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Original Article

Genetic polymorphisms and phenotypic analysis of drug-metabolizing enzyme CYP2C19 in a Li Chinese population

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Abstract: *CYP2C19* is a highly polymorphic gene and CYP2C19 enzyme results in broad inter-individual variability in response to certain clinical drugs, while little is known about the genetic variation of *CYP2C19* in Li Chinese population. The aim of this study was to identify different *CYP2C19* mutant alleles and determine their frequencies, along with genotype frequencies, in the Li Chinese population. We used DNA sequencing to investigate promoter, exons, introns, and 3'UTR of the *CYP2C19* gene in 100 unrelated healthy Li individuals from Hainan Province, China. We also used SIFT and PolyPhen-2 to predict the protein function of the non-synonymous mutation in *CYP2C19* coding regions. We identified 22 different *CYP2C19* polymorphisms in the Li Chinese population, including three novel variants (-254A > G, 17807T > C and 58025C > T). The allele frequencies of *CYP2C19**1A, *1B, *2A and *3A were 50%, 24%, 24.5%, and 1.5%, respectively. The most common genotype combinations were *1A/*1B (48%) and *1A/*2A (49%). Additionally, the mutation Ala161Pro was predicted to be intolerant and possibly damaging by SIFT and PolyPhen-2, respectively. Our results shed new light on *CYP2C19* polymorphisms in Li individuals, which may help to optimize pharmacotherapy effectiveness by providing personalized medicine to this ethnic group.

Keywords: Genetic polymorphism, CYP2C19, Li Chinese population, ethnic groups

Introduction

The cytochrome P450 (CYP450) superfamily is a large and diverse group of enzymes, mainly localized in the endoplasmic reticulum, that metabolize many common therapeutic drugs [1]. CYP2C19 is a member of the CYP2C subfamily of cytochromes P450 and involved in the metabolism of a range of clinically important compounds [2]. These compounds include certain tricyclic antidepressants (e.g., amitriptyline, clomipramine and imipramine), anticonvulsant drugs (e.g., phenytoin and diazepam), antiulcer drugs (e.g., lansoprazole, omeprazole and rabeprazole), benzodiazepines (e.g. quazepam, diazepam and unitrazepam) and specific b-adrenoceptor blockers [3-6].

CYP2C19 is a highly polymorphic gene and genetic variants in the *CYP2C19* might cause changes to the enzyme, thus giving rise to different enzymatic activities and resulting in great intra- and inter-population differences in therapeutic outcomes and adverse drug reactions [7]. To date, at least 34 alleles of *CYP2C19* have been identified. Among them, *CYP2C19*2* and *CYP2C19*3* are the most prevalent alleles and have been associated with decreased metabolism of the substrates (drugs); by contrast, *CYP2C19*17* is less studied and showed increased gene expression and enzyme activity [8]. Previous studies had demonstrated significant inter-individual and inter-ethnic differences in the frequencies of *CYP2C19* alleles and genotypes [9].

The population of China consists of Han Chinese and 55 ethnic minorities currently recognized by the People's Republic of China. Li is one of the most ancient ethnic groups, having their

Table 1. Primers used to amplify regions of *CYP2C19*

Primer name	Primer Sequence (5'-3')	PCR product size (bp)
Promoter_F	GCCTGTTTTATGAACAGGATGA	918
Promoter_R	TAAGACAACCGTGAGCTTGC	
Exon1_F	ACAGAGTGGGCACTGGGACGA	844
Exon1_R	GGTCCTAAACCCACAGCTGCTTCC	
Exon2_3_F	TTGTCTGACCATTGCCTTGA	833
Exon2_3_R	TCTCAGCTTCAAACCCTGCT	
Exon4_F	CCCCAACTATTCTCACCCTTT	916
Exon4_R	AAAGTGTGAATTGAAGGACAAGC	
Exon5_F	TCAGGTTGTGCAAACTCTTTT	908
Exon5_R	CCTTCACTCACTTTTTGATGGA	
Exon6_F	ATGTTGGTAAGTATACAATGTGAGT	386
Exon6_R	TCACACCATTAAATTGGGACAGA	
Exon7_F	TTTTGATTGGAAATTTTAGTCCATT	921
Exon7_R	TCAGTTCTTTCCAAACTGACCT	
Exon8_F	GTCACTGGCCTTAAGCTCATGCCT	718
Exon8_R	CCCAGCCTAGGGGGTGAGGG	
Exon9_F	TGAGAGTAGGGGAGGTGAAGA	907
Exon9_R	GATGACGGGTCAGAAGAAGC	
3'-UTR_F	ACGGATTTGTGTGGGAGAGGGC	674
3'-UTR_R	AATGCTCAGCCAAAATAGCTTCCCT	

