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SHORT COMMUNICATION

Frequencies of genotypes and alleles of the functional SNPs in *CYP2C19* and *CYP2E1* in mainland Chinese Kazakh, Uygur and Han populations

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CYP2C19 **and** ***CYP2E1*** **show great genetic differences between Orientals and Caucasians. The objective of this study was to investigate the genotype and allele distribution patterns of** ***CYP2C19*** **and** ***CYP2E1*** **polymorphisms among healthy participants in mainland Chinese Kazakh, Uygur and Han populations by the PCR–restriction fragment length polymorphism technique. The allele frequencies of** ***CYP2C19*2***, ***CYP2E1*5B*** **and** ***CYP2E1*6*** **were significantly lower in the Chinese Kazakh (15.4, 11.2 and 14.5%, respectively) ($P<0.05$) and Uygur (16.1, 12.1 and 18.8%) ($P<0.05$) populations than that in the Chinese Han population (28.8, 19.4 and 26.2%), but the frequencies of** ***CYP2C19*3*** **were similar among the three populations (8.0, 9.4 and 7.2%). Frequencies of the three combined genotypes, one for predicted CYP2C19 poor metabolizers and two for predicted high levels of CYP2E1 transcription, were significantly lower in the Chinese Kazakh (7.5, 19.6 and 28.0%, respectively) ($P<0.05$, χ^2-test) and Uygur (8.1, 22.8 and 33.6%) ($P<0.05$) populations compared with the Chinese Han population (16.5, 35.9 and 44.7%). The present research shows that frequencies of the functional single-nucleotide polymorphisms in the** ***CYP2C19*** **and** ***CYP2E1*** **genes vary in the Chinese Kazakh, Uygur and Han populations, suggesting that disease susceptibilities or drug responses associated with enzyme activities of CYP2C19 and CYP2E1 may differ in the diverse ethnic populations in mainland China.**

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INTRODUCTION

The cytochrome P450 enzymes (CYP) metabolize many therapeutic drugs, endogenous hormones and xenobiotic toxins/carcinogens. Genetic polymorphisms in the CYP genes may cause differences in enzyme activities or gene expression, which may be responsible for interindividual and interethnic variabilities in drug response and carcinogenetic susceptibility.[1–3]

CYP2C19 is one of the most polymorphic CYP genes in diverse racial groups.[4,5] Two variant alleles account for the majority of the defective genotypes, namely *CYP2C19*2* (rs4244285), which carries a 681G>A change in exon 5 causing an aberrant splice site, and *CYP2C19*3* (rs4986893), which has a 636G>A change in exon 4 producing a premature stop codon. It has been recognized that the prediction of CYP2C19 phenotypes can be achieved by genotyping *CYP2C19*2* and *CYP2C19*3* in a population.[6] On the basis of *CYP2C19* genotypes, individuals can be grouped into poor metabolizer genotypes (PMs, the sum of homozygous and heterozygous genotypes of *CYP2C19*2/*2*, **3/*3* and **2/*3*) and extensive metabolizer genotypes (EMs, *CYP2C19*1/*1*, **1/*2* and **1/*3*).[7] CYP2C19 PMs may suffer undesirable adverse effects with a normal dose of a drug inactivated by CYP2C19, and may also show decreased responses to drugs that need to be activated by CYP2C19.

CYP2E1 is known to metabolize and activate many low molecular weight compounds, drugs and procarcinogens. The two single-nucleotide polymorphisms (SNPs) (−1053C>T, rs3813867 and −1293G>C, rs2031920) in the 5′ flanking transcription regulatory region of this gene are in linkage disequilibrium, namely as *CYP2E1*5B*. This allele is associated with a higher transcriptional level of CYP2E1 expression and an increased risk of hepatocarcinogenetics.[8] Moreover, another SNP of *CYP2E1*6* (7632T>A, rs6413432) was found in intron 6 of the *CYP2E1* gene, and the higher frequency of *CYP2E1*6* was associated with the alcohol-related hepatic disease.[9] Recently, it has been shown that the frequencies of the *CYP2E1*5B* and **6* alleles in Orientals were significantly higher than those in Caucasians.[10]

In our earlier studies, the frequencies of genetic polymorphisms in the *CYP3A5* and *MDR1* (multidrug resistance 1) genes in the Chinese Uygur and Kazakh populations, who reside in the Xinjiang Autonomous Region of northwestern China with genetic admixture between Orientals and Caucasians, were observed and compared with that of

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the Chinese Han population.[11] The purpose of this study was to further investigate the frequencies of the functional SNPs in the *CYP2C19* and *CYP2E1* genes in the three mainland Chinese Kazakh, Uygur and Han populations, and to compare them with those previously reported in the Caucasian population.

