Mol Biol Rep (2012) 39:9423–9433
DOI 10.1007/s11033-012-1807-5

Allele and genotype frequencies of the polymorphic cytochrome P450 genes (*CYP1A1*, *CYP3A4*, *CYP3A5*, *CYP2C9* and *CYP2C19*) in the Jordanian population

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Received: 20 December 2011 / Accepted: 9 June 2012 / Published online: 22 June 2012

Abstract Drug metabolizing enzymes participate in the neutralizing of xenobiotics and biotransformation of drugs. Human cytochrome P450, particularly *CYP1A1*, *CYP2C9, CYP2C19*, *CYP3A4* and *CYP3A5,* play an important role in drug metabolism. The genes encoding the CYP enzymes are polymorphic, and extensive data have shown that certain alleles confer reduced enzymatic function. The goal of this study was to determine the frequencies of important allelic variants of *CYP1A1*, *CYP2C9, CYP2C19, CYP3A4* and *CYP3A5* in the Jordanian population and compare them with the frequency in other ethnic groups. Genotyping of *CYP1A1*(m1 and m2), *CYP2C9* (*2 and *3), *CYP2C19* (*2 and *3), *CYP3A4*5*, *CYP3A5* (*3 and *6), was carried out on Jordanian subjects. Different variants allele were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP). *CYP1A1* allele frequencies in 290 subjects were 0.764 for *CYP1A1*1*, 0.165 for *CYP1A1*2A* and 0.071 for *CYP1A1*2C*. *CYP2C9* allele frequencies in 263 subjects were 0.797 for *CYP2C9*1*, 0.135 for *CYP2C9*2* and 0.068 for *CYP2C9*3*. For *CYP2C19*, the frequencies of the wild type (*CYP2C19*1*) and the nonfunctional (*2 and *3) alleles were 0.877, 0.123 and 0, respectively. Five subjects (3.16 %) were homozygous for *2/*2. Regarding *CYP3A4*1B*, only 12 subjects out of 173 subjects (6.9 %) were heterozygote with none were mutant for this polymorphism. With respect to *CYP3A5*, 229 were analyzed, frequencies of *CYP3A5*1,*3 and *6 were 0.071, 0.925 and 0.0022, respectively. Comparing our data with that obtained in several Caucasian, African-American and Asian populations, Jordanians are most similar to Caucasians with regard to allelic frequencies of the tested variants of *CYP1A1*, *CYP2C9, CYP2C19, CYP3A4* and *CYP3A5*.

Keywords Polymorphism · Genotype · Alleles frequencies · Jordanian population · CYP450

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Introduction

The cytochrome P450 enzymes (CYP) play a central role in the metabolism of many therapeutic agents. Differences in the activities of these enzymes are thought to be responsible for individual variability in response and/or toxicity to numerous drugs. Among the CYP enzymes many isoforms exhibit genetic polymorphisms; examples include 1A1, 2C9, 2C19, 3A4, and 3A5. Different populations and different ethnicities differ greatly in the genotype and allele frequencies of many of the metabolizing enzymes including the CYP enzymes.

The *CYP1A1* gene, located on chromosome 15q24.1. It comprises seven exons and six introns and encodes a 512–amino acid protein [1]. It plays a key role in phase I metabolism of polycyclic aromatic hydrocarbons to their ultimate DNA-binding forms [2]. A great part of the inter-individual and inter-ethnic differences in relation to

xenobiotic effects is now attributable to genetic differences in their metabolism [3–5].

Three restriction fragment length polymorphic (RFLP) variants have received the most attention: m1 (*MspI* RFLP-*CYP1A1**2A-(T6235C)-rs4646903); m2 (*Bsrd1* RFLP-*CYP1A1**2C-(A4889G)-rs1048943- Ile462Val); and m3 (*MspI* RFLP-*CYP1A1**3-(T5639C)-rs4986883). The rare *Val* and *M2* alleles of the *CYP1A1* gene have been associated with increased individual cancer risk [6, 7]. Ethnic differences have been observed in the distribution of the *CYP1A1* polymorphic genotypes [8] with the m1 and m2 polymorphisms being much more frequent in Asians compared to Caucasians and African-Americans [9, 10].

