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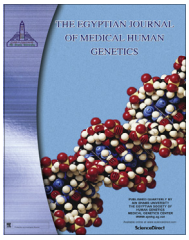

ORIGINAL ARTICLE

Association of CYP3A4 and CYP3A5 polymorphisms with Iranian breast cancer patients

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KEYWORDS

Breast cancer;
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Abstract *Background:* Polymorphisms of different gene have been reported to be associated with cancer including breast cancer. Hospitalization rate for breast cancer has increased over the years in Iran.

Aim: The aim of this study was to examine whether polymorphisms in the CYP3A4 and CYP3A5 genes affect the risk of developing breast cancer.

Subjects and methods: The genotype distribution and allele frequencies of four CYP3A4*1A, CYP3A4*1B, CYP3A5*1 and CYP3A5*3 single-nucleotide polymorphisms were determined in 250 subjects from the general population in Ahvaz city (southwest of Iran) including 200 healthy subjects and 50 individuals affected with breast cancer.

Results and conclusion: The genotype frequency of *CYP3A4*1A/*1A* (A/A) in both case and control groups was 100%; however, there was no subject with either *CYP3A4 * 1A/ * 1B* (A/G) or *CYP3A4*1B/*1B* (G/G) genotype. For *CYP3A5* gene, *CYP3A5*3/*3*mutant homozygote genotype frequency was found to be 99% (n = 198) and 98% (n = 49) in control and patient groups respectively. *CYP3A5*1/*1* wild-type genotype was calculated to be 1% (n = 2) in the control group and 2% (n = 1) in the case group. No. *CYP3A5*1/*3* heterozygote genotype was detected in the both groups. The results showed that there was no association between breast cancer, *CYP3A5* (P-value = 0.561) and *CYP3A4* allele distribution.

1. Introduction

The numerous endogenous compounds such as estrogen and testosterone are metabolized by a heme-containing enzyme named cytochrome P450 (CYP) [1,18]. CYP3A subfamily

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isoforms activate plenty of procarcinogenic polycyclic aromatic hydrocarbon dihydrodiols and metabolize N0-nitrosonornicotine [2]. Polymorphisms of *CYP3A* gene involved in carcinogen metabolism may affect individual variation in cancer susceptibility [3,4] and the response to anticancer therapy [5,6]. Moreover, the CYP3A gene participates in metabolism of many pharmaceutical and recreational drugs; therefore, it has been widely studied in industrialized populations. CYP3A subfamily has two predominant isoforms including CYP3A4 and CYP3A5 enzymes which are expressed in human liver, small intestine jejunum, colon, breast, prostate and pancreas [7–12]. Both genes have variant alleles all occurring at low frequencies in various ethnic populations [13]. Several SNPs affecting enzyme function have been reported for CYP3A5 gene [14].

It has been shown that a frequent single nucleotide polymorphism (SNP) of CYP3A5gene, 6896A > G, is associated with CYP3A5 enzyme production and activity [14]. The G > A mutation in intron 3 of the gene leading to a splice defect of the mRNA produces an unstable and nonfunctional protein. The mutated allele and the wild type were named *CYP3A5*3*(rs776746) and *CYP3A5*1*, respectively. Only individuals carrying at least one *CYP3A5*1* allele can express high levels of CYP3A5 enzyme [15]. *CYP3A5*3* allele on the other hand, causes alternative splicing and blocks protein production resulting in either reduced or lost CYP3A5 enzyme activity [8,16]. CYP3A4 is the major CYP in human hepatic tissue and also expressed in the breast which has an important role in the oxidation of both testosterone (2β-, 6β-, or 15β-hydroxytestosterone) and estrogen (4- and 16α-hydroxylation) [17,18]. *CYP3A4* exhibits a common variant in the 5′-flanking region (−290) designated *CYP3A4*1B*(rs2740574) [19]. In comparison with the wild-type *CYP3A4*1A*, *CYP3A4*1B* shows about a 2-fold increase in enzyme activity [18]. *CYP3A4*1B* leads to an amino acid change resulting in altered protein function and is associated with a variety of cancers including prostate cancer and leukemia in individuals treated with epipodophyllotoxin [20–22]. Although *CYP3A4*1B* causes an amino acid change, there is no significant difference between the *CYP3A4*1B* variant and the wild-type enzymes in the metabolism of testosterone, progesterone, or 7-benzyloxy-4 (trifluoromethyl) coumarin [23]. Not only inter-individual differences in the expression level resulting in tumor development have been connected with *CYP3A5* and *CYP3A4* polymorphisms, but polymorphism frequencies also differ remarkably among different human populations [24,25]. Even though these polymorphisms are well characterized in different populations, there is not enough data about the Iranian ethnic group. Furthermore, the association study of these polymorphisms with breast cancer is the first cross-sectional investigation in the world. The aim of the present study is addition valuable data to association studies of *CYP3A5* and *CYP3A4* with cancer susceptibility. We were going to study the possible association of CYP3A5*3 and CYP3A4*1B SNPs with breast cancer.

