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CYP3A5*3 and MDR-1 C3435T single nucleotide polymorphisms in six Chinese ethnic groups

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The prevalent CYP3A5 *3 and the functional multi-drug resistance gene (MDR1) C3435T show marked interethnic variation among Orientals, Caucasians and Africans. This study aimed to investigate the distribution of CYP3A5*3 and MDR1 C3435T among Chinese ethnic groups. Genotypes of the CYP3A5*3 and MDR1 C3435T were determined in 839 unrelated healthy Chinese subjects by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays. Frequencies *($P < 0.05$)* of CYP3A5*3 variant alleles observed in Uygur Chinese, Kazakh Chinese and Tibetan Chinese (88.1%, 84.5% and 80.7%, respectively) were Significantly higher than those in Han Chinese, Wa Chinese and Bai Chinese (67.3%, 56.3% and 70.2%, respectively). Significantly higher 3435T variant frequencies *($P < 0.05$)* were observed in Uygur Chinese (58.4%) and Kazakh Chinese (56.8%) compared with Han Chinese (44.2%), Tibetan Chinese (43.9%), Wa Chinese (45.8%) and Bai Chinese (44.2%). These results indicate that there were marked ethnic differences in the mutant frequencies of CYP3A5*3 and MDR1 C3435T among Chinese ethnic groups. Frequencies of those variants observed in Uygur Chinese, Kazakh Chinese, Tibetan Chinese, Wa Chinese and Bai Chinese were intermediate between those seen in Han Chinese and African-American.

1. Introduction

The CYP3A enzymes are richly expressed subfamily of cytochrome P450 s in human liver and intestine. This subfamily comprises four enzymes: CYP3A4, CYP3A5, CYP3A7, and CYP3A43 (Guengerich 1999). Among them, CYP3A43 is expressed at very low levels in adult livers; CYP3A7 is a fetal protein and is much lower than CYP3A4 and CYP3A5, but can also be present in small amounts in some adult livers (Tateishi et al. 1999; Domanski et al. 2001). Thus, CYP3A4 and CYP3A5 are regarded as predominant functional forms of human CYP3A. They are involved in the oxidation, peroxidation, and reduction of approximately 50% of commonly used drugs, including cancer chemotherapeutic drugs, human immunodeficiency virus protease inhibitors, calcium channel antagonists, immunosuppressants, and cholesterol-lowering drugs. They are also involved in the metabolism of either carcinogens or toxic chemicals, as well as endogenous substances (Thummel and Wilkinson 1998). Therefore, CYP3A, in particular CYP3A4 and CYP3A5, may be an important metabolic contributor to drug efficacy or bioactivation of potential toxic substrates, as well as drug-drug interactions.

Several studies reported that the genetic factor of the interindividual variability in CYP3A activity exceeds 80% and most of these genetic polymorphisms are expressesed as single nucleotide polymorphisms (SNPs) (Evans and Relling 1999; Ozdemir et al. 2000). Therefore, many studies have been focused on the detection of CYP3A4 and CYP3A5 mutant alleles which can effect the catalytic activity of CYP3A.

It is reported that there are a number of functional polymorphisms found in CYP3A4 and CYP3A5. A total of 28 SNPs in CYP3A4 were identified and racial variability was observed for the frequency of individual SNPs. CYP3A4*15 was identified only in black populations with an allelic frequency of 4%. CYP3A4*17 and CYP3A4*3 were identified in Caucasians with allelic frequencies 2% and 4%, respectively. CYP3A4*18 and CYP3A4*19 were only observed in Asians at allelic frequencies of 2% (Dai et al. 2001).

Though several SNPs are found in CYP3A5, analysis of human liver CYP3A5 cDNA revealed that only people with at least one CYP3A5*1 allele express large amounts of CYP3A5 (Kuehl et al. 2001). The most common polymorphism is CYP3A5*3, which is designated by a genomic 6986A_G transition within intron 3, which produces a truncated protein with loss of enzyme activity (Yu et al. 2004).

