

# Genetic Polymorphism of Cytochrome p450 (2C19) Enzyme in Iranian Turkman Ethnic Group

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## Abstract

**Objective:** Different findings indicate that CYP2C plays a clinical role in determining interindividual and interethnic differences in drug effectiveness. The ethnic differences in the frequency of CYP2C19 mutant alleles continue to be a significant study topic. The aim of the present study was to assess the frequency of allelic variants of CYP2C19 in Turkman ethnic groups and compare them with the frequencies in other ethnic populations.

**Methods:** The study group included 140 unrelated healthy ethnic Turkman subject referred to the Health Center. Genotyping of CYP2C19 alleles (CYP2C19\*1, CYP2C19\*2, and CYP2C19\*3 alleles) was carried out by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism technique

**Results:** The allele frequency of CYP2C19\*1, CYP2C19\*2 and CYP2C19\*3 were 56.43%, 23.57% and 20%, respectively. The result also showed that 39.7% of subjects expressed the CYP2C19\*1/\*1 genotype. While 42.1%, 9.3%, 9.3% and 1.4% expressed CYP2C19\*1/\*2, CYP2C19\*1/\*3, CYP2C19\*2/\*2 and CYP2C19\*3/\*3 genotypes, respectively. The genotype CYP2C19\*2/\*3 was not expressed in this study population. The findings suggested that 10% of subjects were poor metabolizers by expressing CYP2C19\*2/\*2 and CYP2C19\*3/\*3 genotypes. Fifty one percent of subjects were intermediate metabolizers having CYP2C19\*1/\*2, CYP2C19\*2/\*3 and CYP2C19\*1/\*3 genotypes and 37.86% were found to be extensive metabolizers expressing CYP2C19\*1/\*1 genotype. The frequency of intermediate metabolizers genotype was high (51%) in Turkman ethnic groups.

**Conclusion:** This study showed that the determined allelic variants of CYP2C19 (CYP2C19\*2 and CYP2C19\*3 mutations) in Turkman ethnic group are comparable to other populations. These findings could be useful for the clinicians in different country to determine optimal dosage and effectiveness of drugs metabolized by this polymorphic enzyme.

**Keywords:** CYP2C19 genetic polymorphism; Iranian Turkman ethnic group; polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP).

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## Introduction

There are at least four isoforms of human CYP2C subfamily in mankind. The main forms are principally 2C8, 2C9, 2C18 and 2C19. Their related genes are located on chromosome 10.<sup>1,2</sup> It has been shown that drug metabolism is directly related to genetic polymorphism and gene mutations manipulate the enzyme activities responsible for the drugs metabolism. Such enzyme activity modulation can present itself in three scenario of high, low and zero activities.<sup>3-5</sup> From drug related genetic pattern, the human gene are sub-grouped into few phenotypes of poor (or slow) metabolizers (PM), intermediate metabolizers (IM), extensive (or rapid) metabolizers (EM), and ultrarapid metabolizers (UM).<sup>6</sup> There are various reports of drugs which adversely affect human metabolism, resulting either from drug toxicity or long-lasting therapeutic effect of some drugs even consumption at therapeutic dosage in poor or slow metabolizer phenotypes. The ultra rapid metabolizer phenotype probably does not demonstrate the related therapeutic effect and this may be the reason why some drugs do not produce any therapeutic effect even in genetically susceptible subjects. This manifestation of specific phenotypes is related to the pharmacogeneticity of particular polymorphism of poor or slow, extensive or rapid and ultra-rapid metabolizer. It has been shown that about 3% of Caucasians express the poor metabolizer phenotypes S-mephenytoin, however literature review in this regards shows slight differences.<sup>7,8</sup> Other studies indicated that East Asian subjects express the poor metabolizer phenotypes at higher frequency. Some researchers have indicated that 18-23% of Japanese,<sup>9,10</sup> 15-17% of Chinese<sup>11,12</sup> and 12-16% Koreans express the poor metabolizer phenotype.<sup>13,14</sup> The same index for Black African was reported to be 4-7%.<sup>15</sup> Reports suggest that the poor metabolizer phenotype is an autosomal recessive trait which is inherited.<sup>8</sup> Same reports have considered CYP2C19\*2 and CYP2C19\*3 to be the dominant poor metabolizer phenotype for malfunction of CYP2C19 alleles.<sup>16,17</sup> Among East Asians, CYP2C19\*2 is the major allele and it dominates about 75% of the defective alleles.<sup>16</sup> These allele defections for Caucasians account for 93% of population.<sup>18</sup> CYP2C19\*3 is the phenotype which comprises approximately 25% of the defective gene among East Asians which was initially found in a Japanese poor metabolizer population.<sup>17</sup> But it was discovered that the above mentioned phenotype is significantly rare among non-East Asian sub-population.<sup>19</sup> The incidence of

