(Table 6. Contd....)

Allele	Nucleotide Change	Amino Acid Change	Population	Allele Frequency	Number of Subjects	Functional Effect	Reference
*3	1334T>C	M445T	Caucasian	0.005	213	No apparent change in activity (*in vitro*)	Eiselt *et al.* 2001
			Caucasian	0.042	24	No apparent change in activity (*in vitro*)	Dai *et al.* 2001
						No change in activity (*in vitro*)	Lee *et al.* 2005
			European	0.021	94		Garsa *et al.* 2005
*4	352A>G	I118V	Chinese	0.015	102	Reduced activity (**4*:n=3, *in vivo*)	Hsieh *et al.* 2001
			Chinese	0.033	211	Reduced activity (**4*:n=8, *in vivo*)	Wang *et al.* 2005
			Chinese	0.004	387		Wen *et al.* 2004
			Chinese	0.024	451		Liu *et al.* 2005
*5	653C>G	P218R	Chinese	0.010	102	Reduced activity (**5*:n=2, *in vivo*)	Hsieh *et al.* 2001
			Chinese	0.007	387		Wen *et al.* 2004
			Chinese	0.007	451		Liu *et al.* 2005
*6	830_831insA	frame-shift	Chinese	0.005	102	Reduced activity (**6*:n=1, *in vivo*)	Hsieh *et al.* 2001
			Chinese	0.005	387		Wen *et al.* 2004
			Malay	0.005	104		Chowbay *et al.* 2003
			Indian	0.005	101		Chowbay *et al.* 2003
			Japanese	0.001	416		Fukushima-Uesaka *et al.* 2004
*7	167G>A	G56D	Caucasian	0.014	213	No apparent change in activity (*in vitro*)	Eiselt *et al.* 2001
*8	389G>A	R130Q	Caucasian	0.003	150	No holoprotein (*in vitro*)	Eiselt *et al.* 2001
*9	508G>A	V170I	Caucasian	0.002	212	No apparent change in activity (*in vitro*)	Eiselt *et al.* 2001
*10	520G>C	D174H	Caucasian	0.002	212	Reduced activity? (*in vitro*)	Eiselt *et al.* 2001
			Caucasian	0.020	53		Lamba *et al.* 2002
			African-American	0.020	21		Lamba *et al.* 2002
			Mexican	0.050	10		Lamba *et al.* 2002
*11	1088C>T	T363M	Caucasian	0.003	149	Reduced holoprotein level (*in vitro*)	Eiselt *et al.* 2001
			Japanese	0.002	416		Fukushima-Uesaka *et al.* 2004
						Reduced activity (*in vitro*)	Murayama *et al.* 2002
*12	1117C>T	L373F	Caucasian	0.003	149	Altered activity depending on the substrates (*in vitro*)	Eiselt *et al.* 2001

(Table 6. Contd....)

Allele	Nucleotide Change	Amino Acid Change	Population	Allele Frequency	Number of Subjects	Functional Effect	Reference
**13*	1247C>T	P416L	Caucasian	0.003	149	No holoprotein (*in vitro*)	Eiselt *et al.* 2001
**14*	44T>C	L15P	unknown	0.060	8	Unknown	Lamba *et al.* 2002
**15*	485G>A	R162Q	African	0.042	24	Unknown	Dai *et al.* 2001
**16*	554C>G	T185S	Mexican	0.050	10		Lamba *et al.* 2002
			Japanese	0.050	10		Lamba *et al.* 2002
			Japanese	0.014	416		Fukushima-Uesaka *et al.* 2004
						Reduced activity (*in vitro*)	Murayama *et al.* 2002
			Japanese			Reduced activity (**16*:n=9, *in vivo*)	Nakajima *et al.* 2006
**17*	566T>C	F189S	Caucasian	0.021	24	Reduced activity (*in vitro*)	Dai *et al.* 2001
			Caucasian	ND	100	Markedly reduced activity (*in vitro*)	Lee *et al.* 2005
**18*	878T>C	L293P	Asian	0.021	24	Increased activity (*in vitro*)	Dai *et al.* 2001
			Japanese	0.028	416		Fukushima-Uesaka *et al.* 2004
						Increased activity (*in vitro*)	Murayama *et al.* 2002
						No change in activity (*in vitro*)	Lee *et al.* 2005
			Chinese	0.008	387		Wen *et al.* 2004
**19*	1399C>T	P467S	Asian	0.021	24	No apparent change in activity (*in vitro*)	Dai *et al.* 2001
						No change in activity (*in vitro*)	Lee *et al.* 2005
**20*	1461_1462insA	frame-shift	Brazilian	unknown	unknown	No holoprotein (*in vitro*)	Westlind-Johnsson *et al.* 2006

