Int J Clin Exp Pathol 2016;9(10):10657-10663
www.ijcep.com /ISSN:1936-2625/IJCEP0037007

Original Article

Genetic polymorphism analysis of CYP2J2 drug-metabolizing enzyme in a Chinese Zhuang population

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Received August 1, 2016; Accepted August 21, 2016; Epub October 1, 2016; Published October 15, 2016

Abstract: CYP2J2 is a sole member of the cytochrome P450 (CYP) 2J subfamily of monooxygenases, which metabolized lots of therapeutic agents and compounds. Detection of *CYP2J2* variant alleles, and knowledge about their allelic frequency in Zhuang ethnic groups, is important to establish the clinical relevance of screening for these polymorphisms to optimize pharmacotherapy. We directly used DNA sequencing to investigate the promoter, exons and surrounding introns, and 3'-untranslated region of the *CYP2J2* gene in 100 unrelated healthy Zhuang individuals and identified 16 different *CYP2J2* polymorphisms in the Zhuang population, in which including one novel variants detected in intron 2 (59907828 C>T). And we determined the allele frequencies of *CYP2J2*1* and *CYP2J2*7* were 95.5% and 4.5%, respectively. Our results summarized related information on *CYP2J2* polymorphisms in Zhuang individuals and provide new data about Zhuang populations to enrich the pharmacogenomic database.

Keywords: *CYP2J2*, ethnic groups, genetic polymorphism, Zhuang ethnic

Introduction

CYP2J2 is a member of cytochrome P450 (CYP) family and is the only member of human cytochromes P450II J subfamily [1]. CYP2J2 converting arachidonic acid to regioselective epoxyeicosatrienoic acids, which play important functions in maintaining homeostasis by controlling anti-inflammation, vasodilatation, relaxation of smooth muscle, angiogenesis and other important biological processes [2]. CYP2J2 expressed in many different tissue such as heart, liver, kidney, lung and pancreas, especially expressed at high levels in the human heart, predominantly in cardiac myocytes and endothelial cells lining small and large coronary arteries [3]. Some study identified CYP2J2 metabolism more than 100 marketed therapeutic medications and potential substrates in *vitro*, such as terfenadine, astemizole, amiodarone and tamoxifen [4, 5].

The physiopathological implications and pharmacokinetic relevance of *CYP2J2*, superimposed with the observation of a large degree of interindividual variation in its expression [6], indicate that the genetic polymorphisms of *CYP2J2* could partly modulate predisposition to some diseases, as well as might contribute to varied clinical response to some treatments. Some independent studies have separately characterized its sequence variations in multiple ethnic populations [7-9], but identified only a few rare mutations with varied catalytic activities, apart from *CYP2J2*7* which according to the Human Cytochrome P450 Allele Nomenclature Committee (http://www.cypalleles.ki.se/). Previous studies had demonstrated significant inter-individual and inter-ethnic differences in the frequencies of *CYP2J2* diversity alleles and genotypes.

The Zhuang ethnic minority, as one of the 16 largest minority group of China, is comprises

Table 1. Primers used to amplify regions of CYP2J2

Primer name	Primer sequence (5'-3')	DNA size for PCR (bp)
UTR & Exon 1	ACAGCAAGATGAGACTACCGAG	783 bp
Exon 2	CTCATGCCTTGCTCTAGGGAC	779 bp
Exon 3	GTGCATTCCTAGTGTTTACCATAC	788 bp
Exon 4	AGCATTGCATATGACAGAGGTGG	856 bp
Exon 5	AACACTCAACCAGTGCTCAGAT	776 bp
Exon 6	CAAATCTGTCTCGTTCACATCC	827 bp
Exon 7	GAGCTGCCTCACTCCTTCTAC	850 bp
Exon 8	CCAAGCCCTACTGAAACTGACC	688 bp
Exon 9	CTTCTATGGTCCTACACCCTGC	869 bp
Exon 9 & UTR	CCCAGCTCTACTGTCTCGTC	778 bp

about 16.93 million people [10]. Zhuang ethnic have their own spoken and written language which mainly distributed in Guangxi, Yunnan, Guangdong and Guizhou provinces in southeast China. The Zhuang language belongs to the Tai language family of Austro-Asiatic language group (http://www.ethnologue.com). To the best of our knowledge, no genotype information on *CYP2J2* mutants in Zhuang ethnic population is available. We systematically screened the whole *CYP2J2* genes from 100 healthy, unrelated Zhuang people for explored their polymorphisms and compared their frequencies with previous observations of other ethnic groups. We hope to provide a better knowledge of CYP2J2 variants and an available database for develop personalized medicine in Zhuang ethnic patients.

