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Genetic polymorphism analysis of cytochrome P4502E1 (CYP2E1) in a Chinese Tibetan population

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Abstract

Cytochrome P4502E1 (CYP2E1) gene genetic polymorphisms vary markedly in frequency among different ethnic and racial groups.

We studied the genotype distributions and allele frequencies of 3 *CYP2E1* polymorphisms: *CYP2E1**1A, *CYP2E1**7A, and *CYP2E1**7C by polymerase chain reaction technique in a sample of 100 healthy subjects representing Tibetan population.

The frequencies of *CYP2E1**1A, *7A, and *7C alleles were 0.705, 0.125, and 0.170, respectively. Compared with other populations, we found that the allele frequencies of the variants −352A>G (rs2070672) and −333A>T (rs2070673) in this Tibetan population have significant differences compared with European-American, African-American, Japanese, Korean, and other different geographic areas in Chinese Han population. Furthermore, the results of protein prediction revealed that the variant 6397G>A (rs61710826) could influence the protein structure and function.

These findings in this study would be valuable for pharmacogenetics for drug therapy and drug discovery. However, further studies in larger samples are warranted to confirm our results.

Abbreviations: CYP2E1= cytochrome P4502E1, DNA = deoxyribonucleic acid, EDTA = ethylene diamine tetraacetic acid, PCR = polymerase chain reaction, PolyPhen-2 = polymorphism phenotyping v2, SIFT = sorting intolerant from tolerant.

Keywords: *CYP2E1* gene, genetic polymorphism, Tibetan population

1. Introduction

The cytochrome P450 (CYP450) enzymes play a central role in the oxidative metabolisms of exogenous and endogenous compounds, including drugs, food additives, industrial solvents, and pollutants, converting them to reactive metabolites.[1] Besides detoxification, many CYP isoforms catalyze the metabolic activation of procarcinogens to their ultimate carcinogenic forms.[2] However, CYP450 enzymes show extensive structural differences due to genetic polymorphisms in the corresponding genes, which give rise to the absence of gene product, enzymes with increased, reduced or altered activity, or alteration in enzyme regulation, which may be responsible for interindividual and interethnic variabilities in drug response and carcinogenetic susceptibility.[3–5] Therefore, the individualized drug therapy based on genotype analysis can effectively reduce adverse effects and improve drug efficacy. Some genotype–phenotype analysis of CYP450 gene, such as *CYP3A4*,[6] and *CYP2C19*[7,8] have been reported in Chinese minority population.

The cytochrome P4502E1 (CYP2E1), as a member of the cytochrome P450 superfamily, is responsible for the metabolic activation of many low-molecular weight compounds, such as ethanol, benzene, vinyl chloride, and N-nitrosamines.[9,10] Compared with other cytochromes P450, the CYP2E1 enzyme has a relatively high redox potential and can induce peroxidation (lipid and NADPH dependent) or other oxidative stress causing the production of reactive oxygen species.[11,12] Therefore, the CYP2E1 enzyme is considered an important source of reactive oxygen species in alcohol-induced liver injury.[13] In addition, it has been reported that endogenous and exogenous substrates, which might be associated with human susceptibility to toxicity and carcinogenicity caused by industrial and environmental chemicals, can regulate the CYP2E1 level.[14] The human *CYP2E1* gene is located in 10q24.3-qter region of chromosome 10.[15] Some polymorphisms in the *CYP2E1* have been reported to be associated with the risk of cancer[16,17] and other diseases.[18,19] However, previous studies demonstrated that the alleles and genotypes frequencies of *CYP2E1* polymorphisms

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have significant differences among different ethnic and racial groups.[20–22] The *CYP2E1* polymorphisms can cause the differences of interindividual drug metabolism and liver injury, or even severe adverse drug reaction.

