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ORIGINAL ARTICLE

The high prevalence of the poor and ultrarapid metabolite alleles of CYP2D6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 in Taiwanese population

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Abstract Genetic polymorphisms of drug metabolizing enzymes, such as cytochromes P450 (CYPs), play major roles in the variations of drug responsiveness in human. The aim of this study is to identify the high prevalence (minor allele frequencies >1%) of the abnormal metabolite alleles of CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 in the Taiwanese population. The genotyping of the functional single nucleotide polymorphisms (SNPs) of CYPs were conducted by direct exon sequencing in 180 Taiwanese volunteers. Twenty-one unique SNPs including three newly identified SNPs were detected in the Taiwanese population. Six of the 21 SNPs in five genes showed frequencies more than 1%. The results indicated that it could be very useful and important in developing an inexpensive, convenient, and precise genotyping method for the high prevalence of CYPs metabolizing abnormal alleles in the Taiwanese population.

Keywords CYP2C9 · CYP2C19 · CYP2D6 · CYP3A4 · CYP3A5 · SNP · Taiwanese population

Introduction

Personalized medicine based on an individual's genetic make-up has been becoming a reality as the need for pharmacogenomics has moved from the research setting into the clinical laboratory (Jannetto et al. 2004). However, the selection of appropriate technologies to perform personalized medicine is extremely critical, and requires careful consideration of several factors including prior knowledge of the polymorphisms, sensitivity, and specificity of the methods used, clinical sample requirements, clinical utilities, and the development cost.

Cytochrome P450 (P450) is responsible for most enzymatic oxidation reactions, and is often rate-limited for the fate of a drug in the body. Therefore, it is expected that dysfunction of P450 may lead to unexpected drug effects and toxicity (Nagata and Yamazoe 2002). Several key drug-metabolizing enzymes, such as P450 (CYP) 2D6, 2C9, 2C19, 3A4, and 3A5, are inherited mutations (or polymorphisms) that lead to different drug responses (Weinshilboum 2003; Evans and McLeod 2003). Polymorphisms of human drug metabolism are associated with specific phenotypes and genotypes. The phenotype is distinguished by the activities or contents of an enzyme. Individuals who have normal metabolic activity are called extensive metabolizers (EM) whereas individuals with defective metabolic activity are called poor metabolizers (PM; Meyer 1990). It has been reported that phenotypes associated with genetic variations often contribute to differences in drug metabolism and the dynamics of drug–drug interactions (Solus et al. 2004).

Although pharmacogenomic intervention cannot assume to be cost-effective for all clinical practice, some key aspects of cost-effectiveness of pharmacogenomics were described (Phillips and Van Bebber 2004). One aspect previously described is the

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prevalence of a specific genetic mutation in a population because testing was no longer cost-effective for lower mutation prevalence (Eckman et al. 2002). In this study, we screened the single nucleotide polymorphism associated with enzyme activity of CYP 2D6, 2C9, 2C19, 3A4, and 3A5, and identified a high prevalence of functional polymorphism in the Taiwanese population. The study was the first comprehensive polymorphism analysis of drug-metabolizing cytochrome genes to be performed in the Taiwanese population. The data would allow us to develop an inexpensive and simple genotyping method for detecting the high prevalence of PM and ultrarapid metabolizer (UM) alleles in the Taiwanese/Asian population.

Materials and methods

DNA preparation

Genomic DNA was extracted from 180 unrelated Han-Chinese volunteers living in Taiwan. Clinical samples were collected with written informed consent from all the participants recruited. DNA was isolated from blood samples using QIAamp DNA Blood kit (QIAGEN, Valencia, CA, USA) according to the manufacturer's instructions. The quality of the isolated genomic DNA was checked using agarose gel electrophoresis analysis, the quantity was determined by spectrophotometer, and stored at –80°C until use.

SNP genotyping by sequencing

Fragments of DNA flanking the genomic region of the selected SNPs were amplified by ABI 9700 thermal cycler using two pairs of forward and reverse primers. The information regarding primers and genotyped SNPs is listed in Table 1. The fragments of polymer chain reaction (PCR) products were sequenced by an ABI 3700 automatic sequencer according the manufacturer's protocol (Applied Biosystems, Foster City, CA, USA). The sequence data were analyzed using PolyPhred software to identify the potential candidate SNPs. The potential SNPs were manually checked to ensure the presence of a true SNP and the allele of each individual. Three independent manual confirmations were performed for all the sequence data and only those data that were confirmed were subjected to the subsequent statistical analysis. The identified SNPs and related primers are listed in Table 1.