CYP2C9 and *CYP2C19* enzymes constitute 50 %, and 16 %, respectively of the CYP2C subfamily [11]. The two genes are located on chromosome 10q24 [12]. *CYP2C9* is a phase I drug-metabolizing CYP450 enzyme isoform [13], it is responsible for the catalyses of the oxidation and metabolic clearance of up to 15–20 % of clinically important drugs [14, 15] including phenytoin, warfarin, tolbutamide, losartan, and a large number of nonsteroidal anti-inflammatory-drugs [16, 17]. Changes in amino acids in this enzyme can affect its activity and produce individual variability in the concentration and/or dosage requirements of prototypic *CYP2C9* substrates as warfarin and clopidogrel, respectively [18, 19].

The gene coding for the *CYP2C9* enzyme is highly polymorphic, including functional variants of major pharmacogenetic importance. Thirteen variant alleles have been reported to date [13]; however, only two amino acids substitutions, the non-synonymous variants *CYP2C9*2* (rs1799853-Arg144Cys) and *CYP2C9*3* (rs1057910-Ile359Leu), are recognized in humans as main *CYP2C9* variants [17, 20]. *CYP2C9*2* and *CYP2C9*3* have reduced catalytic activity compared with wild type (*CYP2C9*1*) [21, 22]. The frequency of *CYP2C9* allelic variants has been reported to differ among Caucasian, African, and Asian populations. The allele frequencies of *CY2C9*2* and *CYP2C9*3* tend to be greater in Caucasian populations than in African-American and Asian populations [20–24]. The *CYP2C9*2* allelic variant was not found in East Asians including Chinese and Japanese [23, 24].

CYP2C19 metabolizes several therapeutically important drugs, namely omeprazole, lansoprozole, imipramine, clopidogrel and diazepam [25, 26]. Among different variants, two alleles with separate mutations have been associated with defective enzyme in Caucasian. The first is *CYP2C19*2* (rs4244285-G681A/C), which has a mutation in exon 5 causing a splice site. The other variant allele is *CYP2C19*3* (rs4986893-G636A) with a point mutation in exon 4 producing a premature stop codon. The most commonly mutated allele is *CYP2C19*2* in Caucasian poor metabolizers (PMs) [27] whereas, *CYP2C19*3*, is rare among Caucasian subjects [28].

The *CYP3A* locus consists of four genes, *CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43*, all of which reside in a 231-kb region of chromosome 7q21.1 [29]. In adults, *CYP3A4* and *CYP3A5* are predominant among the four known isoforms whether in liver or intestine [30]. All genes show high degree of polymorphic expression [31]. Genetic variation within the *CYP3A* genes may contribute to inter-individual variability in drug metabolism. It has been suggested up to 60 % of the variability in *CYP3A4* activity may be because of a genetic component [32]. The most prevalent polymorphism in *CYP3A4* is (*CYP3A4*1B*) (rs2740574) occurs in the 5 V flanking region of the gene, it involves an A > G transition at -293 position from the transcription start site [33]. Large ethnic differences have been reported in this single nucleotide polymorphism (SNP) [30, 33].

CYP3A5 is expressed in a polymorphic manner in 10–29 % of adult livers [34, 35]. Several polymorphic variants in *CYP3A5* (chromosome 7q22.1) appear to have a functional effect on CYP3A5 activity. *CYP3A5*3* (rs776746) polymorphism occurs in intron 3 of *CYP3A5*, creating a cryptic splice site leading to the inclusion of a novel exon, and ultimately a premature stop codon, which leads eventually to very low amount of CYP3A5 protein [35, 36]. The *CYP3A5* allele 6986A > G (*CYP3A5*3*) is associated with reduced clearance of drugs such as simvastatin, lovastatin, midazolam, cyclosporine and tacrolimus [33, 37, 38].