Materials and methods

Subjects

We recruited a random sample of 100 healthy, unrelated Zhuang between October and December 2014 from the Wenshan of Yunnan Province. All participants were Zhuang ethnic people residing in the Wenshan county of China, and they had at least three generations of Zhuang paternal ancestry. All subjects were deemed healthy based on their medical history and a physical examination. The purpose and experimental procedures of the study were explained to all individuals, and written informed consent was obtained from all participants prior to sample donation. The study protocol was performed in accordance with the Declaration of Helsinki and was approved by The Ethics Committees of The First People's Hospital of Yunnan Province.

PCR and DNA sequencing

Genetic polymorphisms of *CYP2J2* in the Zhuang study group were screened by direct DNA sequencing. Briefly, 5 ml venous blood separately was collected in EDTA tubes and genomic DNA was extracted from leukocytes using the GoldMag nanoparticles method (GoldMag Ltd., Xi'an, China) according to the manufacturer's instructions. Primers listed in **Table 1** were designed to amplify the 5' flanking regions, all exons, and partly introns of the *CYP2J2* gene. Thermal cycling conditions were as follows: an initial denaturation step at 95°C for 15 min was followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 55-64°C for 30 s, and extension at 72°C for 1 min. A final extension step was performed at 72°C for 3 min. Purified PCR products were sequenced directly using the ABI Prism BigDye Terminator Cycle Sequencing Kit version 3.1 (Applied Biosystems, Foster City, CA), on an ABI Prism 3100 sequencer (Applied Biosystems, Foster City, CA).

Data analysis

Sequencher 4.10.1 (http://www.genecodes.com/) software was used to initially analyze the sequences including manual management, fragment assembly, and mutation detection. The Human Cytochrome P450 (CYP) Allele Nomenclature Database describes *CYP2J2* variants according to the NCBI reference sequence AF272142.1. Allelic frequency comparisons between Zhuang ethnic population and other populations were performed using the Chi-squared test with a significance level set at P=0.05. Haploview software (version 4.2) was used to assess linkage disequilibrium (LD) and Hardy-Weinberg equilibrium for each genetic variant. Haplotypes were constructed from the selected SNPs and haplotype frequencies were derived for the Zhuang population.

Results

Genetic variants

Seventeen different *CYP2J2* polymorphisms were determined in our study subjects, One of

Table 2. Frequency distribution of CYP2J2 polymorphisms in Zhuang population

Nucleotide change	Position	Region	SNP	Allele	Amino-acid effect	Frequency (%)
G>T	59893278	Promoter	rs890293	*7	Decreased	0.09
C>T	59893484	Exon 1	rs2229189		Phe61=	0.12
G>A	59893630	Intron 2	rs3738474		No translated	0.08
G>C	59907633	Intron 2	rs11572245		No translated	0.08
G>A	59907717	Intron 2	rs149199403		No translated	0.01
C>T	59907828	Intron 2	/	Novel	No translated	0.03
A>G	59907994	Intron 3	rs372402076		No translated	0.03
C>T	59908103	Exon 4	rs76900855		Phe197=	0.01
A>C	59911461	Intron 4	rs1570693		No translated	0.24
G>A	59911701	Intron 5	rs1155002		No translated	0.34
T>G	59911800	Intron 5	rs2271800		No translated	0.24
C>A	59915763	Exon 6	rs2229191		Arg321=	0.08
C>T	59915765	Intron 6	rs527342446		No translated	0.01
T>C	59915912	Intron 6	rs2271798		No translated	0.24
G>A	59926564	3'UTR	rs776582105		No translated	0.02
C>T	59926822	3'UTR	rs4388726		No translated	0.09
A>G	59952634	3'UTR	rs11572327		No translated	0.05

Table 3. Allele and genotype frequencies of CYP2J2 in Zhuang population

Gene	Allele	Number	Phenotype	Frequency (%)
CYP2J2	*1	191	Normal	95.5%
	*7	9	Decreased	4.5%
Total number		200		100.0%
	Genotype			
	*1/*1	91	Normal	91.0%
	*1/*7	9	Decreased	9.0%
Total number		100		100.0%

which was novel: the nonsynonymous mutations 59907828C>T was in intron 2. The variant have not previously been reported in the NCBI database or in the Human CYP Allele Nomenclature Committee tables (**Table 2**).

