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Review

Individual and ethnic differences in CYP2C19 activity in Chinese populations[1]

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Inter-individual difference in drug response is a clinically important problem encountered in the use of many drugs[1]. One of its major causes is variability in the activities of drug-metabolizing enzymes of the liver. Both genetic and nongenetic factors can contribute to the variability largely. In recent years，among the drug-metabolizing enzymes，cytochrome P-4502C19（CYP2C19）has become a subject of extensive studies concerning individual and ethnic variation in drug metabolism.

Genetic polymorphism of CYP2C19 represents one of the best-studied examples of the determinants responsible for the pronounced individual and ethnic differences in response to the affected drugs. The polymorphism was first identified in 1984 by the study of the family of a volunteer who had experienced unusual sedation after normal doses of mephenytoin（MP）[2]. Since then，the polymorphic deficiency of *S*-mephenytoin（*S*-MP）4′-hydroxylase，its frequency，inherited trait and molecular mechanisms，and the association of its deficiency with other drug metabolisms has been extensively explored in many different ethnic groups[3]. *S*-MP 4′-hydroxylase was ultimately identified to be CYP2C19 several years later[4,5]. In addition，the importance of nongenetic factors as a cause of variation in CYP2C19 activity has also been recognized in the last few years. While the mechanisms of differences in CYP2C19 activity are being continuously determined，what should be emphasized now is that an ever-increasing number of clinically important drugs are found to be completely or partially metabolized by CYP2C19.

In this review，we mainly summarize recent studies carried out in our laboratory on individual and ethnic variations in CYP2C19 activity in Chinese populations，their mechanisms，and the role of CYP2C19 in the metabolism of certain currently used drugs.

GENETIC POLYMORPHISM OF CYP2C19 IN CHINESE POPULATIONS

Population studies of MP have suggested that individuals can be divided into two sub-groups，extensive（EM）and poor metabolizers（PM）[6]. PM is deficient in *S*-MP 4′-hydroxylase that is now termed CYP2C19. There exists marked ethnic differences in the incidence of this polymorphic deficiency，with PM representing 3 % – 5 % of Caucasian populations but 18 % – 23 % of Oriental populations[6].

In collaboration with Takashi Ishizaki of the National Medical Center of Japan，our earlier work confirmed that both the Chinese Han population and the Japanese population have a greater incidence of PM phenotype for CYP2C19（17.4 % and 22.5 %，respectively）[7] as compared to the Caucasian populations[6]. There was no statistically significant difference in the incidence of PM between the two Oriental populations. However，Chinese EM showed a significantly lower excretion of 4′-hydroxymephenytoin（4′-OH-MP）than Japanese EM，and the mode of the distribution histogram of the Chinese EM for MP 4′-hydroxylation was skewed compared with that of the Japanese EM. These results suggest that ethnic differences in enzyme activity of CYP2C19 exist between different Oriental groups with a similar ethnic origin

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residing in the same geographic area.

China is a multi-national country with 55 ethnic minorities besides the Han majority. Each of these nationalities has unique genetic, cultural, dietetic, and environmental characteristics that affect the enzyme activity of CYP2C19. Inspired by previous results obtained from the Chinese and Japanese[7] populations, simple phenotyping[8,9] and genotyping[10,11] methods were developed to define the similarity and differences in CYP2C19 polymorphism among the Chinese nationalities. The incidence of PM and the enzyme activity of CYP2C19 were compared among five Chinese ethnic groups: Han, Bai, Dong, Miao, and Dai. The frequency of PM in the Han was significantly higher than in the Dong[10] and Dai, and marginally higher than that in the Bai[11,12] populations (Tab 1). In addition, Lou *et al* reported a PM incidence of 10.2 % in a Zhuang population[13], which is also lower than that in Han population studied by us. Using the *S/R* ratio of MP as a sensitive index for CYP2C19 activity, it was found that the Han EM had a higher enzyme activity of CYP2C19 than the Dong[10] and Dai EM (unpublished data) (S/R: 0.23 ± 0.02 *vs* 0.29 ± 0.02 and 0.28 ± 0.017, respectively, $P < 0.05$), but similar to that of the Bai EM (S/R: 0.21 ± 0.01, $P > 0.05$)[11]. These results suggest that different Chinese ethnic groups may exhibit somewhat different sensitivities to drugs metabolized by CYP2C19. It should be noted that our result of the PM incidence in Han is concluded from a relatively small population ($n = 101$). The results reported by Ruan *et al* (13.5 %, $n = 148$)[14] and Lou *et al* (14.6 %, $n = 137$)[15] are lower than ours. Since the phenotypes of CYP2C19 in our studies were confirmed by genotyping, the overlap of distribution frequencies of EM and PM in those other phenotyping studies[14,15] is a possible explanation for the discrepancy. On the other hand, our data in the Han population should be re-examined with greater sample size.