The multidrug resistance-1 (MDR1) gene that encodes an integral membrane protein, P-glycoprotein (P-gp), a member of the ATP-binding cassette transporters, locates on chromosome 7, consists of a core promoter region and 28 exons (Sakaeda et al. 2003). MDR1 gene is expressed at very high levels in the adrenal glands and kidneys, at intermediate levels in the lung, liver, lower jejunum, colon and rectum and at low levels in many

Table 1: Genotype and allelic distribution of CYP3A5*3 and MDR1C3435T in six Chinese ethnic groups

SNPs	Ethnicity	Genotype Frequency%(n)			Allele Frequency%(n[a])	
CYP3A5*3		*1/*1	*1/*3	*3/*3	*1	*3
	Chinese Han	15.9(18)	33.7(38)	50.4(57)	32.7	67.3
	Chinese Uygur	0 (0)	23.9(21)	76.1(67)	11.9	88.1
	Chinese Kazakh	1.8(2)	27.3(30)	70.9(78)	15.5	84.5
	Chinese Wa	16.9 (24)	53.5(76)	29.6(42)	43.7	56.3
	Chinese Bai	10.8(14)	38.0(49)	51.2(66)	29.8	70.2
	Chinese Tibetan	4.7(12)	29.2(75)	66.1(170)	19.3	80.7
MDR1 C3435T		CC	CT	TT	C	T
	Chinese Han	20.4(23)	70.8(80)	8.8(10)	55.8	44.2
	Chinese Uygur	6.8(6)	70.5(62)	22.7(20)	41.6	58.4
	Chinese Kazakh	9.1(10)	68.2(75)	22.7(25)	43.2	56.8
	Chinese Wa	31.7(45)	45.1(64)	23.2(33)	54.2	45.8
	Chinese Bai	30.2(39)	51.2(66)	18.6(24)	55.8	44.2
	Chinese Tibetan	25.7(66)	56.8(146)	17.5(45)	54.1	43.9

other tissues (Cordon-Cardo et al. 1989). The distribution of P-gp in normal tissue suggests that P-gp plays a role in excreting toxic xenobiotics and metabolites into urine, bile and intestinal lumen. At the blood-brain barrier, P-gp limits the brain accumulation of many drugs including digoxin, ivermectin, vinblastine, dexamethasone, cyclosporin A, domperidone and loperamide (Schinkel et al. 1996).

There is highly individual variation in P-gp expression. Recently, a functional single nucleotide polymorphism (SNP) resulting in a C to T transition has been described in exon 26 (C3435T), where the homozygous T allele is associated with more than two-fold lower duodenal P-gp protein expression levels compared with CC samples (Hoffmeyer et al. 2000). It is reported that the distribution of the MDR1 genotype at exon 26 was 35.1 % C/C, 52.6 % C/T, and 12.3 % T/T in healthy Japanese subjects and there was no gender or age effect on the distribution (Sakaeda et al. 2001). Although ethnic variation has been observed for most SNPs, the population frequency of C3435T in different ethnic groups has not been evaluated.

Interethnic differences in the distribution of CYP3A5 and MDR1genetic variants may contribute to explore variability in disposition of CYP3A or P-gp substrates. Therefore, the CYP3A5*3 and C3435T SNP was assessed in 839 Chinese healthy subjects (113 Han, 88 Uygur, 110 Kazakh, 142 Wa, 129 Bai and 257 Tibetan) in this study in order to investigate the distribution of CYP3A5*3 and MDR1 C3435T among Chinese ethnic groups.

2. Investigations and results

*2.1. Frequency in CYP3A5*3 single nucleotide polymorphisms (SNPs)*

The allelic frequencies of CYP3A5*3 were in Hardy-Weinberg equilibrium ($P > 0.05$) for six ethnic groups. As shown in Table 1, there was no significant difference of CYP3A5*3 variant frequencies between Uygur Chinese and Kazakh Chinese, Tibetan Chinese and Kazakh Chinese, Bai Chinese and Han Chinese.

The homozygous CYP3A5*3/*3 variants were more common in Uygur Chinese, Kazakh Chinese and Tibetan Chinese than those in Han Chinese, whereas heterozygous *1/*3 and homozygous *1/*1 genotypes were less common in Uygur Chinese, Kazakh Chinese and Tibetan Chinese than in Han Chinese and Bai Chinese. The homozygous CYP3A5*3/*3 variants were the lowest in Wa Chinese. Significantly higher frequencies of CYP3A5*3 variant alleles were observed ($P < 0.05$; Table1) in Uygur Chinese, Kazakh Chinese and Tibetan Chinese than those in Han Chinese and Bai Chinese. Lowest frequencies of CYP3A5*3 variant alleles were observed ($P < 0.05$; Table1) in Wa Chinese. This was consistent with what was reported previously that CYP3A5*3 allele was observed at intermediate frequencies in Uygur Chinese (84.8%) and Kazakh Chinese (86.6%), relative to Han Chinese (72.7%) (Li et al. 2007).