2. Subjects and methods

2.1. Subjects

A total of 250 subjects were included in the study consisting of 200 female healthy individuals aged 24–70 years (mean age 44.89 ± 14.30) and 50 unrelated patients suffering from breast cancer aged 20–65 years (mean 41.98 ± 13.91) collected at the Hospitals of Jundishapur University (Ahvaz-southwest of Iran). Ethical approval for this study was obtained from the Ethics Committee of Jundishapur University of Medical Sciences, Ahvaz, Iran.

2.2. Genotype analysis

Whole-blood genomic DNA was extracted using the diatom DNA kit (IsoGene, Russia), according to the manufacturer's recommendations. The DNA quantity and quality were determined by Nano-Drop (ND1000; NanoDrop Technologies, Wilmington, DE) and proved to be implemented efficiently as template for PCR. Then, they were stored at −20 °C until genotyping. To genotype the A6986G polymorphism in the *CYP3A5* gene, polymerase chain reaction (PCR) (Bio-Rad Company – T100™ Thermal Cycler Model) based on the restriction fragment length polymorphism (RFLP) was used as described by Tsuchiya et al. method [26]. The designed primers for *CYP3A5* were F: 5′-ATGGAGAGTGGCATA GGAGATA-3′ and R: 5′-TGTGGTCCAAACAGGGAAGA AATA-3′. Reaction mixtures consisted of 40–50 ng DNA, 1.5 mM master mix, 10 pmol each primer and 1 U Taq polymerase (Qiagen Company), and deionized water to a volume of 25 µl. The PCR for amplifying *CYP3A5* was carried out by the following: initial heating at 94 °C for 10 min, 40 cycles of 94 °C for 30 s, 56 °C for 45 s, and 72 °C for 30 s and a final extension at 72 °C for 5 min. Afterward, the PCR products (130 bp) were digested with restriction enzyme *SspI* (Fermentas, USA, Catalogue number: ER0771). When the A allele of *CYP3A5* was present, it was divided into 107 and

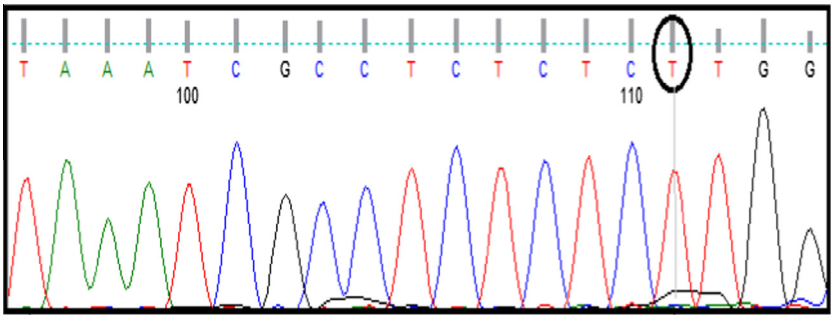

Figure 1 Chromatogram of *CYP3A4*1A* sequence result by Chromas program. Homozygote individuals for A/A genotype present only one peak.

