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Distinct genotype distribution and haplotype profiles in *MDR1* gene among Chinese Han, Bai, Wa and Tibetan ethnic groups

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P-Glycoprotein (P-gp, encoded by *MDR1* gene) plays an important role in determining bioavailability and pharmacologic effects of many drugs. There is increasing evidence that P-gp activity may be genetically determined. In this study, we investigated the genotype distribution and the haplotype profiles of *MDR1* gene in Chinese Han, Bai, Wa and Tibetan subjects. Much lower frequencies of the 1236T allele and the 2677T allele were found in Wa subjects than those in other three ethnic groups, while the 2677A allele was found about 6-fold more frequently in Han subjects than in subjects of other three ethnic groups. The Han, Bai and Tibetan subjects share the same three predominant haplotypes (T-T-T, T-G-C and C-G-C), and T-T-T is the highest and accounts for more than one third of the number of haplotypes in the subjects from each ethnic group. However, T-T-T was less common than T-G-C, T-G-T and C-G-C and occurring at only 13.8% in Wa subjects, furthermore, higher frequencies of T-G-T, C-T-C, C-G-T and C-T-T were observed in Wa subjects compared to those in other three ethnic groups. Frequencies of C-A-C and T-A-C in Han subjects were higher than those in other three ethnic groups. The findings of this study will be of some relevance in predicting *MDR1* phenotype and pharmacokinetics as well as pharmacodynamic effects of many commonly used drugs that are P-gp substrates in these four Chinese ethnic groups.

1. Introduction

P-Glycoprotein (P-gp), encoded by multidrug resistance gene (*MDR1*), is a transmembrane transporter that belongs to the superfamily of the adenosine triphosphatase-binding cassette (ABC) transporters. It serves as a potent efflux pump for a wide range of chemically divergent substrates, including chemotherapeutic agents, antihypertensive agents, anthracycline antibiotics, glucocorticoids, antiviral drugs, immunosuppressants, antidepressants, neuroleptics, opioids and many others (Marzolini et al. 2004; Kaya et al. 2005). The clinical importance of P-gp was first recognized in cancer chemotherapy resistance (Gottesman et al. 1996; Ambudkar et al. 1999) and later determined to has considerable impact on bioavailability, tissue concentration, and pharmacologic effects of many drugs (Schinkel 1997; Ambudkar et al. 1999; Fromm 2000). Therefore, expression levels and function integrity of P-gp directly affect plasma levels and intracellular concentrations of drugs and thereby plays an important role in efficacy and toxicity of drug treatment.

There is increasing evidence that genetic polymorphisms in *MDR1* gene may affect P-gp activity and expression levels and thus modulate its function. China is a multiracial country with a Han ethnic majority group and fifty-five ethnic minority groups with unique genetic backgrounds. Significant intra-ethnic differences in genotype frequencies of cytochrome P450 s (CYP2B6 (Guan et al. 2006) and CYP3A5 (Lai et al. 2011), thiopurine S – methyltransferase (TPMT) (Zhang et al. 2004) and glutathione S-transferase (GST) (Zhong et al. 2005) have been reported in previous studies of our lab. Our pilot study in *MDR1* gene has found that the frequency of a single nucleotide polymorphism (SNP) in exon 26 (3435C > T) differ among ethnic groups (Lai et al. 2011). 3435C > T is the most extensively studied SNP in *MDR1* gene and is the best characterized in terms of its association with the expression and/or function in the tissues, and also with pharmacokinetics and pharmacodynamics, however, there are still discrepancies in the results of all these studies (Hoffmeyer et al. 2000; Kim et al. 2001; Sakaeda et al. 2001; Fellay et al. 2002). Since 3435C > T is a synonymous mutation not resulting in a change in amino acid sequence, suggesting 3435C > T may not be the single causal modulator of the observed functional differences but rather may be in strong linkage disequilibrium with other causal polymorphisms. Multiple studies have demonstrated two synonymous mutations in exon 12 (1236C > T) and exon 26 (3435C > T) and a non-synonymous mutation in exon 21 (2677G > T/A) were found to be linked, and occurred in 62% of European Americans and 13% of African-Americans, respectively (Kim et al. 2001; Tang et al. 2002; Kroetz et al. 2003; Allabi et al. 2005), suggesting that the functional effects may be rather haplotype dependent. Indeed, superiority of haplotype analysis in predicting pharmacokinetics of some drugs and a risk of disease development were demonstrated by several clinical studies (Johne et al. 2002; Chowbay et al. 2003; Atanasova et al. 2004; Tan et al. 2005). Therefore, the aim of the present study was to characterize variability in the genotype distribution and the haplotype profiles of *MDR1* gene in four distinct Chinese populations-Han, Bai, Wa and Tibetan.

