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Genotype and allele frequency of *CYP2C19*17* in a healthy Iranian population

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Abstract

Background: Cytochrome P450 2C19 (CYP2C19) is important in metabolism of wide range of drugs. *CYP2C19*17* is a novel variant allele which increases gene transcription and therefore results in ultra-rapid metabolizer phenotype (URM). Distribution of this variant allele has not been well studied worldwide. The aim of present study was to investigate allele and genotype frequencies of *CYP2C19*17* in a healthy Iranian population and compare them with other ethnic groups.

Methods: One hundred eighty healthy unrelated Iranian volunteer took part in this study and were genotyped for *CYP2C19 *2, *3, *17* (-3402) by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and *CYP2C19*17* (-806) by a nested-PCR assays. The distribution of *CYP2C19*17* polymorphism in Iranian population was then compared with other ethnic groups.

Results: The *CYP2C19*17* allele frequency was 21.6% in Iranian population. Among studied subjects 5.5% were homozygous for CYP2C19*17 and phenotyped as ultra-rapid metabolizers; 28.8% were genotyped as *CYP2C19*1*17* (extensive metabolizers) and 3.3% as *CYP2C19*2*17* (intermediate metabolizers).

Conclusion: The *CYP2C19*17* genetic distribution in Iranian population is similar to Middle East or European countries. The high frequency of *CYP2C19*17* in Iranian population highlights the importance of this new variant allele in metabolism of CYP2C19 substrates. Thus, future association studies are required to reveal clinical consequence of this genetic polymorphism in carrier individuals.

Keywords: CYP2C19, Genotyping, Iranian, Polymorphism, Polymerase chain reaction.

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Introduction

The cytochrome P450 2C19 (CYP2C19) is important in metabolism of a wide range of drugs including proton pump inhibitors (omeprazole), tricyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (citalopram), anticonvulsant S-mephenytoin and anti-platet drugs (clopidogrel) (1-3).

Genetic polymorphism of CYP2C19 was identified by its considerable effect in metabolism of S-mephenytoin, resulting in poor metabolizer (PM) and extensive metabolizer (EM) (4). The EM phenotype is attributed to wide type allele *(CYP2C19*1)*. The PM is assigned to *CYP2C19*2* which is defined as a mutation in exon 5 *(CYP2C19, 681G>A)* and causes a splice

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site and *CYP2C19*3 (CYP2C19, 636G>A)* which creates a stop codon in exon 4 (5). In 2006 a novel variant allele, *CYP2C19*17* was reported by Sim et al. (6) which is specified by a double mutation in promoter region *(CYP2C19 -806C>T* and *-3402C>T)* (2), these mutations lead to increased gene transcription and therefore ultra-rapid metabolizer phenotype (URM) (7-9).

Few studies have reported allelic frequency of *CYP2C19*17* and its effect on clinical response to CYP2C19 substrates (8,10-13). *CYP2C19*17*17* genotype has been found to increase clinical response to clopidogrel treatment by better anti-platelet activity and therefore was associated with higher risk of bleeding (14); In treatment of peptic ulcer, URM phenotype, caused therapeutic failure by increasing proton pump inhibitor metabolism (15) and PM phenotype led to greater acid suppression (16,17).

Several studies show inter-ethnic differences in distribution of this variant allele (1,6,17). The allele frequency of *CYP2C19*17* was estimated 18% in Swedish, 4% in Chinese (6) and 1.7% in Japanese people (1). To our best knowledge, no study has been conducted to evaluate distribution of this new variant allele in Iranian population. Thus, the present study aims to investigate allele and genotype frequencies of *CYP2C19*17* variant in the Iranian population and compare these frequencies with other ethnic groups. These findings would help us to estimate importance of this new polymorphism in variable response to CYP2C19 substrates between Iranian individuals.

Methods

Subjects and DNA extraction

One hundred and eighty unrelated healthy Iranian volunteers (60 women and 120 men) with the mean age of 36 years (ranging between 20 and 55) and average body weight of 63 kg (ranging between 45 and 89) took part in this study. A randomize prospective cross sectional design was used to recruit participants. All subjects were students or stuffs of faculty of pharmacy from four different cities in Iran. They signed written informed consent before attending this project. The study protocol was confirmed by ethics committee of Tehran University of Medical Sciences.