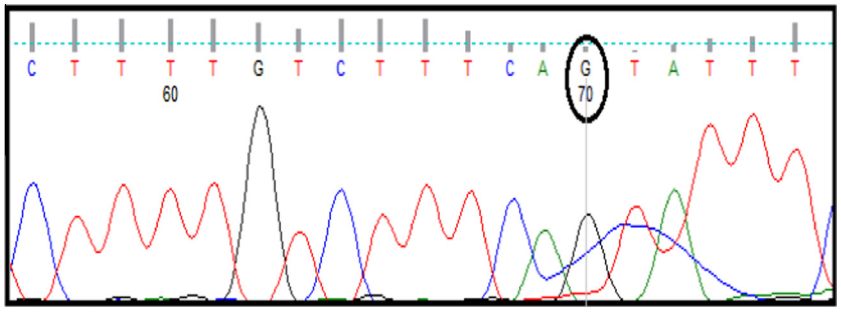

Figure 2 Chromatogram of *CYP3A5*3* sequence result by Chromas program. Homozygote individuals for G/G genotype present only one peak.

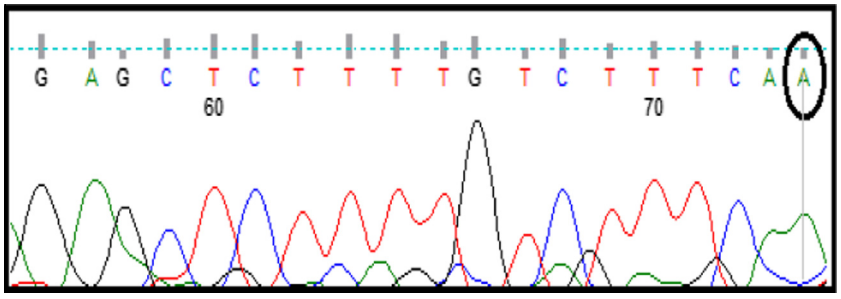

Figure 3 Chromatogram of *CYP3A5*1* sequence result by Chromas program. Homozygote individuals for A/A genotype present only one peak.

23 fragments and visualized by electrophoresis in 2.5% agarose gel. Unlikely, two-step PCR-RFLP assay was carried out for genotyping of a *CYP3A4*1A/B* SNP at the promoter region. First, 319-bp PCR product was produced, then secondary PCR using nested primers amplified 168-bp PCR product. As mentioned earlier, PCR reaction mixtures were prepared. The designed primers used for the first PCR reaction were FI: 5′-CTGGAGCTGTGGCTTGTTGG-3′ and RI: 5′-CGAAGCAGGGCTGGAGCTGC-3′. For amplifying, the PCR conditions were: 95 °C for 1 min for an initial denaturation, 40 cycles of 95 °C for 45 s, 63 °C for 30 s, and 72 °C for 30 s and a final extension at 72 °C for 5:30 min. Nested primers used for the secondary PCR reaction were FII: 5′-GGACAGCCATAGAGACAAGGCCA-3′ and RII: 5′-CACTCACTGACCTCCTTTGAGTTCA-3′. Amplification conditions of the first and second PCR reactions were alike. *Scr*FI restriction enzyme (Fermentas; USA) digestion of the secondary PCR product results in *CYP3A4*1A* homozygote's (168-bp fragment) and *CYP3A4*1B* homozygote's (146-bp and 22-bp fragments) which were shown by 2.5% agarose gel. Several samples were randomly selected and directly sequenced to validate the results of the study (Figs. 1–3).

2.3. Statistical analysis

The χ^2-test was used to determine if the allele and genotype frequencies of polymorphisms fit the Hardy–Weinberg equilibrium and to compare the obtained results between healthy and affected subjects. Analysis was performed with SPSS software (Statistical Package for the Social Sciences, version 18, SSPS Inc., Chicago, IL, USA), with *P*-values < 0.05 as the statistical significance. The obtained results were compared between different populations.

3. Results

In the present study, the allele and genotype frequencies of *CYP3A4*1B/*1A* and *CYP3A5*3/*1* SNPs were determined in 250 subjects from the general population in Ahvaz city

Table 1 Allele and genotype frequencies of CYP3A4 and CYP3A5 genes in breast cancer patients and healthy subjects in Iranian population.