own spoken and written language. Li population, living mainly in Hainan Island, is geographically isolated from other ethnic groups in the region. To our knowledge, no genotype information on *CYP2C19* mutants in this population is available. We systematically screened the whole *CYP2C19* genes of 100 healthy, unrelated Li people for polymorphisms and compared their allelic frequencies with previous observations of other ethnic groups, hoping to offer recommendations pertaining to the drug substrates of *CYP2C19* in the Li population.

Materials and methods

Subjects

One hundred healthy, unrelated Li Chinese (50 males and 50 females) were recruited between March 2013 and October 2014 from Hainan Provincial People's Hospital. All participants were Li Chinese residing in the Hainan province, and they had at least three generations of Li paternal ancestry. Subjects with any type of medical illness, organ transplant, drug or alcohol addiction, and pregnant females were excluded from the study. These exclusion criteria were used to minimize controllable factors that may have influenced genetic variation in the genes of interest.

The purpose and experimental procedures of the study were explained to all participants, and written informed consent was obtained from all individuals prior to sample donation. The study protocol was performed in accordance with the Declaration of Helsinki and was approved by The Ethics Committees of Hainan Provincial People's Hospital.

PCR and DNA sequencing

A blood sample (5 mL) was taken from each subject into an EDTA tube and genomic DNA was extracted using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Ltd.) according to the manufacturer's instructions. Primers for PCR were designed to amplify the 5' flanking regions, all exons, and all introns of the *CYP2C19* gene, and their sequences are provided in **Table 1**. Polymerase chain reaction (PCR) for all single nucleotide polymorphisms (SNPs) was performed in 10 μL reactions with 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 as follows: a initial denaturation step of 15 min at 95°C, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 55-64°C for 30 s, extension at 72°C for 1 min, and a final extension at 72°C for 3 min. The PCR products were sequenced using the ABI PrismBigDye Terminator Cycle Sequencing Kit version 3.1 (Applied Biosystems) on an ABI Prism3100 sequencer (Applied Biosystems).

Data analysis

Sequencher 4.10.1 (http://www.genecodes.com/) software was used to initially analyze the sequences including manual curation, fragment assembly, and mutation detection. We named the *CYP2C19* variants based on the nucleotide reference sequence NG_008384.2 and CYP allele nomenclature (http://www.cypalleles.ki.se/). Allelic frequency comparisons between Li Chinese population and other popu-