Five ml venous blood sample was taken from each subject and transferred into tubes containing 10 µl of 10% ethylene diamine tetra-acetic acid (EDTA). Genomic DNA was obtained from peripheral blood leucocytes by salting out method (using supersaturated 6M NaCl solution) (18). The extracted DNA was dissolved in sterile distilled water and stored at 4°C until the day of analysis.

*Genotyping of CYP2C19*2 (681G>A), CYP2C19*3 (636G>A) and CYP2C19*17 (-3402C>T)*

The genotyping of *CYP2C19*2 (681G>A), CYP2C19*3 (636G>A),* and *CYP2C19*17 (-3402C>T)* polymorphisms was performed by modified PCR-RFLP assays as originally described by De Morais et al. (19) and Sim et al. (6). The PCR reaction mixture (25 µl) was consisted of 250 ng template DNA, 1× PCR buffer, 2 mM MgCl2, 0.2-0.8 µM of each specific forward and reverse primers, 0.2 mM dNTPs, 1 Unit of Taq DNA polymerase (CinnaGen, Iran) and sterile distilled water. The PCR reaction was carried out in an Eppendorf PCR system gradient master cycler (Hamburg, Germany). Thermal profile for DNA amplification was as follows: the initial denaturation at 94° C for 2 min; then 35 cycles of denaturation at 94°C for 45 seconds, annealing at 53° C for 40 seconds, and extension at 72°C for 30 seconds; final extension at 72° C for 5 min eventually applied to cycling. All three PCR reactions were amplified by similar thermal profile. The PCR product of each reaction was digested by specific restriction endonuclease (New England Biolabb, UK). The details of primers sequence and restriction enzymes are summarized in Table 1. SmaI digested the 169 bp fragment to 120 and 49 bp fragments in wild type (wt) carriers of

Table 1. Primer sequences, PCR products, restriction endonucleases, and digested fragments

Gene	Primer Sequence	PCR product (bp)	Restriction endonuclease, T (ºC)	Restriction Pattern (bp)
CYP2C19*2	5'-AATTACAACCAGAGCTTGGC-3' (F) 5'-TATCACTTTCCATAAAAGCAAG-3' (R)	169	SmaI, 25	Wt:120, 49 Het:169, 120, 49 Mt: 169
CYP2C19*3	5'-TATTATTATCTGTTAACTAATATGA-3' (F) 5′-ACTTCAGGGCTTGGTCAATA-3' (R)	329	BamHI, 37	Wt:233, 96 Het:329, 233, 96 Mt: 329
CYP2C19*17 (-3402C>T)	5′-AATAAAGATGACCTTGATCTGG-3' (F) 5′-TCTCCTGAAGTGTCTGTAC-3' (R)	500	MnlI, 37	Wt: 280, 224 Het:500,280, 224 Mt: 500
CYP2C19*17 (-806C>T)[a] I	5′-GCCCTTAGCACCAAATTCTC-3' (F_1) 5′-ATTTAACCCCCTAAAAAAACACG-3' (R_1)	470	–	–
CYP2C19*17 (-806C>T)[b] II	5′-TCTGTTCTCAAAGC-3' (F_2 wt) 5′-TCTGTTCTCAAAGT-3' (F_3 mt)	200	–	–

F (Forward primer), R (Reverse primer), bp (Base pair), Wt (wild type), Mt (mutant), Het (heterozygous)
CYP2C19*17(-806C>T) genotyping was performed by semi-nested PCR technique. [a] $R_1 + F_1$ primers were used for first PCR (I) amplification (470 bp). [b] In second PCR (II), $R_1 + F_2$ primers were used for amplification of -806C (wide type) allele and $R_1 + F_3$ primers were used for amplification of -806T (mutant) allele (200 bp).

*CYP2C19*1*. BamHI yielded 233 and 96 bp fragments in wild type carriers of *CYP2C19*1*. MnlI resulted in 280 and 224 bp fragments in wt subjects for *CYP2C19*1*. While the homozygous carriers of *CYP2C19*2, *3* and **17* were resistant to digestion by related enzymes and resulted in single band in the 2.5% agarose gel stained with ethidium bromide (Table 1).