ND: not detected.

the promoter region, resulting in reduced enzymatic activity [Rodriguez-Antona *et al.*, 2005], and lowered systemic clearance of midazolam [Wandel *et al.*, 2000]. Other studies, however, suggested no changes (or rather an increase) in enzyme activity both *in vivo* [Ball *et al.*, 1999; Hesselink *et al.*, 2004] and *in vitro* [Westlind *et al.*, 1999]. A recent report also showed its association with even higher expressions of mRNA and protein and enzymatic activity [Schirmer *et al.*, 2006]. At least part of this discrepancy *in vivo* might be explained by the linkage between *CYP3A4*1B* and *CYP3A5*1* (wild-type) as discussed below.

In contrast to the **1B* allele, nonsynonymous polymorphisms were relatively rare in all ethnic groups (Table 6). The allele **2* with a S222P change showed a higher *K*m and lower *V*max for nifedipine, resulting in a 6 to 9-fold reduction of intrinsic clearance *in vitro* [Sata *et al.*, 2000]. However, no significant change was observed in testosterone 6β-hydroxylase activity. This allele was found at frequencies of 0.027 in Finnish [Sata *et al.*, 2000] and 0.045 in Portuguese [Cavaco *et al.*, 2003]. *CYP3A4*3* (M445T) had no functional changes for chlorpyrifos [Dai *et al.*, 2001], testosterone and progesterone [Eiselt *et al.*, 2001], and nifedipine [Lee *et al.*, 2005] when the variant enzyme was expressed in *E. coli*. *CYP3A4*4* to **6* were found only in Asians. *CYP3A4*4* (I118V) has been detected at 0.01 to 0.03 frequencies only in Chinese, but has not been detected in 416 Japanese subjects [Fukushima-Uesaka *et al.*, 2004]. The subjects with the **4* allele showed a reduced ratio of urine 6β-hydroxycortisol to free cortisol, suggesting reduced enzyme activity [Hsieh *et al.*, 2001; Wang *et al.*, 2005]. Furthermore, heterozygous **4* patients showed significantly increased lipid-lowering effects of simvastatin compared with homozygous **1* patients [Wang *et al.*, 2005]. Two Chinese subjects with heterozygous **5* (P218R) also showed a reduced ratio of urine 6β-hydroxycortisol to free cortisol [Hsieh *et al.*, 2001]. *CYP3A4*5* was detected at ~1% frequency only in Chinese, but not in 416 Japanese [Fukushima-Uesaka *et al.*, 2004]. *CYP3A4*6* allele, a rare allele detected in Chinese, Japanese,