Tab 1. Genetic polymorphism of CYP2C19 in five Chinese ethnic groups. [b]$P < 0.05$ *vs* Han nationality.

Nationality	*n*	EM	PM	% PM	*Reference*
Han	101	81	20	19.8	*Reference* 11
Dong	244	217	27	11.1[b]	*Reference* 10
Miao	219	183	36	16.4	Unpublished
Bai	202	175	27	13.4	*Reference* 11
Dai	193	175	18	9.3[b]	Unpublished

OVERALL INCIDENCE OF PM IN CHINESE POPULATIONS

During the past 10 years, the polymorphism of CYP2C19 has been extensively studied in several Chinese populations[7,10-16]. To overview and re-evaluate those separate series data with the same objective and trait is necessary. By a method of meta-analysis, the overall estimate of PM at 14.32 % (CI: 12.26 % – 16.38 %) was achieved based on 1117 determinations for MP 4′-hydroxylation including almost all studies based on Chinese subjects[17].

MOLECULAR MECHANISMS OF THE CYP2C19 POLYMORPHISM IN CHINESE POPULATIONS

Up to now, two defective alleles, designated as *CYP2C19 * 2* (m1) and *CYP2C19 * 3* (m2), have been characterized as the main genetic defect in the PM of MP. The *CYP2C19 * 2*, which accounts for 75 % – 85 % of the defective alleles in both white and Japanese PM, has been shown to be a G→A mutation at bp 681 in exon 5 of wild-type *CYP2C19 * 1*[18]. This mutation results in an aberrant splice site and shifts the reading frame, thereby producing an early-stop codon and a truncated protein. The *CYP2C19 * 3* involves a G→A mutation at bp 636 in exon 4 that also creates a premature stop codon and a truncated protein[19]. This second mutation accounts for the remaining defective alleles in Japanese PM but appears to be extremely rare in white persons.

CYP2C19 **allele frequencies in Chinese populations** The intensive studies on the molecular mechanisms of CYP2C19 polymorphism in Japanese and Caucasian impelled us to document them in Chinese populations. The mechanisms of CYP2C19 polymorphism were elucidated in the Dong minority at first[10,20]. The two defective alleles, previously described in Japanese PM[18,19], were together found in Dong PM and accounted for 100 % of the poor metabolizer alleles. The *CYP2C19 * 2* and *CYP2C19 * 3* represent 86.8 % and 13.2 % of the mutant alleles in this ethnic group, respectively. Similar results were then achieved in the Han majority (83.2 % and 16.8 %, respectively) and Bai minority (82.5 % and 16.7 %, respectively)[11]. Of 101 Han subjects, 20 (19.8 %) were classified as PM phenotypically, and 100 % of these phenotypes could be explained by *CYP2C19 * 2* and/or *CYP2C19 * 3*.