*Genotyping of CYP2C19*17 (-806C>T)*

The *CYP2C19*17 -806C>T* mutation was analyzed by semi-nested PCR approach as described by Sim et al. with a few modifications (6). The first PCR reaction mixture and thermal protocol (PCR I) was identical to what described earlier for *CYP2C19*2,*3* and **17*(-3402); R_1 and F_1 primers (Table 1) yielded a 470 bp product. 0.5 µl of PCR I product was then included in second allele-specific PCR reactions (PCR II). Primer F_2 (wt) or primer F_3 (mt) were used with primer R_1 to differentiate between -806C (*CYP2C19*1)* and -806T (*CYP2C19*17*) alleles, respectively. The reaction mixture (15 µl) of PCR II (one reaction for each allele) was similar to that of first reaction, except for using 2.5 mM MgCl2. The second reaction (PCR II) was performed with initial denaturation at 94º C for 1 min, and then 15 cycles at 94ºC for 15 seconds, annealing at 53º C for 20 seconds and extension at 72º C for 30 seconds. The 200 bp PCR products (wt or mt) were separated by 2.5% agarose gel.

Statistical analysis

The allele frequency differences between populations were estimated using Chi-squar test and two tailed Fisher's exact test. The 95% confidence intervals (CIs) were calculated using Confidence Interval Analysis software. The relation of sex and genotype was analyzed by two tailed Fisher's exact test. The observed and expected frequencies were calculated using Hardy-Weinberg equation. The two tailed Fisher's exact test was used to assess genotype frequencies deviation in the studied population from Hardy-Weinberg equilibrium. In all statistical analysis $p<0.05$ was considered as significant difference.

Results

The *CYP2C19*17* allele was identified in 78 out of 180 volunteer with the frequency of 21.6% (95% CI: 17.5 – 26.3). 10 subjects were homozygous for *CYP2C19*17* (5.5%, 95% CI: 2.7-10 %), 52 subjects (28.8%, 95% CI: 22.4-36.1 %) were heterozygous for *CYP2C19*17* and 75 subjects (41.7%, 95% CI: 34.4-49.2%) were found to be homozygous for *CYP2C19*1*. The genotype and allele frequencies of CYP2C19 are reported in Table 2. The dis-

Table 2. CYP2C19 genotype and allele frequencies and expected phenotype in 180 healthy Iranian individuals

CYP2C19 Genotype	Number of subjects		Frequency (%)	95% CI	Predicted Phenotype	Expected frequency by Hardy-Weinberg low [a] (%)
	Men (120)	Women (60)				
*17*17	5	5	5.5	2.7-10.0	URM	4.84
*1*17	37	15	28.8	22.4-36.1	EM	28.6
*1*1	53	22	41.7	34.4-49.2	EM	42.3
*1*2	20	13	18.3	13.0- 24.7	IM	17.0
*2*17	4	2	3.3	1.23-7.1	IM	5.7
*2*2	2	2	2.2	0.6-5.5	PM	1.70
Alleles	No. of alleles		Frequency (%)	95% Confidence Interval		
CYP2C19*17	78		21.6	17.5-26.3		
CYP2C19*1	235		65.3	60.1-70.2		
CYP2C19*2	47		13.1	9.7-16.9		
CYP2C19*3	0		0	0		

Abbreviations: UM, Ultra-rapid metabolizer, Het-EM, Heterozygous extensive metabolizer, EM, Extensive metabolizer; IM, Intermediate metabolizer; PM, Poor metabolizer. CI: Confidence Interval

[a] Observed and expected frequencies were not statistically different (p>0.05).

tribution of *CYP2C19*17* and *CYP2C19*2* polymorphisms were not statistically different in the studied men and women (p>0.05). The expected frequencies of CYP2C19 genotypes in Iranian population in this study, had no significant deviation from the Hardy-Weinberg equilibrium (p>0.05). Complete linkage disequilibrium was observed in -806 C>T with that of -3402C>T and this observation was in accordance with previously published studies (1,6,13,20). Both -806 C>T and -3402C>T mutations were not observed in subjects homozygous for *CYP2C19*2* and accordingly *CYP2C19*2* allele was not detected in subjects homozygous for *CYP2C19*17.*

*CYP2C19*2* allele was present in 43 individuals (with the frequency of 13.1%; 95% CI: 9.7-16.9 %). Four subjects were homozygous for *CYP2C19*2* (2.2%, 95% CI: 0.6-5.5%) and 39 subjects were heterozygous for *CYP2C19*2* (21.6%, 95% CI: 15.8-28.4%). Six out of these 39 subjects had both *CYP2C19*17* and *CYP2C19*2* alleles (3.3%, 95% CI: 1.2-7.1%) and were genotyped as *CYP2C19*2*17,* and the rest of 33 subjects were combination of *CYP2C19*1* and *CYP2C19*2* alleles (18.3%; 95% CI: 13.0-24.7%) and were genotyped as *CYP2C19*1*2. CYP2C19*3* was not identified in our study population.

