healthy and unrelated Turkish subjects who were 54 men and 55 women aged between 18-65 years. The study was executed according to Good Clinical Practices and the Helsinki declaration.

Genotyping

*CYP2C8*4* polymorphism was conducted as per method defined by Minhas et al. [3] with minor modifications. Polymerase chain reaction (PCR) amplification for *CYP2C8*4* was performed using the forwad and reverse primers: 5'-AAAGTAAAAGAACACCAAGC-3' and 5'-AAACATCCTTAGTAAATTACA-3', respectively. PCR was done in a 25-µl reaction mixture which contain 300 to 500 ng of genomic DNA, 10 x PCR buffer, 0.2 mM each deoxynucleotide triphosphate, 10 pmol of each primer, 1.25 unit of Taq polymerase, and 1.5 mM $MgCl_2$ (Fermentase) on the Thermal Cycler (Thermo, UK). The PCR process was as follows: 94 ˚C for 5 min for initial denaturation, and then 30 cycles of 94°C for 30 sec, 54 °C for 30 sec, 72 ˚C for 30 sec, followed by a final elongation at 72°C for 5 min. PCR products (167 bp) electrophoresed on a 2 % agarose gel including ethidium bromide (500 ng/ml) which make the products visible, and then the 10 µl PCR product was cut in 15 minutes at 65°C using 10 U of Fast Digest Taq I restriction enzyme with the proper buffer in total volume of 20 µl. The variant genotype was digested to 136 and 31 bp fragments while the wild type genotype was digested to 83, 53, and 31 bp fragments (Figure 1). 2.5 % agarose gel with ethidium bromide was used to evaluate the digested fragments. For a quality assurance, 10% of the samples at random was reanalyzed, which provide 100% concordance.

Statistical analysis

Allelic and genotypic frequencies were calculated using genotype counting method. The expected and observed frequencies of *CYP2C8*4* were compared using chi-square (X^2) test based on Hardy–Weinberg equilibrium. Chi-square test was employed to compare the allele frequencies determined from the current investigation with the prior findings of other populations. Besides, comparison of baseline characteristics between genotypes was performed using chi-square test and Mann-Whitney U test, as appropriate. Statistical analysis were carried out using IBM SPSS computer software for Windows 25.0. $p<0.05$ was considered to be statistically significant.

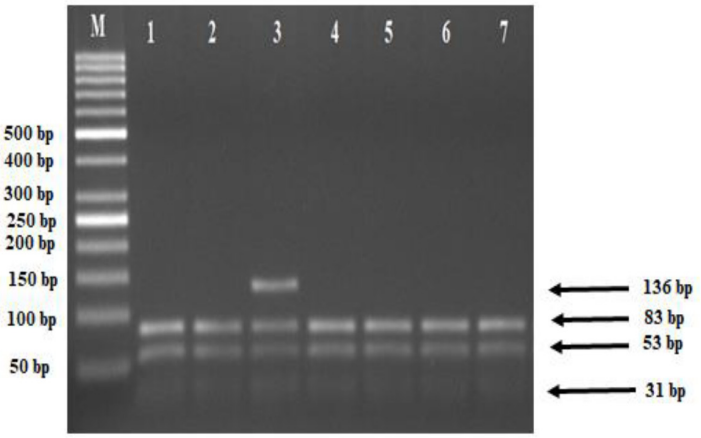

Figure 1. Genotyping for the *CYP2C8*4* polymorphism by restriction fragment length method. Lane M: Marker (50 bp); Lane 1,2, 4-7: wild type genotype (83, 53, 31 bp). Lane 3: heterozygous genotype (136, 83, 53, 31 bp)

Results

Analysis of CYP2C8 polymorphism was carried out with 109 healthy unrelated individuals. As illustrated in Table 1, of the 109 subjects, 55 (51 % of them) were women, while 54 (49 % of them) were men. The mean body weight with standard deviation (SD) of the subjects participating in the study is 70.92 ± 13.20 kg. The mean body mass index (BMI) with SD is 24.49 ± 3.70 kg/m^2. The mean height with SD is 169.67 ± 8.28 cm. Besides, 91 subjects (83%) were <40 years of age, while 18 subjects (17%) were ≥40 years of age. There was no statistical difference between the genotypes in terms of baseline properties ($p>0.05$).

