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GENETIC POLYMORPHISM OF CYP2C19 IN A SAMPLE OF IRAQI POPULATION

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ABSTRACT

Background: *CYP2C19 is responsible for the metabolism of a wide variety of medications this enzyme encoded by highly polymorphic gen.* ***Aim:*** *the aim of this study was to determine the frequencies of CYP2C19*1*2*3 and*17 in a sample of Iraqi population.* ***Methods:*** *This study was conduct in 221 Iraqi subjects. DNA was extracted from blood sample and detection of CYP2C19*1*2*3 and*17 was done by using TaqMan assay.* ***Results:*** *The frequencies for CYP2C19*1, CYP2C19*17, CYP2C19*2 and CYP2C19*3 were 65.1%, 19.5%, 15.2% and 0.2 respectively. Regarding phenotype the frequencies of EM, IM, UM and PM were 43.9 %, 27.1%, 27.1% and 1.9% respectively.* ***Conclusions:*** *The most common variant allele in this study was CYP2C19*17 and the EM was the most common phenotype*

KEY WORDS

Cytochrome P450 - Iraqi - pharmacogenetics - polymorphism - SNP

INTRODUCTION

The CYP2Cs form an important subfamily of CYP enzymes that are responsible for metabolizing about 20% of most therapeutic drugs [1]. P450 2C19 is a member of four P450 2C monooxygenases that are encoded by a cluster of genes which began as gene duplication and divergence on chromosome 10. In human liver three of these P450s, 2C19, 2C9, and 2C8, are expressed. They significantly contribute to hepatic capacity to metabolize drugs [2]. CYP2C19 hydroxylates a wide variety of drugs like clopidogrel, lansoprazole, diazepam, barbiturates, nelfinavir, omeprazole, cyclophosphamide, and clonazepam [1]. *CYP2C19* is extremely polymorphic and can cause difference in drug response. There are about 24 mutant allelic variants of *CYP2C19* are known till now, of which *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* are the most common [3].

Among *CYP2C19* defective alleles the most frequently founded one in human populations are *CYP2C19*2* (rs4244285). The *CYP2C19*2* is a defective allele that carries a 681G<A single base substitute in exon 5 causing an alternate splice site consensus and by this it eliminates the catalytic activity on all substrates [4]. The other important defective allele is *CYP2C19*3* (rs4986893), this has an adenine substituted for a guanine at base 636 (636G>A) in exon 4, forming a premature stop codon [4]. The *CYP2C19*17* allele (c.-806C>T; rs12248560) on the contrary results in increased activity as a result of enhanced transcription [5]. Several researches have investigated the frequency of different *CYP2C19* alleles worldwide. The allele frequency of *CYP2C9*2* was reported to be about 50% in Asians, 19% in American populations, 34% in Africans and 18% in Caucasians [6-9]. The allele frequency of CYP2C9*3 among the Asian, African and Caucasian populations was <7 %, <1 % and 1 %, respectively [10] The *CYP2C19*17* genotype was found in 22,0 % of the Norse (Pedersen et al 2010), 25,7 % of the Germans [11], 20,0 % of the Swedes [12], 4,0 % of the Chinese [5], 0,3 % of the Koreans [13], 1,3 % of the Japanese [12], 25.7 % of Saudi Individuals [14].

CYP2C19 enzyme activity are considered to be normal when two *CYP2C19*1* alleles are present

*(CYP2C19*1/*1)*; *CYP2C19* Intermediate Metabolizer (IM) phenotype is expected by the existence of one *CYP2C19* allele with normal function and one *CYP2C19* allele with decreased function or one *CYP2C19* allele with increased function and one *CYP2C19* allele with decreased function *(CYP2C19*1/*2, *1/*3, *2/*17, *3/*17)*; *CYP2C19* Poor Metabolizer (PM) phenotype is expected when two CYP2C19 non-functional alleles *CYP2C19*2* or *CYP2C19*3* are present (*CYP2C19*2/*2, *2/*3, *3/*3*). In contrast presence of Heterozygosity or homozygosity for the increased function *CYP2C19*17* allele is associated with CYP2C19 increased activity that will lead to an ultra-rapid metabolizer phenotype (UM) [15].

MATERIAL AND METHODS

Subject

Two hundred and twenty one of unrelated Iraqi nationality and Arab ethnicity (127 male and 94 female, aged 19 to 85 years) were enrolled in this study. Ethical approval of this study obtained from the Research and Ethics Committee of Medical College / Al-Nahrain University. All subjects included in this study informed about the test that will done in this study.