SNP	Patient group (n = 50)		Control group (n = 200)		**p-value for Hardy–Weinberg equilibrium
	*N	%	N	%	
CYP3A5					
*3/*3(G/G)	49	98	198	99	0.561
*1/*3(A/G)	0	0	0	0	
*1/*1(A/A)	1	2	2	1	
CYP3A5*3(G) allele	49	98	198	99	
CYP3A5*1(A) allele	1	2	2	1	
CYP3A4					
*1A/*1A(A/A)	50	100	200	100	
*1A/*1B(A/G)	0	0	0	0	
*1B/*1B(G/G)	0	0	0	0	
CYP3A4*1A(A) allele	50	100	200	100	
CYP3A4*1B(G) allele	0	0	0	0	

* N = population size.
** *P*-values express whether Iranian population is similar to respective populations.

(southwest of Iran) including 200 healthy subjects and 50 individuals affected with breast cancer. The genotype frequency of *CYP3A4*1A/*1A* (A/A) in the both case and control groups was 100%; however, there was no subject with either *CYP3A4 * 1A/ * 1B* (A/G) or*CYP3A4*1B/*1B* (G/G) genotype. Since all subjects had the same genotype (A/A), χ^2-test was not performed in order to statistically analyze the genotype frequencies of *CYP3A4* gene in the studied population. For *CYP3A5* gene, *CYP3A5*3/*3*mutant homozygote genotype frequency was found to be 99% ($n = 198$) and 98% ($n = 49$) in control and patient groups respectively. *CYP3A5*1/*1* wild-type genotype, on the other hand, was calculated to be 1% ($n = 2$) in the control group and 2% ($n = 1$) in the case group. No *CYP3A5*1/*3* heterozygote genotype was detected in both groups.

CYP3A5*3 (G) allele frequencies were 99% in healthy individuals and 98% in patients. Moreover, allele frequency of CYP3A5*1 (A) was 1% and 2% in the control group and patient group respectively. The results showed that there was no statistical difference between cases and control and that the *CYP3A5* (*P*-value = 0.561) and *CYP3A4* genotypes were not detected among certain groups (Table 1).

4. Discussion

Breast cancer is the most prevalent malignancy among Iranian women [27]. Many genetic-conditions such as sickle cell disease and thalassemias are well known in Iran. Therefore it was assumed that genetic conditions may have a significant impact on breast cancer. The present study was conducted to explore the probable association between cancer-related polymorphisms with the risk of breast cancer among Iranian population. In addition, determination of CYP3A4 and CYP3A5 variant alleles and knowledge about their allelic frequency in Iranian population may lead to individualized drug dosing and improved breast cancer therapeutics.

CYP3A5 genotype and allele frequencies were compared between this study and other studies done on different ethnic populations in the world. Iran is a country which has a large population with different ethnic groups; therefore, the studied population in Ahvaz city (southwest of Iran) can be compared to the population investigated in Shiraz city (south of Iran) [27]. The results of χ^2-test showed that there was no significant difference in the genotype frequencies of *CYP3A5* between the two populations (*P*-value = 0.082). The present study was also compared with other Asian populations, and the comparison showed that *CYP3A5* genotype distribution differed from Chinese (*P*-value < 0.0001) [28,29] and Japanese populations (*P*-value < 0.0001) [30]. Genotype frequencies of *CYP3A5* were also significantly different from Europeans such as Poland (*P*-value < 0.0001) [31], Dutch Caucasian (*P*-value < 0.0001) [32], Spain (*P*-value < 0.0001) [33], Bosnia, and Herzegovina (*P*-value < 0.0001) [34]. There were significant differences between this study and the studies on Americans such as American Indians (*P*-value < 0.0001) [35] and Brazilians (*P*-value < 0.0001) [36]. Genotype distribution of *CYP3A5* was also different from African countries, including Cameroon and South Africa (*P*-value < 0.0001) [37] (Table 2). So our study indicated that there were noticeable interethnic variations in the frequencies of alleles and genotype for the *CYP3A5* polymorphisms among Iranian populations and African, American and Asian populations.