Malay and Indian, has an insertion of adenine between 830 and 831, resulting in a frame-shift from E277 and an immature stop codon at 285 [Hsieh *et al.*, 2001]. Thus, the variant enzyme is most likely to be non-functional. A patient heterozygous for this allele showed a reduced urine 6β-hydroxycortisol/free cortisol ratio [Hsieh *et al.*, 2001]. *CYP3A4*7* (G56D), **8* (R130Q), and **9* (V170I) were detected only in Caucasians [Eiselt *et al.*, 2001]. The **8* variant exhibited no holoprotein formation in *E. coli*, although its apoprotein was slightly expressed. *CYP3A4*10* (D174H) was found in Caucasians, African-Americans, and Mexicans but not in Japanese. The variant protein exhibited a slightly reduced testosterone and progesterone hydroxylase activity at a low substrate concentration (25 μM) [Eiselt *et al.*, 2001]. *CYP3A4*11* (T363M) is a rare allele detected in Caucasians and Japanese, and its recombinant protein had reduced holoprotein levels [Eiselt *et al.*, 2001]. When expressed in a human liver cell line, HepG2, the variant enzyme had ~40% decrease in intrinsic clearance (*V*max/*K*m) for the testosterone 6β-hydroxylation reaction [Murayama *et al.*, 2002]. Both *CYP3A4*12* (L373F) and **13* (P416L) with reduced expression levels were detected only in Caucasians with very low frequencies [Eiselt *et al.*, 2001]. Functional significance of *CYP3A4*14* (L15P) and **15* (R162Q) has not been reported until now. *CYP3A4*16* (T185S) was found in Japanese and Mexicans with 0.01 to 0.05 frequencies. The CYP3A4.16 proteins expressed in HepG2 cells exhibited about 50% reduction in the intrinsic clearance (*V*max/*K*m) in testosterone 6β-hydroxylation activity with about 60% decrease in *V*max [Murayama *et al.*, 2002]. Very recently, we have shown for the first time that heterozygous **16* patients administered paclitaxel show significantly reduced 3'-*p*-hydroxypaclitaxel/paclitaxel AUC ratio and increased 6α-hydroxypaclitaxel/paclitaxel AUC ratio, suggesting that *CYP3A4*16* is indeed a low-activity allele [Nakajima *et al.*, 2006]. *CYP3A4*17* (F189S) detected in Caucasians had a low activity to testosterone and almost negligible activities for chlorpyrifos and nifedipine *in vitro* [Dai *et al.*, 2001; Lee *et al.*, 2005]. *CYP3A4*18* allele (L293P) was found in Asians at 0.01 to 0.03 frequencies. The CYP3A4.18 protein exhibited increased activities for testosterone and chlorpyrifos, but was unchanged for nifedipine compared with wild-type CYP3A4 enzymes [Dai *et al.*, 2001; Lee *et al.*, 2005]. Our *in vitro* analysis revealed that increased activity for testosterone was attributed to an increased *V*max [Murayama *et al.*, 2002]. However, the *in vivo* activity did not alter in Japanese heterozygotes [Nakajima *et al.*, 2006]. *CYP3A4*19* (P467S) in Asians catalyzes testosterone, chlorpyrifos and nifedipine similar to that of the wild-type enzymes [Dai *et al.*, 2001; Lee *et al.*, 2005]. The most recently identified **20* allele, found in a Brazilian patient, is defective, but was not detected in 413 Caucasian, 195 African and 230 Chinese samples [Westlind-Johnsson *et al.*, 2006]. Overall, functionally important and relatively frequent (≥1%) alleles are **4*, **16* and **18* (and probably **5*) for Asians (at least for East Asians) and **2* for Caucasians.

Since nonsynonymous polymorphisms are relatively rare, the transcriptional regulatory regions have also been analyzed. It has been shown that CYP3A4 induction is mediated by pregnane/steroid X receptor (PXR/SXR), constitutive androstane receptor and the vitamin D receptor (VDR) through binding to the distal xenobiotic-responsive enhancer module (XREM) (-7.7 kb and –7.3 kb upstream of the transcriptional start site), and to the proximal promoter region, especially to the proximal PXR/SXR response element (-169 to -152 from the transcriptional start site) [Goodwin *et al.*, 1999, 2002; Drocourt *et al.*, 2002]. Hepatocyte nuclear factor-4α also binds to the region immediately upstream of XREM and increases basal and the above transcriptional factor-mediated reporter gene expression [Tirona *et al.*, 2003]. However, no functional polymorphism has been found in these transcriptional factor-binding elements in Japanese [Fukushima-Uesaka *et al.*, 2004]. Recently, Matsumura *et al.* [2004] reported that a TGT insertion between –11,129 and -11,128 (from the transcriptional start site) resulted in the disruption of transcriptional factor USF1 binding and a 36% reduction of enhancer activity. This polymorphism was detected at a 0.031 frequency in 511 French subjects, but not in 131 Japanese subjects, suggesting that this polymorphism is an important factor in regulating CYP3A4 activity in Caucasians.