The expression of *CYP3A5* can be reduced by quite a few other alleles in addition to *CYP3A*3*. The *CYP3A5*6* (rs10264272) is a 14690G > A synonymous mutation (Lys–Lys) that causes the formation of a splice variant mRNA. Exon 7 is deleted, resulting in a frame shift and a truncated protein [36]. The frequency of this SNP have been found to be 17 % in African–Americans and is absent in Asians [33].

The frequencies of the important allelic variants in the *CYP1A1*, *CYP3A4, CYP3A5 CYP2C9* and *CYP2C19,* genes have been studied in many ethnicities, and the data, so far, show striking interethnic variation in the distribution of these variants. However, no information is available for the Jordanian population. In the present study, we report here the allele frequencies of *CYP1A1* (*2A and *2C), *CYP2C9* (*2 and *3), *CYP2C19* (*2 and *3), *CYP3A4*1B*, and *CYP3A5* (*3 and *6), in a sufficiently large sample of the Jordanian population, providing a basis for future clinical studies concerning variability in the response and/or toxicity to drugs known to be substrates for these enzymes and proteins. To our knowledge this is the first genotyping study of cytochrome P450 polymorphisms in the Jordanian population reported to date.

While native Jordanians are mostly descended from people of villagers and Bedouin descent originating in the

Table 1 List of the primers, PCR conditions and restriction enzymes used in the identification of the designated SNPs

SNPs of interest	Primers sequence	PCR conditions[a]	Enzyme[b]
*CYP3A4*B*	F: gacagccatagagacaagggga	Annealing temp 60 °C	*MboII*
	R: ggtttccatggccaagtctg		
*CYP3A5*3*	F: catgacttagtagacagatga	Annealing temp 55 °C	*SspI*
	R: ggtccaaacagggaagaaata		
*CYP3A5*6*	F: tggaagatgattcagcagatagt	Annealing temp 55 °C	*DdeII*
	R: gtggggtgttgacagctaaag		
*CYP1A1*2A*	F[c]: ggctgagcaatctgacccta	Annealing temp 63 °C	*MspI*
	R[c]: taggagtcttgtctcatgcct		
*CYP1A1*2C*	F[c]: ctgtctccctctggttacaggaagc		*BsrdI*
	R[c]: ttccacccgttgcagcaggatagcc		
*CYP2C9*2*	F: gatggaaaacagagacttacaga	Annealing temp 58 °C	*Sau69I*
	R: cacacacagcacaaatatgt		
*CYP2C9*3*	F: tgcacgaggtccagagatgc	Annealing temp 60 °C	*NsiI*
	R: gatactatgaatttgggacttc		
	F: tgcacgaggtccagaggtac		*KpnI*
	R: gatactatgaatttgggacttc		
*CYP2C19*2*	F: gcttttatactatcaaaagcagg	Annealing temp 58 °C	*AVaI*
	R: gtaaacacaaaactagtcaatg		
*CYP2C19*3*	F: atcatttagcttcaccctgtga	Annealing temp 60 °C	*NiaIV*
	R: gg gattctagctgatgagacag		

[a] PCR conditions; first denaturation at 95 °C for 5 min, then 35–40 cycles of denaturation (95 °C for 1 min), annealing and extension (72 °C for 1 min). A final extension step at 72 °C for 10 min was done

[b] Manufacturer condition were followed

[c] Reference of primer design is based on Cascorbi et al. [46]

Arabian Peninsula [39], ethnically, the Jordanians represent a mixed stock. Most of the population is Arab (approximately 98 %) with 1 % of the population is Armenian, and another 1 % is Circassian. There are also small Kurd, Druze, and Chechen minorities [40, 41].