Table 1: Frequencies of *MDR1* single nucleotide polymorphisms (SNPs) in Chinese Han (n = 144), Bai (n = 134), Wa (n = 143) and Tibetan (n = 241) ethnic groups

SNPs	Ethnicity	Genotype frequency %(n)						Allele frequency %(n[a])		
MDR1 exon 12		CC		CT		TT		C	T	
1236C > T	Han	5.5 (8)		39.6 (57)		54.9 (79)		25.3 (73)	74.7 (215)	
	Bai	11.9 (16)		34.3 (46)		53.7 (72)		29.1 (78)	70.9 (190)	
	Wa	14.0 (20)		48.9(70)		37.1 (53)		38.5 (110)	61.5 (176)	
	Tibetan	7.0 (17)		44.0 (106)		49.0 (118)		29.0 (140)	71.0 (342)	
MDR1 exon 21		GG	GT	GA	TT	AT	AA	G	T	A
2677G > T/A	Han	13.2 (19)	41.7 (60)	13.2 (19)	19.4 (28)	12.5 (18)	0.0 (0)	40.6 (117)	46.5 (134)	12.9 (37)
	Bai	23.9 (32)	51.5 (69)	4.5 (6)	20.1 (27)	0.0 (0)	0.0 (0)	51.9 (139)	45.9 (123)	2.2 (6)
	Wa	34.3 (49)	48.9 (70)	1.4 (2)	12.6 (18)	2.1 (3)	0.7 (1)	59.5 (170)	38.1 (109)	2.4 (7)
	Tibetan	20.7 (50)	57.3 (138)	2.5 (6)	18.3 (44)	0.8 (2)	0.4 (1)	50.6 (244)	47.3 (228)	2.1 (10)
MDR1 exon 26		CC		CT		TT		C	T	
3435C > T	Han	34.7 (50)		51.4 (74)		13.9 (20)		60.4 (174)	39.6 (114)	
	Bai	29.1 (39)		51.5 (69)		19.4 (26)		54.9 (147)	45.1 (121)	
	Wa	31.5 (45)		44.7 (64)		23.8 (34)		53.8 (154)	46.2 (132)	
	Tibetan	24.9 (60)		57.7 (139)		17.4 (42)		53.7 (259)	46.3 (223)	

[a] Number of alleles.

2. Investigations and results

Genotype data were available from a total of 662 subjects: 144 Han, 134 Bai, 143 Wa and 241 Tibetan populations. Table 1 shows the genotype and allelic frequencies in 1236C > T, 2677G > T/A and 3435C > T by ethnic groups. In each ethnic group, and for each locus, the distribution was consistent with Hardy–Weinberg equilibrium (each $P > 0.05$).