Several studies by other investigators[21-23] recently confirmed that the *CYP2C19 * 2* accounted for most mutant *CYP2C19* alleles in Han, and that *CYP2C19 * 3* could partially explain these mutant alleles. Furthermore, of the 202 Bai subjects, 27 (13.4 %) were classified as PM phenotypically, and only one appeared to be an outlier. The outlier was finally found to be a heterozygote with a *CYP2C19 * 2* and a new mutant allele consisting of a C→T mutation at bp 1297 in exon 9. This mutation, which is now designated as *CYP2C19 * 5*, results in the substitution of Arg_{433}→Trp_{433} in the heme-binding region and may produce an inactive protein. Recently, it was also concluded that the *CYP2C19 * 2* and *CYP2C19 * 3* accounted for all mutant alleles in the Dai minority (90.7 % and 9.3 % respectively, unpublished data). It should be noticed that several other rare mutations of *CYP2C19* are found in Caucasian populations[24]. Nevertheless, they were not detected in Chinese populations. Although the *CYP2C19* allele frequencies in Chinese Han, Dong, Bai, and Dai subjects are somewhat different, they as a whole suggest that the molecular mechanisms of the CYP2C19 polymorphism in Chinese populations are almost the same (Tab 2).

Tab 2. *CYP2C19* allele frequencies in Chinese Han, Dong, Bai, and Dai subjects.

Nationality	Allele	PM genotype	EM genotype	Total population
Han	wt	–	0.698 (113)	0.559 (113)
	*CYP2C19 * 2*	0.8 (32[a])	0.259 (42)	0.366 (74)
	*CYP2C19 * 3*	0.2 (8)	0.043 (7)	0.074 (15)
Dong	wt	–	0.727 (80)	0.541 (80)
	*CYP2C19 * 2*	0.895 (34)	0.227 (25)	0.399 (59)
	*CYP2C19 * 3*	0.105 (4)	0.045 (5)	0.060 (9)
Bai	wt	–	0.794 (278)	0.688 (278)
	*CYP2C19 * 2*	0.759 (41)	0.18 (63)	0.257 (104)
	*CYP2C19 * 3*	0.222 (12)	0.026 (9)	0.052 (21)
	*CYP2C19 * 5*	0.019 (1)	0 (0)	0.0025 (1)
Dai[b]	wt	–	0.734 (257)	0.666 (257)
	*CYP2C19 * 2*	0.889 (32)	0.243 (85)	0.303 (117)
	*CYP2C19 * 3*	0.111 (4)	0.023 (8)	0.031 (12)

wt: wild type. [a]represents the number of alleles. [b]unpublished data.

Gene dose effect on CYP2C19 activity The PM in the Dong had a much higher *S/R* ratio of MP compared with that of the EM (0.98 ± 0.02 *vs* 0.29 ± 0.02, $P < 0.01$). Moreover, within the EM, the heterozygotes had a higher *S/R* ratio compared with the homozygotes (0.33 ± 0.03 *vs* 0.24 ± 0.03, $P < 0.05$). These results suggest that the homozygous EM have a higher enzyme activity of *S*-MP hydroxylase than the heterozygous EM and the heterozygous EM than the PM in the Dong minority. Therefore, an apparent gene dose effect on CYP2C19 activity was first found in this ethnic group[10,25]. This gene dose effect was further confirmed in the population studies of the Han[11], Bai[11], and Dai nationality (unpublished data).

NONGENETIC FACTORS THAT INFLUENCE THE ENZYME ACTIVITY OF CYP2C19

There exist statistically significant individual differences in the activity of *S*-MP 4′-hydroxylase in subgroups with the same genotype in the Han, Dong, Bai and Dai, indicating effects of nongenetic factors on the enzyme activity of CYP2C19. A few definite nongenetic determinants responsible for the variation of CYP2C19 activities have been identified so far.

Induction of CYP2C19 Rifampicin is a potent unspecific inducer of many CYP450 isoforms. Treating EM and PM of *S*-MP 4′-hydroxylation with rifampicin, using MP as a probe, we reported that the enzyme activity of CYP2C19 was inducible in EM[26]. In a recent study, after treatment with rifampicin daily for 22 d, the *S/R* ratios in the PM with *CYP2C19 * 2* was decreased by $9.6\% \pm 5.7\%$ ($P < 0.05$), and the amount of 4′-OH-MP excreted in the urine was increased by $80.1\% \pm 48.0\%$ ($P < 0.05$)[27]. These results showed that the CYP2C19 in the PM with *CYP2C19 * 2* can be induced by rifampicin. In this study, it was also found that the amount of 4′-OH-MP excreted in the urine in homozygous EM was increased by $203.9\% \pm 42.5\%$, while that in heterozygous EM was only increased by $69.6\% \pm 4.1\%$, suggesting the effect of gene dose on the inducibility of CYP2C19[27]. The relation of induction effect of rifampicin on CYP2C19 to *CYP2C19 * 2* and gene dose represents best example of the co-operation between genetic and nongenetic factors to determine the activity of drug-metabolizing enzyme.