CYP3A5 expressers (sum of CYP3A5*1/*1 and *1/*3 genotypes) were significantly more common ($P < 0.05$; Table 1) in Han Chinese (49.6%) than those in Uygur Chinese (23.9%), Kazakh Chinese (29.1%) and Caucasians (20.0%) (Kuehl et al. 2001). In addition, frequency of CYP3A5 expressers in Han Chinese were close to other reported Oriental populations, such as Bai Chinese (48.8%) and Japanese (39.5%) (Fukuen et al. 2002).

Frequencies of the CYP3A5*3 allele were observed in Uygur Chinese (88.1%) and Kazakh Chinese (84.5%), at frequencies intermediate between Han Chinese (67.3%) and values reported for Caucasians (90.8%) (Kuehl et al. 2001). In addition, the frequency of CYP3A5*3 variant allele was similar between Han Chinese and other reported Oriental populations, such as Japanese (76.7%) (Fukuen et al. 2002). As shown in Table 2, a lower frequency of the CYP3A5*3 allele was observed in African-American (55.0%) (Kuehl et al. 2001). There was no significant difference of CYP3A5*3 allele frequencies among Uygur Chinese, Kazakh Chinese, Caucasians (Kuehl et al. 2001), Dutch Caucasian (van Schaik et al. 2002) and Spaniards (Gervasini et al. 2005).

2.2. Frequency of MDR1 3435 single nucleotide polymorphisms (SNPs)

The allelic frequencies of MDR1C3435T were in Hardy-Weinberg equilibrium ($P > 0.05$) for three ethnic groups. As shown in Table 1, there was no significant difference in MDR1 C3435T variant frequencies between Uygur Chinese and Kazakh Chinese, Wa Chinese and Bai Chingese and Tibetan Chinese.

In MDR1 exon 26 (C3435T), a much higher frequency of the homozygous TT variant was observed in Uygur Chinese, Kazakh Chinese, Wa Chinese, Bai Chinese, and Tibetan Chinese, compared with Han Chinese, with a much lower frequency of the homozygous CC wild type in Uygur Chinese and Kazakh Chinese compared with Han Chinese, Wa Chinese, Bai Chinese and Tibetan Chinese.

Table 2: Allelic and genotype distribution of CYP3A5 among ethnic populations

Ethnicity	Genotype Frequency%(n)			Allele Frequency%(n[a])	
	*1/*1	*1/*3	*3/*3	*1	*3
Chinese Han	15.9	33.7	50.4	32.7	67.3
Chinese Uygur	0	23.9	76.1	11.9	88.1
Chinese Kazakh	1.8	27.3	70.9	15.5	84.5
Chinese Wa	16.9	53.5	29.6	43.7	56.3
Chinese Bai	10.8	38	51.2	29.8	70.2
Chinese Tibetan	5	29.4	65.6	19.7	80.3
Japanese[a]	7	32.5	60.5	23.3	76.7
Caucasian[b]	0.3	17.7	82	9.2	90.8
Dutch Caucasian[c]	0.2	16.7	83.1	8.3	91.7
Spaniard[d]	2.8	12.4	84.7	0.9	90.1
African-American[b]	25	40	35	45	55

[a] Fukuen et al. (2002);
[b] Kuchi et al. (2001);
[c] van Suhaik et al. (2002);
[d] Gesvasini et al. (2005)

Significantly higher 3435T allele frequencies were observed in Uygur Chinese and Kazakh Chinese compared with Han Chinese, Wa Chinese, Bai Chinese and Tibetan Chinese *($P < 0.05$;* Table 1*)*. Other studies reported that a significantly higher MDR1 3435T variant frequency was observed in Uygur Chinese (52.8%), than in Kazakh Chinese (39.8%) and Han Chinese (37.9%) (Li et al. 2007). The frequency of MDR1 3435T variant allele in Chinese Uygur (58.4%) and Kazakh (56.8%) was more consistent with that in Caucasians (53.9%) (Ameyaw et al. 2001). The frequency of the MDR1 3435T variant allele of Han Chinese was similar to that reported in other Oriental populations, such as Japanese (40.6%) (Tanabe et al. 2001). The frequency of MDR1 3435T variant allele was much lower in African-American (16%) (Schaeffeler et al. 2001) than that in other reported populations.