Table 2. Frequency distribution of *CYP2C19* polymorphisms in 100 Li subjects

NO.	SNP	Position	Nucleotide change	Region	Allele	Frequencies		Amino-acid effect
1	rs190944530	-283	G > T	Promoter		9/100	9%	No translated
2		-254	A > G	Promoter	Novel 1	1/100	1%	No translated
3	rs17885098	99	C > T	Exon 1		91/94	96.80%	Pro33Pro[a]
4	rs17878649	12306	G > A	Intron 1		1/100	1%	No translated
5	rs145328984	12401	C > T	Exon 2		1/100	1%	Arg73Cys[b]
6	rs12769205	12662	A > G	Intron 2		55/100	55%	No translated
7	rs181297724	12834	G > C	Exon 3		3/99	3.03%	Ala161Pro[b]
8		17807	T > C	Exon 4	Novel 2	1/98	1.02%	Asp165Asp[a]
9	rs4986893	17948	G > A	Exon 4	*CYP2C19**3A	3/98	3.06%	Trp212Ter[b]
10	rs184151290	18074	C > T	Intron 4		1/98	1.02%	No translated
11	rs7088784	18911	A > G	Intron 4		5/100	5%	No translated
12	rs4244285	19154	G > A	Exon 5	*CYP2C19**2A	53/100	53%	Pro227Pro[a]
13	rs12571421	19520	A > G	Intron 5		53/100	53%	No translated
14		58025	C > T	Intron 6	Novel 3	5/100	5%	No translated
15	rs28399513	79936	T > A	Intron 6		53/100	53%	No translated
16	rs3758580	80160	C > T	Exon 7	*CYP2C19**2A	53/100	53%	Val330Val[a]
17	rs3758581	80161	A > G	Exon 7		100/100	100%	Ile331Val[b]
18	rs4917623	87106	C > T	Intron 7		61/94	64.89%	No translated
19	rs17886522	87313	A > C	Exon 8	*CYP2C19**3A	3/100	3%	Gly417Gly[a]
20	rs17882572	87594	G > T	Intron 8		3/100	3%	No translated
21	rs17885052	87620	A > T	Intron 8		5/100	5%	No translated
22	rs191493794	90647	C > T	3'-UTR		5/100	5%	No translated

[a]Synonymous mutations; [b]non-synonymous mutations.

Table 3. Allele and genotype frequencies of *CYP2C19* in Li population

		Total (N = 100)	Frequency	Phenotype
Allele	*1A	100	50.00%	Normal
	*1B	48	24.00%	Normal
	*2A	49	24.50%	None
	*3A	3	1.50%	None
Genotype	*1A/*1B	48	48.00%	Normal enzyme activity
	*1A/*2A	49	49.00%	Decreased enzyme activity
	*1A/*3A	3	3.00%	Decreased enzyme activity

lations were performed using the Chi-squared test with a significance level set at P = 0.05 [10]. HAPLOVIEW 4.1 (http://broad.mit.edu/mpg/haploview) was used to assess linkage disequilibrium (LD) and Hardy-Weinberg equilibrium for each genetic variant [11]. Haplotypes were constructed from the selected SNPs and haplotype frequencies were derived for the Li population.

Transcriptional prediction

We analyzed non-synonymous SNPs in the *CYP2C19* coding regions to predict the corresponding protein function. Two algorithms, SIFT (Sorting Intolerant From Tolerant, http://sift.bii.a-star.edu.sg/) and PolyPhen-2 (Polymorphism Phenotyping v2, http://genetics.bwh.harvard.edu/pph2/), were used to perform the functional prediction of non-synonymous SNPs [12]. Each variant was given a score based on the impact of its mutation on protein function. The SIFT divided results into four 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). PolyPhen-2 results were divided into three categories: benign, possibly damaging and probably damaging.

Results

Genetic variants

We sequenced *CYP2C19* from our study subjects and successfully identified a total of 22 *CYP2C19* polymorphisms in this population.

Table 4. Allele frequencies of *CYP2C19* in different populations

Populations	Total Number	Allele frequency (%)			References
		*CYP2C19**1	*CYP2C19**2	*CYP2C19**3	
Asians					
Chinese Li	100	74.00	24.50	1.50	Present study
Chinese Han	100	67.50	25.50	2.00	[13]
Chinese Dai	193	66.30	30.30	3.40	[14]
Japanese	140	53.90**	35.00	11.10**	[15]
Korean	103	67.00	21.00	12.00**	[16]
Vietnamese	90	62.00	24.00	14.00**	[17]
Thai	121	59.90*	35.10	5.00	[17]
Caucasians					
Swedish	175	76.60	23.10	0.30	[18]
Russian	290	88.30**	11.40**	0.30	[19]
Italian	360	88.90**	11.10**	0.00*	[20]
Bolivian	778	92.10**	7.80**	0.10**	[21]
Faroese	312	97.10**	2.90**	0.00*	[22]
Africans					
Tanzanian	251	81.50	17.90	0.60	[23]
Ethiopian	114	84.00	14.00	2.00	[24]
Zimbabwean	84	86.90*	13.10	0.00	[25]

$^{**}P < 0.01$, compared with the data of the present study; $^{*}P < 0.05$, compared with the data of the present study.