Allele and genotype frequency

Two *CYP2J2* alleles were detected in the Zhuang study group (**Table 3**) which including CYP2J2*1 and CYP2J2*7. The *CYP2J2*1* allele had the highest frequency (95.5%), the frequency of the *CYP2J2*7* is only 4.50%. We also found two *CYP2J2* genotypes distribute in the Zhuang ethnic group. Individuals with the wild genotype CYP2J2*1/*1 genotype have normal enzyme activity, and the frequency of the genotype is 91% in our study. However heterozygous genotype CYP2J2*1/*7 is 9%, which leads to decreased enzyme activity. According to Haploview analysis, all allele and genotype frequencies (**Table 3**) conformed Hardy-Weinberg equilibrium.

Inter-population comparisons

We further compared *CYP2J2* allele distribution patterns among Zhuang ethnic, some populations from different ethnic groups and the data of CYP2J2 in 1000 Genomes Project. Different major alleles, which including the wild-type allele *CYP2J2*1* and the prevalent allele *CYP2J2*7*, were analyzed in our study. We found that the allele frequency of wild-type *CYP2J2*1* was significantly higher than *CYP2J2*7*. Except for the Taiwanese and STU population, lower mutant allele frequencies were observed (mutation frequency: 1.61-6.77%) in Asian populations. Among Caucasians, similar mutant allele frequencies were shown in German, Spanish, and American populations (mutation frequency: 4.95-9.91%) and were slightly higher than in Asians. In African Ancestry populations, the mutant allele frequencies were significant higher than in Caucasians (mutation frequency: 10.42-20%) (**Table 4**).

Linkage disequilibrium analysis

Haploview was used to assess LD between pairs of loci. The extent of LD for each pair of

Table 4. Allele frequencies of CYP2J2 in different populations

Population		Sample size	Allele frequency (%)						Reference
			*1	*4	*5	*7	*8	*9	
Zhuang ethnic		100	95.50%			4.50%			Present study
Russian		227	95.16%			4.84%			[22]
Tatars		178	96.35%			3.65%			
Bashkirs		102	98.53%			1.47%			
Ovambos		186	93.28%			6.72%			[23]
Mongolians		118	96.61%			3.39%			
Japanese		338	93.79%			6.21%			
Americans		116	90.09%			9.91%			[19]
Germans		960	93.54%			6.46%			[24]
Germans		255	94.51%			5.49%			[15]
Spanish		89	93.26%			6.74%			[25]
African-Americans		102	88.73%			11.27%			[26]
African-Americans		73	86.30%			13.70%			[19]
Koreans		271	95.76%			4.24%			[7]
Chinese		384	97.40%			2.60%			[27]
Taiwanese		200	88%			12%			[17]
African Ancestry	ACB	96	89.06%		0.52%	10.42%			1000 Genomes Project
	ASW	61	81.97%		1.64%	16.39%			
	ESN	99	81.82%			18.18%			
	GWD	113	84.52%		0.44%	15.04%			
	LWK	99	85.85%	0.51%		13.64%			
	MSI	85	78.24%		1.76%	20.00%			
	YRI	108	84.26%		0.46%	15.28%			
American	CLM	94	94.68%			5.32%			
	MXL	64	96.87%			3.13%			
	PEL	85	99.41%			0.59%			
	PUR	104	93.75%			6.25%			
East Asia	CDX	93	98.39%			1.61%			
	CHB	103	95.63%			4.37%			
	CHS	105	93.81%			6.19%			
	JPT	104	96.16%			2.40%	1.44%		
	KHV	99	97.98%			2.02%			
European	CEU	99	94.95%			5.05%			
	FIN	99	92.93%			7.07%			
	GBR	91	95.05%			4.95%			
	IBS	107	93.93%			6.07%			
	TSI	107	94.86%			5.14%			
South Asia	BEB	86	99.24%			0.76%			
	GIH	103	94.66%			5.34%			
	ITU	102	93.63%			5.88%		0.49%	
	PJL	96	92.19%			6.77%		1.04%	
	STU	102	90.20%			9.80%			