3. Discussion

The current study revealed that there were marked interethnic differences in the distributions of MDR1 and CYP3A5 polymorphisms among Chinese ethnic groups, which may have important clinical implications. For frequencies of CYP3A5*3 and MDR1 C3435T, variants were observed in Uygur Chinese and Kazakh Chinese at frequencies intermediate between those seen in Han Chinese and Caucasians. This is consistent with the previous conclusion that Uygur and Kazakh have a genetic composition between Eurasians and Orientals according to Alu insertion polymorphisms (Xiao et al. 2002), mitochondrial DNA linkage analysis (Comas et al. 2004) and vitamin D receptor genetic polymorphism (Zhang et al. 2001).

In fact, the highest frequency of CYP3A5*1 allele is found in African-Americans (Kuehl et al. 2001). The CYP3A5*3 variant allele and homozygote are more frequent in Caucasians and Dutch Caucasians than in Han Chinese and much less common in African-Americans. Similarly, our study indicated that there were marked interethnic variations in the frequencies of alleles and genotypes for the CYP3A5 polymorphism among different Chinese ethnic populations. As mentioned previously that only people with at least one CYP3A5*1 allele express large amounts of CYP3A5, non-Caucasians, such as African-Americans and Han Chinese may be more likely to experience higher clearance of some drugs metabolized by CYP3A and less likely to experience drug toxicities. Moreover, because CYP3A5 have varying degrees of specificity and catalytic activity toward some substrates, the proposed detection assays are useful and reliable for screening the CYP3A5 related SNPs in pharmacogenetic research.

The 3435 TT genotype was not detected in the 206 Ghanaians studied, but accounted for 1∼4.5%, 4% and 6% in the African-American, Kenyan and Sudanese subjects, respectively (Ameyaw et al. 2001; Schaeffeler et al. 2001). It shows that the mutant T allele, which results in decreased P-gp levels, is relatively rare in populations with African ancestry, but exists at higher frequencies in Caucasian, Chinese and Japanese populations. The determination of variations in the MDR1 gene polymorphism has implications for the use of numerous drugs that are substrate of P-gp.

The variant frequency of these polymorphisms among different ethnic groups may contribute to drug efficiency and toxicity. For example, cyclosporine, tacrolimus, sirolimus and everolimus are immunosuppressive agents widely administered in patients who receive organ transplants. It is essential to undertake close drug monitoring programs for these drugs, which are characterized by a narrow therapeutic index. CYP3A5 and P-gp appear as important determinants of the metabolism of these drugs. Therefore, there may have evident correlation between functional SNPs in CYP3A5 and MDR1 and disposition of these drugs.

The people with at least one CYP3A5*1 allele (regarded as CYP3A5 expressers), were more common in African-Americans than Caucasians. This different distribution may affect the administration of some drugs between African-Americans and Caucasians. It has been reported that oral bioavailability of these drugs in African-Americans was 20–50% lower than in Caucasians or Non-African-Americans and resulted in higher dose requirements in African-Americans to maintain similar average concentrations of the respective immunosuppressant (Dirks et al. 2004). The data for another study indicated that long-term graft survival rates were poorer in African-Americans, even though cyclosporine dosages and blood levels were comparable to those in Caucasians (First et al. 1996). According to our data and those reported previously, we can hypothesise that Uygur Chinese and Kazakh Chinese may have high blood concentrations of the respective immunosuppressant compared with Han Chinese, and may require lower doses of the respective immunosuppressant than Han Chinese.

It has been reported that MDR-1 (3435CC) polymorphisms are associated with cyclosporine pharmacokinetics and dose requirements in the first few days after renal transplantation in 88 Iranian renal transplant patients (Azarpira et al. 2006). The data in Hauser's study indicated that kidney transplant patients with the 3435CC genotype require significantly higher cyclosporine

doses than patients with the 3435TT genotype (Hauser et al. 2005). Therefore, we can also infer that Uygur Chinese and Kazakh Chinese may have higher blood concentrations and require lower drug doses of the respective immunosuppressant than Han Chinese on account of a lower frequency of the homozygous CC wild type in Uygur Chinese and Kazakh Chinese compared with Han Chinese.