Three of the polymorphisms had not previously been reported in either the NCBI database or the Human Cytochrome P450 Allele Nomenclature Committee tables (**Table 2**). -254A > G was in the promoter region, 17807T > C was a synonymous mutation in exon 4, and 58025C > T was in the intron 6.

Allele frequency and genotype frequency

Four *CYP2C19* alleles were detected in the Li study group (**Table 3**). The *CYP2C19**1A allele had the highest frequency (50%), followed by the *CYP2C19**1B allele (24.00%), and the *CYP2C19**2A allele (24.50%). The last allele, *CYP2C19**3A, was relatively rare with frequencies of only 1.50%.

We also detected three *CYP2C19* genotypes, with a frequency range from 3.00% to 49.00% in this Li population. Individuals with the wild-type *1/*1 genotype have normal enzyme activity, and this genotype was the relatively prevalent (48.00%) in our study group. Other identified genotypes included the heterozygous genotype *1/*2 (49.00%) and *1/*3 (3.00%), which leads to decreased enzyme activity. According to Haploview analysis, all allele and genotype frequencies (**Table 3**) were in Hardy-Weinberg equilibrium.

Inter-population comparisons

We further compared *CYP2C19* allele frequencies between our data and previously published data from different countries and ethnic groups in east Asia [13-16], south Asia [17], Europe [18-22] and Africa [23-25] (**Table 4**). Our results showed that the frequency of the wild-type allele, *CYP2C19**1, in our study group was significantly lower ($P < 0.01$) than in Caucasian populations, but was highest in Asian groups. Furthermore, the frequencies of *CYP2C19**2 and *CYP2C19**3 were significantly higher ($P < 0.05$) among those of Chinese descent compared with Caucasians. Additionally, we found no significant differences between Li Chinese and Africans.

Linkage disequilibrium analysis

We performed LD analysis using Haploview with confidence intervals to define LD blocks (**Figure 1**). The extent of LD for each pair of SNPs was measured by the D' value, which was most accurate when minor allele frequencies (MAFs) were greater than 5%. Haplotype analysis identified one LD blocks within *CYP2C19*, and very strong linkage was found between rs4244285, rs12571421, novel variant 58025C > T, rs28399513 and rs3758580.

Predicted protein function of the non-synonymous mutation

We identified four non-synonymous mutation of *CYP2C19* in our study group, Arg73Cys, Ala161Pro, Trp212Ter and Ile331Val. Trp212Ter was excluded because it is a termination of protein sequence. Analysis using SIFT of the Arg73Cys and Ala161Pro variants indicated that they were intolerant (score = 0.01), while the variant Ile331Val was identified as tolerant (score = 0.29). PolyPhen-2 results for the