As demonstrated in Table 2, the genotype frequencies of the homozygous wild type, heterozygous and homozygous variant were 95.4%, 4.6% and 0.0%, respectively. Besides, the frequencies of wild type and variant alleles were 0.977 and 0.023, respectively. The genotype frequencies did not deviate from the Hardy-Weinberg equilibrium ($p>0.05$).

Discussion

In this study, allele and genotype frequencies of *CYP2C8*4* polymorphism were detected in the Turkish population and the results were compared with other population frequencies. To our knowledge, this is the first investigation to detect the genotype and allele frequencies of the *CYP2C8*4* polymorphism in the Turkish population. The genotype frequencies of *CYP2C8*4* polymorphism were 95.4% for wild type, 4.6% for heterozygous, 0.0% for mutant genotypes while the allele frequencies of wild type and variant were 0.977 and 0.023, respectively.

As seen in the Table 3, the frequencies obtained in this study

Table 1. Baseline characteristics of the subjects participating in the study

	Total	Homozygous wild type	Heterozygous	Homozygous variant	*p* value
Gender		**n (%)**			
Women	55 (51)	53 (96)	2 (4)	0 (0)	0.632[a]
Men	54 (49)	51 (94)	3 (6)	0 (0)	
Age range (years)					
< 40	91 (83)	86 (95)	5 (5)	0 (0)	0.309[a]
≥ 40	18 (17)	18 (100)	0 (0)	0 (0)	
		mean±SD			
Body weight (kg)	70.92 ± 13.20	71.30 ± 13.40	63.2 ± 2.17	-	0.213[b]
BMI (kg/m²)	24.49 ± 3.70	24.58 ± 3.75	22.82 ± 2.08	-	0.356[b]
Height (cm)	169.67 ± 8.28	169.8 ± 8.33	166.8 ± 7.26	-	0.263[b]

BMI: Body mass index, mean±SD is mean±standart deviation.
[a]Chi-square, [b]Mann-Whitney U test.

Table 2. Distribution of genotype and allele frequencies of *CYP2C8*4* polymorphism in the Turkish population

Genotype	n (Observed)	Genotype frequencies, %	n (Expected)	Allele frequencies
Homozygous wild type	104	95.4	104.1	Wild type: 0.977
Heterozygous	5	4.6	4.8	Variant: 0.023
Homozygous variant	0	0.0	0.1	X^2: 0.06 df = 1; p>0.05
Total	109	100	109	

were compared with the results of 1000 Genomes Project [12] and previous studies [3,7,13-20]. According to this, there were significant differences between the variant allele frequency in Turkish population and the frequencies in European ancestry with range of 0.067 to 0.081 (p<0.05), inclusiving Finnish in Finland (FIN), British, German, Sweden and Iberian populations in Spain (IBS), but no significant difference was between the results and those of Czech (*p>0.05*) and Toscani in Italy (TSI) (*p>0.05*). Besides, no significant differences were noted between Turkish population and American ancestry with range of 0.012 to 0.024 (*p>0.05*), inclusiving Puerto Rican in Puerto Rico (PUR), Mexican Ancestry in Los Angeles, California (MXL), Colombian in Medellin, Colombia (CLM) and Peruvian in Lima, Peru (PEL). The *CYP2C8*4* variant allele frequency range from 0.00 to 0.040 in Black ancestry and there were significant difference between Turkish population and African populations (p<0.05), including Malaysian Indians, Ghanaian, Luhya in Webuye, Kenya (LWK) while no significant differences were between Turkish population and the other African populations (*p>0.05*), including African American, North Indians, Zanzibar, Yoruba in Ibadan, Nigeria (YRI), Esan in Nigeria (ESN).

*CYP2C8*4* polymorphism is no present in East Asian populations, inclusiving Japanese, Southern Han Chinese, China (CHS), Kinh in Ho Chi Minh City, Vietnam (KHV), Chinese Dai in Xishuangbanna, China (CDX), Han Chinese in Bejing, China (CHB), Japanese in Tokyo, Japan (JPT). Besides, the polymorphism is absent or low frequencies in South Asian population. Hence, there were significantly differences between Turkish population and East Asian ancestry and South Asian ancestry, excluding Sri Lankan Tamil in the UK (STU).