LDs and Haplotype Structures of the CYP3A Cluster

The *CYP3A5*, *CYP3A7*, *CYP3A4*, and *CYP3A43* genes are located on chromosome 7 (7q21.1) in this order. Extreme interethnic variability exists in CYP3A5 expression, and this variation has been shown to be mostly due to IVS3-237A>G (6986A>G) in intron 3, designated *CYP3A5*3*. This polymorphism generates an incorrectly spliced mRNA and a non-functional protein [Kuehl *et al.*, 2001]. This allele has reported in the frequencies of 0.06-0.84 in Africans, 0.85-0.95 in Caucasians, 0.59-0.82 in Asians, 0.71-0.85 in Hispanics, and 0.79-0.82 in Pacific Islanders (summarized in Table 7). Thus, there is extreme variation in allele frequencies in Africans. This allele was known to be associated with reduced midazolam hydroxylation [Kuehl *et al.*, 2001] and clearance [Wong *et al.*, 2004], increased AUC of alprazolam [Park *et al.*, 2006], and reduced oral clearance of sirolimus [Le Meur *et al.*, 2006]. We analyzed haplotype structures of *CYP3A4* in 416 Japanese subjects [Fukushima-Uesaka *et al.*, 2004] and *CYP3A5* in 187 Japanese subjects [Saeki *et al.*, 2003]. Overall, 25 haplotypes were inferred in *CYP3A4*. Then, the association between the *CYP3A4* and *CYP3A5* haplotypes was analyzed [Fukushima-Uesaka *et al.*, 2004]. In Japanese, LD analysis of *CYP3A4* and *CYP3A5* showed strong linkages of polymorphisms between both genes. The *CYP3A4* haplotypes containing the IVS10+12G allele (such as **1A*) are very closely linked to *CYP3A5*3*. Inversely, most of the *CYP3A4* haplotypes with IVS10+12A (such as **1G*) are linked to *CYP3A5*1*. Thus, these results suggested that, in a Japanese population, genotyping the IVS10+12 position in *CYP3A4* can predict whether the subject has *CYP3A5*3* although the IVS10+12G>A polymorphism itself lacks functional significance [Nakajima *et al.*, 2006]. In addition, the low-activity haplotype *CYP3A4*16B* (with T185S and IVS10+12G>A) is perfectly linked with *CYP3A5*1E* (with IVS9+77G>T), but not with **3*. We also found that a *CYP3A7* SNP -425G>C (A of the translational start site of *CYP3A7* is numbered +1) was perfectly linked with a *CYP3A5* haplotype containing IVS2-102C>T and IVS11+177C>T [Fukushima-Uesaka *et al.*, 2004]. These results suggested that *CYP3A4*, *CYP3A5*, and *CYP3A7* (in the order

Table 7. Allelic Frequencies of *CYP3A5*3* (IVS3-237A>G) in Different Ethnic Populations

Population	Allele Frequency	Number of Subjects	Reference
Caucasians			
Caucasian-American*	0.85	27	Kuehl *et al.* 2001
Dutch¶	0.92	500	van Schaik *et al.* 2002
Caucasian-Canadian¶	0.93	77	Roy *et al.* 2005
French*	0.91	29	Thompson *et al.* 2004
Russian*	0.92	25	Thompson *et al.* 2004
Italian (Sardinian)*	0.95	28	Thompson *et al.* 2004
Africans			
African-American¶	0.55 0.27	20 45-50	Kuehl *et al.* 2001 Hustert *et al.* 2001
Nigerian (Yoruba)*	0.06	25	Thompson *et al.* 2004
Senegalese (Mandenka)*	0.31	24	Thompson *et al.* 2004
Algerian (Mozabite)*	0.84	29	Thompson *et al.* 2004
Zimbabwean	0.78	100	Roy *et al.* 2005
Asians			
Japanese	0.71 0.77 0.74 0.76	45-50 200 196 187	Hustert *et al.* 2001 Fukuen *et al.* 2002 Hiratsuka *et al.* 2002 Saeki *et al.* 2003
Chinese	0.73 0.76	45-50 108	Hustert *et al.* 2001 Balram *et al.* 2003
Korean*	0.70	45-50	Hustert *et al.* 2001
Malay¶	0.61	98	Balram *et al.* 2003
Indian¶	0.59	90	Balram *et al.* 2003
Cambodian*	0.73	11	Thompson *et al.* 2004
Pakistani (Kalash)*	0.76	25	Thompson *et al.* 2004
Palestinian	0.82	51	Thompson *et al.* 2004
Hispanics			
Mexican (Maya)*	0.71	24	Thompson *et al.* 2004
Brazilian (Karitiana)*	0.77	24	Thompson *et al.* 2004
Colombian*	0.85	13	Thompson *et al.* 2004
Pacific islanders			
Papua New Guinean*	0.79	17	Thompson *et al.* 2004
Melanesian (Bougainville)*	0.82	22	Thompson *et al.* 2004