Inhibition of CYP2C19 Most CYP450 isoforms can not only be induced but also be inhibited by certain foreign compounds including clinically used drugs. Some *in vivo* and *in vitro* drug-drug interactions suggest that fluvoxamine, a widely used drug in the treatment of major depression, may have an inhibitory effect on CYP2C19 activity. Using MP and metoprolol as probe drugs, we

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studied the effect of fluvoxamine on the activities of CYP2C19 and CYP2D6 in healthy subjects[29]. Administration of a therapeutic dose of fluvoxamine caused a significant increase in the *S/R* ratio of MP and a reduction in the excretion of 4′-OH-MP in 0 – 8 h urine. In contrast, fluvoxamine had no effect on either the 0 – 8 h urinary metoprolol/α-hydroxymetoprolol ratio or the 0 – 8 h urinary recovery of α-hydroxymetoprolol. These results indicate that fluvoxamine is an inhibitor of CYP2C19 but not CYP2D6 *in vivo*.

Certain dietary habits are also capable of inhibiting CYP450. In a study principally designed to study the *N*-demethylation of diazepam[28], the EM of MP were also subgrouped on the basis of alcohol intake to determine the effect of alcohol on CYP2C19 activity. The mean *S/R* ratio of nine drinkers who had consumed 50 – 500 mL alcohol per day for a period of 2 – 13 years was significantly higher than that of 7 non-drinkers (0.30 ± 0.11 *vs* 0.14 ± 0.08, $P < 0.01$). In addition, four of the nine drinkers had the highest *S/R* ratios of MP out of the 16 EM. These unexpected results suggest that long-termed ingestion of ethanol could decrease the enzyme activity of CYP2C19.

Effect of gender on CYP2C19 activity Gender is an important nongenetic factor affecting hepatic metabolism of certain drugs in human beings[30]. To seek the evidence for or against the effect of gender on CYP2C19 activity, the CYP2C19 activity was compared in women and men from a randomly selected and unrelated healthy Chinese population who were phenotyped and genotyped[31]. Of 116 females, 13 (11.2 %) were classified as PM phenotypically, and of 128 males, 14 (10.9 %) were PM. There was no statistically significant gender difference in the incidence of PM between females and males. However, in all phenotyped EM the *S/R* ratio of males was significantly greater than that of females (0.28 ± 0.17 *vs* 0.24 ± 0.15, $P = 0.030$). In addition, in the EM genotyped as homozygotes, females had a significantly lower *S/R* ratio than that of males (0.22 ± 0.14 *vs* 0.33 ± 0.09, $P = 0.046$), and in the heterozygous EM, this ratio was only slightly lower in females ($P > 0.05$). It was also found that the frequency of homozygous EM was 18.4 % higher in females than in males, though there was no significant difference ($P > 0.05$). From these results, it is concluded that in the phenotyped EM subgroup the CYP2C19 activity was significantly greater in females than that in males and this was caused, at least in part, by the higher enzyme activity and relatively high prevalence of homozygous EM in the female subgroup.

ROLE OF CYP2C19 IN DRUG METABOLISM

A number of clinically important drugs are metabolized by CYP2C19 including the biguanide antimalarials, omeprazole, citalopram, and certain barbiturates[32]. In addition, the metabolism of propranolol, diazepam, and certain tricyclic antidepressants also appears to be decreased in the PM of MP, albeit to a lesser extent[32]. In efforts to extend the clinical implication of CYP2C19 polymorphism, the role of CYP2C19 in the metabolism of certain drugs was studied or re-examined in Chinese subjects or liver microsomes.