CYP 2C19 genotyping

For genetic study 2.5 ml of the blood was drawn from each subject and transferred in to EDTA containing tube. DNA was extracted by using a kit provided by promega (ReliaPrep™ Blood gDNA Miniprep System**).** DNA extraction was done according to manufacturer's instructions. CYP2C19 *2,*3 and *17 were determined by TaqMan assay using STRATAGENE-MX3005P.

PCR amplification for all three SNP was done in 20 µL reactions with about 80ng of template DNA, 1X KAPA PROBE FAST qPCR Master Mix Universal, 600nm each primer, 400nm each probe, and deionized water. The thermal condition of the reaction began with denaturation at 95° C for 10 min, followed by 40 cycles of denaturation at 95°C for 30 sec, annealing, and extension at 60° C for 1 min. at the end of amplification results were obtained from the software supplied with STRATAGENE-MX3005P. As a quality control of the genotyping, 20 per cent of the total sample genotyped was sequenced.

RESULTS

The frequency of CYP2C19 alleles, genotype and phenotype in all subject enrolled in this study are shown in table 3-12. The most frequent allele was CYP2C19*1(288/441, 65%). CYP2C19*1*1 was the most frequent genotype (97/221, 44%). The most frequent variant allele was CYP2C19*17 (86/441, 19.5%). CYP2C19*17 where classified as 51 (23.1%) heterozygous for CYP2C19*1*17, 17 (7.7%) heterozygous for CYP2C19*2*17 and 9 (4.1%) homozygous for the CYP2C19*17*17. The second most common variant allele in this study was CYP2C19*2 (67/442, 15.2%), these allele are distributed as 43(19.5%) heterozygous for CYP2C19*1*2, 17 (7.7%) heterozygous for CYP2C19*17*2 and 3 (1.4%) homozygous for CYP2C19*2*2. There was only on CYP2C19*3 allele in this study which was heterozygous for CYP2C19*2*3. Regarding phenotype the frequencies of EM, IM, UM and PM were 43.9 %, 27.1%, 27.1% and 1.9% respectively. Based on Hardy-Weinberg equilibrium there was no statistical difference in the actual and expected frequency distribution (P>0.05)

Table 1: Frequencies of CYP2C19 alleles and genotypes in Iraqi population sample (n=221)

CYP2C19	Allele	Actual		95% CI	Expected by Hardy-Weinberg law	
		Number	Frequency		Number	Frequency
Alleles	*1	288	0.652	0.607-0.696	N/A	N/A
	*2	67	0.152	0.118-0.185	N/A	N/A
	*3	1	0.002	0.000-0.007	N/A	N/A
	*17	86	0.195	0.158-0.203	N/A	N/A
	Total	442	1.000	N/A	N/A	N/A
Phenotypes	Genotype					
EM	*1*1	97	0.439	0.373-0.504	93.828	0.425
	*1*17	51	0.231	0.175-0.286	56.036	0.254
	*17*17	9	0.041	0.015-0.067	8.367	0.038
	*1*2	43	0.195	0.142-0.247	43.656	0.198
	*2*17	17	0.077	0.042-112	13.036	0.059
	*1*3	0	0.000	N/A	0.652	0.003
	*3*17	0	0.000	N/A	0.195	0.001
	*2*2	3	0.014	0.000-0.029	5.078	0.023
	*2*3	1	0.005	0.000-0.013	0.152	0.001
	*3*3	0	0.000	N/A	0.001	0.000
	Total	221	1.000		221.000	1.000

DISCUSSION

This study is the first to characterized the phenotype and genotype of CYP 2C19 in Iraqi population. The genetic polymorphism of CYP2C19 has been shown to have the most striking interethnic variation of a CYP so far. The PM frequency ranges from 2 to 7% in Caucasians, 14–25% in Asians, and 60% in the Vanuatu [16,17]. In this study the CYP2C19*2 frequency was 15.1%. This frequency was similar to that of Saudi Arabian 15 % [18] and higher than those reported in Caucasians (14.7%), Egyptian (11.0%) [19], while it was lower than Asians (30%) as shown in table 2**.** Moreover, this study revealed that the CYP2C19*3 frequency was 0.2% (only one subject). However there is limited numbers of studies have reported CYP2C19*3 in populations other than the Asians. CYP2C19*3 was reported in the Egyptian population 0.2% [19], and Swedish population 0.3% [20], 0.7% [21]. CYP2C19*3 has been considered as an Asian mutation allele and after genotyping for CYP2C19*2 it was responsible for the remaining alleles in Asian PMs [19].