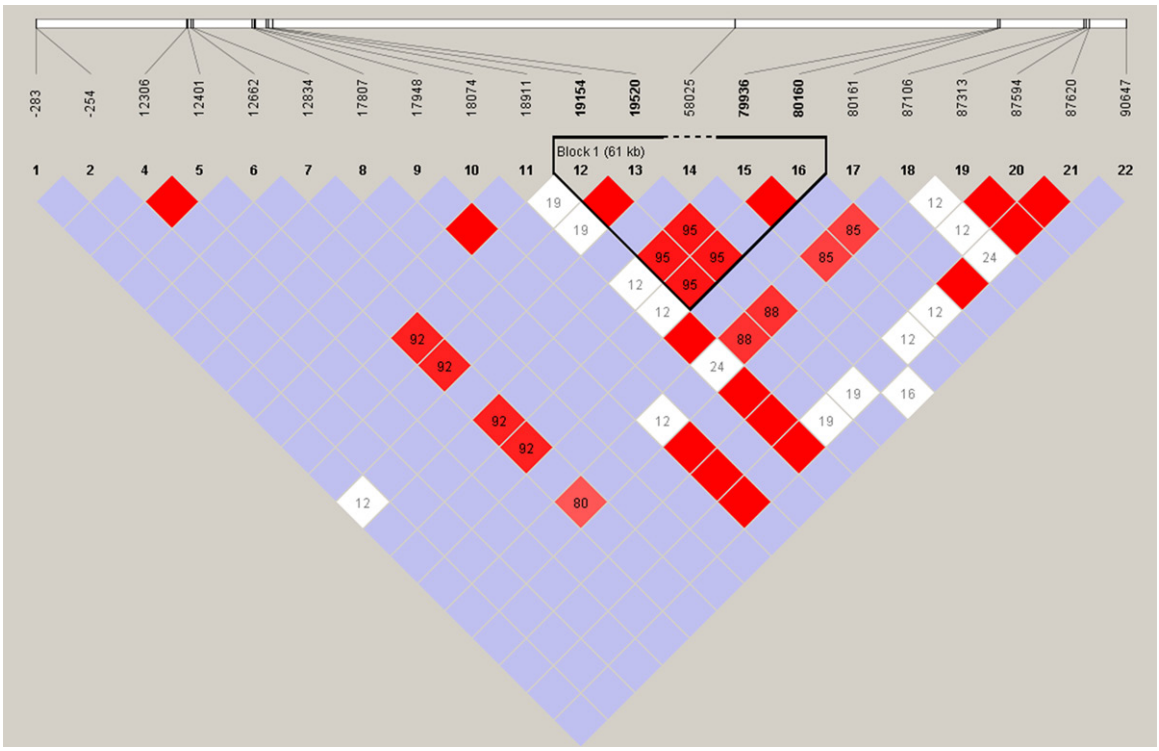

Figure 1. Linkage disequilibrium analysis of *CYP2C19*. LD is displayed by standard color schemes, with bright red for very strong LD (LOD > 2, D' = 1), pink red (LOD > 2, D' < 1) and blue (LOD < 2, D' = 1) for intermediate LD, and white (LOD < 2, D' < 1) for no LD.

Arg73Cys and Ile331Val revealed that both mutations were benign; while Ala161Pro was identified as possibly damaging. PolyPhen-2 utilized two models (HumDiv and HumVar), in which the latter is more rigorous in its false discovery rate. So the HumVar dataset was usually used to predict protein function (**Figure 2**). The protein function prediction results from SIFT and PolyPhen-2 analysis of the Arg73Cys were inconsistent. However, the protein function prediction results of the Ala161Pro and Ile331Val variants were highly consistent.

Discussion

Genetic polymorphisms in *CYP2C19* are highly involving in the metabolism of many clinically prescribed drugs and may give rise to important inter-individual and inter-ethnic differences in patient responsiveness and adverse drug reactions [26]. All of these years, several study has determined *CYP2C19* genetic polymorphisms in Han Chinese populations, few studies to date have focused on ethnic minorities in China, especially Li Chinese. We identified 22 genetic variants including three novel polymorphisms, four alleles, and three genotypes of *CYP2C19* in our study Li Chinese population, and compared these data with previous observations of other ethnic groups. Therefore, our results provide a better understanding of *CYP2C19* polymorphisms and a potential database for promoting personalized medicine in Li Chinese population.

The frequency of the wild-type *CYP2C19* allele (*CYP2C19**1) in the Li Chinese study population was significantly lower ($P < 0.01$) than in Caucasian populations, which was consistent with findings in previous studies on the Asian populations [27, 28]. *CYP2C19**2 and *CYP2C19**3 have been determined as null alleles and resulting in the total absence of enzyme activity and *1/*2, *1/*3 genotypes have been associated with decreased enzyme activity in previous studies [29]. The occurrence of *CYP2C19**2 in the Li subjects in our study was significantly higher ($P < 0.01$) than that reported for Caucasians, which suggested the pharmacological or toxicological properties of medications that are metabolized by *CYP2C19* are likely to differ between Li Chinese and Caucasian populations. Interestingly, the allele frequency of *CYP2C19* in our Li group has no significant differences compared with