In exon 12 of the *MDR1* gene, the frequencies of the variant allele (61.5%) and of the TT variant (37.1%) for the 1236C > T polymorphism were lower in Wa subjects compared with Han (74.7%; 54.9%), Bai (70.9%; 53.7%), and Tibetan subjects (71.0%; 49.0%), respectively ($P < 0.05$ or $P < 0.01$). At 3435C > T in exon 26, the C and T allele frequencies were similar in the four ethnic groups (each $P > 0.05$), while Wa subjects and Tibetan subjects have significantly different genotype frequencies (31.5% vs. 24.9%, 44.7% vs. 57.7%, and 23.8% vs. 17.4, $P = 0.048$). There are wide variations in genotype frequencies and allele frequencies of 2677G > T/A in exon 21 among the four ethnic groups. Much lower frequency of the wild-type GG genotype and higher frequencies of the GA and AT variants were observed in Han subjects compared to those in other three ethnic groups, while much higher frequency of the wild-type GG genotype and lower frequency of the TT variant were found in Wa subjects compared to those in other three ethnic groups. The AA variant was found to be rare in all four ethnic groups, being detected in 0.7% of Wa subjects and 0.4% of Tibetan subjects and missing in Han and Bai subjects. The A allele was about 6-fold more frequently found in Han subjects (12.9%) than in Bai (2.2%), Wa (2.4%) and Tibetan (2.1%) subjects whilst the G allele was less common in Han subjects (40.6%) than in Bai (51.9%), Wa (59.5%) and Tibetan (50.6%) subjects. The frequencies of the G and T alleles were highest and lowest, respectively, in the Wa subjects compared with Han, Bai and Tibetan subjects.

Strong linkage disequilibrium among the three SNPs was observed and the haplotype profiles of these three SNPs significantly differed in the four ethnic groups (each $P < 0.01$) (Table 2). Haplotype structure analysis of these three SNPs was statistically inferred by a Bayesian approach using the program PHASE2.1. Eleven out of twelve possible haplotypes were observed in Han, Wa and Tibetan subjects, compared with nine in Bai subjects. T-T-T, T-G-C and C-G-C were major haplotype and together they shared 73.3%, 74.1% and 82.3%, respectively, of the number of haplotypes in Han, Bai and Tibetan subjects.

Table 2: Estimated frequencies of *MDR1* haplotypes in Chinese Han (n = 144), Bai (n = 134), Wa (n = 143) and Tibetan (n = 241) ethnic groups

Haplotypes	Estimated frequency %			
	Han	Bai	Wa	Tibetan
C-G-C	14.3	21.0	14.9	24.2
C-G-T	0.6	1.1	8.1	1.8
C-T-C	0.9	4.2	8.5	1.3
C-T-T	0.5	0.5	5.9	1.1
C-A-C	8.9	2.2	0.5	0.5
C-A-T	0.0	0.0	0.5	0.0
T-G-C	23.2	19.7	19.2	20.2
T-G-T	2.4	10.1	17.2	4.1
T-T-C	9.4	7.8	10.0	7.0
T-T-T	35.8	33.4	13.8	37.9
T-A-C	3.3	0.0	0.7	0.6
T-A-T	0.6	0.0	0.6	1.4

T-T-T (13.8%) was less common than T-G-C (19.2%), T-G-T (17.2%) and C-G-C (14.9%) in Wa subjects, furthermore, higher frequencies of T-G-T, C-T-C, C-G-T and C-T-T were observed in Wa subjects compared to those in other three ethnic groups. Frequencies of C-A-C and T-A-C in Han subjects were higher than those in other three ethnic groups. We also observed two haplotypes that have been rarely reported in Asian population: the C-A-T haplotype only occurring in one of Wa subject, and the T-A-T haplotype were found in Han, Wa and Tibetan subjects but missing in Bai subjects.