Based on the CYP2C19 genotypes, subjects were divided into 4 previously defined phenotypes (2); the summary of predicted phenotypes is shown in Table 2. Homozygous carriers of *CYP2C19*17* allele were categorized as ultra-rapid metabolizers (URM). Subjects with *CYP2C19*1*17* and *CYP2C19*1*1* genotypes were designated as extensive metabolizer (EM). Individuals with *CYP2C19*2*17* and *CYP2C19*1*2* genotypes were classified as intermediate metabolizers (IM) and homozygous carrier of *CYP2C19*2* were stratified as poor metabolizers (PM).

The allele and genotype frequencies of CYP2C19 in this study were also compared with previously published reports. Data are summarized in Table 3 and Table 4. According to the data in the Table 3, the allele frequency of *CYP2C19*17* in this study was not statistically different from European and Middle East countries. For example, the frequency of *CYP2C19*17* allele was 20% in Swedish, 20.1 % in Danish, 22% in Norwegian, 19.6% in Greek, 24.4% in Turkish and 25.7% in Saudi Arabian people (6,9,21,23) while in the East and South Asia like Korea, Thailand and Japan, there was an statistically significant difference in allele frequency of *CYP2C19*17* with European and Middle East countries (p< 0.05) (1,24,25).

Discussion

CYP2C19 is an important factor in the pharmacokinetic of CYP2C19 substrates like clopidogrel, imipramine, escitalopram and proton pump inhibitors (PPIs) (12,13,15,20, 28). *CYP2C19*17* variant

Table 3. Comparison of CYP2C19 allele frequencies between Iranians and different populations

Population	Sample size	CYP2C19 Allele Frequency (%)					Reference
		19*17	19*1	19*2	19*3	Others	
Iranian	180	21.7	65.3	13.0	0	0	Present study
Japanese	165	1.3 [a]	57.9	27.9 [a]	12.8 [a]	0	1
Swedish	314	18.0	NR	NR	0	0	6
Ethiopian	190	18.0	NR	NR	0	0	6
Chinese	68	4.0 [a]	NR	NR	0	0	6
Danish	276	20.1	64.9	15.0	0	0	9
Faroese	311	15.4 [a]	65.9	18.7 [a]	0	0	9
Norwegian	309	22.0	62.8	15.2	0	0	9
Polish	78	28.2	56.4 [a]	15.4	0	0	10
Greek	283	19.61	67.32	13.07	0	0	21
Saudi Arabian	201	25.7	62.9	11.2	0	0	22
Turkish	244	24.4	65.6	10.0	0	0	23
Korean	150	0.3 [a]	61.0	28.0 [a]	11.0 [a]	0	24
Swedish	185	20.0	64.0	16.0	0	0	24
Thai	1051	4.0 [a]	63.0	27.0 [a]	6	0	25
Indian	206	17.9	42.0 [a]	40.2 [a]	0	0	26
Korean	271	1.5 [a]	60.0	28.4 [a]	10.1 [a]	0	27
German	186	25.5	59.3	15.2	0	0	28
Ashkenazi Jewish	342	13.0	70.0	12.0	0	4.1	29
African American	149	19.0	63.0	12.0	0	4.6	29
Hispanic	346	10.0 [a]	75.0	10.0	0	1.74	29

NR: Not reported

[a] Represent statistically significant difference in comparison to present data ($p<0.05$)

Table 4. Comparison of CYP2C19 genotype frequencies between Iranians and different populations

Population	Sample Size	CYP2C19 genotype frequency (%)						Reference
		17*17	1*17	1*1	2*17/3*17	1*2/1*3	2*2/2*3/3*3	
Iranian	180	5.5	28.9	41.7	3.3	18.3	2.2	Present Study
Japanese	165	0.0	1.1 [a]	35.5	1.5	43.8 [a]	18.8 [a]	1
Danish	276	5.1	22.8	44.2	7.3	18.5	2.2	9
Faroese	311	3.5	16.4 [a]	46	7.4	23.5	3.2	9
Norwegian	309	4.9	26.5	39.5	7.8	20.1	1.3	9
Greek	283	3.2	28.6	44.17	4.3	17.8	2.1	21
Saudi Arabian	201	7.0	30.4	40.3	7.0	14.5	0.4/0.4	22
Turkish	244	6.6	30.3	44.3	5.3	12.3	1.2	23
Thai	1051	0.0	4.3 [a]	40.7	0.0	35.1 [a]/6.85	7.32 [a]/5.61/0.1	25
Indian	206	1.2 [a]	20.7	16.1 [a]	12.6 [a]/0	31.0 [a]/0	18.4 [a]	26
Korean	271	0.0	1.1 a	35.7	1.4 a/0.3	36.5 a/10.7	5.9/7.0/1.1	27