Briefly, *CYP2C8*4* variant allele is dominant in European ancestry with a range of 0.023 to 0.081. However, the variant allele is absent in East Asian ancestry and is absent and/or low frequency in South Asian and Black ancestry. The *CYP2C8*4* allele frequencies are variable among different populations. Therefore, this polymorphism can bring about inter- and intra- population variations in drug pharmacokinetics, efficacy and toxicity and predisposition to complex diseases.

Dorado et al. [21] examined influence of CYP2C8 and CYP2C9 genotypes on metabolism of diclofenac in 142 healthy Spanish individuals. They reported that the urinary concentration ratio of diclofenac/5-hydroxydiclofenac was more elevated in subjects with *CYP2C8*4* or *CYP2C8*3* allele when compared to subjects with *CYP2C8*1*/*1 (p<0.05). Thus, it was conluded that CYP2C8 genotypes had an effect on diclofenac metabolism *in vivo*. Barratt et al [22] investigated the impacts of the *CYP2C8*4* and *CYP2C8*3* polymorphisms on metabolism of imatinib and plasma imatinib concentrations in 210 chronic myeloid leukaemia patients receiving 400–800 mg of imatinib per day. They reported that patients carrying *CYP2C8*3* and *4 alleles had significantly more elevated (p<0.01) and lower (p<0.01) metabolic ratios,

Table 3. Allele frequencies of CYP2C8*4 in dissimilar populations

	Populations	Sample size	Allele frequencies		References
			Wild-type allele	Variant allele	
WHITE					
European	Turkish	109	0.977	0.023	The present study
	Finnish in Finland (FIN)*	99	0.919	0.081	[12]
	British*	107	0.925	0.075	[13]
	German*	122	0.926	0.074	[14]
	Sweden*	652	0.933	0.067	[15]
	Iberian populations in Spain (IBS)*	107	0.935	0.065	[12]
	Czech	161	0.941	0.059	[7]
	Toscani in Italy (TSI)	107	0.953	0.047	[12]
American	Puerto Rican in Puerto Rico (PUR)	104	0.976	0.024	[12]
	Mexican Ancestry in Los Angeles, California (MXL)	64	0.977	0.023	[12]
	Colombian in Medellin, Colombia (CLM)	94	0.984	0.016	[12]
	Peruvian in Lima, Peru (PEL)	85	0.988	0.012	[12]
BLACK					
African	African American	165	0.988	0.012	[16]
	North Indians	251	0.960	0.040	[3]
	Zanzibar	165	0.994	0.006	[17]
	Yoruba in Ibadan, Nigeria (YRI)	108	0.995	0.005	[12]
	Esan in Nigeria (ESN)	99	0.990	0.010	[12]
	Luhya in Webuye, Kenya (LWK)*	99	1.000	0.000	[12]
	Ghanaian (Africa)*	204	1.000	0.000	[18]
	Malaysian Indians*	123	1.000	0.000	[19]
ASIANS					
East Asian*	Japanese	360	1.000	0.000	[20]
	Southern Han Chinese, China (CHS)	105	1.000	0.000	[12]
	Kinh in Ho Chi Minh City, Vietnam (KHV)	99	1.000	0.000	[12]
	Chinese Dai in Xishuangbanna, China (CDX)	93	1.000	0.000	[12]
	Han Chinese in Bejing, China (CHB)	103	1.000	0.000	[12]
	Japanese in Tokyo, Japan (JPT)	104	1.000	0.000	[12]
South Asian	Sri Lankan Tamil in the UK (STU)*	102	1.000	0.000	[12]
	Punjabi in Lahore, Pakistan (PJL)	96	0.990	0.010	[12]
	Indian Telugu in the UK (ITU)	102	0.990	0.010	[12]
	Bengali in Bangladesh (BEB)	86	0.994	0.006	[12]

Differences in allele frequencies were evaluated by X^2 test.
Significant at *$p<0.05$ when compared with the current investigation.