The Tibetan population is a minority ethnic group in China with unique lifestyle, diverse genetic background, dietary habit, culture, and geographical environment. According to 2014 Census, Tibetans with a population of 2.2 million live mostly in the Tibet Autonomous Region and the 10 Tibetan Autonomous Prefectures in Gansu Qinghai, Sichuan, and Yunnan provinces of China. We systematically screened some *CYP2E1* gene polymorphisms of 100 healthy, unrelated Tibetans for polymorphisms and compared the allelic frequencies with those in the ethnic China population. Our study hope to find corresponding phenotypes and offer recommendations pertaining to the drug substrates of *CYP2E1* in the Tibetan population.

2. Materials and methods

2.1. Subjects

A total of 100 unrelated Tibetan Chinese healthy subjects consisted of 50 males and 50 females were recruited for the population genetics study. The subjects selected were deemed healthy based on their medical history and a physical examination. All participants resided in the Xinjiang Autonomous Region of China and had the Tibetan paternal ancestry for at least 3 generations. The study protocol was approved by the Ethics Committee of Xizang Minzu University and performed in accordance with the Declaration of Helsinki. We informed each subject about the experimental procedures and the purpose of the study and written informed consent was obtained from all participants before enrollment in the study.

2.2. PCR and DNA sequencing

Five milliliter peripheral venous blood sample was collected from each participant in EDTA (ethylene diamine tetraacetic acid) containing vacuumed tube, and the genomic DNA (deoxyribonucleic acid) was extracted from the of the using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Ltd., Xi'an, China) according to the manufacturer's instructions. The primers for polymerase chain reaction (PCR) were designed to amplify the exons and the 3′-untranslated region of the *CYP2E1* gene using a standard procedure, and the sequences are listed in Table 1.

PCR was performed in a total volume of 10 μL reactions containing 5 μL HotStar Taq Master Mix, 1 μL of template DNA, 0.5 μL each primer (5 μM), and 3 μL deionized water. Thermal cycling conditions were at 95°C for 15 minutes (denaturation), followed by 35 cycles at 95°C for 30 seconds (denaturation), 55°C to 64°C for 30 seconds (annealing), 72°C for 1 minute (extension), and a final extension at 72°C for 3 minutes to hold. The PCR products were purified by incubating with 0.5 mL shrimp alkaline phosphate (Roche, Basel, Switzerland), 1.5 mL deionized water, and 8 mL HotStar PCR product, for a total volume of 10 mL, at 38°C for 30 minutes, followed by heat inactivation at 80°C for 15 minutes. The purified PCR products were directly sequenced using an ABI Prism BigDye Terminator Cycle Sequencing Kit version 3.1 (Applied Biosystems Inc., Foster City, CA) on an ABI Prism3100 sequencer (Applied Biosystems). We used specific primers to detect deletions and duplications of *CYP2E1*.

Table 1

Primers used for *CYP2E1* amplification.

Region	Forward primer	Reverse primer
UTR&Exon1	CTCAGACAAACCTCCTCATCAGAC	GTCGCTCCAGGATGCTATCAAT
Exon2	GACGTGAGGAGCCGGAGT	TGGACGAAGCCACCTGTACC
Exon3	GTGGGAGGTGTTCTTGGAGT	ACGAAAGATAGTGAATGTCTGAACC
Exon4	TGCGTATCTGCTGCCTAGC	GTGTCCTTCTTGGGCACCAT
Exon5	TATGTGATAGACAGGACTGCAA	GGCTTCTCCTCAGACAAAATG
Exon6	GGAGCCCACACTGATTTCCC	ACTGGGACATTATCTTCTCTGTCAT
Exon7	TGGATGGATGGAGGGGTTTAT	TGGAAACCCCCAGTGAAGAAT
Exon8	AAGAGCCTCAGCAGATAGTGC	GGCTTTGATGCTTCCTGTGATG
Exon9&UTR	CCGCTTCCCCTAGTCTCACT	TGAAGTTGTGTGATCCTAGATGGAA

2.3. Data analysis

The initial analyses of the sequences including base calling, fragment assembly, and detection of SNPs, insertions, and deletions were used in the Sequencher 4.10.1 (http://www.genecodes.com/) software. The Human Cytochrome P450 (CYP) Allele Nomenclature Database describes *CYP2E1* variants according to the NCBI reference sequence: NC_000010.11 and CYP allele nomenclature (http://www.cypalleles.ki.se/). The differences of allelic frequencies between Tibetan and other ethnic populations were compared using the χ^2 test with a significance level set at 0.05. Hardy–Weinberg equilibrium for each genetic variant and Linkage disequilibrium (LD) between loci pairs were assessed using Haploview software (version 4.2).[23] The haplotypes were constructed from the selected SNPs and the haplotype frequencies were derived for the Tibetan population.