SNPs was measured by the D' value, which was most accurate when minor allele frequencies (MAFs) were greater than 5%. The overall LD of our Zhuang ethnic group across the *CYP2J2* gene is depicted in **Figure 1**. Haplotype analysis identified two LD blocks within *CYP2J2*, and very strong linkage was found between rs59907633 and rs59907994.

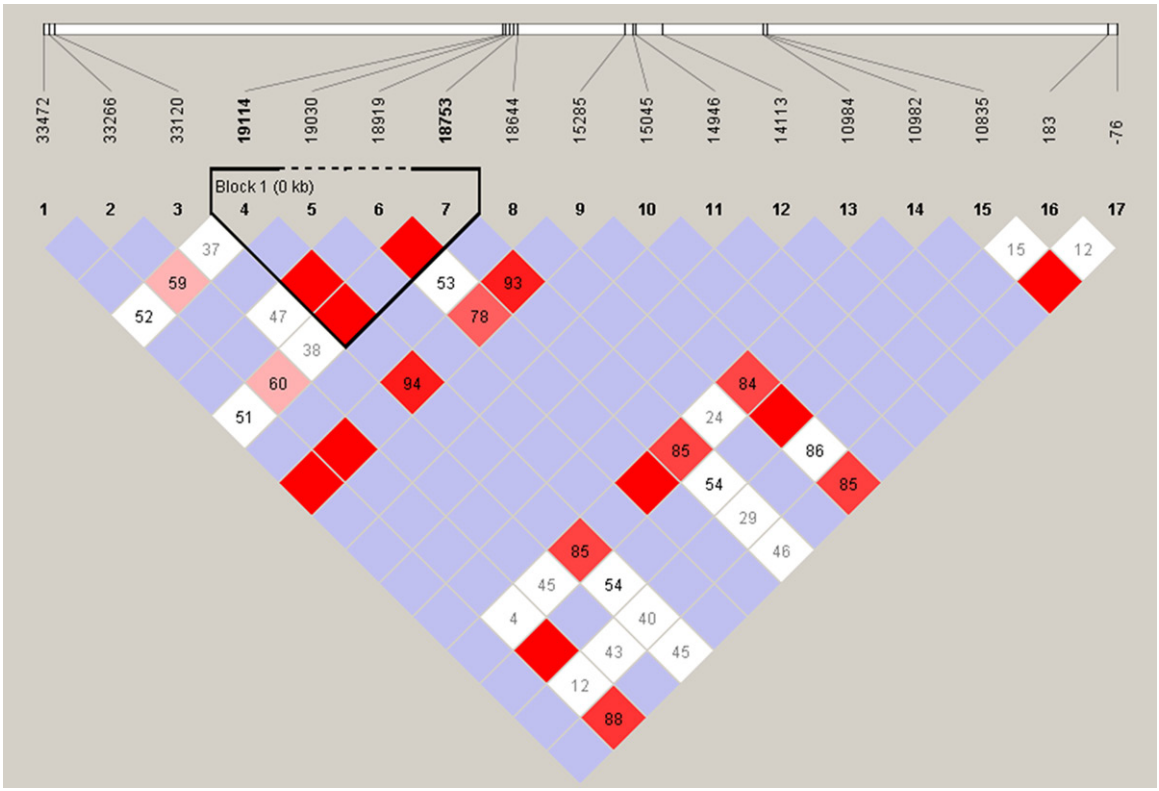

Figure 1. Linkage disequilibrium (LD) analysis of CYP2J2 genetic polymorphisms. LD is indicated by bright red (very strong: LOD>2, D'=1), light red (LOD>2, D'>1), and blue (LOD<2, D'=1) for intermediate LD, and white (none: LOD<2, D'<1).