¶Significant differences ($P<0.01$, chi-square test) in allele frequencies between the Japanese population and each ethnic population. When plural studies were undertaken for each ethnic population, combined data were used for comparison. The multiple comparison was corrected by Bonferroni's method.

*Not statistically analyzed due to the small number of subjects (<50 subjects).

3A5-3A7-3A4 on chromosome 7) are in the same LD block in Japanese.

In Caucasians, a close linkage between *CYP3A4*1A* and *CYP3A5*3* (inversely, *CYP3A4*1B* and *CYP3A5*1*) was

also observed [Plummer *et al.*, 2003; Zeigler-Johnson *et al.*, 2004]. A weaker linkage was also observed in African-Americans. The *CYP3A4*1B* and **1G* alleles were very closely linked in Caucasians [Schirmer *et al.* 2006], and no **1B* allele was detected in Japanese. Therefore, the linkage patterns between *CYP3A4* and *CYP3A5* are similar between Caucasians and Japanese. Similar LD patterns between *CYP3A4* and *CYP3A5* were also reported by a different group [Thompson *et al.*, 2004], where haplotype structures were shown to be different between African-Americans and non-African-Americans (Europeans and Han Chinese). The same group extended the analysis to all four genes in the *CYP3A* cluster using the 224 detected polymorphisms for 3 ethnic groups [Thompson *et al.*, 2006]. In Han Chinese and Europeans, strong LDs were observed among *CYP3A5*, *CYP3A7* and *CYP3A4*, but only between *CYP3A5* and *CYP3A7* in African-Americans. In all populations, LD decays substantially between *CYP3A4* and *CYP3A43* [Thompson *et al.*, 2006]. Thus, in the two non-African populations, the LD profiles of the *CYP3A* locus are relatively similar. Another group reported the LD patterns and haplotype structures of the *CYP3A* locus for 5 different ethnic groups (African-Americans, African Sans, European Caucasians, Chinese, and Japanese) [Schirmer *et al.*, 2006]. Strong LDs were also observed for the *CYP3A5-CYP3A7-CYP3A4* region in European Caucasians and Japanese, and their most frequent haplotype was similar. The tendency observed in Chinese was similar, but the LD between *CYP3A7* and *CYP3A4* was far weaker than in European Caucasians and Japanese. In African-Americans and African Sans, strong linkages were not detected between the *CYP3A7* and *CYP3A4* regions. The *CYP3A43* region forms discrete LD blocks in African-Americans and African Sans. The 5'-part of *CYP3A4* was in LD with *CYP3A43* in European Caucasians. In Chinese and Japanese, strong linkages were not observed in this region. This paper also described haplotype structures of the entire *CYP3A* cluster region and revealed that the most common haplotype was the same among Caucasians, Japanese and Chinese although the linkages downstream of the *CYP3A43* gene were different.

The clinical importance of these linkages among the *CYP3A* genes has not been investigated. However, the linkage between *CYP3A4*1B* and *CYP3A5*1* is probably important if a substrate drug is metabolized by both enzymes. In Japanese, the low-activity haplotype *CYP3A4*16B* was perfectly linked with *CYP3A5*1*, but not **3*, suggesting that the resulting expression of CYP3A5 can compensate for decreased CYP3A4 activity.