the poor metabolizer phenotype in European whites,<sup>7</sup> and the residents of Vanuatu Island as well as Melanesia subjects,<sup>20</sup> at a rate of 3-5% and 70%, respectively. The incidence of CYP2C19\*2 and CYP2C19\*3 alleles among north Indian subjects was reported to be as 29.7% and 0.00%, respectively.<sup>21</sup> In an other study, the frequency of CYP2C19\*2 and CYP2C19\*3 alleles among South Indian of Tamil, Telgu, Kannada, and Malayalam backgrounds were reported to be 35% and 1%, respectively.<sup>22</sup> The narrow therapeutic index of some drugs in particular are important safety in determining the drug metabolic capacity indications of some individual by applying the necessary phenotype and genotype standards to provide a safe guard for susceptible subjects. The aim of this study was to assess the distribution of CYP2C19 allele and genotypic variants among the Turkman ethnic group in comparison with other populations.

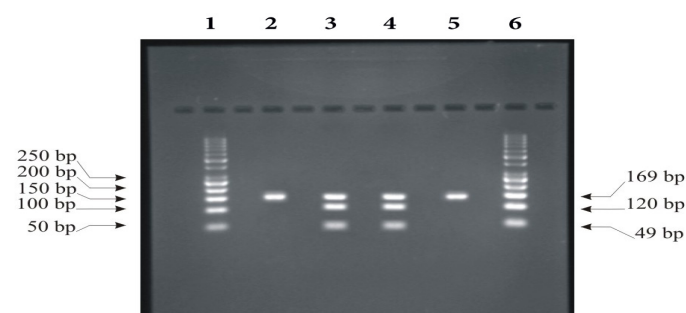
## Methods

The study group included 140 unrelated healthy subjects of Turkman origin (people who speak Turkman as a native language and population inbreeding people) who were referred to the Health Center in Gonbadkavoos (located in North Eastern Iran, South East of the Caspian Sea). This present study, set to establish the prevalence of CYP2C19 variants in a sample of Turkman ethnic group and compare the collected data with other populations. Ethical approval was obtained from the ethics committee of Golestan University of Medical Sciences and informed consent was obtained from all participants.

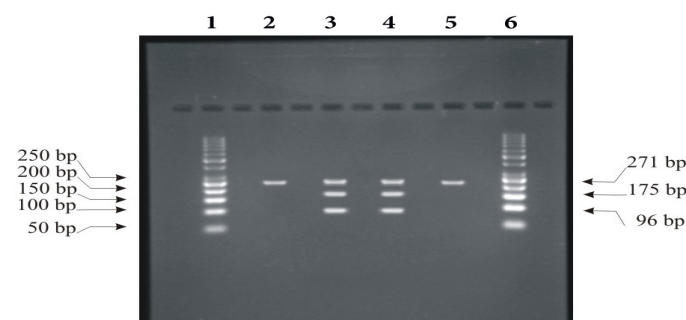
Five milliliters of venous blood was sampled from each subject and collected into EDTA tubes. Extraction of DNA from peripheral white blood cells was done by salting out method.<sup>23</sup> DNA extract was dissolved in sterilized distilled water and samples were kept in -20°C until analysis by polymerase chain reaction (PCR).