2.4. Transcriptional prediction

We predicted the protein function of nonsynonymous SNPs (nsSNPs) in *CYP2E1* coding regions used the online tools SIFT (Sorting Intolerant from Tolerant, http://sift.bii.a-star.edu.sg/) and PolyPhen-2 (Polymorphism Phenotyping v2, http://genetics.bwh.harvard.edu/pph2/). The SIFT results were divided into 4 categories based on these scores: tolerant (0.201–1.00), borderline (0.101–0.20), potentially intolerant (0.051–0.10), and intolerant (0.00–0.05).[24] PolyPhen-2 results were divided into 5 categories: benign (0.00–0.15), possibly damaging (0.15–0.85), and probably damaging (0.85–1.00).[25] The prediction accuracy of SIFT and PolyPhen-2 was 63% and 75%, the false positive rate is 19% and 9%, respectively.

3. Results

3.1. Genetic variants

We sequenced *CYP2E1* from our study subjects and successfully identified a total of 23 *CYP2E1* polymorphisms in the Tibetan population. Three polymorphisms were not previously reported in either the NCBI database or the Human Cytochrome P450 Allele Nomenclature Committee tables. Two of the novel polymorphisms (971C>T and 6179C>T) were within in the introns, and the other (11598C>A) was in the 3′UTR, as shown in Table 2.

3.2. Alleles and genotypes frequencies

Three alleles and 3 genotypes of *CYP2E1* were identified on the basis of the polymorphisms found in the Chinese Tibetan

Table 2

Frequency distribution of *CYP2E1* polymorphisms in 100 Tibetan subjects.

SNP	New alleles	Gene position	Region	Nucleotide change	Amino-acid effect	Frequency % (n)	Flanking sequence
rs2070672	*7C	−352	Promoter	A>G	No translated	35	CCGTTGTCTA R CCAGTGCCAA
rs2070673	*7A, *7C	−333	Promoter	A>T	No translated	59	AAAGGGCAGG W CGGTACCTCA
	Novel	971	Intron 1	C>T	No translated	4	CTTTTCCCCA Y GTCCCTCTGG
rs41299408		987	Intron 1	C>A	No translated	2	TCTGGGTTCT M TAGAGCAACA
rs41299410		1036	Intron 1	C>T	No translated	2	TAGAGCCCCG Y ACCTCCTCGC
rs72862138		1074	Intron 1	G>C	No translated	1	TTCTAGCCAC S GGTCTCCGCA
rs943975		1361	Intron 2	T>C	No translated	31	ATTATAGTAA Y AGCATCCGAA
rs2070674		4441	Intron 2	C>T	No translated	33	CAGGGACCTA Y GGACAAGGAG
rs6413421		4912	Intron 3	T>C	No translated	3	TCCTCTTTCA Y CAGTCATCAA
rs576234120		5005	Intron 4	C>T	No translated	1	AACATAGCTT Y GAGGGGTGTT
	Novel	6179	Intron 5	C>T	No translated	1	TTTCTGGGAG Y CTCAGTTTCC
rs61710826		6397	Exon 6	G>A	Gly288Ser	1	CACAATGGAC R GTATCACCGT
rs28371746		6444	Exon 6	C>A	Thr303=	1	GGACAGAGAC M ACCAGCACAA
rs943976		6634	Intron 6	A>G	No translated	100	TGAGATGGCT R GATGCACTGC
rs371936931		9926	Intron 7	C>A	No translated	1	TGCCAGGGAG M AGGATGGGGG
rs8192777		9972	Intron 7	T>G	No translated	30	GGTCACTGAG K GGAAGGGCTG
rs2070676		10238	Intron 7	C>G	No translated	31	TCCTTCAACT S GAAATATACT
rs2070677		10275	Intron 7	A>T	No translated	31	TATTCAAAAC W ACATTCTTCA
rs2515641		10463	Exon 8	C>T	Phe421=	31	ATGGAAAGTT Y AAGTACAGTG
rs7081484		11591	3′UTR	C>T	No translated	1	ACACCCTGAA Y CCCCCGCTTT
	Novel	11598	3′UTR	C>A	No translated	1	GAACCCCCCG M TTTCAAACAA
rs2480257		11610	3′UTR	T>A	No translated	82	TTCAAACAAG W TTTCGAATTG
rs2480256		11615	3′UTR	A>G	No translated	82	ACAAGATTTC R AATTGTTTGA