Results

Six SNPs associated with the PM/UM phenotype had a high prevalence in the Taiwanese population

We investigated the frequencies of five P450 genes of PM/UM-associated alleles in 180 Han-Chinese volunteers in Taiwan. As Table 1 showed, 21 SNPs were detected by our screening in the Taiwanese population. Three SNPs, VGV 3030 in CYP2C19 exon 1, VGV1995 in CYP3A4 exon 11, and VGV2643 in CYP2D6 intron 5, were the newly identified SNPs in the current study. Six of the 21 SNPs in five genes associated with PM/UM phenotypes showed a frequency of more than 1% (Table 1). Compared with other ethnic populations, the allele frequencies of six SNPs associated with PM/UM in the Taiwanese population are similar to those of other Asian populations (Chinese–Asian, Japanese, Korean), but different from the Caucasian and African–American populations (Table 2). In Table 2, the total numbers of participants analyzed are less than 180 for some genes because those participants with missing genotyping or an ambiguous genotype calling were not analyzed.

High prevalence PM/UM genotype frequencies in the Taiwanese population

The high prevalence (frequencies more than 1%) of genotypes associated with abnormal metabolic rates are listed in Table 3. We did not find the homozygous CYP2C9*3 and CYP2D6*5 alleles in this study. We detected several participants who were heterozygous with both CYP2C19*2 and *3 loci. Nevertheless, we could not determine whether or not these two inactive alleles are on the same chromosome or on a different one. The participants who were heterozygous with both CYP2C19*2 and *3 loci should be defined as PM according to the haplotype analysis in the Japanese population because CYP2C19*2 and *3 were suggested to exist exclusively on the same chromosome in this previous report (Fukushima-Uesaka et al. 2005). In general, the PM, IM (intermediate metabolizer), EM and UM phenotypic categories correspond to two inactive alleles, one inactive allele, two normal active alleles, and two over-active alleles respectively. Because the CYP2D6*10 allele reduces, but does not abolish enzyme activity, being homozygous with CYP2D6*10 therefore represents the IM phenotype.

Table 1 Single nucleotide polymorphisms (SNPs) of five cytochrome P-450 genes (newly identified SNPs) by polymer chain reaction (PCR)d-based sequencing methods