CYP3A4 genotype distribution was also compared between Iranian population and other Asians. The χ^2-test results showed that there was considerable similarity genotype distribution of *CYP3A4* gene in the population investigated in Shiraz city. As all subjects in both groups had the (A/A) genotype, no statistical analysis was carried out [27]. In contrast,

Table 2 The comparison between *CYP3A5* genotype and allele frequencies in Iran and other countries.

Population	*N**	*CYP3A5* genotype frequency(%)			*P*-value**	References
		*3/*3 (G/G)	*3/*1 (G/A)	*1/*1 (A/A)		
Asian						
Iranian(Ahvaz city)	200	198	0	2		This study
Iranian(shiraz city)	100	98	2	0	0.082	[27]
Chinese(2005)	302	190	90	2	< 0.0001	[28]
Chinese(2014)	240	116	103	21	< 0.0001	[29]
Japanese	400	242	130	28	< 0.0001	[30]
European						
Poland	100	93	7	0	< 0.0001	[31]
Dutch Caucasian	1000	831	167	2	< 0.0001	[32]
Spanish	163	135	27	1	< 0.0001	[33]
Bosnia& Herzegovina	139	120	19	0	< 0.0001	[34]
American						
American Indian	94	80	13	1	< 0.0001	[35]
Brazilian	799	500	263	36	< 0.0001	[36]
African						
Cameroon	72	0	25	47	< 0.0001	[37]
South African	155	14	41	100	< 0.0001	[37]

* N = population size,
** *P*-values express whether Iranian population is similar to respective populations.

CYP3A4 genotype frequencies were significantly different from Mixed-Ancestry (*P*-value < 0.0001) [38] and Jordanian populations (*P*-value < 0.0001) [39]. The result of Chi-square test demonstrated that the genotype distribution of *CYP3A4* remarkably differed from European countries, including Poland (*P*-value = 0.001) [31] and Bosnia and Herzegovina (*P*-value = 0.001) [34]. There was also a noticeable difference between Iranian and Spanish populations (*P*-value < 0.0001) [33]. In addition, the genotype frequencies of *CYP3A4* were different between this study and American Indian population (*P*-value = 0.003) [35]. The comparison between *CYP3A4* genotype frequencies in this study and the studies on African countries, including Cameroon (*P*-value < 0.0001) [37], South Africa (*P*-value < 0.0001) [37], Xhosa (*P*-value < 0.0001) [38], and Khoisan (*P*-value < 0.0001) [38] showed there was considerable dissimilarity (Table 3). Our study indicated that there were noticeable interethnic variations in the frequencies of alleles and genotype for the *CYP3A4* polymorphisms among Iranian populations and European and African populations.

The allele and genotype frequencies in CYP3A enzymes may contribute greatly to variation in oral bioavailability and systemic clearance of CYP3A substrates including numerous common therapy drugs and endogenous molecules such as the oxidation of testosterone and the hydroxylation of estrogens [40]. There was a difference in the frequencies of breast cancer in different ethnic groups. Epidemiological evidence reported the relationship of breast cancer frequency (cases per 100,000). The alleles and genotypes frequencies were found significantly different among African, American, Asian and Caucasian populations [40]. The incidence of breast cancer in Iranian women was 22 per 100,000 and the incidence rate of breast cancer in Iran was raised to 93 cases per 100,000 in 2013 [41]. This incidence (in 2007) was less than the incidence rate in African, American, Asian and Caucasian populations (Fig. 4) [40]. Although few studies have investigated a role for CYP3A enzymes activity in breast cancer risk, taken together, previous studies suggest evidence that the major polymorphic variants in CYP3A4 may be associated with steroid metabolism related to breast cancer.