Methods

Subjects

Apparently healthy unrelated Jordanian subjects that participated in different genotyping studies were selected from many hospitals (Jordan University hospital, Al-Bashair Hospital and Royal medical service). Each subject gave a sample of about 1 ml of blood after detailed explanation of the purpose of the study; a consent form was also obtained from each subject. Genomic DNA was isolated from the blood using Wizard Genomic® (DNA purification kit) (Promega Corporation, USA). The isolated DNA samples were prepared for genotyping.

Genotyping

Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) that were used to identify different single nucleotide polymorphisms (SNPs) (CYP1A1 (m1 (*2A) and m2 (*2C)), CYP2C9 (*2 and *3), CYP2C19 (*2 and *3), CYP3A4*1B, CYP3A5 (*3 and *6), primers, restriction enzymes and the condition of PCR are summarized in Table 1. Findings of the PCR-RFLP were validated by:

*Every time PCR reactions were done a negative control was run simultaneously. A negative control contains all PCR components except the DNA template.
*The sequence of the reverse, forward or both primers of (CYP2C9, CYP2C19, CYP3A4, and CYP3A5) differed from original nucleotide sequence at that region of the genomic DNA, to create an internal control site (ICS). The ICS serves to make sure that when the restriction enzyme dose not cut, it does so because of the sequence and not because it is not functioning properly. If the restriction enzyme is functional, it will always cut the PCR product at ICS irrespective of sequence of SNP.
*Around 15 % of all samples were repeated to confirm findings of the PCR-RFLP.
*The PCR-RFLP results (CYP3A4, and CYP3A5) were confirmed by direct DNA sequencing using BigDye Terminator Cycle Sequencing on 3730xl DNA sequencer (Macrogene® Co., Korea).

Statistical analysis

Allele and genotype frequencies for different alleles among Jordanian population were estimated from the results of the above PCR-RFLP test. This estimation was according to formulas reported previously [42]. Genotype and allele frequency were matched to expectation by Hardy-Weinberg

Table 2 Demographic data for all subjects enrolled in the presents study

SNP studied	Number	Age	Gender (number)	
		Mean ± SD	Men	Women
CYP1A1	290	58.91 ± 11.81	162	128
CYP2C9	263	58.37 ± 13.45	136	127
CYP2C19	158	47.65 ± 12.20	125	33
*CYP3A4*1B*	173	37.7 ± 11.99	115	58
CYP3A5	229	34.62 ± 11.69	166	63

Equilibrium, differences in allele frequencies between Jordanians and other ethnic populations were assessed using χ^2 test [43]. A p value below 0.05 was considered statistically significant throughout the population comparisons. Table 2

The minimum sample size needed to accomplish the objectives of the study was calculated based on the following equation [44]

$$N = P * Q\ (Z_\alpha + Z_\beta)^2/\Delta^2$$

where N is the sample size needed; P is the reported frequency of the allele at that SNP; Q is (1 − P); Z_α is the critical value at type 1 error; Z_β is the critical value at type 2 error; and Δ is the acceptable margin of error.

Based on previously reported frequencies among Caucasians and assuming $\alpha = 5$ % and $\beta = 20$ % and $\Delta = 4$ to 5 %, then the minimum sample size needed for estimation of the less-frequent allele type of *CYP1A1, CYP2C9, CYP2C19, CYP3A4* and *CYP3A5* was 242, 218, 143, 156, and 207 respectively.

Results

CYP1A1

The frequencies of *CYP1A1* alleles among 290 Jordanian subjects were as follows; *CYP1A1*1* (76.4 %), *CYP1A1*2A* (16.6 %) and *CYP1A1*2C* (7.1 %). The distribution of *CYP1A1* genotypes is summarized in Table 3.

CYP2C9

The frequencies of *CYP2C9* alleles among 263 Jordanian subjects were as follows; *CYP2C9*1* (79.7 %), *CYP2C9*2* (13.5 %), and *CYP2C9*3*(6.8 %). The distribution of *CYP2C9* genotypes is summarized in Table 3.