Gene	Primer name	Sequence (5′–3′)	PCR ID	Size	Detect changes	Allele	Polymorphism location	Effect	Minor allele frequency
CYP2C9	O7679	TAGTTTCGTTTCTCTTCCTGTTA	O7679 + O7680	246	C430T	CYP2C9*2	Exon 3, R144C	PM	ND
	O7680	AAATGTTTCCAAGAATGTCAGTA							
	O7681	CAGAGCTTGGTATATGGTATGTA	O7681 + O7682	348	818delA	CYP2C9*6	frame shift	PM	ND
	O7682	TACTGATTGACCAGTTAAACATC							
	O7683	CTAAAGTCCAGGAAGAGATTGA	O7683 + O7684	250	A1075C	CYP2C9*3	Exon 7, I359L	PM	C:3.8%
	O7684	ATGATACTATGAATTTGGGGACT			C1080G	CYP2C9*5	Exon 7, D360E	PM	ND
CYP2C19	O8566	CAAAGAGGCACACACACTTA	O8566 + O8567	390	A1G	CYP2C19*4	GTG initiation codon		ND
	O8567	AACAAAAGCCTTTCAAAGTA			C18G[a]	VGV3030	Exon 1		G:1.63%
					C99T				C:5.98%
	O5538	AACTGTATCTCCTTTTCTAGCTCT	O5538 + O5539	535	G276C		Exon 2, E92D		ND
	O5539	GAAAGGTCAGTGATAGAGAGTATG			T358C	CYP2C19*8	Exon 3, W120R	PM	ND
					G395A	CYP2C19*6	Exon 3, R132Q	PM	ND
					G431A	CYP2C19*9	Exon 3, R144H	PM	ND
					G449A	CYP2C19*11	Exon 3, R150H		ND
					G481C	VGV2001	Exon 3, A161P		C:0.54%
	O5540	TCTGTTAACAAATATGAAGTGTTT	O5540 + O5541	351	G636A	CYP2C19*3	Exon 4, W212end	PM	A:2.2%
	O5541	TCTAGGCAAGACTGTAGTATTCA							
	O5542	TTGGCATATTGTATCTATACCTTT	O5542 + O5543	303	C680T	CYP2C19*10	Exon 5, P227L	PM	ND
	O5543	CTAGTCAATGAATCACAAATACG			G681A	CYP2C19*2	Exon 5, splicing site	PM	A:28.9%
	O5544	ACTTGTGTCTTGTCAGCTAAAGT	O5544 + O5545	251	C990T				T:28.2%
	O5545	GAGGAATAAAAGAACATGGAGTT			A991G		Exon 7, I331V		A:3.4%
	O5546	CCTCTTATTACTTCGTCTATCTGT	O5546 + O5547	500	C1228T	CYP2C19*13	Exon 8, R410C		ND
	O5547	TAATTCTCCAAAACCCACTAAT			A1251C				C:2.2%
	O5548	ATATTCTGTCTGTGCCAGTTATAG	O5548 + O5549	362	C1297T	CYP2C19*5A	Exon 9, R433W	PM	ND
	O5549	CAGAAGAAGCATCACAGATAGT							
CYP2D6	O5550	ACACAGCAGGTTCACTCAC	O5550 + O5551	499	G31A		Exon 1, V11M		ND
	O5551	GTATAAATGCCCTTCTCCAG			G77A	CYP2D6*43	Exon 1, R26H		ND
					C82T	CYP2D6*22	Exon 1, R28C		ND
					C100T	CYP2D6*10	Exon 1, P34S	IM	C:34.4%
					G124A	CYP2D6*12	Exon 1, G42R	PM	ND
	O11531	CCCCGCCCCACGATCAGGAG	O11530 + O11532	518	T843G		Intron 1		T:24.8%
	O11532	GCCCCGCCCACTCGTCACAAG			G883C	CYP2D6*11	Intron 1, splicing defect	PM	ND
					C957T	CYP2D6*23	Exon 2, A85V		ND
					C974A		Exon 2, L91M		ND
					A984G		Exon 2, H94R		ND
					C997G		Exon 2		ND
					C1039T		Exon 2		C:39.0%
	O5554	CACGGAAATCTGTCTCTGTC	O5554 + O5555	278	C1023T		Exon 2, T107I	IM	ND
	O5555	TTCAAATAGGACTAGGACCTGTA							
	O5556	CTTCTCCGTGTCCACCTT	O5556 + O5557	494	T1707 del	CYP2D6*6A	Exon 3, frameshift	PM	ND
	O5557	CCTTCTTACAGTGGGGTCT			G1758T	CYP2D6*8	Exon 3, stop codon	PM	ND
					G1758A	CYP2D6*14	Exon 3, G169R	PM	ND
					G1846A	CYP2D6*4	Intron 3, splicing defect	PM	ND
					G1976A		Exon 4, G212E		ND
	O5552	CCCGTTCTGTCTGGTGTA	O5552 + O5553	605	T2470C		Exon 5		ND