Regarding CYP2C19*17 we found that the frequency of CYP2C19*17 was 19.4. The allele frequency of CYP2C19*17 in Iraqi population was similar to that found in African Americans 21% [22], Danish 20.1% [23]and Greece 19.6 [24]. While it was slightly lower than Saudi Arabia 25% [14], German 25.5% [11] and Polish 27.2% [25]Lower frequencies of CYP2C19*17 were reported for in East and South Asian groups (Chinese, Japanese, and Koreans), the CYP2C19*17 allele frequencies (range: 1.2% -1.5%) [26 , 27].

Based on the genotype results, the classification of patients was made according to their metabolizer phenotype. Phenotype classifications divided patients into those who were extensive (normal) metabolizers, intermediate metabolizers, poor metabolizers and rapid metabolizers.

Our result revealed that the EM phenotype in 221 Iraqi subjects was 43.9% while the frequency of IM in our study was 27.15%, in addition our study demonstrate that the frequency of PM and UM were 1.8% and 27.15% respectively. Similar results were obtained by Leena et al and Goldstein et al in Saudi Arabian population [14, 18].

In addition the result of this study was similar to that obtained in pan-ethnic population. The metabolic rate in pan- ethnic population include the following: 41% of populations were extensive metabolizer, 27.57% as intermediate metabolizer, 27.8% as ultrarapid metabolizer and 3.46 as poor metabolizer [28].

In Asian populations the frequencies of poor and intermediate metabolizer were higher than that observed in this study while ultrarapid metabolizer was lower. In Thai population the frequencies of

intermediate, poor and ultrarapid metabolizer were 41.95%, 13.03% and 4.3% respectively [29]. In Korean population the frequency of poor and intermediate metabolizer were 12%, 42% respectively [30]. This can be explain by Lower frequencies of CYP2C19*17 and higher frequencies of CYP2C19*3 in these population [12, 26, 27].

CONCLUSION

In term of genotyping, the most frequent allele in a sample of Iraqi population was CYP2C19*1, while the most frequent variant allele was CYP2C19*17. In term of phenotype, Extensive metabolizer was the most frequent phenotype of CYP2C19, while Ultrarapid and intermediate metabolizer have the same frequency

Table 2: Ethnic variation of *CYP2C19* (1, *2, *3,* and **17*) in the present study and publications**

population	Number	Alleles frequency of *CYP2C19*				Reference
		*1	*2	*3	*17	
Iraqi population	221	65.1	15.2	0.2	19.4	Our study
Saudi Arabians	97	85	15	***0.00***	NA	[18]
Saudi Arabians	201	62.8	11.5	NA	25.7	[14]
Egyptians	494	88	12	6	NA	[19]
Jordania	78	84	16	0.0	NA	[31]
Lebanese	161	83.6	13.4	3	NA	[32]
Tunisian region	100	88.5	11.5	NA	NA	[33]
Iranian:Tehran	200	86	14	0	NA	[34]
Iranian:Turkman	140	56.4	23.5	20	NA	[35]
Japanese	217	61.2	27.4	10.8	NA	[36]
Japanese	265	70.8	27.9	NA	1.3	[12]
Chinese	121	49.5	45.5	4.5	NA	[37]
Chinese	384	73.9	24.9	NA	1.2	[26]
Koreans	103	67.4	20.9	11.7	NA	[30]
Thai	774	68	29	3	NA	[38]
Thais	1051	63	27	6	4	[29]
Burmese	127	66	30	4	NA	[38]
Malaysians	142	66	28	6	NA	[39]
German	237	59.3	15.2	NA	25.5	[11]
Danish	276	64.9	15.0	NA	20.1	[23]
Polish	125	61.2	11.6	NA	27.2	[25]
Greece	283	79.4	NA	NA	19.6	[24]
Swedish	310	81.2	18.8	0	NA	[21]
Italians	360	88.9	11.1	0	NA	[40]
Croatians	200	85	15	0	NA	[41]
Belgian	121	90.9	9.1	0	NA	[42]
Islands	5538	22.3	63.3	14.4	NA	[43]
Ethiopians	114	83	14	3	NA	[44]
Tansanians	251	81	18	1	NA	[45]
Russians	290	88.3	11.4	0.3	NA	[46]
African-American	114	79	NA	NA	21.0	[22]
African Americans	517	81	19	0	NA	[47]
Americans	100	80	11	0	9	[48]

NA: not analyzed

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