Genotyping of CYP2C19 alleles (CYP2C19\*1, CYP2C19\*2, and CYP2C19\*3 alleles) was carried out by Polymerase Chain Reaction (PCR)-Restriction Fragment Length Polymorphism (RFLP) technique.<sup>24</sup> PCR was done in 25 microliter mixture containing PCR buffer 10 mM Tris-HCl, pH 9, 1.5 mM MgCl<sub>2</sub> (Fermentase, Burlington; Canada), 50 mM KCl (Fermentase, Burlington; Canada), 10 mM deoxyribonucleotide triphosphate (dNTP) mix, 5 U/μl Taq polymerase (Fermentase, Burlington; Canada), 5 pM of each primer (Bioneer; Korea), 500 ng DNA (Genomic; Korea) and sterile distilled water. PCR was carried out in a genetix CG palm-thermocycler (New Delhi; India). PCR products (10μl) were digested with restriction enzymes (Fermentase; Burlington; Canada), (SmaI for CYP2C19\*2 and BamHI for CYP2C19\*3) at 30°C and 37°C for 16 hrs for complete digestion, respectively. Primers amplification was done as described by De Morais et al.<sup>17</sup> The DNA fragments were electrophoresed (Apelex, France) on a 2% (for CYP2C19\*3) and 3% (for CYP2C19\*2) agarose gel and stained with Ethidium bromide. Bands were detected by a short wavelength UV transluminator, photographed using a Polaroid Gel Camera with Polaroid black and white film. The CYP2C19\*2 mutation was detected using

sense primer 5'-AATTACAACCAGAGCTTGGC-3' and antisense primer 5'-TATCACTTTCCATAAAAGCAAG-3'. The detection of CYP2C19\*3 was carried out using sense primer 5'-AAATTGTTTCCAATCATTTAGCT-3' and antisense primer 5'-ACTTCAGGGCTTGGTCAATA-3'. The PCR amplification conditions for CYP2C9\*2 and CYP2C9\*3 were as follow: Initial denaturation, Number of cycle(s), Denaturation, Extension and Final extension step, which were 94°C, 300 sec.; 37; 94°C, 60 sec.; 72°C, 30 sec. and 72°C, 300 sec., respectively. The annealing temperature and time for CYP2C9\*2 and CYP2C9\*3 were 55°C, 30 sec. and 52°C, 45 sec., respectively. The Products of PCR before and after restriction enzyme digestion for CYP2C9\*2 and CYP2C9\*3 genotypes are summarized in Fig. 1 and 2, respectively.



**Figure 1:** PCR-restriction enzyme (SmaI digestion) fragmentation patterns on the agarose gel is stained by ethidium bromide for CYP2C19\*2 from subjects representing \*1/\*1, \*1/\*2, \*1/\*2, and \*1/\*1 genotypes (From 2 to 5 wells, left to right on the agarose gel). DNA ladder was loaded in well 1 and the sizes of the PCR-restriction fragments were loaded in well 6.



**Figure 2:** PCR-restriction enzyme (BamHI digestion) fragmentation patterns on agarose gel is stained by ethidium bromide for CYP2C19\*3 from subjects representing \*1/\*1, \*1/\*3, \*1/\*3, and \*1/\*1 genotypes (From 2 to 5 wells, left to right on the agarose gel). DNA ladder was loaded in well 1 and the sizes of the PCR-restriction fragments were loaded in well 6.

Statistical analysis was done to evaluate allele frequencies of CYP2C19 in Turkman subjects alongside other ethnic groups. The 95% confidence intervals (95% CI) for frequency of the variant alleles of each gene were determined. The observed genotype frequencies of CYP2C19 were observe and compared with expected frequencies according to the Hardy-Weinberg law. Differences in allele frequencies and PM genotype frequencies between the

Turkman ethnic group and other populations from various area were measured by Fisher exact test. Data was analysed using SPSS version 16.0. and statistical significance was considered at  $p < 0.05$ .