Table 1 continued

Gene	Primer name	Sequence (5′–3′)	PCR ID	Size	Detect changes	Allele	Polymorphism location	Effect	Minor allele frequency
	O5553	TGTCCCAGCAAAGTTCAT			G2483T	CYP2D6*33	Exon 5, A237S		ND
					A2549 del	CYP2D6*3A	Exon 5, frameshift	PM	ND
					2613-5 del AGA (3-bp deletion)	CYP2D6*9	Exon 5, K281del	IM	ND
					G2663A[a]	VGV2643	Intron 5		A:3.8%
					C2850T		Exon 6, R296C		T:16%
					A2935C	CYP2D6*7	Exon 6, H324P	PM	ND
	O5558	AGGTGAAGAAGAGGAAGAGC	O5558 + O5559	291	G3853A	CYP2D6*27	Exon 8, E410K		A:32.4%
	O5559	ACTCATCACCAACCTGTCAT							
	O11368	TCTTCTTCACCTCCCTGCTG	O11368 + O11372	793	G4180C		Exon 9, S486T		G:25.9%
	O11372	TGTACAGCAGCATCCCTGAG			C4401T				C:39.7%
					G4481A				A:14.0%
	O11361	GTTATCCCAGAAGGCTTTGCAGGCTTCA	O11361 + O711362	5100		CYP2D6*5[b]	CYP2D6 deleted		*5: 5.5%
	O11362	GCCGACTGAGCCCTGGGAGGTAGGTA							
	O11363	CAGGCATGAGCTAAGGCACCCAGAC	O11363 + O11364	3200					
	O11364	CACACCGGGCACCTGTACTCCTCA							
CYP3A4	O5562	GTTCCTGTTTAACACATTTTCTAC	O5562 + O5563	271	A352G	CYP3A4*4	Exon 5, I118V		ND
	O5563	TGTGATCTTATTTTATACCTGTCC			G389A	CYP3A4*8	Exon 5, R130Q		ND
	O5564	CTAGTAGATCTGAAAGTCTGTGG	O5564 + O5565	401	C554G	CYP3A4*16	Exon 7, T185S		ND
	O5565	CAAATGTACTACAAATCACTGAAC			T566C	CYP3A4*17	Exon 7, F189S	PM	ND
					C653G	CYP3A4*5	Exon 7, P218R		ND
	O5566	GCTTCACTTAGATTTCTCTTCAT	O5566 + O5567	250	T878C	CYP3A4*18	Exon 10, L293P	UM	C:1.1%
	O5567	ACTCACCTTATTGGGTAAAACT							
	O5568	TTAGTACTGCATGGACTGAGTTA	O5568 + O5569	407	C1088T	CYP3A4*11	Exon 11, T363M		ND
	O5569	CAAGCAAATAATTATACAACCAC			G1089A[a]	VGV1995	Exon 11		A:0.5%
					C1117T	CYP3A4*12	Exon 11, L373F		ND
					C1247T	CYP3A4*13	Exon 11, P416L		ND
CYP3A5	O5570	GTACATATTACCTCCCTCTCTTG	O5570 + O5571	269	C3705T	CYP3A5*3B	Exon 2, H30Y		ND
	O5571	TTTACTGATGGAACTAAGCTGAT							
	O7701	TATGTAATCCATACCCCTAGTTG	O7701 + O7702	258	A6986G	CYP3A5*3	intron 3, splicing defect, premature stop after aa 102	PM	A:30.8%
	O7702	AACATTATGGAGAGTGGCATAG							
	O5572	ATTCAGCAGATAGTTCTGAAAGT	O5572 + O5573	304	A14665G	CYP3A5*4	Exon 7, Q200R		ND
	O5573	GAAAGAAATAATAGCCCACATAC							
	O5574	GATTATCCAATTCTGTTTCTTTC	O5574 + O5575	341	C27289A	CYP3A5*2	Exon 11, T398N		ND
	O5575	CGATTGTCATGTAGATTAAGAGA							
	O5576	CATGTAACTCTGTGGTTTTTATG	O5576 + O5577	323	A29782G	CYP3A5*3J	Exon 12, I456V		ND
	O5577	CCCATAGAATGAATTATTAAAAGA							
	O5578	TCCATATGCTTGTTTAACTATTG	O5578 + O5579	308	T31551C	CYP3A5*3F	Exon 13, I488T		C:0.5%
	O5579	TACATAATGCACAACACTCTACA			C31611T	CYP3A5*1D			C:26.6%

The related information refers to the homepage of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee (http://www.imm.ki.se/CYPalleles/)

PM poor metabolizers, *IM* intermediate metabolizers, *UM* ultrarapid metabolizers, *ND* no polymorphism was detected

[a] Newly identified SNP

[b] The detection methods and primer design were described in Hersberger et al. (2000)