UGT1A1 AND OTHER UGT1AS

Glucuronidation, catalyzed by UGTs, is one of the critical steps in the detoxification and elimination of various endogenous and exogenous compounds [Radominska-Pandya *et al.*, 1999, Tukey and Strassburg, 2000]. Glucuronidation accounts for about 35% of phase II drug metabolism [Evans and Relling, 1999]. As for the genes encoding UGTs, the four subfamilies, *UGT1*, *UGT2*, *UGT3* and *UGT8*, have been identified in humans [Mackenzie *et al.*, 2005]. As the *UGT1* subfamily, the *UGT1A* gene complex, located on chromosome 2q37, spans approximately 200 kb and consists of 9 active and 4 inactive first exons (in the following order: *UGT1A12P*, *1A11P*, *1A8*, *1A10*, *1A13P*, *1A9*, *1A7*, *1A6*, *1A5*, *1A4*, *1A3*, *1A2P* and *1A1*) and common exons 2 to 5. One of the 9 active first exons (namely, *1A1* and *1A3* to *1A10*) can be used in conjunction with the common exons [Tukey and Strassburg, 2000]. The UGT1A *N*-terminal domains (encoded by the first exons) determine the substrate-binding specificity, and the *C*-terminal domain (encoded by exons 2 to 5) is important for binding to UDP-glucuronic acid [Radominska-Pandya *et al.*, 1999]. The first exons, encoding substrate-binding domains, confer the substrate specificity of UGT1A isoforms, and the 5'-flanking region of each exon 1 is presumed to independently regulate the expression of each isoform. UGT1A1, 1A3, 1A4, 1A6, and 1A9 are expressed in liver as well as extrahepatic tissues such as colon [Tukey and Strassburg, 2000]. Recently, UGT1A5 was reported to be also expressed in liver and intestine at low levels and shown as catalytically active [Finel *et al.*, 2005]. In contrast, UGT1A7, 1A8, and 1A10 are expressed only in extrahepatic tissues including esophagus, stomach, small intestine and colon [Tukey and Strassburg, 2000; Basu *et al.*, 2004]. Substantial interindividual differences were detected in mRNA, protein and activity levels of UGT1A isoforms [Ritter *et al.*, 1999; Congiu *et al.*, 2002].

UGT1A1 Polymorphisms and Segmental Haplotypes

A number of genetic polymorphisms including SNPs in *UGT1As* have been identified and publicized in the UDP-Glucuronosyltransferase (UGT) Alleles Nomenclature Home Page (http://galien.pha.ulaval.ca/alleles/alleles.html, as of July 14, 2006), and some of them are known to affect glucuronidation rates [Guillemette, 2003 for review]. UGT1A1 is known to be the principal isoform for the glucuronidation of bilirubin and SN-38, an active metabolite of the anticancer drug irinotecan [Ando and Hasegawa, 2005]. To date, 64 alleles were reported in this isoform, most of which are rare and related to two severe familial forms of unconjugated hyperbilirubinemia syndromes (Crigler-Najjar types I and II). However, several genetic polymorphisms are relatively common and involved in altered drug metabolism. $A(TA)_nTAA$ number polymorphisms in the TATA box region (-54 to -39 from the translational start codon) include four variant alleles (n=5, *UGT1A1*36*; n=6, wild-type; n=7, *UGT1A1*28*; n=8, *UGT1A1*37*). *In vitro* and *in vivo* studies showed that increasing the TA repeat number leads to a decrease in the transcriptional activity of *UGT1A1*. Given the transcriptional activity of n=6 was defined as 100%, those of n=5, 7, and 8 were approximately 130%, 65% and 50%, respectively [Beutler *et al.*, 1998]. The frequencies of these repeat polymorphisms in various populations are summarized in Table 8. *UGT1A1*28* was distributed at 0.35-0.56 frequencies in Africans, 0.26-0.39 in Caucasians, and 0.07-0.19 in East and South-East Asians, and 0.25-0.49 in South and Middle East Asians. While the frequencies in South and Middle East Asians were comparable to Caucasians, there were no remarkable differences between East and South-East Asians. *UGT1A1*36* and **37* were detected at 0.01-0.12 frequencies in Africans and 0-0.02 in Caucasians, but not found in Asians. *UGT1A1*28* is known to be associated with an increased risk of SN-38 (an active irinotecan metabolite)-induced toxicity [Ando *et al.* 2000] as well as a mild type of inherited unconjugated hyperbilirubinemia syndrome