population (Table 3). All the *CYP2E1* alleles and genotype frequencies were in the Hardy–Weinberg equilibrium. The most frequent alleles in the Tibetan populations were the wild-type allele *CYP2E1*1A (70.5%), followed by the *CYP2E1*7C allele (17.0%) and the *CYP2E1*7A allele (12.5%). Individuals with the wild-type *1A/*1A genotype have normal enzyme activity, and this genotype was the most prevalent (41.0%) in the Chinese Tibetan population. Other identified genotypes included the heterozygous *1A/*7C genotype (34.0%) and the *1A/*7A genotype (25.0%).

3.3. Linkage disequilibrium analysis

We used the Haploview to perform LD analysis with confidence intervals to define LD blocks. The extent of LD for each pair of SNPs was measured by the D' and r^2 values. The minor allele frequencies (MAFs) were >5% due to SNPs with lower frequencies have little power to detect LD. Haplotype analysis identified 4 LD blocks within *CYP2E1*, and very strong linkages were found between −352A>G (rs2070672) and −333A>T (rs2070673), 1361T>C (rs943975) and 4441C>T (rs2070674), 9972T>G (rs8192777), 10238C>G (rs2070676), 10275A>T (rs2070677) and 10463C>T (rs2515641), 11610T>A (rs2480257), and 11615A>G (rs2480256), as shown in Figure 1.

Table 3

Alleles and genotype frequencies of *CYP2E1* in Tibetan population.

Allele	Total (n = 200)	Phenotype	Frequency (%)
*1A	141	Normal	70.5
*7A	25		12.5
*7C	34		17.0
Genotype	Total (n = 100)	Phenotype	Frequency (%)
*1A/*1A	41	Normal	41.0
*1A/*7A	25		25.0
*1A/*7C	34		34.0

3.4. Interpopulation comparisons

We further compared *CYP2E1* polymorphisms distribution patterns between Tibetan population and previously published data from different countries in China.[26] The results showed that the frequencies of the −352A>G (*CYP2E1*7C) and the −333A>T (*CYP2E1*7A and *7C) in our study group were significantly higher ($P < 0.05$) than most of other groups. Furthermore, compared them with the frequencies in other ethnic populations,[21,22] we found that the −352A>G and the −333A>T were significant differences compared with African-American, European-American, and Korean, as shown in Table 4.

3.5. Predicted protein function of the nonsynonymous mutation

The protein prediction results of the nonsynonymous variant 6397G>A from the SIFT analysis indicated that substitution at position 288 from Gly to Ser is predicted to be tolerated with a score of 0.25. The result performed by PolyPhen-2 analysis showed that this mutation is predicted to be probably damaging with a score of 0.945 (HumDiv) and a score of 0.613 (HumVar), as shown Figure 2.