respectively, compared to *CYP2C8*1*/*1 patients, and also that plasma imatinib concentrations were more than 50% in subjects with *CYP2C8*1*/*4 according to subjects with *CYP2C8*1*/*1 and *CYP2C8*3*. Consequently, it was concluded that CYP2C8 genotype significantly changes metabolism of imatinib in patients. Jernström et al. [15] explored the frequencies of CYP2C8 and *CYP2C9* polymorphisms associated with properties of breast tumor and disease-free survival in 652 Swedish patients who had breast cancer. They found that *CYP2C8*4* was significantly related with a less incidence of lymph node involvement. Daly et al. [23] reported that *CYP2C8*4* variant allele was related with an increment risk for diclofenac hepatotoxicity since this polymorphism could increase level of reactive diclofenac metabolites which cause hepatotoxicity. Besides, Lazarska et al. [24] notified that *CYP2C8*4* indicated a reduced activity of about 35% in the intrinsic clearance of diclofenac acyl glucuronide hydroxylation compared to the wild-type enzyme. In an investigation of 93 patients with ovarian cancer by Bergmann et al. [25], it was declared that *CYP2C8*4* had effect on paclitaxel pharmacokinetics. On the other hand, Bahadur et al. [13] declared that for paclitaxel, median *CYP2C8*4* metabolic activity is lower compared to wild-type enzyme despite not statistically significant. Henningsson et al. [26] investigated relationship of CYP2C8, *ABCB1, CYP3A5 and CYP3A4* polymorphisms with the paclitaxel pharmacokinetics in 97 Caucasian patients with cancer and declared that the evaluated variant alleles were not relationship with paclitaxel pharmacokinetics. Marsh et al. [27] reported that in 93 breast cancer patients administering paclitaxel at high dose, no relationship between pharmacokinetics of paclitaxel and CYP2C8 genotypes was observed. Besides, Niemi et al. [28] examined the influence of CYP2C8 polymorphisms on the pharmacodynamics and pharmacokinetics of repaglinide in 28 healthy volunteers and declared that *CYP2C8*4* polymorphism had no impact on repaglinide clearance.

Genetic polymorphism may influence pharmacokinetics and pharmacodynamics of many drugs, and thus cause inter- and intra-population variations in drug efficacy and safety and/or adverse reactions. Evaluation of genetic polymorphism may help personalized of drug dosage, disease management, and improved therapeutics [1].

Conclusion

The study indicates the allele and genotype frequencies of *CYP2C8*4* polymorphism in a healthy Turkish population and comparison of the obtained frequencies with those of other ethnic groups. The determination of this polymorphism may ensure useful data about the pharmacokinetics, efficacy and/or toxicity of its substrates and predisposition to some diseases and may help to improve personalized therapy in the future and contributes to epidemiological studies.

Competing interests
The authors declare that they have no competing interest.

Financial Disclosure
This study received no financial support.

Ethical approval
The present study was approved by the Ethics Committee of Mersin University (20/11/2019, protocol no: 2019/515).