Table 2 Allele frequencies in different ethnic populations

Allele	Taiwanese (*n*)	Chinese–Asian	Japanese	Korean	Caucasian	African–American
CYP2C9*3	0.025 (180)	0.026 (Sullivan-Klose et al. 1996)	0.021 (Nasu et al. 1997)	0.011 (Yoon et al. 2001)	0.06–0.09 (Scordo et al. 2001; Sullivan-Klose et al. 1996)	0.005 (Sullivan-Klose et al. 1996)
CYP2C19*2	0.324 (179)	0.32 (Goldstein et al. 1997)	0.23 (Goldstein et al. 1997)	0.209 (Herrlin et al. 1998)	0.129–0.144 (Goldstein et al. 1997; Shimizu et al. 2003)	0.25 (Goldstein et al. 1997)
CYP2C19*3	0.05 (179)	0.055 (Goldstein et al. 1997)	0.104 (Goldstein et al. 1997)	0.116 (Herrlin et al. 1998)	0 (Goldstein et al. 1997; Shimizu et al. 2003)	0 (Goldstein et al. 1997)
CYP2D6*5	0.055 (173)	0.072 (Ji et al. 2002)	0.003–0.062 (Kubota et al. 2000; Fukuda et al. 2005)	0.017 (Roh et al. 2001)	0.02 (Sachse et al. 1997)	
CYP2D6*10	0.656 (173)	0.47–0.516 (Armstrong et al. 1994; Ji et al. 2002)	0.386 (Kubota et al. 2000)	0.538 (Roh et al. 2001)	0.015–0.05 (Armstrong et al 1994; Sachse et al. 1997)	
CYP3A4*18	0.034 (178)	0.01–0.1 (Dai et al. 2001; Hu et al. 2005)	0.013 (Yamamoto et al. 2003)		0 (Dai et al. 2001)	
CYP3A5*3	0.692 (180)	0.73–0.75 (Lee et al. 2003; van Schaik et al. 2002)	0.71 (van Schaik et al. 2002)	0.7 (van Schaik et al. 2002)	0.91 (Lee et al. 2003; van Schaik et al. 2002)	0.27 (van Schaik et al. 2002)

Table 3 Genotype frequencies of six SNPs identified in the present study

Gene	Genotype	Number of individuals	Frequency	Phenotype interpretation
CYP2C9	CYP2C9*1/*1	171	0.950	EM
	CYP2C9*1/*3	9	0.050	IM
CYP2 C19	CYP2C19*1/*1	65	0.365	EM
	CYP2C19*1/*2	80	0.449	IM
	CYP2C19*1/*3	12	0.067	IM
	CYP2C19*2/*2	15	0.084	PM
	CYP2C19*2/*3	6	0.034	PM
CYP2D6	CYP2D6*1/*1	24	0.139	EM
	CYP2D6*1/*5	7	0.040	IM
	CYP2D6*1/*10	45	0.260	EM
	CYP2D6*5/*10	12	0.069	IM
	CYP2D6*10/*10	85	0.491	IM
CYP3A4	CYP3A4*1/*1	168	0.944	EM
	CYP3A4*1/*18	8	0.045	EM
	CYP3A4*18/*18	2	0.011	UM
CYP3A5	CYP3A5*1/*1	16	0.089	EM
	CYP3A5*1/*3	79	0.439	IM
	CYP3A5*3/*3	85	0.472	PM

EM extensive metabolizers

Discussion

The likely response of an individual to a drug, such as the risk of a toxic event, is thus a complex equation involving multiple variables. However, inherited unique genetic polymorphisms (usually inactivating) are one of the major causes of variations in drug responsiveness (Evans and Johnson et al. 2001). It has been reported that the drug dosages used in clinical trials with east Asian participants are typically lower than those used in trials with western participants (Yu et al. 1996; Ross et al. 2001). Selecting polymorphisms with high frequencies of drug-metabolizing enzymes in different populations is a necessary and critical task. Therefore, an easy-to-use tool urgently needs to be developed by integrating the population's specific DME polymorphisms for clinical practice in the near future.

CYP2D6*5 represents deletion of the CYP2D6 gene and its frequency is larger than 1% in the Taiwanese population. Theoretically, the genotype frequency of homozygous CYP2D6*5 is about 0.3% (0.055^2) and represents the PM phenotype. However, we could not find homozygous CYP2D6*5 in this study. Similarly, CYP2D6*10 is another high frequency allele representing the IM phenotype in this study population. Most Taiwanese are homozygous CYP2D6*10 and belong to the IM phenotype. Both transheterozygous CYP2D6*5/*10 and homozygous CYP2D6*10/*10 represent the IM phenotype. Because of this, in the Taiwanese population it is likely that the IM

transheterozygous genotyping with CYP2D6*5/*10 could be wrongly genotyped as CYP2D6*10/*10 due to having the same IM classification.