In this study, the results indicate that the distribution of CYP3A5*3 and MDR1 C3435T variants, observed in Uygur Chinese and Kazakh Chinese, are different from those seen in Han Chinese, which suggest that evaluation of CYP3A and MDR1 genotype status may be a valuable tool in identifying individuals who may have altered drug absorption. Detection of CYP3A5 and MDR1 variant alleles and knowledge about their allelic frequency in specific ethnic groups are important to lead to individualized drug dosing and improved therapeutics. Prospective studies are now required to determine the utility of CYP3A5 and MDR1 C3435T genotype for individualizing therapy and administration. Therefore, it is important to characterize the variability of CYP3A5 and MDR1 genotype frequency in different ethnic populations.

4. Experimental

4.1. Chemical and reagents

Restriction enzymes were purchased at Roche Diagnostics (Beijing, China) or New England Biolabs (Beverly, MA). Thermoscript RT-PCR System was from Invitrogen, and Taq polymerase from QIAGEN (Beijing, China), and PCR dNTPs from Invitrogen. The water used was of Milli-Q grade purified by a Milli-Q UV Purification System (Millipore, Bedford, MA, USA). All other chemicals and reagents were of analytical or HPLC grade as appropriate.

4.2. Study population

Venous blood samples (1.5 ml) were obtained from unrelated healthy Han Chinese (all college students, n = 113; 74 males and 39 females; mean age: 18.1 ± 0.6 years with a range of 17–23 years), Uygur Chinese (all college students, n = 88; 34 males and 54 females; mean age: 18.4 ± 0.4 years with a range of 17–21 years), Kazakh Chinese (n = 110; 62 males and 48 females; mean age: 38.1 ± 12.2 years with a range of 15–55 years), Wa Chinese (n = 142; 69 males and 73 females; mean age: 21.3 ± 0.6 years with a range of 15–51 years), Bai Chinese (n = 129; 60 males and 69 females; mean age: 26.1 ± 9.8 years with a range of 17–85years) and Tibetan Chinese (n = 257; 127 males and 130 females; mean age: 25.1 ± 10.7 years with a range of 18–70 years). The volunteers were from Sun Yat-sen University, Guangdong Province, PR China and Polytechnic College of Xinjiang Uygur Autonomous Region, Xinjiang Province, PR China and the People's Hospital, Xinhua Hospital of Xinjiang Kazakstan Autonomous Region, Xinjiang Province, PR China and Cangyuan county, Jianchuan county and Xianggelila county, Yunnan Province. These subjects were healthy based upon medical history, clinical investigations, and routine laboratory parameters. The ethnicity of all volunteers was confirmed by their social and culture characteristics and official identity information. 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 participants.

4.3. DNA extraction

Total DNA was extracted from peripheral leukocytes from the subjects by the phenol-chloroform extraction method as described previously (Chomczynski and Sacchi 1987). The DNA concentrations were determined using the GeneQuant photometer (Amersham Biosciences Inc., Piscataway, NJ). The purity of DNA was 99.5%.

4.4. PCR amplification, genotyping

Polymerase chain reaction (PCR) followed by restriction fragment length polymorphism analysis was used for genotyping MDR1 exon 26 (C3435T) and CYP3A5*3 (A6986G in intron 3) variant alleles as described previously (Fukuen et al. 2002; Ameyaw et al. 2001).

A PCR assay using forward primer (5'-CAT GAC TTA GTA GAC AGA TGA C-3') and reverse primer (5'-GGT CCA AAC AGG GAA GAA ATA -3') was performed in a 50 μl of reaction system for detecting CYP3A5*3. The PCR product of 293 bp was obtained and was digested by restriction enzyme SspI.

Primers were designed from known sequences of MDR1 exon 26 (Genbank accession nos: J05168 and AC 005068). A PCR assay using forward primer MDR1F (5'-TGC TGG TCC TGA AGT TGA TCT GTG AAC-3') and reverse primer MDR1R (5'-ACA TTA GGC AGT GAC TCG ATG AAG GCA-3') was performed with 50 μl with 20 ng genomic DNA, 10 × PCR buffer, 200 μM dNTPs and 1 unit of Taq polymerase. The PCR product of 248 bp was obtained and was digested by restriction enzyme MboI.

4.5. Statistical analysis

Analysis of data was performed using the computer software SPSS for Windows (Version 13.0). The frequencies of each SNPs were assessed for deviation from Hardy-Weinberg equilibrium and were compared between different Chinese ethnic groups using X^2 test. The results were considered significant when $p < 0.05$. The differences in genotype frequency between different ethnic groups of Chinese were tested with X^2 test.

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