## Results

The data revealed mean ages of the participants to be  $29.73 \pm 9.11$  years old. Allele and genotype frequencies of CYP2C19 gene among the Turkman ethnic group are shown in Tables 1 and 2. The allele frequency of CYP2C19\*1 (Wild type), CYP2C19\*2 and CYP2C19\*3 were 56.43% (95% CI: 48.15-64.36), 23.57% (95% CI: 17.31-31.25) and 20% (95% CI: 14.22-27.36), respectively. CYP2C19\*1 was the most frequently (56.43%) determined allele in Turkman ethnic groups. The observed frequencies of CYP2C19 genotypes in Turkman ethnic group were found to be in the Hardy-Weinberg equilibrium (Table 2). The results showed that 39.7% of subjects expressed the CYP2C19\*1/\*1 genotype (95% CI: 30.25-46.11). While 59 (42.1%), 13 (9.3%), 13 (9.3%) and 2 (1.4%) subjects expressed the CYP2C19\*1/\*2 (95% CI: 34.28-50.42), CYP2C19\*1/\*3 (95% CI: 5.51-15.24), CYP2C19\*2/\*2 (95% CI: 5.51-15.24) and CYP2C19\*3/\*3 (95% CI: 0.3-5) genotypes, respectively. There was no expression CYP2C19\*2/\*3 (0%) genotype. Out of the alleles, CYP2C19\*1/\*2 (42.1%) was the most frequently observed mutant allele. Table 3 shows the prevalence of the predicted phenotypes of CYP2C19, which were as follow: 10.7% of subjects were PM carrying the CYP2C19\*2/\*2 and CYP2C19\*3/\*3 genotypes (95% CI: 5.5-15). Fifty one percent of subjects were IM carrying the CYP2C19\*1/\*2, CYP2C19\*2/\*3 and CYP2C19\*1/\*3 genotypes (95% CI: 43-60). Which 37.86% were found to be EM expressing the CYP2C19\*1/\*1 genotype (95% CI: 29.72-45.99). IM genotype frequency was high (51%) in the Turkman ethnic group.

**Table 1:** Allele frequencies of CYP2C19 gene among Turkman ethnic groups ( $n = 140$ ).

Variant allele	n	Frequency (%)	95% CI
CYP2C19*1	79	56.43	48.15-64.36
CYP2C19*2	33	23.57	17.31-31.25
CYP2C19*3	28	20	14.22-27.36

**Table 2:** Genotype frequencies of CYP2C19 gene among Turkman ethnic groups ( $n = 140$ ).

Genotype	n	Observed frequency %	Expected frequency % by Hardy-Weinberg law
CYP2C19*1/*1	53	37.9(30.25-46.11)	40.41
CYP2C19*1/*2	59	42.1(34.28-50.42)	38.6
CYP2C19*1/*3	13	9.3(5.51-15.24)	7.72
CYP2C19*2/*2	13	9.3(5.51-15.24)	9.22
CYP2C19*2/*3	-	0(-)	3.69
CYP2C19*3/*3	2	1.4(0.3-5)	0.37

**Table 3:** Prevalence of CYP2C19 predicted phenotypes in Turkman ethnic groups ( $n = 140$ ) [ $\chi^2$  test,  $p > 0.05$ ].

Genotype	predicted phenotype	Frequency (%)	95% CI
CYP2C19*1/*1	EM	37.86	29.72-45.99
CYP2C19*1/*2, CYP2C19*1/*3 and CYP2C19*2/*3	IM	51	43-60
CYP2C19*2/*2 and CYP2C19*3/*3	PM	10.7	5.5-15

EM: Extensive metabolizers, IM: Intermediate metabolizers, PM: poor metabolizers.

## Discussion

The Turkman ethnic group is a unique population in Iran, due to their population inbreeding, these people were considered to be particularly important in investigating the allele frequencies and genotype distributions of some variants of a pharmacogenetic interest. This is the first study based on the CYP2C19 genotype distribution in this ethnic group. There have been many reports on the genetic polymorphisms of CYP2C. Some studies have reported that the hydroxylation metabolism of S-mephenytoin showed genetic polymorphism.<sup>53,54</sup> It was also determined that this enzyme catalyzes the metabolism of some drugs such as S-mephenytoin, methylphenobarbital, omeprazole, phenytoin, imipramine, proguanil, propranolol and diazepam.<sup>55</sup> It has also reported that CYP2C shows a possible clinical role in determining interindividual and interethnic differences in drug effectiveness.