MATERIALS AND METHODS

A total of 359 unrelated mainland Chinese healthy participants, including 103 Chinese Han, 107 Chinese Kazakh and 149 Chinese Uygur, were recruited for the genotyping study. Each participant had the same ethnic origin for at least three generations. All the Chinese Uygur and Kazakh participants resided in the Xinjiang Autonomous Region of China. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Beijing University. Written informed consent was obtained from all participants.

CYP2C19 and *CYP2E1* genotyping were performed by PCR followed by restriction fragment length polymorphism similar to previously described methods with little modifications.[5,10] Fragments of the genomic regions of the selected SNPs were amplified by a PTC-100 Peltier Thermal Cycler (MG Research Inc., Waltham, MA, USA). The detailed information regarding primers, conditions and products of PCR amplification, and restriction endonuclease digestion for genotyped SNPs is listed in Table 1.

Distributions of genotypes and alleles were compared by χ^2 and Fisher's exact tests between different ethnic groups. $P<0.05$ was considered to be significant in the comparison.

RESULTS AND DISCUSSION

Both frequencies of the *CYP2C19* and *CYP2E1* genotypes met the Hardy–Weinberg equilibrium in three ethnic groups. Similarly, frequencies of the *CYP2C19* and *CYP2E1* alleles were within the 95% confidence interval.

The genotype distributions of *CYP2C19* in the three mainland Chinese ethnic groups are shown in Table 2. The frequencies of the *CYP2C19* PM genotypes in the Chinese Kazakh (7.5%, $P<0.05$) and

Table 1 Selected primers, conditions and products of PCR amplification and restriction endonuclease digestion for the *CYP2C19* and *CYP2E1* genotyping

SNPs	*Primer sequence*	*Tm/extention time*	*PCR product (bp)*	*Restriction endonuclease*	*Incubation temperature*	*Digested product (bp)*
*CYP2C19*2* (681 G>A)	F:CAGAGCTTGGCATATTGTATC R:GTAAACACACAACTAGTCAATG	53 °C/20 s	321	*Sma I*	30 °C	212, 109
*CYP2C19*3* (636 G>A)	F:TATGAAGTGTTTTATATCTAATGTTTACTCA R: ACTTCAGGGCTTGGTCAATATAGA	50 °C/45 s	309	*BamH I*	37 °C	213, 96
*CYP2E1*5B* (−1293G>C; −1053C>T)	F: CCAGTCGAGTCTACATTGTCA R: TTCATTCTGTCTTCTAACTGG	53 °C/60 s	410	*Rsa I or Pst I*	37 °C	360, 50 or 290, 120
*CYP2E1*6* (7632T>A)	F: AGTCGACATGTGATGGATCCA R: GACAGGGTTTCATCATGTTGG	63 °C/45 s	375	*Dra I*	37 °C	249, 126

Table 2 Frequencies of the *CYP2C19* genotypes and alleles in mainland Chinese Han (n=103), Kazakh (n=107) and Uygur (n=149) ethnic populations, compared with those reported earlier in Caucasians (n=360)[5]