CYP3A4*1B in Iranian population is lower than its frequencies in Hispanic population (0.000 in this study). Frequencies of the CYP3A4*1B variant among African Americans is 0.817, among Caucasian is 0.096, among Hisponish is 0.107, among Asian is 0.000 and unknown in Native Americans. The five populations frequencies of CYP3A4*1B are poorly correlated with breast cancer incidence (*P*-value > 0.1). The results show no association with breast cancer and CYP3A4*1B polymorphism and comparison between Incidence rates of breast cancer in five different ethnic groups, therefore there is no association between breast cancer and frequency of CYP3A4 enzymes activity in most populations.

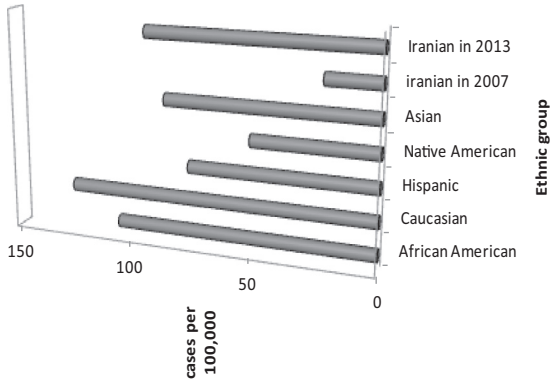

Figure 4 Comparison between Incidence rates of breast cancer in five different ethnic groups and Iranian population.

Table 3 The comparison between *CYP3A4* genotype and allele frequencies in Iran and other countries.

Population	*N*[*]	*CYP3A4* genotype frequency (%)			*P*-value[**]	References
		*1A/*1A (A/A)	*1A/*1B (A/G)	*1B/*1B (G/G)		
Asian						
Iranian(Ahvaz city)	200	200	0	0		This study
Iranian(shiraz city)	100	100	0	0	–	[27]
Jordanian	173	161	12	0	< 0.0001	[39]
Mixed-Ancestry	65	19	32	14	< 0.0001	[38]
European						
Poland	100	95	5	0	0.001	[31]
Spanish	163	149	14	0	< 0.0001	[33]
Bosnia& Herzegovina	138	131	7	0	0.001	[34]
American						
American Indian	94	90	4	0	0.003	[35]
African						
Cameroon	69	41	26	2	< 0.0001	[37]
South African	153	78	47	28	< 0.0001	[37]
Xhosa	65	5	25	35	< 0.0001	[38]
Khoisan	29	2	10	17	< 0.0001	[38]

[*] N = population size.
[**] *P*-values express whether Iranian population is similar to respective populations.

5. Conclusion

In conclusion, the results obtained show that 98% of our sample do not carry a mutant allele. Ethnic and geographic differences may explain discrepancies in the prevalence of *CYP3A4* and *CYP3A5* polymorphisms. Genotype distribution studies could provide valuable information to help further investigations of association between polymorphisms and several types of cancer. A large database may allow for a more precise estimate of these associations.

6. Conflict of interest

We have no conflict of interest to declare.