Table 8. Frequencies of TATA Box Polymorphism of *UGT1A1* in Different Ethnic Populations

Population	Allele Frequency				Number of Subjects	Reference
	**36*	Wild-Type	**28*	**37*		
	$A(TA)_5TAA$	$A(TA)_6TAA$	$A(TA)_7TAA$	$A(TA)_8TAA$		
Caucasians						
Sardinian[#]	ND	0.743	0.257	ND	70	Hall *et al.* 1999
European[#]	ND	0.613	0.387	ND	71	Beutler *et al.* 1998
Caucasian[¶]	0.005	0.698	0.295	0.002	101	Lampe *et al.* 1999
	0.009	0.616	0.366	0.009	56	Innocenti *et al.* 2002
	0.017	0.588	0.388	0.007	147	Kaniwa *et al.* 2005
	0.004	0.659	0.337	ND	132	Innocenti *et al.* 2005
Caucasian-Brazilian[¶]	0.007	0.662	0.324	0.007	71	Fertrin *et al.* 2002
Africans						
African-American[¶]	0.035	0.470	0.426	0.069	101	Beutler *et al.* 1998
	0.080	0.520	0.380	0.020	200	Guillemette *et al.* 2000a
	0.038	0.500	0.346	0.115	56	Innocenti *et al.* 2002
	0.044	0.446	0.446	0.064	149	Kaniwa *et al.* 2005
African-Brazilian[¶]	0.065	0.519	0.407	0.009	54	Fertrin *et al.* 2002
Pygmy Mbenzele (Cameroon)*	0.036	0.333	0.560	0.071	42	Hall *et al.* 1999
Kenyan[¶]	0.100	0.444	0.444	0.013	80	Premawardhena *et al.* 2003
at Ivory coast[¶]	0.061	0.466	0.358	0.115	74	Premawardhena *et al.* 2003
Asians						
Japanese	ND	0.903	0.097	ND	150	Kaniwa *et al.* 2005
	ND	0.914	0.086	ND	116	Kanai *et al.* 2005
	ND	0.870	0.130	ND	301	Saeki *et al.* 2006
Koreans	ND	0.873	0.127	ND	324	Ki *et al.* 2003
	ND	0.932	0.068	ND	81	Han *et al.* 2006
Chinese	ND	0.840	0.160	ND	89	Balram *et al.* 2002
Taiwanese	ND	0.876	0.124	ND	218	Huang *et al.* 2002
Thai	ND	0.844	0.156	ND	96	Boyd *et al.* 2006
Vietnamese	ND	0.916	0.084	ND	83	Premawardhena *et al.* 2003
Malay	ND	0.920	0.080	ND	50	Yusoff *et al.* 2006
	ND	0.812	0.188	ND	93	Balram *et al.* 2002
Indonesian	ND	0.808	0.192	ND	60	Premawardhena *et al.* 2003
Indian[¶]	ND	0.649	0.351	ND	84	Balram *et al.* 2002
	ND	0.592	0.408	ND	119	Premawardhena *et al.* 2003
Sri lankan[¶]	ND	0.506	0.493	ND	229	Premawardhena *et al.* 2003
Yemenite[¶]	ND	0.746	0.254	ND	61	Premawardhena *et al.* 2003

(Table 8. Contd....)

Population	Allele Frequency				Number of Subjects	Reference
	36	Wild-Type	*28*	*37*		
	A(TA)$_5$TAA	A(TA)$_6$TAA	A(TA)$_7$TAA	A(TA)$_8$TAA		
Lebanese*	ND	0.643	0.357	ND	42	Premawardhena *et al.* 2003
Hispanics*	0.011	0.614	0.375	ND	44	Hall *et al.* 1999
Parakana Indian*	ND	0.672	0.328	ND	32	Fertrin *et al.* 2002

ND: not detected.