Change in CYP expression can affect drug response and activity. The ethnic differences in the frequency of CYP2C19 mutant alleles continues to be a significant study topic.<sup>56</sup> In this current study, we assessed the distribution of CYP2C19 variants in the Turkman ethnic group and compared the data with those from other populations. The CYP2C19\*2 variant was the most allele among Turkman ethnic groups. The frequency of this variant was 23.57% in the present study. Its frequency was lower than the figures reported from Chinese (45.5%),<sup>27</sup> Japanese (27.4%),<sup>28</sup> Thai (29%),<sup>30</sup> Karen (28%),<sup>30</sup> Malaysians (28%),<sup>31</sup> Filipino (29%),<sup>32</sup> Vanuatu and other Pacific islands (63.3%),<sup>51</sup> as well as Australian Aborigines (35.5%).<sup>52</sup> The frequency of CYP2C19\*2 has been reported to range from 20.9% to 45.5%, 12%-15%, 35.5%-63.3%, 9.1%-15.9%, 13%-19.1%, 7.8%, 14%-18.8%, 10.9%-19% and 13%-14% in East Asian,<sup>27-32</sup> West Asian,<sup>32-34</sup> Oceanian,<sup>51,52</sup> European,<sup>33,38,39</sup> North American and Canadian,<sup>32,40</sup> South American (Bolivian),<sup>41</sup> Scandinavian,<sup>42-44</sup> African<sup>38,45-50</sup> and Iranian,<sup>25,26</sup> respectively. The frequency of the CYP2C19\*3 allele (20%) was high among the Turkman ethnic group when compared with some East and West Asians,<sup>27,31-34</sup> Oceanian,<sup>51,52</sup> European,<sup>33,38,39</sup> North American and Canadian,<sup>32,40</sup> South American (Bolivian),<sup>41</sup> Scandinavian,<sup>42-44</sup> African<sup>38,45-50</sup> and Iranian<sup>25,26</sup> populations, respectively. All combinations of alleles are shown in Tables 4 and 5. These results appear to suggest that CYP2C19\*2 and CYP2C19\*3 mutations are distinctive in different

ethnic groups. Some studies have shown that the CYP2C19\*2 and CYP2C19\*3 mutant alleles are collaborated with reduced enzyme activity. Clinical studies have shown that patients with CYP2C19\*2 allele showed lower levels of the metabolite's activities. This causes

a decrease in platelet inhibition activity and higher rates of cardiac occurrences.<sup>57</sup> According to various studies, the functional loss of CYP2C19 allelic variants is not in favor of cardiovascular systems following clopidogrel therapeutical regimen.<sup>58-60</sup>

**Table 4:** Comparison of allele frequencies of CYP2C19 of the Turkman ethnic group with different populations.

Population study	Sample size	Allele frequency % ( <i>p</i> -value versus Turkman ethnic group)		
		1	2	3
<b>Iran</b>				
Turkman	140	56.43	23.57	20
Iranian(Tehran) <sup>25</sup>	200	86	14(0.04)	0(<0.001)
Iranian (Southern) <sup>26</sup>	150	86.73	13(0.001)	1(<0.001)
<b>East Asia</b>				
Chinese <sup>27</sup>	121	50	45.5 (<0.001)	4.5(0.005)
Japanese <sup>28</sup>	217	61.8	27.4(NS)	10.8(0.013)
Koreans <sup>29</sup>	103	67.5	20.9(NS)	11.7(NS)
Thai <sup>30</sup>	774	68	29(NS)	3(<0.001)
Burmese <sup>30</sup>	127	66	30(NS)	4(<0.001)
Karen <sup>30</sup>	131	71	28(NS)	1(<0.001)
Malaysians <sup>31</sup>	142	66	28(NS)	6(<0.001)
Filipino <sup>32</sup>	52	54	39(0.040)	8(0.042)
<b>West Asia</b>				
Turkish <sup>33</sup>	404	87	12(0.001)	0.4 (<0.001)
Jewish Israel <sup>34</sup>	140	84	15(NS)	1(<0.001)
Saudi Arabia <sup>32</sup>	97	85	15(NS)	0(<0.001)
<b>Europe</b>				
Russians <sup>35</sup>	290	88	11.4 (0.001)	0.3 (<0.001)
Italians <sup>36</sup>	360	88.9	11.1 (0.001)	0 (<0.001)
Croatians <sup>37</sup>	200	85	15 (0.045)	0 (<0.001)
Belgian <sup>38</sup>	121	90	9.1 (0.001)	0 (<0.001)
Germans <sup>33</sup>	328	84	15.9 (0.047)	0.2 (<0.001)
Portuguese <sup>39</sup>	153	87	13 (0.001)	0 (<0.001)
<b>North America and Canada</b>				
Canadian Native Indian <sup>40</sup>	115	80.9	19.1(NS)	0 (<0.001)
Americans <sup>32</sup>	105	87	13(0.044)	0 (<0.001)
<b>South America</b>				
Bolivian <sup>41</sup>	778	92.1	7.8(0.001)	0.1 (<0.001)
<b>Scandinavia</b>				
Faroese <sup>42</sup>	310	81.8	18.8(NS)	0 (<0.001)
Swedish <sup>43</sup>	83	85	14(NS)	0.1 (<0.001)
Danish <sup>44</sup>	239	84	16(NS)	0 (<0.001)
<b>Africa</b>				
African Americans <sup>45</sup>	517	81	19(NS)	0 (<0.001)
Egyptians <sup>46</sup>	247	88.8	10.9(0.001)	0.2 (<0.001)
Ethiopians <sup>47</sup>	114	85	14(NS)	3 (<0.001)
Tansanians <sup>48</sup>	251	81	18(NS)	1 (<0.001)
Zimbabweans <sup>49</sup>	84	87	13(NS)	0 (<0.001)
Venda <sup>50</sup>	76	78.3	21.7(NS)	0 (<0.001)
Beninese <sup>38</sup>	111	87	13(0.027)	0 (<0.001)
<b>Oceania</b>				
Vanuatu and other Pacific islands <sup>51</sup>	5538	22.3	63.3 (0.001)	14.4(NS)
Australian aborigines <sup>52</sup>	227	50.1	35.5 (0.015)	14.3(NS)