Acknowledgments

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References

[1] Nelson DR, Koymans L, Kamataki T, et al. P450 super-family: update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics 1996;6(1):1–42.
[2] Patten CJ, Smith TJ, Friesen MJ, Tynes RE, Yang CS, Murphy SE. Evidence for cytochrome P450 2A6 and 3A4 as major catalysis for N′-nitrosonornicotine a-hydroxylation by human liver microsomes. Carcinogenesis 1997;18(8):1623–30.
[3] Gonzalez FJ. The role of carcinogen-metabolizing enzyme polymorphisms in cancer susceptibility. Reprod Toxicol 1997;11(2–):397–412.
[4] Wenzlaff AS, Cote ML, Bock CH, Land SJ, Santer SK, Schwartz DR, et al. CYP1A1 and CYP1B1 polymorphisms and risk of lung cancer among never smokers: a population-based study. Carcinogenesis 2005;26(12):2207–12.
[5] McFadyen MC, Melvin WT, Murray GI. Cytochrome P450 enzymes: novel options for cancer therapeutics. Mol Cancer Ther 2004;3:363–71.
[6] Murray GI. The role of cytochrome P450 in tumour development and progression and its potential in therapy. J Pathol 2000;192:419–26.
[7] Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 caucasians. J Pharmacol Exp Ther 1994;270(1):414–23.
[8] Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001;27(4):383–91.
[9] Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL, et al. Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. J Pharmacol Exp Ther 1997;283(3):1552–62.
[10] Koch I, Weil R, Wolbold R, Brockmoller J, Hustert E, Burk O, et al. Interindividual variability and tissue-specificity in the expression of cytochrome P450 3A mRNA. Drug Metab Dispos 2002;30(10):1108–14.
[11] Lamba J, Hebert JM, Schuetz EG, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for CYP3A5. Pharmacogenet Genomics 2012;22:555–8. http://dx.doi.org/10.1097/fpc.0b013e328351d47f.
[12] Lee SJ, Goldstein JA. Functionally defective or altered *CYP3A4* and *CYP3A5* single nucleotide polymorphisms and their detection with genotyping tests. Pharmacogenomics 2005;6:357–71. http://dx.doi.org/10.1517/14622416.6.4.357.
[13] Zeng Z, Andrew NW, Arison BH, Luffer-Atlas D, Wang RW. Identification of cytochrome P4503A4 as the major enzyme responsible for the metabolism of ivermectin by human liver microsomes. Xenobiotica 1998;28(3):313–21.
[14] Tsuchiya N, Satoh S, Tada H, Li Z, Ohyama C, Sato K, et al. Influence of CYP3A5 and MDR1 polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplantation 2004;78(8):1182–7.
[15] Hustert E, Haberl M, Burk O, Wolbold R, He YQ, Klein K, et al. The genetic determinants of the CYP3A5 polymorphism. Pharmacogenetics 2001;11(9):773–9.
[16] Ho H, Pinto A, Hall SD, Flockhart DA, Li L, Skaar TC, et al. Association between the CYP3A5 genotype and blood pressure. Hypertention 2005;45(2):294–8.
[17] Niwa T, Yabusaki Y, Honma K, et al. Contribution of human hepatic cytochrome P450 isoforms to regioselective hydroxylation of steroid hormones. Xenobiotica 1998;28:539–47.
[18] Waxman DJ, Attisano C, Guengerich FP, et al. Human liver microsomal steroid metabolism. Identification of the major microsomal steroid hormone 6 beta-hydroxylase cytochrome P-450 enzyme. Arch Biochem Biophys 1988;263:424–36.
[19] Raucy JL. Regulation of CYP3A4 expression in human hepatocytes by pharmaceuticals and natural products. Drug Metab Dispos 2003;31(5):533–9.
[20] Lamba JK, lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev 2002;54(10):1271–94.
[21] Rebbeck TR, Jaffe JM, Walker AH, Wein AJ, Malkowicz SB. Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4. J Natl Cancer Inst 1998;90(16):1225–9.
[22] Felix CA, Walker AH, Lange BJ, Williams TM, Winick NJ, Cheung NK, et al. Association of CYP3A4 genotype with treatment-related leukemia. Proc Natl Acad Sci U.S.A. 1998;95(22):13176–81.
[23] Eiselt R, Domanski TL, Zibat A, Mueller R, Presecan-siedel E, Huster E, et al. Identification and functional characterization of eight CYP3A4 protein variants. Pharmacogenetics 2001;11(5):447–58.
[24] Bolt HM, Roos PH, Their R. The cytochrome P-450 isoenzyme CYP2E1 in the biological processing of industrial chemicals: consequences for occupational and environmental medicine. Int Arch Occup Environ Health 2003;76:174–85.
[25] Ghazaleh SH, Hamid G, Amir J, Fatemeh Z, Seyed A, Mohammad A. CYP2E1*5B, CYP2E1*6, CYP2E1*7B, CYP2E1*2, and CYP2E1*3 Allele Frequencies in Iranian Populations. Asian Pacific J Cancer Prev 2012;13(12):6505–10.
[26] Ko Y, Abel J, Harth V, Brod P, Antony C, Donat S, et al. Association of CYP1B1 codon 432 mutant allele in head and neck squamous cell cancer is reflected by somatic mutation of p53 in tumor tissue. Cancer Res 2001;61(11):4398–404.
[27] Negar A, Mohammad Javad A, Bigan KH, Masumeh D, Afsoon H, Elham A. Study the polymorphism of CYP3A5 and CYP3A4 loci in Iranian population with laryngeal squamous cell carcinoma. Mol Biol Rep 2011;38:5443–8.
[28] Yong-Fang H, Jun H, Guo-Lin Ch, Dan W, Zhong-Qi L, Che Zh, et al. CYP3A5*3 and CYP3A4*18 single nucleotide polymorphisms in a Chinese population. Clin Chim Acta 2005;353:187–92.
[29] Chuan-Jiang L, Liang L, Li L, Hai-Xai J, Ze-Yan Zh, Wei-Mo L, et al. Impact of the CYP3A5, CYP3A4, COMT, IL-10 and POR genetic polymorphisms on tacrolimus metabolism in Chinese renal transplant recipients. PLos One 2014;9(1):e86206.