CYP2C19

The frequencies of *CYP2C19* alleles among 158 Jordanian subjects were as follows; *CYP2C19*1* (87.65 %), *CYP2C19*2* (12.35 %), and *CYP2C19*3*(0). The distribution of *CYP2C19* genotypes is summarized in Table 3.

Table 3 The observed and expected genotype distribution of the tested variants among the Jordanian subjects according to Hardy–Weinberg equilibrium

Tested gene	Observed (*N*)	Expected (*N*)	*p*-value
CYP1A1	290		
*1/*1	200	201	0.53
*1/*2A	51	49	
*2A/*2A	2	3	
*1/*2C	3	3	0.92
*2C/*2C	0	0	
1/*2A/*2C	28		
*2A/*2C	6		
CYP2C9	263		
*1/*1	165	166	1
*1/*2	57	57	
*2/*2	5	5	
*1/*3	32	30	0.2
*3/*3	0	1	
*2/*3	4		
CYP2C19	158		
*1/*1	124	122	0.056
*1/*2	29	34	
*2/*2	5	2	
*1/*3	0	*	
*3/*3	0	*	
*2/*3	0		
*CYP3A4*1B*	173		
*1/*1	161	161.2	0.66
*1/*1B	12	11.6	
*1B/*1B	0	0.2	
CYP3A5	229		
*1/*1	4	1	0.0034
*1/*3	24	30	
*3/*3	200	197	
*1/*6	1	1	0.8
*6/*6	0	0	
*3/*6	0		

Differences between observed and expected were measured by χ^2 test

N total number of subjects

p value ≤ 0.05 indicates deviation of Hardy–Weinberg

*CYP3A4*1B*

Among 173 subjects tested, 161 were homozygous for wild type allele (*CYP3A4*1/*1*, 93.1 %) and 12 individuals were heterozygous for variant allele (*CYP3A4*1B/*1*,

6.9 %). No homozygote was detected in the study samples. Thus, the allele frequency of the *CYP3A4*1B* variant allele among Jordanian population is 3.5 % (Table 3).

CYP3A5

The frequencies of *CYP3A5* alleles among 229 Jordanian subjects were as follows; *CYP3A5*1* (7.2 %), *CYP3A5*3* (92.58 %), *CYP3A5*6* (0.22 %). The distribution of *CYP3A5* genotypes is summarized in Table 3.

All loci examined were in consistent with HWE, with the exception of one loci *CYP3A5*3* (Table 3).

Discussion

CYP1A1

Ethnic differences in *CYP1A1* polymorphisms have been previously reported [3–5, 45] and our results corroborate the ethnic difference in the allelic frequency of *CYP1A1* between Caucasians and Africans (Table 4). The frequency of *CYP1A1* mutations varies among different ethnic groups, with a high prevalence of m1 and m2 in Far East Asian populations and a low rate in Caucasians [46–48]. The m2 is found always linked with m1 [46, 48]. *CYP1A1* allele *2B, containing mutations m1 and m2, was identified to place the carrier at increased risk for lung cancer [46, 49, 50] and both (*2A and *2C) are also known to increase risk for lung cancer [6, 7]. In the current study, both polymorphisms *2A/*2C were found to be carried in 34 subjects (using RFLP). All examined loci of *CYP1A1* were consistent with HWE.

Our results show that the prevalence of *CYP1A1*2A*, and **2C* were closest to the one reported for the Turkish population (Table 4). The observed genotype and allele type is quite different from Asians and Africans.

CYP2C9

The frequency of the *CYP2C9*2* allele in the Jordanian population was 13.5 % which is in a range comparable with other Caucasian populations (Table 5); 8 % in American, 12.5 % in British [20], and 10.6 % in Turkish [51]. It was reported that the *CYP2C9*2* allele occurs at a significantly lower frequency in the African-American population (1 %) [18]. In contrast, the *CYP2C9*2* allele was reported to be absent or at least very rare in the East Asian populations [52, 53].