		Frequency % (n)			
Genotypes and alleles	*Predicted phenotype*	*Chinese Han*	*Chinese Kazakh*	*Chinese Uygur*	*Caucasians*
CYP2C19 genotype					
**1/*1*	EM	43.7 (45)$^{\#\#}$	60.7 (65)$^{*,\#\#}$	57.0 (85)$^{*,\#\#}$	79.4 (286)**
**1/*2*	EM	33.0 (34)$^{\#\#}$	21.5 (23)	22.1 (33)	18.9 (68)**
**1/*3*	EM	6.8 (7)$^{\#\#}$	10.3 (11)$^{\#\#}$	12.8 (19)$^{\#\#}$	0.0 (0)**
	Total EM	83.5 (86)$^{\#\#}$	92.5 (99)$^{*,\#\#}$	91.9 (137)$^{*,\#\#}$	98.3 (354)**
**2/*2*	PM	9.7 (10)$^{\#\#}$	3.7 (4)	3.4 (5)*	1.7 (6)**
**3/*3*	PM	1.0 (1)	1.9 (2)	1.3 (2)	0.0 (0)
**2/*3*	PM	5.8 (6)$^{\#\#}$	1.9 (2)	3.4 (5)$^{\#\#}$	0.0 (0)**
	Total PM	16.5 (17)$^{\#\#}$	7.5 (8)$^{*,\#\#}$	8.1 (12)$^{*,\#\#}$	1.7 (6)**
CYP2C19 allele					
**1*		64.0 (133)$^{\#\#}$	76.6 (164)$^{**,\#\#}$	74.5 (222)$^{*,\#\#}$	88.9 (640)**
**2*		28.8 (60)$^{\#\#}$	15.4 (33)**	16.1 (48)$^{**,\#}$	11.1 (80)**
**3*		7.2 (15)$^{\#\#}$	8.0 (17)$^{\#\#}$	9.4 (28)$^{\#\#}$	0.0 (0)**

Abbreviations: EM, extensive metabolizer; PM, poor metabolizer.
Frequencies of genotypes and alleles were calculated according to the Hardy–Weinberg equation and were within the 95% confidence interval.
$^{*}P<0.05$, $^{**}P<0.01$ compared with Chinese Han group by χ^2 test.
$^{\#}P<0.05$, $^{\#\#}P<0.01$ compared with Caucasians group by χ^2 test.

Table 3 Frequencies of the *CYP2E1* genotypes and alleles in mainland Chinese Han (n=103), Kazakh (n=107) and Uygur (n=149) ethnic populations, compared with those reported earlier in Caucasians (n=264)[10]

		Frequency % (n)			
Genotypes and alleles	*Predicted phenotype*	*Chinese Han*	*Chinese Kazakh*	*Chinese Uygur*	*Caucasians*
CYP2E1genotype					
Rsa I or Pst I site					
**1A/*1A*	Normal	64.1 (66)$^{\#\#}$	80.4 (86)$^{**,\#\#}$	77.2 (115)$^{*,\#\#}$	93.2 (246)**
**1A/*5B*	HTA	33.0 (34)$^{\#\#}$	16.8 (18)$^{**,\#\#}$	21.5 (32)$^{*,\#\#}$	6.1 (16)**
**5B/*5B*	HTA	2.9 (3)	2.8 (3)	1.3 (2)	0.7 (2)
**1A/*5B+*5B/*5B*	Total HTA	35.9 (37)$^{\#\#}$	19.6 (21)$^{**,\#\#}$	22.8 (34)$^{*,\#\#}$	6.8 (18)**
Dra I site					
**1A/*1A*	Normal	55.3 (57)$^{\#\#}$	72.0 (77)*	66.4 (99)$^{\#}$	77.7 (205)**
**1A/*6*	HTA	36.9 (38)$^{\#\#}$	27.1 (29)	29.6 (44)	22.0 (58)**
**6/*6*	HTA	7.8 (8)$^{\#\#}$	0.9 (1)*	4.0 (6)$^{\#}$	0.3 (1)**
**1A/*6+*6/*6*	Total HTA	44.7 (46)$^{\#\#}$	28.0 (30)*	33.6 (50)$^{\#}$	22.3 (59)**
CYP2E1 allele					
Rsa I or Pst I site					
**1A*		80.6 (166)$^{\#\#}$	88.8 (190)$^{*,\#\#}$	87.9 (262)$^{*,\#\#}$	96.2 (508)**
**5B*		19.4 (40)$^{\#\#}$	11.2 (24)$^{*,\#\#}$	12.1 (36)$^{*,\#\#}$	3.8 (20)**
Dra I site					
**1A*		73.8 (152)$^{\#\#}$	85.5 (183)**	81.2 (242)$^{*,\#\#}$	88.6 (468)**
**6*		26.2 (54)$^{\#\#}$	14.5 (31)**	18.8 (56)$^{*,\#\#}$	11.4 (60)**

Abbreviation: HTA, higher transcriptional activity.
Frequencies of genotypes and alleles were calculated according to the Hardy–Weinberg equation and were within the 95% confidence interval.
$^{*}P<0.05$, $^{**}P<0.01$ compared with Chinese Han group by χ^2 test.
$^{\#}P<0.05$, $^{\#\#}P<0.01$ compared with Caucasians group by χ^2 test.