Differences in the allele frequencies were determined by Fisher exact test. NS: No significant differences.

**Table 5:** Comparison of CYP2C19 genotype and poor metabolizer frequency between Turkman ethnic group and other populations.

Study groups	Sample size	Genotype frequency % ( <i>p</i> -value versus Turkman ethnic group)						PM genotype (%)
		*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	
<b>Iran</b>								
Turkman	140	37.9	42.1	9.3	9.3	0	1.4	10
<b>East Asia</b>								
Chinese <sup>27</sup>	121	-	-	-	-	-	-	24 (0.002)
Japanese <sup>28</sup>	217	-	-	-	-	-	-	15.2 (NS)
Koreans <sup>29</sup>	103	-	-	-	-	-	-	11.7(NS)
Thai <sup>30</sup>	774	44.5	42.6	3.7	6.7	2.1	0.4	9.2(NS)
Burmese <sup>30</sup>	127	44.1	39.4	5.5	9.4	1.6	0	11(NS)
Karen <sup>30</sup>	131	51.1	39.7	0.8	7.6	0.8	0	8.4(NS)
Malaysians <sup>31</sup>	142	42	40	6	6	6.3	1	12.7(NS)
Filipino <sup>32</sup>	104	-	-	-	-	-	-	25(NS)
<b>West Asia</b>								
Turkish <sup>33</sup>	404	76	22.3	0.74	0.9	0	0	1(<0.001)
Jewish Israel <sup>34</sup>	140	70.7	26.4	1.4	2	0	0	2.8(0.015)
Saudi Arabia <sup>32</sup>	97	-	-	-	-	-	-	2(0.017)
<b>Oceania</b>								
Vanuatu and other Pacific islands <sup>51</sup>	5,538	-	-	-	-	-	-	61(<0.001)
Australian aborigines <sup>52</sup>	227	-	-	-	-	-	-	25.6(<0.001)
<b>Europe</b>								
Russians <sup>35</sup>	290	78.7	19	0.3	1.7	0.3	0	2(<0.001)
Italians <sup>36</sup>	360	79.4	18.9	0	1.7	0	0	1.7(<0.001)
Croatians <sup>37</sup>	200	73	24	0	3	0	0	3(<0.001)
Belgian <sup>38</sup>	121	83.5	15	0	1.6	0	0	1.6(0.005)
Germans <sup>33</sup>	328	-	-	-	-	-	-	4.3(0.017)
Portuguese <sup>39</sup>	153	-	-	-	-	-	-	1(NS)
<b>North America and Canada</b>								
Canadian Native <sup>40</sup> Indian <sup>32</sup>	115	-	-	-	-	-	-	7(NS)
Americans	105	-	-	-	-	-	-	2(0.011)
<b>South America</b>								
Bolinian <sup>41</sup>	778	85.3	13.5	0.1	1	0	0	1(0.001)
Faroese <sup>42</sup>	310	66.2	31.2	0	3.2	0	0	3.2(0.003)
Swedish <sup>43</sup>	83	71	27	1	1	0	0	1.2(0.011)
Danish <sup>44</sup>	239	71.5	24.7	0	3.8	0	0	3.8(0.014)
<b>Africa</b>								
AfricansAmericans <sup>45</sup>	517	66	30	0	3	0.1	0	3.7(0.002)
Egyptians <sup>46</sup>	247	78.6	20.2	0.4	0.8	0	0	0.8(0.001)
Ethiopians <sup>47</sup>	114	75	19	1	3	3	0	5.3(NS)
Tanzanians <sup>48</sup>	251	66	30	1	3	0	0	3.2(0.005)
Zimbabweans <sup>49</sup>	84	77	19	0	4	0	0	3.6(NS)
Venda <sup>50</sup>	76	61.8	32.9	0	5.3	0	0	7(NS)
Beninese <sup>38</sup>	111	74	26.1	0	0	0	0	0 (<0.001)