The *CYP2C9*3* allele occurred with a frequency of 6.8 % in the Jordanian subjects. This finding is similar to that of other Caucasian populations in which the frequency of the *CYP2C9*3* allele was reported to be 6 % in American, 8.5 % in British and 10.0 % in Turkish (Table 5). Lower frequencies were reported for the *CYP2C9*3* variant in East Asian populations; 1.1–2.1 % in Japanese [52] and Korean [53] and the lowest frequency of *CYP2C9*3* was reported in African-Americans (0.5 %) [20].

Warfarin is an oral anti-coagulant with narrow therapeutic index. It has been recommended that the initial dose and dose adjustment should be based on the genetic polymorphism of *CYP2C9* in addition to *VKORC1* [54]. Patients with *CYP2C9*2* and **3* variants have longer times to dose stabilization and are at higher risk of serious and life-threatening bleeding [55]. The high prevalence of *CYP2C9*2and *3* alleles among Jordanians clearly indicates the benefits of genetic testing of *CYP2C9* in warfarin dosing, allowing physicians to identify patients at high risk for warfarin hyper responsiveness. In addition, our data could be extrapolated to other drugs metabolized by the *CYP2C9.*

CYP2C19

The genetic polymorphism of *CYP2C19* has been shown to have the most interethnic variation with PM frequency

Table 4 Comparison of allele frequencies of *CYP1A1* reported from different ethnic populations

Population	Allele frequency				*p* value	References
	N	*1/*1	*2A	*2C		
Jordanian	290	76.4 %	16.2 %	7.4 %		Current study
Caucasians						
Spanish	265	88.7 %	9.8 %	1.5 %	<0.0001	[7]
Turkish	271	73 %	18.1 %	8.9 %	0.62	[74]
German	880	89.5 %	7.7 %	2.8 %	<0.0001	[46]
Africans	445	77.6 %	21.8 %	0.6 %	<0.0001	[45]
Asians						
Chinese	404	38.9 %	35.5 %	25.6 %	<0.0001	[75]
India (Kashmir)	163	43.1 %	30.3 %	26.6 %	<0.0001	[6]
African-American	278	73.3 %	23.7 %	3.0 %	<0.0001	[76]

Differences in allele frequencies were measured by χ^2 test

N total number of subjects, *NR* not reported

Table 5 Comparison of allele frequencies of *CYP2C9* reported from different ethnic populations

Population	Frequency (p value vs. Jordanian)				p value	References
	N	*1	*2	*3		
Jordanian	263	0.797	0.135	0.068		Current study
Caucasians						
American	100	0.86	0.08	0.06	0.169	[20]
British	100	0.79	0.125	0.085	0.787	[17]
German	118	0.81	0.14	0.05	0.783	[77]
Turkish	499	0.794	0.106	0.100	0.166	[51]
Italian	157	0.80	0.11	0.090	0.593	[78]
Asians						
Japanese	218/140	0.979/0.963	0	0.021/0.036	<0.0001	[51, 52]
Koreans	574	0.989	0	0.011	<0.0001	[53]
Egyptian	247	0.818	0.12	0.062	0.773	[51]
Iranian	200	0.872	0.128	0	0.001	[79]
African-Americans	226	0.970	0.011	0.018	<0.0001	[18]
African						
Ethiopians	150	0.94	0.04	0.02	0.001	[78]
Ghanaian	204	1.00	0	0	<0.0001	[80]

N total number of subjects

Differences in allele frequencies were measured by χ^2 test

ranges from 2 to 7 % in Caucasians, to 14–25 % in Asians [51]. In the present study, we found that the incidence of *CYP2C19*2* among Jordanians (12.3 %) was similar to that found in other Caucasian populations, in Europe, and in Saudi Arabia [56]. Higher frequencies of *CYP2C19*2* were reported for Asian populations [56], Africans and African Americans [51] (Table 6)

The presence of *CYP2C19*3* in one Jordanian subject (0.0) was consistent with other Caucasian populations (Table 6). *CYP2C19*3* has been regarded as an Asian mutation and accounted for the remaining alleles in Asian PMs [51].