Uygur (8.1%, $P<0.05$) populations were significantly lower than that in the Chinese Han population (16.5%), but higher than that reported in the Caucasian population (1.7%, $P<0.01$). The present data support earlier results[7,12–14] and suggest that the frequencies of the *CYP2C19* PM genotypes in the mainland Chinese Kazakh and Uygur populations exist between those in the Chinese Han and Caucasian populations.[15]

As shown in Table 2, the frequencies of the prevalent defective allele of *CYP2C19*2* in both the Chinese Kazakh (15.4%, $P<0.01$) and Uygur (16.1%, $P<0.01$) populations were significantly lower than that in the Chinese Han population (28.8%). It was reported that the allele frequency of *CYP2C19*3* had been regarded as a unique Asian variant allele that accounted for the CYP2C19 PM phenotype in Oriental populations, which are a rare occurrence in the Caucasian populations.[5] In the present results, the *CYP2C19*3* allele was observed in the Chinese Kazakh (8.0%) and Uygur (9.4%) populations, and both frequencies were similar to that of the Chinese Han population (7.2%), but significantly higher than that in the Caucasian population (0%, $P<0.01$). We speculated that the possibly higher frequencies of *CYP2C19*3* in the Chinese Uygur and Kazakh participants might be due to the genetic Eurasian admixture between the Caucasoid and Mongoloid populations, namely genetic excursion induced by emigration along the ancient Silk Road.[16]

As shown in Table 3, at the *CYP2E1* polymorphic sites digested by *Rsa I* or *Pst I* endonucleases, frequencies of the *CYP2E1* genotypes associated with higher gene transcription (the sum of genotypes of heterozygous *CYP2E1*1A/*5B* and homozygous *CYP2E1*5B/*5B*) in the Chinese Han population (35.9%) were significantly higher than that reported earlier in the Caucasian population (6.8%, $P<0.01$).[10] Intermediated frequencies were observed in the Chinese Kazakh (19.6%, $P<0.01$) and Uygur (22.8%, $P<0.05$) populations. Similarly, for *CYP2E1*6* digested by the *Dra I* enzyme, compared with the frequency in the Chinese Han population (44.7%), lower frequencies of CYP2E1 variants (the sum of *CYP2E1*1A/*6* and *CYP2E1*6/*6* genotypes) were observed in the Chinese Kazakh (28.0%, $P<0.05$) and Chinese Uygur populations (33.6%).

Furthermore, the allele frequency of *CYP2E1*5B* in the Chinese Han (19.4%, $P<0.01$), Kazakh (11.2%, $P<0.01$) and Uygur (12.1%, $P<0.01$) populations was significantly higher than that reported in the Caucasian population (3.8%). However, compared with the *CYP2E1*6* allele frequency in the Caucasian population (11.4%), significant differences were observed in the mainland Chinese Han (26.2%, $P<0.01$) and Chinese Uygur (18.8%, $P<0.05$) populations, but no significant difference was observed in the Chinese Kazakh population (14.5%), leading to speculation that this discrepancy might be due to the ethnic complexity of this Eurasian admixed population. The present results support the proposition that the P450 genetic distances were well correlated with the geographic distances across Eurasian populations,[17] and indicate potential relevance to clinical decision making.

In summary, the present research shows that frequencies of the functional SNPs in the *CYP2E1* and *CYP2C19* genes vary among the mainland Chinese Han, Kazakh and Uygur populations. Both of the latter were origins of Eurasian admixture between the Oriental and Caucasian populations. These results suggest that disease susceptibilities and drug responses associated with enzyme activities of CYP2C19 and CYP2E1 may vary in the diverse ethnic populations in mainland China.

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