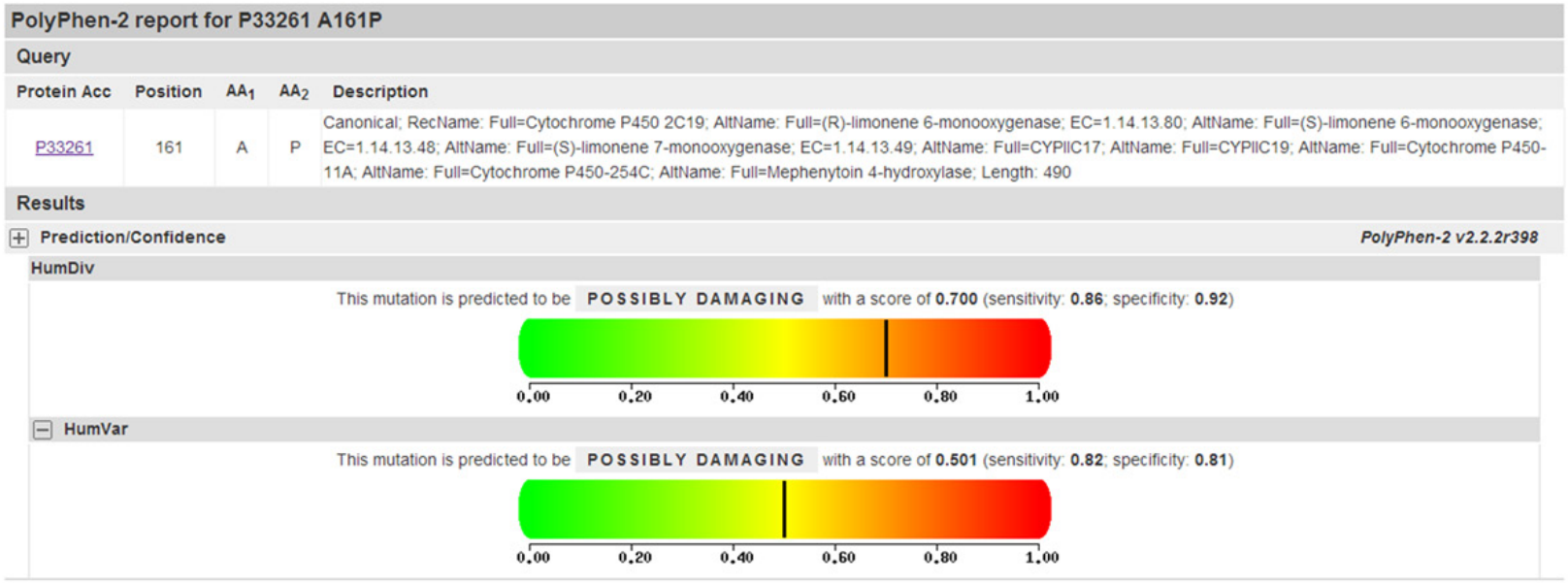

Figure 2. PolyPhen-2 prediction of functional change resulting from an amino acid mutation at position 161.

Africans, which may relate to the similarity of their residences. Hainan Province is in the southernmost point of China, and belongs to tropical and subtropical zones, which was consistent with most part of African territory.

Recent studies have shown that *CYP2C19* polymorphisms have caused a diverse responsiveness to clopidogrel [30]. The risk of cardiovascular events is increased in patients who are PM (poor metabolizer, carrying at least one CYP2C19*2 allele) despite patients receiving adequate doses of an antiplatelet agent, clopidogrel [31]. In our current study, we determined that the allele *2 and *3 are common genetic variant in the Li Chinese population, and individuals who are homozygous carriers for the *2 or *3 allele show decreased enzyme activity compared to the wild type. So clinical treatment used clopidogrel should be more carefully in Li Chinese population.

Analysis of genetic variants in the coding region revealed variant Ala161Pro will affect the protein structure and function, and the results of SITF and PolyPhen-2 were highly consistent. However, the protein prediction results of Arg73Cys from the SIFT and PolyPhen-2 were inconsistent. The prediction accuracy of SIFT and PolyPhen-2 is 63% and 75%, while the false positive rate is 19% and 9%, respectively [12, 32]. Therefore, the results identified here should be confirmed by other means in further studies.