***N*-demethylation of diazepam** Diazepam (DZ) is one of the most commonly prescribed sedative drug for the treatment of anxiety, convulsions and muscle spasm. *N*-demethylation is the major metabolic pathway of diazepam *in vivo* at therapeutic doses. There is evidence that in white and Korean populations the metabolism of both DZ and its *N*-demethylated metabolite desmethyldiazepam (DMDZ) cosegregates with the *S*-MP hydroxylation polymorphism, but the data from a Chinese population conflicts with the findings in white and Korean populations[33]. It has been suggested that this discrepancy might be related to the proportion of heterozygotes in Chinese *vs* Caucasian EM[33]. Thus, the *N*-demethylation of DZ and its relationship to the polymorphic hydroxylation of MP were re-examined in Chinese subjects[28]. The elimination half-lives and the clearance of DZ and DMDZ were correlated significantly to the *S/R* ratio of MP ($r = 0.543$ and 0.522, respectively, $P < 0.05$) and were dependent on MP oxidation phenotype, indicating that DZ and its active metabolite DMDZ are both metabolized by CYP2C19 in the Chinese.

The effect of CYP2C19 gene dose on DZ *N*-demethylation was then evaluated (unpublished data). Among three subgroups genotyped as PM (*CYP2C19 * 2/CYP2C19 * 2*), heterozygous EM (*CYP2C19 * 2/CYP2C19 * 1*) and homozygous EM (*CYP2C19 * 1/CYP2C19 * 1*), the elimination half-lives of DZ and DMDZ for the PM were the longest (84.0 ± 13.7 h), and those for the heterozygous EM were longer than these for the homozygous EM (62.9 ± 9.8 *vs* 20.0 ± 10.8 h, $P < 0.05$). In parallel, the mean clearance of DZ for the PM was the lowest (2.8 ± 0.9 L/h), and that for the heterozygous EM was lower than that for the homozygous EM (7.2 ± 2.6 *vs* 19.5 ± 9.8 L/h, $P < 0.05$). These results suggest that *N*-demethylation of DZ was dependent

on CYP2C19 gene dose. In addition, these results can be used as a direct evidence for the effect of heterozygote proportion on the differences in DZ *N*-demethylase observed between Chinese and Caucasians[33,34].

Side-chain oxidation of propranolol There exist great individual and ethnic differences in disposition of and response to propranolol[1]. Ward *et al* found that the clearance of propranolol *N*-dealkylation, one of propranolol's three major pathways *in vivo*, correlated highly with the polymorphic CYP2C19[35]. Considering certain discrepancies between this *in vivo* study and other *in vitro* studies, we re-examine the correlation between the side-chain oxidation of propranolol and CYP2C19 activity in healthy Chinese[36]. Relationship between MP *S*/*R* ratio or lg (4′-OH-MP/MP) and the clearance of propranolol *N*-dealkylation ($r_s = -0.0484$, $P = 0.8695$; $r_s = -0.1077$, $P = 0.7140$; respectively) had no significant correlation in the EM subjects with a large range of CYP2C19 activities. It is concluded that CYP2C19 is not a principal CYP450 isoform responsible for the *in vivo* side-chain oxidation of propranolol in Chinese.

***N*-demethylation of sertraline** The use of human liver tissue for studying drug metabolism *in vitro* has greatly increased in recent years. It allows investigators using enzyme kinetics and inhibition studies to model the *in vivo* situation of drug metabolism and to determine the enzyme(s) responsible for certain metabolic pathways. The CYP450 isoforms responsible for sertraline *N*-demethylation were unclear until a recently concluded *in vitro* study was reported. This study was designed to define the enzyme kinetics and identify the CYP450 isoform(s) of sertraline *N*-demethylase in human liver microsomes[37]. The kinetics of *N*-demethylase in the EM of CYP2C19 followed a two-enzyme Michaelis-Menten equation, while the kinetics in the PM conformed to a single-enzyme Michaelis-Menten equation lacking high-affinity components. The CYP2C19 and 2C9 selective inhibitors, omeprazole and sulfaphenazole respectively, substantially inhibited *N*-desmethylsertraline formation. Of the five tested monoclonal antibodies to CYP450 isoforms, only anti-CYP2C8/9/19 had an inhibitory effect on this reaction. It is evident that the polymorphic CYP2C19 is the high-affinity isoenzyme which catalyze sertraline *N*-demethylation, while CYP2C9 is one of the low-affinity components responsible for this reaction. Further studies are needed to determine the relative contribution of CYP2C19 and CYP2C9 to sertraline *N*-demethylation *in vivo*.