[30] Fukuen S, Fukuda T, Maune H, Ikenaga Y, Yamamoto I, Inaba T, et al. Novel detection assay by PCR-RFLP and frequency of the CYP3A5 SNPs, CYP3A5*3 and *6, in a Japanese population. Pharmacogenetics 2002;12:331–4.
[31] Dorota Z, Janusz W, Leszek P. Impact of CYP3A4*1B and CYP3A5*3 polymorphisms on the pharmacokinetics of cyclosporine and sirolimus in renal transplant recipients. Ann Transplant 2012;17(93):36–44.
[32] Van Schaik RH, Van der Heiden IP, Van den Anker JN, Lindemans J. CYP3A5 variant allele frequencies in Dutch Caucasians. Clin Chem 2002;48:1668–71.
[33] Guillermo G, Elena G, Jose M, Rosa P, Javier S, Carmen M, et al. Genetic variability in CYP3A4 and CYP3A5 in primary liver, gastric and colorectal cancer patients. BMC Cancer 2007;7:118.
[34] Sabina S, Tanja D, Barbara O, Besim P, Tamer B, Maja M, et al. Analysis of CYP3A4*1B and CYP3A5*3 polymorphisms in population of Bosnia and Herzegovina. Med Glas Ljek Komore Zenico-doboj Kantona 2011;8(1):84–9.
[35] Alison F, LeeAnna LM, Melissa A, Andrea G, Adam G, et al. Pharmacogenetics in American Indian Populations: analysis of CYP2D6, CYP3A4, CYP3A5, and CYP2C9 in the confederated Salish and Kootenai tribes. Pharmacogenet Genomics 2014;23(8):403–14.
[36] Guilherme S, Daniela DV, Ana Beatriz S, Mara H, Maria E, et al. Globa l pharmacogenomics: distribute ion of CYP3A5 polymorphisms and phenotypes in the Brazilian population. PLoS One January 2014;9(1):e83472.
[37] Marelize S, Michelle S, Ambroise W, Luke KR, Nyasha C, Dandara Collet. CYP1A2, CYP2A6, CYP2B6, CYP3A4 and CYP3A5 polymorphisms in two Bantu-speaking populations from Cameroon and South Africa: implications for global pharmacogenetics. Curr Pharmacogenomics Personalized Med 2012;10:43–53.
[38] Britt D, Marieth P, Lundi K, Gloudi A, Anke D, Dana N. Characterization of the genetic variation present in CYP3A4 in three South Africa populations. Front Genet 2013;4.
[39] Al-Motassem Y, Bulatova Nailya R, William N, Nancy H, Said I, Hisham Q, et al. Allele and genotype frequencies of the polymorphic cytochrome P450 genes (CYP1A1, CYP3A4, CYP3A5, CYP2C9 and CYP2C19) in the Jordanian population. Mol Biol Rep 2012;39(10):9423–33.
[40] Keshava C, McCanlies EC, Weston A. CYP3A4 polymorphisms—potential risk factors for breast and prostate cancer: a HuGE review. Am J Epidemiol 2004;160:825–41.
[41] Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, et al. Breast cancer in Iran: an epidemiological review. Breast J 2007;13(4):383–91.