In summary, our results provide a basic profile of *CYP2C19* polymorphisms in the Li Chinese population, and future studies will use a larger sample size of Li Chinese, leading to the enhanced application of personalized medicine in this population.

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Disclosure of conflict of interest

None.

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References

[1] Nelson DR, Zeldin DC, Hoffman SM, Maltais LJ, Wain HM and Nebert DW. Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. Pharmacogenetics 2004; 14: 1-18.

[2] Gerbal-Chaloin S, Pascussi JM, Pichard-Garcia L, Daujat M, Waechter F, Fabre JM, Carrère N and Maurel P. Induction of CYP2C genes in human hepatocytes in primary culture. Drug Metab Dispos 2001; 29: 242-251.

[3] Andersson T, Holmberg J and Walan A. Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. Br J Clin Pharmacol 1998; 45: 369-375.

[4] Gardiner SJ and Begg EJ. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. Pharmacol Rev 2006; 58: 521-590.

[5] Onof S, Hatanaka T, Miyazawa S, Tsutsui M, Aoyama T, Gonzalez F and Satoh T. Human liver microsomal diazepam metabolism using cDNA-expressed cytochrome P450s: role of CYP2B6, 2C19 and the 3A subfamily. Xenobiotica 1996; 26: 1155-1166.

[6] Paveliu MS, Bengea S and Paveliu FS. Individualized drug response related to genetic variations of cytochrome P450 isoforms and other enzymes. Farmacia 2010; 58: 245-254.

[7] Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. Br J Clin Pharmacol 2001; 52: 349-355.

[8] Chang M, Tybring G, Dahl ML and Lindh JD. Impact of cytochrome P450 2C19 polymorphisms on citalopram/escitalopram exposure: a systematic review and meta-analysis. Clin Pharmacokinet 2014; 53: 801-811.

[9] Hu LM, Dai DP, Hu GX, Yang JF, Xu RA, Yang LP, Qian JC, Ge RS and Cai JP. Genetic polymorphisms and novel allelic variants of CYP2C19 in the Chinese Han population. Pharmacogenomics 2012; 13: 1571-1581.

[10] Adamec C. Example of the use of the nonparametric test. Test X2 for comparison of 2 independent examples. Cesk Zdrav 1964; 12: 613.

[11] Barrett JC, Fry B, Maller J and Daly MJ. Haploview: analysis and visualization of LD and hap-