***N*-demethylation of tricyclic antidepressants** *N*-demethylation is the major metabolic pathway of the three tricyclic antidepressants: imipramine, amitriptyline, and clomipramine. It has been suggested that this pathway is associated with *S*-MP hydroxylation[32]. However, the relative contribution of CYP2C19 and other CYP450 isoforms to the pathway of each of the antidepressants have is unclear. Using kinetic analysis and inhibition studies in Chinese liver microsomes, we found that CYP2C19 and CYP1A2 were major CYP450 isoforms mediating amitriptyline *N*-demethylation *in vitro* at substrate concentrations relevant to therapeutic levels *in vivo*[38]. Furthermore, though CYP2C19 has a minor role, the *N*-demethylation of clomipramine is mediated mainly by CYP1A2 and CYP3A4 in Chinese liver microsomes[39]. In addition, fluvoxamine, a selective inhibitor of CYP2C19[29], can inhibit imipramine *N*-demethylation *in vivo* in young Chinese men[40], thereby the contribution of CYP2C19 to this reaction cannot be excluded. The influence of genetic polymorphism of CYP2C19, and the induction and inhibition of CYP2C19 on the pharmacokinetics of tricyclic antidepressants is required to be further investigated upon *in vivo*.

SUMMARY AND FUTURE CONSIDERATIONS

Our past work on CYP2C19 has been focused on the Han majority, and the Dong, Miao, Bai and Dai minority in China. Although each of these nationalities has its own traits, they seem to belong to a common origin. This has been partially confirmed by our previous results as these five nationalities differ in the CYP2C19 activity in EM, but the kinds of genotypes for PM and EM are almost the same and the frequencies of PM in the populations are similar. Nevertheless, in China, many other minorities with a big population have more distant genetic origin from the Han as compared to the Dong, Miao, Bai, and Dai. These minorities include the Mongolian, Vigur, Kazak, Tibetan, and so on. Through further extensive studies in these additional minorities, researchers would not only have a better understanding of the role of genetic factors in individuals and ethnic differences in CYP2C19 activity but also directly benefit these minor people.

It should be noticed that there exist significant differences in CYP2C19 activity in the subgroup with the same genotype. CYP2C19 activity may be influenced by nongenetic factors such as nutrition, sex, age, disease, other drugs, and so on to a great extent. Therefore, the effect of nongenetic factors on variation of CYP2C19

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activity in Chinese population should be further explored.

Detailed knowledge of the genetic polymorphism of CYP2C19 in Chinese population has been obtained for the last 10 years. However, the clinical relevance of this polymorphism is poorly documented in the Chinese. There is an obvious discrepancy between detailed information for CYP2C19 polymorphism and only rudimentary clinical evaluation of the implications of this polymorphism. The availability of phenotyping and genotyping methods should help identify the adverse reactions and toxicity of drugs that are metabolized by CYP2C19 and determine the doses of these drugs according to individual CYP2C19 activity. Moreover, in consideration of the high frequencies of defect in CYP2C19 in Chinese populations, the association of CYP2C19 with drug disposition and response should be particularly extended to more clinically used drugs in China.

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中国人群中 CYP2C19 活性的个体和种族差异[1]

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关键词　美芬妥英；细胞色素 P-450 CYP2C19；多态现象（遗传学）；蒙古人种；药物动力学；等位基因

本文综述了我国，其中主要在我们实验室，近年来对 CYP2C19 的研究结果，包括中国人群中多个民族之间 CYP2C19 的遗传多态性分布及活性比较；中国多个民族中 CYP2C19 遗传多态性的分子机制；一些非遗传因素对 CYP2C19 活性的影响；以及 CYP2C19 在一些重要药物代谢中的作用.

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