4. Discussion

The cytochrome P450 isozyme CYP2E1 are highly relevant in the metabolism of many low-molecular weight drugs, toxicants, and carcinogens, and may give rise to important interindividual and interethnic differences in patient responsiveness and adverse drug reactions. *CYP2E1* gene polymorphisms could be associated with

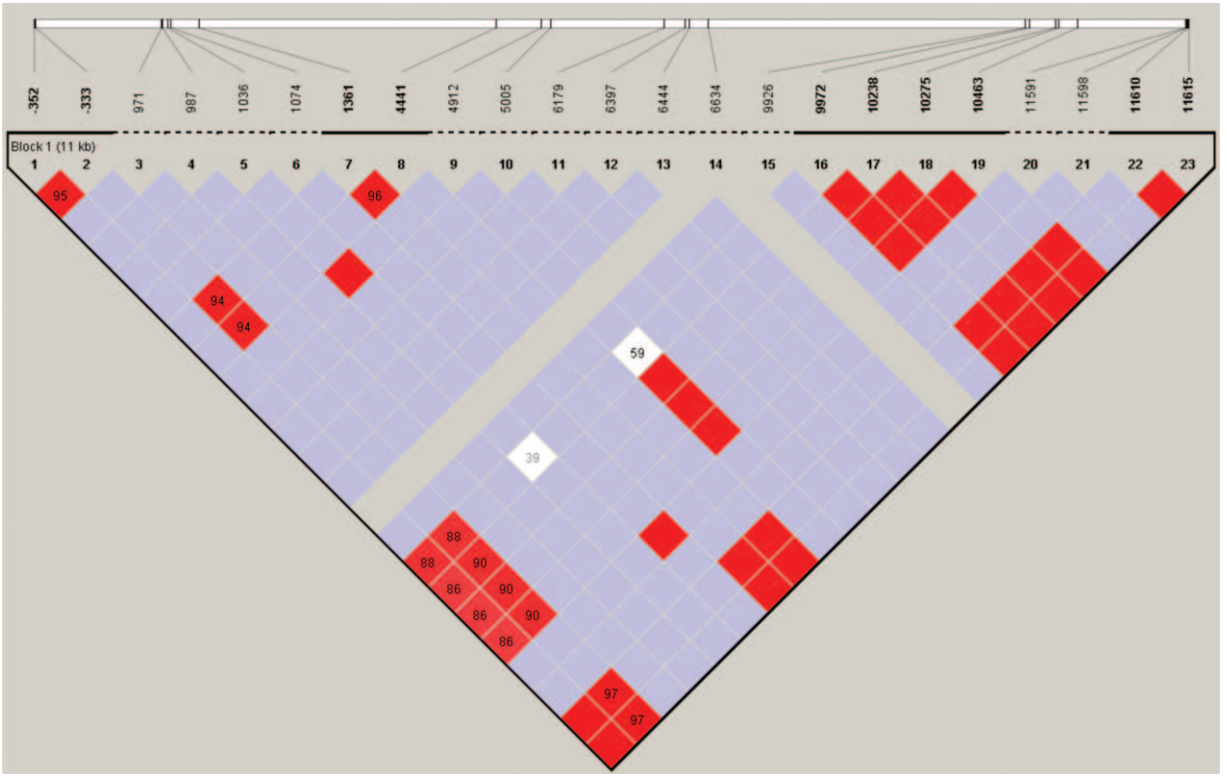

Figure 1. Linkage disequilibrium analysis of *CYP2E1*. LD is displayed by standard color schemes, with bright red for very strong, and blue for intermediate LD, and white for no LD.

the high degree of individual variability in the susceptibility to developing cancer and other diseases related, since polymorphic alleles encode proteins with altered catalytic activities or show differences in gene expression. To better understand the distribution of *CYP2E1* allele and genotype frequencies in the Tibetan populations, we systematically screened the whole *CYP2E1* polymorphisms from 100 healthy, unrelated Tibetans.