References

1. Uckun Z, Baskak B, Ozdemir H, et al. Genotype and allele frequency of CYP3A4 -392A>G in Turkish patients with major depressive disorder. Turk J Pharm Sci. 2018;15:200-6.
2. Sim SC, Ingelman-Sundberg M. The human cytochrome P450 (CYP) allele nomenclature website: a peer-reviewed database of CYP variants and their associated effects. Hum Genomics. 2010;4:278-81.
3. Minhas S, Setia N, Pandita S, et al. Prevalence of CYP2C8 polymorphisms in a North Indian population. Genet Mol Res. 2013;12:2260-6.
4. Marwa KJ, Schmidt T, Sjögren M, et al. Cytochrome P450 single nucleotide polymorphisms in an indigenous Tanzanian population: a concern about the metabolism of artemisinin-based combinations. Malar J. 2014;13:420.
5. Aquilante CL, Niemi M, Gong L, et al. PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 8. Pharmacogenet Genomics. 2013;23:721-8.
6. Daily EB, Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. Pharmacogenomics. 2009;10:1489-510.
7. Pechandova K, Buzkova H, Matouskova O, et al. Genetic polymorphisms of CYP2C8 in the Czech Republic. Genet Test Mol Biomarkers. 2012;16:812-6.
8. Jiang H, Zhong F, Sun L, et al. Structural and functional insights into polymorphic enzymes of cytochrome P450 2C8. Amino Acids. 2011;40:1195-204.
9. Suarez-Kurtz G, Genro JP, de Moraes MO, et al. Global pharmacogenomics: Impact of population diversity on the distribution of polymorphisms in the CYP2C cluster among Brazilians. Pharmacogenomics J. 2012;12:267-76.
10. Vicente J, González-Andrade F, Soriano A, et al. Genetic polymorphisms of CYP2C8, CYP2C9 and CYP2C19 in Ecuadorian Mestizo and Spaniard populations: a comparative study. Mol Biol Rep. 2014;41:1267-72.
11. Korytina G, Kochetova O, Akhmadishina L, et al. Polymorphisms of cytochrome p450 genes in three ethnic groups from Russia. Balkan Med J. 2012;29(3):252-60.
12. 1000 Genomes Project. http://phase3browser.1000genomes.org/ access date 28.11.2019
13. Bahadur N, Learth JBS, Mutch E, et al. CYP2C8 polymorphisms in Caucasians and their relationship with paclitaxel 6α-hydroxylase activity in human liver microsomes. Biochem Pharmacol. 2002;64:1579-89.
14. Weise A, Grundler S, Zaumsegel D, et al. Development and evaluation of a rapid and reliable method for cytochrome P450 2C8 genotyping. Clin Lab. 2004;50:141-8.
15. Jernström H, Bågeman E, Rose C, et al. CYP2C8 and CYP2C9 polymorphisms in relation to tumour characteristics and early breast cancer related events among 652 breast cancer patients. Br J Cancer. 2009;101:1817-23.
16. Jaja C, Bowman L, Wells L, et al. Preemptive genotyping of CYP2C8 and CYP2C9 allelic variants involved in NSAIDs metabolism for sickle cell disease pain management. Clin Transl Sci. 2015;8:272-80.
17. Cavaco I, Strömberg-Nörklit J, Kaneko A, et al. CYP2C8 polymorphism frequencies among malaria patients in Zanzibar. Eur J Clin Pharmacol. 2005;61:15-8.
18. Kudzi W, Dodoo AN, Mills JJ. Characterisation of CYP2C8, CYP2C9 and CYP2C19 polymorphisms in a Ghanaian population. BMC Med Genet. 2009;10:124.
19. Muthiah YD, Lee WL, Teh LK, et al. Genetic polymorphism of CYP2C8 in three Malaysian ethnics: *CYP2C8*2* and *CYP2C8*3* are found in Malaysian

Indians. J Clin Pharm Ther. 2005;30:487-90.

20. Nakajima M, Fujiki Y, Noda K, et al. Genetic polymorphisms of CYP2C8 in Japanese population. Drug Metab Dispos. 2003;31:687-90.

21. Dorado P, Cavaco I, Cáceres MC, et al. Relationship between CYP2C8 genotypes and diclofenac 5-hydroxylation in healthy Spanish volunteers. Eur J Clin Pharmacol. 2008;64: 967-70.

22. Barratt DT, Cox HK, Menelaou A, et al. CYP2C8 genotype significantly alters Imatinib metabolism in chronic myeloid leukaemia patients. Clin Pharmacokinet. 2017;56:977-85.

23. Daly AK, Aithal GP, Leathart JB, et al. Genetics susceptibility to diclofenac-induced hepatotoxicity: contribution of UGT2B7, CYP2C8, and ABCC2 genotypes. Gastroenterology. 2007;132:272-81.

24. Lazarska KE, Dekker SJ, Vermeulen NPE, et al. Effect of UGT2B7*2 and *CYP2C8*4* polymorphisms on diclofenac metabolism. Toxicol Lett. 2018;284:70-8.

25. Bergmann TK, Brasch-Andersen C, Gréen H, et al. Impact of *CYP2C8*3* on paclitaxel clearance: a population pharmacokinetic and pharmacogenomic study in 93 patients with ovarian cancer. Pharmacogenomics J. 2011;11:113-20.

26. Henningsson A, Marsh S, Loos WJ, et al. Association of CYP2C8, CYP3A4, CYP3A5, and ABCB1 polymorphisms with the pharmacokinetics of paclitaxel. Clin Cancer Res. 2005;11:8097-104.

27. Marsh S, Somlo G, Li X, et al. Pharmacogenetic analysis of paclitaxel transport and metabolism genes in breast cancer. Pharmacogenomics J. 2007;7:362-5.

28. Niemi M, Leathart JB, Neuvonen M, et al. Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. Clin Pharmacol Ther. 2003;74:380-7.