The CYP2C19*1/*2 and *1/*3 with the IM classification accounted for about 52% (0.449 + 0.067) of CYP2C19 genotypes. Over 50% of CYP2D6 genotyped individuals were related to the IM phenotype. The abnormal metabolic genotypes of the major drug-metabolizing cytochromes CYP2C9, CYP2C19, and CYP2D6, are usually linked to the IM phenotype. These observations may provide some indication as to why the drug dosages used in clinical trials with east Asian participants are usually lower than those used in trials with western participants.

The genotype of homozygous CYP3A5*3 is classified as PM and occurred in 47.2% Taiwanese. Previous studies on CYP3A5 in vitro and in humans have provided inconsistent information on whether CYP3A5 plays a significant role in the metabolism of CYP3A substrates in vivo (Williams et al. 2003). Further clarification is required to differentiate the relative contributions of CYP3A4 and CYP3A5 in vivo.

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References

Armstrong M, Fairbrother K, Idle JR, Daly AK (1994) The cytochrome P450 CYP2D6 allelic variant CYP2D6J and related polymorphisms in a European population. Pharmacogenetics 4:73–81

Dai D, Tang J, Rose R, Hodgson E, Bienstock RJ, Mohrenweiser HW, Goldstein JA (2001) Identification of variants of CYP3A4 and characterization of their abilities to metabolize testosterone and chlorpyrifos. J Pharmacol Exp Ther 299:825–831

Eckman MH, Singh SK, Erban JK, Kao G (2002) Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. Med Decis Making 22:108–124

Evans WE, Johnson JA (2001) Pharmacogenomics: the inherited basis for interindividual differences in drug response. Ann Rev Genomics Hum Genet 2:9–39

Evans WE, McLeod HL (2003) Pharmacogenomics—drug disposition, drug targets, and side effects. N Engl J Med 348:538–549

Fukuda T, Maune H, Ikenaga Y, Naohara M, Fukuda K, Azuma J (2005) Novel structure of the CYP2D6 gene that confuses genotyping for the CYP2D6*5 allele. Drug Metab Pharmacokinet 20:345–350

Fukushima-Uesaka H, Saito Y, Maekawa K, Ozawa S, Hasegawa R, Kajio H, Kuzuya N, Yasuda K, Kawamoto M, Kamatani N, Suzuki K, Yanagawa T, Tohkin M, Sawada J (2005) Genetic variations and haplotypes of CYP2C19 in a Japanese population. Drug Metab Pharmacokinet 20:300–307

Goldstein JA, Ishizaki T, Chiba K, de Morais SM, Bell D, Krahn PM, Evans DA (1997) Frequencies of the defective CYP2C19 alleles responsible for the mephenytoin poor metabolizer phenotype in various Oriental, Caucasian, Saudi Arabian and American black populations. Pharmacogenetics 7:59–64

Herrlin K, Massele AY, Jande M, Alm C, Tybring G, Abdi YA, Wennerholm A, Johansson I, Dahl ML, Bertilsson L, Gustafsson LL (1998) Bantu Tanzanians have a decreased capacity to metabolize omeprazole and mephenytoin in relation to their CYP2C19 genotype. Clin Pharmacol Ther 64:391–401

Hersberger M, Martin-Jaun J, Rentsch K, Hansler E (2000) Rapid detection of the CYP2D6*3, CYP2D6*4, and CYP2D6*6 alleles by tetra-primer PCR and of the CYP2D6*5 allele by multiplex long PCR. Clin Chem 48:1072–1077

Hu YF, He J, Chen GL, Wang D, Liu ZQ, Zhang C, Duan LF, Zhou HH (2005) CYP3A5*3 and CYP3A4*18 single nucleotide polymorphisms in a Chinese population. Clin Chim Acta 353:187–192

Jannetto PJ, Laleli-Sahin E, Wong SH (2004) Pharmacogenomic genotyping methodologies. Clin Chem Lab Med 42:1256–1264

Ji L, Pan S, Wu J, Marti-Jaun J, Hersberger M (2002) Genetic polymorphisms of CYP2D6 in Chinese mainland. Chin Med J (Engl) 115:1780–1784