[a] Represent statistically significant difference in comparison to present data ($p<0.05$)

that was identified by Sim et al. and reported to be associated with higher metabolic activity of CYP2C19. This variant allele has a different genetic distribution in various ethnic groups (6). Several studies have shown the effect of *CYP2C19*17* polymorphism on treatment of peptic ulcer disease (10,15,20,30). The data in the different studies indicate that *CYP2C19*17*17* is associated with 2.1 fold lower omeprazole plasma concentration and therefore the efficacy of PPIs like omeprazole is decreased in *CYP2C19*17*17* individuals (10,15,20). Musumba et al. investigated the effect of C*YP2C19*17* allele on occurrence of peptic ulcer disease (PUD) and showed increased prevalence of PUD in patient with *CYP2C19*17*17* genotype in comparison to *CYP2C19*1*1* genotype (30). *CYP2C19*17* allele also leads to lower risk of breast cancer by increasing estrogen metabolism (31).

The distribution of *CYP2C19*17* polymorphism has not been well estimated worldwide. The main goal of present study was to investigate allele and genotype frequencies of *CYP2C19*17* in Iranian population. In this study the allele frequency of *CYP2C19*17, *2* and **1* were 21.6%, 13.1% and 65.3% respectively which is in agreement with previous study in our lab for *CYP2C19*2* and **1* (32). In our previ-

ous study subjects that were genotyped as *CYP2C19*1*17* and *CYP2C19*17*17* in this study were identified as *CYP2C19*1*1*; so, if genotype frequencies of *CYP2C19*1*17* and *CYP2C19*17*17* (28.8% and 5.5%) is deduced from *CYP2C19*1*1* genotype frequency in previous report (75%), the similar frequency for *CYP2C19*1*1* (40.55%) is attained. Accordingly, people with *CYP2C19*2*17* in this study were defined as *CYP2C19*1*2* in previous report, so, if we recalculate the *CYP2C19*1*2* genotype frequency by deduction of the *CYP2C19*2*17* frequency in this study (3.3%) form *CYP2C19*1*2* genotype frequency in the previous study (22%), the frequency of 18.7% for *CYP2C19*1*2* is obtained which is similar to the result of this study (18.3%).

Based on the results of this study, there is not a significant difference in distribution of *CYP2C19*17* variant allele in Iranian population compared with European and other Middle East countries. In contrast, east and south Asian people have significantly lower frequency of this polymorphism than Iranians.

*CYP2C19*2* allele reduces enzyme activity and *CYP2C19*17* allele increases enzyme activity (6). In this study, subjects with *CYP2C19*2*17* were categorized as IM. Few studies have reported effect of *CYP2C19*2*17* on metabolic capacity of this enzyme (2,13,21,26). In the study by Gurbel et al. (2) the *CYP2C19* activity in stented patients treated with clopidogrel was similar in both *CYP2C19*2*17* and *CYP2C19*1*2* genotypes. Therefore, it was concluded that in patients carrying both **2* and **17* alleles the reduction of enzyme activity by **2* allele is more predominant than induction of enzyme activity by **17* allele, consequently, in this study *CYP2C19*2*17* genotype was classified as IM.

Finally, although genotype-based phenotype prediction is not the best and complete way for estimation of protein activity because other factors like sex, age and associated disease, combination therapy and environmental factors may influence this relationship, the high frequency of *CYP2C19*17* in Iranian population makes this new variant allele suitable candidate for association studies and help us to reveal clinical consequences of this genetic polymorphism in carrier individuals.

Conclusion

The allele frequency of *CYP2C19*17* in Iranian population is 21.6% and is similar to Middle East or European countries. The high frequency of *CYP2C19*17* allele in Iranian population highlights the importance of this new variant allele in metabolism of CYP2C19 substrates. Future association studies are required to reveal clinical consequence of this genetic polymorphism in carrier individuals.

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