lotype maps. Bioinformatics 2005; 21: 263-265.
[12] Ng PC and Henikoff S. Accounting for human polymorphisms predicted to affect protein function. Genome Res 2002; 12: 436-446.
[13] Zhou Q, Yu X, Lin H, Wang L, Yun Q, Hu S and Wang D. Genetic polymorphism, linkage disequilibrium, haplotype structure and novel allele analysis of CYP2C19 and CYP2D6 in Han Chinese. Pharmacogenomics J 2009; 9: 380-394.
[14] He N, Yan FX, Huang SL, Wang W, Xiao ZS, Liu ZQ and Zhou HH. CYP2C19 genotype and S-mephenytoin 4'-hydroxylation phenotype in a Chinese Dai population. Eur J Clin Pharmacol 2002; 58: 15-18.
[15] Kimura M, Ieiri I, Mamiya K, Urae A and Higuchi S. Genetic polymorphism of cytochrome P450s, CYP2C19, and CYP2C9 in a Japanese population. Ther Drug Monit 1998; 20: 243-247.
[16] Roh HK, Dahl ML, Tybring G, Yamada H, Cha YN and Bertilsson L. CYP2C19 genotype and phenotype determined by omeprazole in a Korean population. Pharmacogenetics 1996; 6: 547-551.
[17] Yamada S, Onda M, Kato S, Matsuda N, Matsuhisa T, Yamada N, Miki M and Matsukura N. Genetic differences in CYP2C19 single nucleotide polymorphisms among four Asian populations. J Gastroenterol 2001; 36: 669-672.
[18] Chang M, Dahl ML, Tybring G, Gotharson E and Bertilsson L. Use of omeprazole as a probe drug for CYP2C19 phenotype in Swedish Caucasians: comparison with S-mephenytoin hydroxylation phenotype and CYP2C19 genotype. Pharmacogenetics 1995; 5: 358-363.
[19] Gaikovitch EA, Cascorbi I, Mrozikiewicz PM, Brockmöller J, Frötschl R, Köpke K, Gerloff T, Chernov JN and Roots I. Polymorphisms of drug-metabolizing enzymes CYP2C9, CYP2C19, CYP2D6, CYP1A1, NAT2 and of P-glycoprotein in a Russian population. Eur J Clin Pharmacol 2003; 59: 303-312.
[20] Scordo MG, Caputi AP, D'Arrigo C, Fava G and Spina E. Allele and genotype frequencies of CYP2C9, CYP2C19 and CYP2D6 in an Italian population. Pharmacol Res 2004; 50: 195-200.
[21] Bravo-Villalta HV, Yamamoto K, Nakamura K, Bayá A, Okada Y and Horiuchi R. Genetic polymorphism of CYP2C9 and CYP2C19 in a Bolivian population: an investigative and comparative study. Eur J Clin Pharmacol 2005; 61: 179-184.
[22] Halling J, Petersen MS, Damkier P, Nielsen F, Grandjean P, Weihe P, Lundgren S, Lundblad MS and Brøsen K. Polymorphism of CYP2D6, CYP2C19, CYP2C9 and CYP2C8 in the Faroese population. European J Clin Pharmacol 2005; 61: 491-497.
[23] Herrlin K, Massele AY, Jande M, Alm C, Tybring G, Abdi YA, Wennerholm A, Johansson I, Dahl ML and Bertilsson L. Bantu Tanzanians have a decreased capacity to metabolize omeprazole and mephenytoin in relation to their CYP2C19 genotype. Clin Pharmacol Ther 1998; 64: 391-401.
[24] Persson I, Aklillu E, Rodrigues F, Bertilsson L and Ingelman-Sundberg M. S-mephenytoin hydroxylation phenotype and CYP2C19 genotype among Ethiopians. Pharmacogenetics 1996; 6: 521-526.
[25] Masimirembwa C, Bertilsson L, Johansson I, Hasler JA and Ingelman-Sundberg M. Phenotyping and genotyping of S-mephenytoin hydroxylase (cytochrome P450 2C19) in a Shona population of Zimbabwe. Clin Pharmacol Ther 1995; 57: 656-661.
[26] Kobori L, Kohalmy K, Porrogi P, Sárváry E, Gerlei Z, Fazakas J, Nagy P, Járay J and Monostory K. Drug-induced liver graft toxicity caused by cytochrome P450 poor metabolism. Br J Clin Pharmacol 2008; 65: 428-436.
[27] Chen L, Qin S, Xie J, Tang J, Yang L, Shen W, Zhao X, Du J, He G and Feng G. Genetic polymorphism analysis of CYP2C19 in Chinese Han populations from different geographic areas of mainland China. Pharmacogenomics 2008; 9: 691-702.
[28] Ota T, Kamada Y, Hayashida M, Iwao-Koizumi K, Murata S and Kinoshita K. Combination analysis in genetic polymorphisms of drug-metabolizing enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A5 in the Japanese population. Int J Med Sci 2015; 12: 78-82.
[29] Desta Z, Zhao X, Shin JG and Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinetics 2002; 41: 913-958.
[30] Lin R, Zhang L, Zhang P, Zhou L, Liu T, Li Y, Zhang W, Wang W and Zhang J. Influence of CYP2C19 loss-of-function variants on the metabolism of clopidogrel in patients from northwestern China. J Clin Pharm Ther 2015; 40: 308-314.
[31] Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, Payot L, Brugier D, Cayla G and Beygui F. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009; 373: 309-317.
[32] Ng PC and Henikoff S. Predicting the effects of amino acid substitutions on protein function. Annu Rev Genomics Hum Genet 2006; 7: 61-80.