Kubota T, Yamaura Y, Ohkawa N, Hara H, Chiba K (2000) Frequencies of CYP2D6 mutant alleles in a normal Japanese population and metabolic activity of dextromethorphan *O*-demethylation in different CYP2D6 genotypes. Br J Clin Pharmacol 50:31–34

Lee SJ, Usmani KA, Chanas B, Ghanayem B, Xi T, Hodgson E, Mohrenweiser HW, Goldstein JA (2003) Genetic findings and functional studies of human CYP3A5 single nucleotide polymorphisms in different ethnic groups. Pharmacogenetics 13:461–472

Meyer UA (1990) Genetic polymorphisms of drug metabolism. Fundam Clin Pharmacol 4:595–615

Nagata K, Yamazoe Y (2002) Genetic polymorphism of human cytochrome P450 involved in drug metabolism. Drug Metabol Pharmacokinet 17:167–189

Nasu K, Kubota T, Ishizaki T (1997) Genetic analysis of CYP2C9 polymorphism in a Japanese population. Pharmacogenetics 7:405–409

Phillips KA, Van Bebber SL (2004) A systematic review of cost-effectiveness analyses of pharmacogenomic interventions. Pharmacogenomics 5:1139–1149

Roh HK, Chung JY, Oh DY, Park CS, Svensson JO, Dahl ML, Bertilsson L (2001) Plasma concentrations of haloperidol are related to CYP2D6 genotype at low, but not high doses of haloperidol in Korean schizophrenic patients. Br J Clin Pharmacol 52:265–271

Ross AM, Gao R, Coyne KS, Chen J, Yao K, Yang Y, Qin X, Qian S, Yao M, TUCC Investigators (2001) A randomized trial confirming the efficacy of reduced dose recombinant tissue plasminogen activator in a Chinese myocardial infarction population and demonstrating superiority to usual dose urokinase: the TUCC trial. Am Heart J 142:244–247

Sachse C, Brockmoller J, Bauer S, Roots I (1997) Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet 60:284–295

Scordo MG, Aklillu E, Yasar U, Dahl ML, Spina E, Ingelman-Sundberg M (2001) Genetic polymorphism of cytochrome P450 2C9 in a Caucasian and a black African population. Br J Clin Pharmacol 52:447–450

Shimizu T, Ochiai H, Asell F, Shimizu H, Saitoh R, Hama Y, Katada J, Hashimoto M, Matsui H, Taki K, Kaminuma T, Yamamoto M, Aida Y, Ohashi A, Ozawa N (2003) Bioinformatics research on inter-racial difference in drug metabolism. I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CYP2C19. Drug Metab Pharmacokinet 18:48–70

Solus JF, Arietta BJ, Harris JR, Sexton DP, Steward JQ, McMunn C, Ihrie P, Mehall JM, Edwards TL, Dawson EP (2004) Genetic variation in eleven phase I drug metabolism genes in an ethnically diverse population. Pharmacogenomics 5:895–931

Sullivan-Klose TH, Ghanayem BI, Bell DA, Zhang ZY, Kaminsky LS, Shenfield GM, Miners JO, Birkett DJ, Goldstein JA (1996) The role of the CYP2C9-Leu359 allelic variant in the tolbutamide polymorphism. Pharmacogenetics 6:341–349

Van Schaik RH, van der Heiden IP, van den Anker JN, Lindemans J (2002) CYP3A5 variant allele frequencies in Dutch Caucasians. Clin Chem 48:1668–1671

Weinshilboum R (2003) Inheritance and drug response. N Engl J Med 348: 529–537

Williams JA, Cook J, Hurst SI (2003) A significant drug-metabolizing role for CYP3A5? Drug Metab Dispos 31:1526–1531

Yamamoto T, Nagafuchi N, Ozeki T, Kubota T, Ishikawa H, Ogawa S, Yamada Y, Hirai H, Iga T (2003) CYP3A4(*)18: it is not rare allele in Japanese population. Drug Metab Pharmacokinet 18:267–268

Yoon YR, Shon JH, Kim MK, Lim YC, Lee HR, Park JY, Cha IJ, Shin JG (2001) Frequency of cytochrome P450 2C9 mutant alleles in a Korean population. Br J Clin Pharmacol 51:277–280

Yu HC, Chan TY, Critchley JA, Woo KS (1996) Factors determining the maintenance dose of warfarin in Chinese patients. QJM 89:127–135