3. Discussion

It is well recognized that different patients respond in different ways to the same medication, and it is estimated that genetics can account for 20 to 95 percent of variability in drug disposition and effects (Evans and McLeod 2003). The discovery of genetic polymorphisms in genes encoding drug-metabolizing enzymes, drug transporters or drug targets has contributed significantly to the understanding of the inter-individual variability in dose-concentration relationships and drug response (Chowbay et al. 2003). Therefore, pharmacogenetic testing achieves an increas-

Table 3: Polymerase chain reaction-restriction fragment length polymorphism genotyping

SNP	Primer sequence	Amplicon size (bp)	Restriction enzyme
1236 C > T	F: 5′-TAC CCA TCT CGA AAA GAA GTT AAG G-3′ R: 5′-GAA AGA TGT GAA TGT GAC TGC TGA T-3′	381	*HaeIII*
2677 G > T/A	F: 5′-TGC AGG CTA TAG GTT CCA GG-3′ R: 5′-GAA GAA CAG TGT GAA GAC AAT GGC-3′	463	*BseYI* *BsrI*
3435C > T	F: 5′-TGC TGG TCC TGA AGT TGA TCT GTG AAC-3′ R: 5′-ACA TTA GGC AGT GAC TCG ATG AAG GCA-3′	248	*MboI*

ing impact in the individualization of drug treatment and could therefore contribute significantly to enhanced drug safety and efficacy (Pfost et al. 2000).

MDR1 genetic polymorphisms have been extensively studied in different countries, and remarkable ethnic variations in the frequencies of *MDR1* variant alleles have been reported. In this study, the frequencies of the 1236T and 2677A variant alleles in Chinese Han, Bai, Wa and Tibetan subjects were significantly higher than those for Caucasians (Hoffmeyer et al. 2000; Cascorbi et al. 2001; Kim et al. 2001) and Africans (Kim et al. 2001). The 3435T variant allele was much more frequent in our study populations (39.6%–46.3%) than Africans (10%–27%) whilst less frequent in our study populations than in Caucasians (46%–52%) (Hoffmeyer et al. 2000; Ameyaw et al. 2001; Cascorbi et al. 2001; Kim et al. 2001; Schaeffeler et al. 2001). Furthermore, intra-ethnic differences among the four Chinese ethnic groups were also significant and should not be neglected. The frequencies of both 1236T variant allele and 1236TT variant were lower in Wa subjects than those for the other three ethnic groups. Relatively higher frequencies of homozygous 3435CC and 3435TT genotype and lower frequency heterozygous 3435CT were observed in Wa subjects than those in Tibetan subjects. Of the three allelic variants in exon 21, the A allele and G allele was more common in Han subjects and Wa subjects, respectively, while and the G allele and T allele was less common in Han subjects and Wa subjects, respectively.

There is growing evidence that haplotype analysis was superior to SNP analysis in predicting *MDR1* phenotype (Johne et al. 2002), thus it is of critical clinical significance to investigate the haplotype profiles of *MDR1* gene in our study populations. Both the kinds and frequencies of haplotypes differed significantly among the four ethnic groups ($P < 0.001$), and Bai subjects have the least number of haplotypes (nine vs. eleven compared to other three ethnic groups). The Han, Bai and Tibetan subjects share the same three predominant haplotypes (T-T-T, T-G-C and C-G-C), and T-T-T is the highest and accounts for more than one third of the number of haplotypes in the subjects from each ethnic group (35.8% for Han subjects, 33.4% for Bai subjects, and 37.9% for Tibetan subjects, respectively). However, T-T-T was less common than T-G-C, T-G-T and C-G-C and occurring at only 13.8% in Wa subjects, furthermore, higher frequencies of T-G-T, C-T-C, C-G-T and C-T-T were observed in Wa subjects compared to those in other three ethnic groups. Interestingly, while Wa subjects have the lowest frequency of 2677T variant allele among the four ethnic groups, they have the most even frequency distribution of haplotype including 2677T allele. Such marked intra-ethnic differences suggesting that Wa subjects may have different origin and may exhibit a response profile to P-gp substrates that is different from those of other three ethnic groups. Chowbay et al. (2003) found that T-T-T haplotype carriers had higher cyclosporine A exposure than C-G-C haplotype carriers in heart transplant recipients. Our previous study in renal transplant recipients revealed that T-G-T haplotype carriers had a significantly lower dose-adjusted through blood concentration of cyclosporine A than in the non-carriers when patients were co-treated with diltiazem (Wang et al. 2009). Significantly lower frequency of T-T-T haplotype and relatively higher frequency of T-G-T haplotype suggesting that Wa subjects may suffer from less susceptibility to cyclosporine A and higher doses are needed. The frequencies of two haplotypes including 2677A allele (C-A-C and T-A-C) in Han subjects were highest among the four ethnic groups, because of the significantly higher frequency of 2677A allele in Han subjects compared to those in other three ethnic groups. The effects of these two haplotypes on P-gp activity and expression levels have not yet been demonstrated and need further study.