We identified 22 genetic variants including 3 novel polymorphisms, 3 alleles (*1A, *7A, and *7C), and 3 genotypes (*1A/*1A, *1A/*7A, and *1A/*7C) of *CYP2E1* in our study Tibetan Chinese population. We also compared 2 major allelic polymorphisms (−352A>G, SNP rs2070672 and −333A>T, SNP rs2070673) with previous observations of other ethnic populations and found that −352A>G and −333A>T were different from those of European-American, African-American, Japanese, Korean, and other different geographic areas of Mainland China Han populations. These differences of polymorphisms distribution could be attributed to the origin and geographical isolation experienced by different ethnic populations, as well as their dietary habits and lifestyles, all of which may affect *CYP2E1* polymorphisms. However, no significant difference was found between −352A>G and −352A>G in the Tibetan and Han Chinese populations. It is probably because that the sample size is relatively small for a population genetics research and the reference studies have variable quality. In addition, it has been reported that −333A>T exists at similar frequencies in European population, with the highest frequency among Africans.

Table 4

Comparison of *CYP2E1* alleles in different populations.

Population	Total number	Allele frequencies (%)		References
		352A>G	333A>T	
Tibetan	100	35.0	59.0	[26]
Shantou	100	18.8**	45.3	
Shanghai	100	14.1**	40.1**	
Shenyang	100	18.8**	35.9**	
Xi'an	100	21.9*	36.5**	
Chinese	400	18.4**	46.7	[21]
European	268	—	17.0**	
African	268	—	80.0**	
African-American	48	11.5**	26.0**	[22]
European-American	48	2.1**	15.6**	
Han Chinese	48	25.0	46.9	
Japanese	48	22.9	44.8*	
Korean	96	21.8*	40.4**	

* $P<0.05$, compared with the data of the present study.
** $P<0.01$, compared with the data of the present study.

The protein prediction results revealed that the variant 6397G>A could influence the protein structure and function, and the results of SITF (tolerant, score = 0.25) and PolyPhen-2 (damaging, score = 0.945) were inconsistent. The inconsistency of functional prediction may be due to that different algorithms are based on different training data, each has its own strength and weakness. In addition, a bioinformatics study of phenotype prediction of deleterious nonsynonymous single-nucleotide polymorphisms in human alcohol metabolism-related genes showed that the mutation 6397G>A is predicted to be borderline (SIFT, score = 0.18) and benign (PolyPhen-2, score = 0.254).[27] The reason for the difference is not clear. The results identified here should be confirmed by other means in further studies.

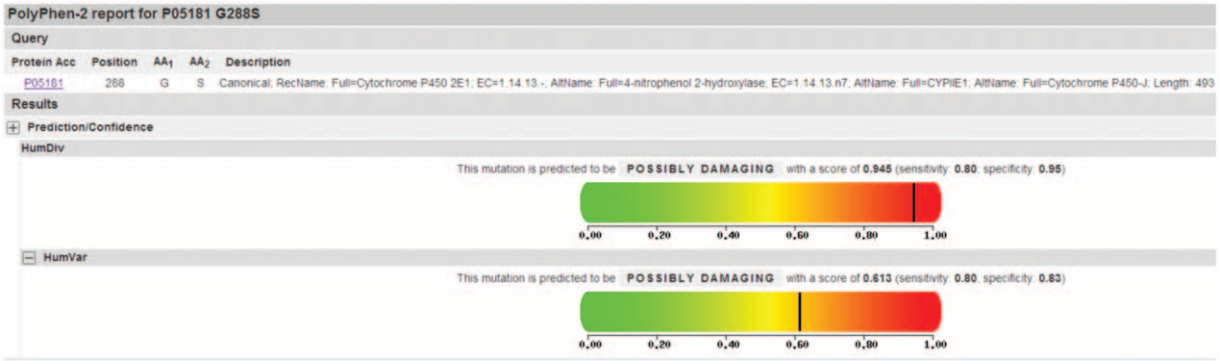

Figure 2. PolyPhen-2 prediction of functional change resulting from an amino acid mutation at position 288.

5. Conclusions

In conclusion, our results provide new information regarding *CYP2E1* genetic polymorphisms in Chinese Tibetan population. These findings in this study would be value for further study in assessing the susceptibility of different populations to diseases related to *CYP2E1* polymorphisms and determining whether it is necessary to design different therapeutics and toxicological protocols to reduce the risk of population, including pharmacogenetics for drug therapy and drug discovery. Further studies in larger groups are warranted to confirm our results.

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