Discussion

Analyses of individual phenotypes and genotypes for the genes are responsible for sensitivity to xenobiotics pointed to racial, ethnic, and geographical differences in the responses to pharmaceuticals and other toxic compounds [11, 12]. In this context, especially in China, which is a multinational state, evaluation of the population frequencies of the gene variants responsible for xenobiotic transformation are essential for further investigation of complex diseases and determination of the roles of climatic and geographical condition in their development. We identified 17 genetic variants including one novel polymorphism, two alleles, and two genotypes of *CYP2J2* in our Zhuang ethnic population, and compared these data with previous observations of other ethnic groups. Therefore, our results provide a better understanding of *CYP2J2* polymorphisms and a potential database for promoting personalized medicine in Zhuang ethnic population.

CYP2J2 is located on human chromosome 1p31.3-31.2 [13], currently, hundreds *CYP2J2* polymorphisms have been identified (http://www.ncbi.nlm.nih.gov/snp). As one of the most relevant polymorphism in terms of frequency and functional importance, rs890293 (G/T), is located at -76 bp in the CYP2J2 promoter region [14]. Some studies showed that rs890293 is associated with susceptibility to various diseases which including coronary artery disease [15], atherosclerosis [16], myocardial infarction [17], and essential hypertension [18].

CYP2J2 contributes to metabolizing arachidonic acid and epoxyeicosatrienoic acids (EETs) to physiologically epoxides. The expression levels and the distribution pattern of CYP2J2 may have powerful effects on tissue homeostasis and play a role in the pathogenesis of diseases such as vascular disorders and cancers [19]. Based on previous study, the CYP2J2 mRNA levels reflects CYP2J2 abundance which is greatest in the small intestine > heart > skeletal > muscles > kidney > salivary > glands > lungs > liver [20].

The variations of human *CYP2J2* genes in some groups had reported by previous study through

direct sequencing its coding and regulatory regions, only found a few rare mutations in the coding region [21]. And from these mutations, only one common variant CYP2J2*7 exists ethnically different allele frequency with identified functional. Liu et al found that the wild-type *CYP2J2* promoter was twice active compared with mutant allele *CYP2J2*7*, and CYP2J2*7 will protect the binding of Sp1 transcription factor to the promoter region which leads to the decreased promoter activity [17]. EETs lead to hyperpolarization and vascular relaxation by activate smooth muscle potassium channels, but lack the study about the association of CYP2J2*7 polymorphism with coronary artery disease (CAD) in different ethnics.

In our current study, all the populations are characterized by a high frequency of *CYP2J2*1* genotype, we determined that the allele *CYP2J2*7* is a common genetic variant in the Zhuang ethnic. The *CYP2J2*7* polymorphic profiles in the Zhuang populations were similar to Asia populations. Therefore, the drug dosage of allergic diseases, such as ebastine (which is metabolized by *CYP2J2*), should be adjusted according the wild-type dosages applied to the Zhuang population used as a starting point and reference the regular dosages of Asia populations. On the other hand, Taiwanese showed different allele frequency (mutation frequency: 12%) compared with other Asian populations. Moreover, different groups showed a different mutation frequency compared with the others. These results suggest that there is a certain genetic heterogeneity in the worldwide distribution about *CYP2J2* polymorphisms.

This study has some limitations. Its main limitation is the relatively small sample size; 100 health samples, were recruited, which is insufficient for a population study. Additionally, in-depth studies are needed to confirm the functional importance of the CYP2J2 polymorphisms and to elucidate its role in more detail.

In conclusion, this is the first study about direct sequencing the CYP2J2 variants of Zhuang ethnic group. Our data provide some of the first information regarding *CYP2J2* genetic polymorphisms in Zhuang individuals. With the continuous accumulation of pharmacogenomics data, subsequent studies should be going on which will focus on identifying *CYP2J2* variants in a larger sample size of Zhuang ethnic group and lead to the establishment of appropriate personalized treatment strategies, including appropriate drugs and correct dosages for the Zhuang population.

Acknowledgements

This work is supported by the Educational Department Scientific Research Key Fund of Engineering of Yunnan Province (2014Z038).

Disclosure of conflict of interest

None.

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