In conclusion, our finding in Chinese Han, Bai, Wa and Tibetan ethnic groups provides evidence for racial heterogeneity in *MDR1* polymorphisms in Chinese. This study will be of some relevance in predicting *MDR1* phenotype and pharmacokinetics as well as pharmacodynamic effects of many commonly used drugs that are P-gp substrates and then help for the future application of pharmacongenomic-based algorithms to subjects of these four Chinese ethnic groups.

4. Experimental

4.1. Subjects

The subjects were 662 healthy, unrelated individuals including 144 Han Chinese (99 males and 45 females; mean age: 20.1 ± 0.6 years with a range of 18–26 years), 134 Bai Chinese (65 males and 69 females; mean age: 26.1 ± 9.8 years with a range of 18–60 years), 143 Wa Chinese (70 males and 73 females; mean age: 21.3 ± 0.6 years with a range of 18–51 years) and 241 Tibetan Chinese (117 males and 124 females, mean age: 25.1 ± 10.7 years with a range of 18–60 years). The Han subjects were from Guangdong Province, while Bai, Wa and Tibetan subjects were from Yunnan Province, and the ethnicity of them was confirmed by their social and culture characteristics and official identity information. These subjects were healthy based on medical history, clinical investigations, and routine laboratory parameters. Ethical approval of this study was obtained from the Ethical committee of Sun Yat-sen University, Guangzhou, PR China and written informed consent was obtained from all subjects.

4.2. DNA extracting and genotyping

Venous blood samples (1.5 ml) were collected into EDTA-containing tubes. Total genomic DNA was extracted from peripheral leukocytes according to the method described previously (Loparev et al. 1991). The subjects were genotyped for the *MDR1* SNPs 1236 C > T, 2677 G > T/A and 3435 C > T using published polymerase chain reaction (PCR) restriction fragment length polymorphism methods (PCR-RFLP) (Ameyaw et al. 2001; Haufroid et al. 2004; Elens et al. 2007). PCR amplification was carried out in a total reaction volume of 25 μl containing 50 ng genomic DNA, 2 μl dNTPs (0.25 mmol/l), 1 ul each of primer (10 μl mol/l), 2.5 μl $10 \times$ Ex Taq buffer (Mg^{2+} Plus), 0.75 U Ex Taq DNA polymerase. The PCR-amplified products were digested with restriction enzymes and analyzed after gel electrophoresis. Details regarding the primer sequences, amplicon sizes and restriction enzymes used are shown in Table 3. Correctness of genotyping was confirmed by DNA sequencing for two cases of each genotype.

4.3. Statistical analysis

Allele and genotype frequencies for the various SNPs in each ethnic group were assessed for deviation from Hardy–Weinberg equilibrium using χ^2 test or Fisher's exact test (two sided). The statistical sig-

nificance of the differences between groups was calculated by the χ^2 test or Fisher's exact test (two sided). Statistical analysis was performed in SPSS system for Windows version 13.0 (SPSS Inc, Chicago, IL, USA). *P*-values less than 0.05 were considered as statistically significant. Linkage disequilibrium between the different pairs of SNPs were estimated on the online software SHEsis (http://analysis.bio-x.cn/myAnalysis.php). Haplotypes were statistically inferred using an algorithm based on Bayesian inference by the program PHASE 2.1 (http://www.stat.washington.edu/stephens/phase/download.html).

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