Differences in the allele frequencies were determined by Fisher exact test. NS: No significant differences.

In a separate study, it was shown that CYP2C19 allelic variants functional loss did not have any adverse effect on the safety and efficacy of clopidogrel among patients with acute coronary diseases.<sup>61</sup> Comparison of the Turkman ethnic group with other ethnic populations indicates differences and resemblances in

the distribution of CYP2C19 allele and PM genotype. The differences may be associated with racial origin, geographical distribution and environmental factors, etc. Differences in the frequency of CYP2C19 polymorphism in different populations have epidemiologic importance. The frequency of CYP2C19\*2 is

reported to be around 10% worldwide. Studies have shown that the frequency of CYP2C19\*2 generally increases sequentially from Western Asia, Iran to India and Melanesian (with higher than 75% rate). On the other hand, CYP2C19\*3 frequency exhibits the same direction. The increase begins in Eastern Asia with the highest prevalency in Melanesia with 33%, but it has been observed that its frequency in other part of the world is very low (lower and/or equal to 1%). The frequency of CYP2C19 variant can be as high as 90% in other regions of the world.<sup>62</sup>

CYP2C19 polymorphism is related to metabolism of some important drugs.<sup>55,56</sup> CYP 2C19 phenotypes are reported to affect clinical benefit of several drugs, such as proton pump inhibitors, clopitogrel, sertraline, escitalopram, moclobemide and voriconazol.<sup>63</sup> Gastric acid-related abnormalities can be treated with the drug inhibitors and the proton pump inhibitors are sequentially metabolized by CYP2C19 in the liver. CYP2C19 from different genetic backgrounds metabolize the above mentioned drug differently and studies have shown that Japanese and Caucasians poor metabolizers respond properly to the drug with therapeutic dosage, but extensive metabolizers have been shown to have no effect on the above drug at therapeutic dosage.<sup>64-66</sup> In a recent clinical trial study, the advantage of CYP2C19 genotype sub-population in having a good response to the proton pump inhibitor in therapeutic dosage was confirmed.<sup>67</sup> The finding from another study indicated that Asian populations represent slower metabolism of diazepam than Caucasians. This may depend on the high frequency of the mutant CYP2C19\*2 and CYP2C19\*3 alleles in Asian populations.<sup>56</sup> Toxic doses of diazepam may arise as the result of slower metabolism in PMs. Thus, extra care must be taken with the dosage of diazepam in Asian populations. Subjects with the variants CYP2C19\*2 or CYP2C19\*3 can demonstrate abnormality in metabolism for drugs such as diazepam, with adverse drug reactions.

The present study showed that PM genotype frequency was highly (10.7%) expressed among the Turkman ethnic group when compared with West Asian,<sup>32-34</sup> Europeans,<sup>33,35-39</sup> North and South Americans,<sup>32,40,41</sup> as well as Scandinavians,<sup>42-44</sup> and Africans.<sup>45-49</sup> While PM genotype frequency in the Turkman ethnic group was lower than some East Asian<sup>27-32</sup> and Oceanian<sup>51,52</sup> populations. Moreover, our study showed that the frequency of poor metabolizers in the Turkman ethnic group (10.7%) is relatively close to Thai (9.2%) and Burmese (11%) populations.<sup>30</sup>

## Conclusion

This study confirms the ethnic differences in the CYP2C19 allele and genotype frequencies. Our results also showed that the determined allelic variants of CYP2C19 (CYP2C19\*2 and CYP2C19\*3 mutations) in the Turkman ethnic group are comparable to other populations. Overall, the determination of CYP2C19 variants in different ethnic groups can be very useful for clinicians to determine the optimal dosage and efficacy of drugs metabolized by this polymorphic enzyme.

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