The importance of genotyping *CYP2C19 *2* and **3* has been highlighted by the United States Food and Drug Administration (FDA) which recommends that Clopidogrel therapy in populations with a high prevalence of those ''risk'' alleles be carefully administered [57]. Moreover, some investigators have shown associations between the

Table 6 Comparison of allele frequencies of *CYP2C19* reported from different ethnic populations

Population	Frequency (p value vs. Jordanian)				p value	References
	n	*1	*2	*3		
Jordanian	158	0.877	0.123	0		Current study
Caucasians						
American	105	0.871	0.129	0	0.811(NS)	[51]
German	140	0.85	0.15	0	0.388(NS)	[51]
Turkish	100	0.86	0.13	0.01	0.044	[81]
Greek	283	0.87	0.13	0	0.751(NS)	[82]
Asians						
Japanese	140	0.54	0.35	0.11	0.00001	[52]
Koreans	103	0.675	0.209	0.116	0.00001	[51]
Egyptians	247	0.888	0.11	0.002	0.795(NS)	[51]
Saudi Arabia	97	0.85	0.15	0	0.427(NS)	[51]
Iranian	200	0.86	0.14	0	0.583(NS)	[79]
Lebanese	161	0.863	0.134	0.003	0.866 (NS)	[83]
Gaza strip	200	0.913	0.058	0.03	0.012	[84]
African- Americans	108	0.75	0.25	0	0.002	[51]
African						
Ghanaian	204	0.94	0.06	0	0.038	[80]

N total number of subjects

Differences in allele frequencies were measured by χ^2 test

NS indicates that there were no significantly differences (p-value ≤ 0.05)

CYP2C19 polymorphism and certain types of cancers (e.g., esophagus, stomach, lung and bladder cancers)[58, 59].

*CYP3A4*1B*

*CYP3A4*1B* allele frequency varies among different ethnic groups and has lower frequency among Caucasians (Table 7). Recently, *CYP3A4*1B* allele was found to be associated with lower CYP3A4 metabolism capacity. This lower capacity is explained by reduction of *CYP3A4* expression due to presence of A-392G SNP which suggests that *CYP3A4*1B* diminishes the binding affinity of a transcription factor, resulting in lower transcriptional activity and therefore, lower enzyme activity [60].

Table 7 Comparison of allele frequencies of *CYP3A4*1B* reported from different ethnic populations

Population	*N*	Frequency	*p* value	Reference
Jordanian	173	0.035		Current study
Caucasians				
Europe	95	0.04	0.63	[85]
British	200	0.065	0.27	[86]
Turkish	186	0.014	0.32	[86]
Spanish	177	0.04	0.99	[87]
Asians				
Chinese	108	0	0.085	[86]
Vietnam	78	0.02	0.99	[88]
African-Americans	80	0.35	< 0.0001	[86]
African	95	0.82	<0.0001	[85]
Ghanaian	203	0.714	<0.0001	[80, 89]

Differences in allele frequencies were assessed by χ^2 test or Fisher exact test

N total number of subjects

The current study shows an allelic frequency of this SNP of 3.5 % among Jordanian population. Another study had been conducted among Jordanian population and found an allelic frequency of this SNP with 11.1 % [61] which is consistent with that reported previously for Caucasians (Table 4). The *CYP3A4*1B* allelic frequency varies among different ethnic groups: 0 % in Chinese and Taiwanese; 9.3–11 % in Hispanic Americans [33]; 2–9.6 % in Caucasians [62]; and 35–67 % in African Americans [30, 36].

There is debatable association of this variant with prostate cancer [63], chemotherapy-related leukemia [64], breast or ovarian cancer [65]. The presence of the *CYP3A4*1B* allele was shown to increase risk for Small Cell Lung Cancer in women [66].

CYP3A5

As mentioned previously, and in contrast to *CYP3A4*, the *CYP3A5* enzyme is known to be expressed in only a small percentage of Caucasian individuals (10–30 %) and this has been linked to a common transition in intron 3 and results in nonfunctional protein [36].

Due to the importance of this SNP (*CYP3A5*3*) as a determinant for the expression of *CYP3A5* gene in Caucasians, the current study estimated the allelic frequency of this SNP. In the Jordanian population the allelic frequency of this SNP was 92.58 %, which is fully consistent with that for other Caucasian populations [30, 67]. The prevalence of this SNP was 89–91 % in Caucasian-Americans; 92–94 % in European-Caucasians; 60–66 % in Hispanics, 71–75 % in East Asian populations (Chinese, Japanese, Koreans); 55–65 % in South Asians (Malay and Indians); and 29–35 % in African-Americans [33] (Table 8).

Contrary to examined HWE in all previously tested loci, we found a significant difference between the observed and

Table 8 Comparison of allele frequencies of *CYP3A5* reported from different ethnic populations

Population	Frequency (*p* value vs. Jordanian)					
	n	*1	*3	*6	*p* value	References
Jordanian	229	0.072	0.9258	0.0022		Current study
Caucasians						
Europe	95	0.06	0.94	0	0.791(NS)	[85]
German	500	0.082	0.917	0.001	0.731(NS)	[67]
French	NR	NR	0.813	NR		[90]
Asians						
Japanese	265	0.26	0.74	0	0.00001	[91]
Koreans	194	0.276	0.724	0	0.00001	[92]
Chinese	108	0.25	0.75	0	0.00001	[93]
Indian/Malays	90/98	0.40	0.60	0	0.00001	[93]
African-Americans	NR	0.60	0.27	0.13	0.00001	[35]
Africans	95	0.72	0.12	0.16	0.00001	[85]
Ghanaians	203	0.71	0.15	0.14	0.00001	[89]

Differences in allele frequencies were measured by χ^2 test

NS indicates that there were no significantly differences (p-value ≤ 0.05)

NR not reported, *N* total number of subjects

the expected frequencies with regard to *CYP3A5*3*. The findings could be spurious. If only one sample was *1/*3 instead of *1/*1, the χ^2 will change from 8.5 to 4.1 and the p value will change from 0.003 to 0.04. Alternatively, this evolution can be explained by genetic drift that occurs when the population size is limited and therefore by chance, certain alleles increase or decrease in frequency. Allele frequencies in small populations do not generally reflect those of larger populations since too small of a set of individuals cannot represent all of the alleles for the entire population [68, 69]. Only a single locus out of nine examined loci deviated from HWE.

*CYP3*6* allele, which encodes for aberrantly spliced CYP3A5 enzyme was found in 0.22 % of Jordanian population resembling results found in other Caucasian populations [30, 67].

Conclusion

The current study has led to the determination of common allelic variants of a number of important metabolizing enzymes namely *CYP1A1*; *CYP2C9; CYP2C19; CYP3A4; CYP3A5* in Jordanian population. Some of these variant alleles, to our knowledge, are being reported for the first time among the Jordanian population. The frequencies obtained are comparable to data previously reported in other populations of Caucasian origin but differ from that observed in African and Asian populations. Comparably, a mitochondrial genetics analysis revealed that Jordanians, carry genetic variants similar to other Caucasians [70]. This is of importance as it has been demonstrated in many studies that allele frequencies of the metabolic genes are not randomly distributed throughout the human population but follow diverse ethnic and/or geographic-specific patterns [4, 71–73]. The findings of current study supported by other studies all over the globe provide merits to suggest the use of genetic polymorphisms of CYP450 SNPs as markers for ethnicity and ancestral origin.

Acknowledgments The authors would like to thank all who participated in the study. This study was supported in part by unconditional grant from the Deanship of Scientific Research (Jordan University, Jordan). The study sponsors had no part in the study design, data collection, data analysis, data interpretations or in the writing of the manuscript. The sponsors had no role in the decision to submit the paper for publication.

Conflict of interest None of the authors has any financial or personal relationships that could potentially be perceived as influencing our research.

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