[¶]Significant differences (P<0.01, chi-square test) in allele frequencies between the Japanese population and each ethnic population. Between Japanese and Caucasian or African populations, all four alleles were compared. Between Japanese and other Asian populations, only A(TA)$_6$TAA and A(TA)$_7$TAA were compared. When plural studies were undertaken for each ethnic population, combined data were used for comparison. The multiple comparison was corrected by Bonferroni's method.

*Not statistically analyzed due to the small number of subjects (<50 subjects).

[‡]Not applicable for chi-square test.

(Gilbert's syndrome) [Bosma *et al.*, 1995; Monaghan *et al.*, 1996]. Another *1A1* polymorphism 211G>A (G71R, **6* allele) in exon 1 is also a causative factor for Gilbert's syndrome [Aono *et al.*, 1995], reduced metabolic activity to SN-38 [Gagne *et al.*, 2002; Jinno *et al.*, 2003a], and lower tumor response and higher incidence of grade 4 neutropenia in Koreans [Han *et al.*, 2006]. This allele is found at intermediate frequencies (0.13-0.24) in East Asians, and at low (0.01-0.10) levels in South-East Asians, but hardly found in Caucasians and Africans (Table **9**). In addition, *1A1*60* allele (-3279T>G) is located in the distal enhancer region (so called phenobarbital–responsive enhancer module) and shows reduced transcriptional activity [Sugatani *et al.*, 2002]. The frequencies of this allele are very high (0.85) in Africans, high (0.35-0.55) in Caucasians, and moderate (0.17-0.34) in Asians (Table **10**). A minor allele **27* (686C>A, P229Q) was reported to be associated with Gilbert's syndrome in Asians [Aono *et al.*, 1995], but its effect on enzymatic activity is marginal *in vitro* [Jinno *et al.*, 2003a]. Using these alleles, haplotypes were estimated for *UGT1A1* exon 1 in Japanese, Caucasians, and African-Americans (Fig. **4**) [Sai *et al.*, 2004; Kaniwa *et al.*, 2005 for detail]. The **28* (A(TA)$_7$ TAA), **36* (A(TA)$_5$TAA), and **37* (A(TA)$_8$TAA) alleles were found to be linked with the **60* allele (-3279T>G) in most cases forming **28b* (and **28c*), **36b*, and **37b* haplotypes, respectively. The **27* allele (686C>A, P229Q), detected only in Asians, was exclusively harbored by the **28b* haplotype (forming **28c* haplotype), suggesting that its association with Gilbert's syndrome may be due to its linkages with A(TA)$_7$TAA and -3279T>G. The **6* (211G>A, G71R) and **28* (A(TA)$_7$TAA) alleles are mutually exclusive. The wild-type haplotype **1a* is less frequent in African-Americans (0.15), but about half of the Caucasians or Asians has this active haplotype (Table **11**). The frequencies of **28* haplotypes were more than 0.34 in Caucasians and African-Americans, but less than 0.14 in Asians. The **60a* haplotype was frequent in African-Americans (0.30-0.33) but less frequent in Asians (0.14-0.23) and Caucasians (0.09-0.14). The **6* haplotypes were found only in Asians with 0.13-0.24 frequencies.

In addition to the *UGT1A1* exon 1, segmental haplotypes for *UGT1A8, 1A10, 1A9, 1A7, 1A6, 1A4, 1A3*, and common exons 2-5 were estimated in Japanese [Sai *et al.*, 2004; Saeki *et al.*, 2005; 2006]. Thomas *et al.* also sequenced the *UGT1A* complex including *1A5* for 92 Caucasians and 46 Asians, and estimated segmental haplotypes of these populations separately [Thomas *et al.*, 2006]. The haplotype configurations for all segments of the complex were significantly different between Caucasians and Asians.

LDs and Haplotype Structures of UGT1A Gene Complex

Co-occurrence of the segmental haplotypes with functional changes in the *UGT1A* complex could lead to a cooperative alteration in glucuronidation activity. Using the genetic variations obtained from 196 Japanese subjects, linkage disequilibrium analysis was performed for the *UGT1A* gene complex [Saeki *et al.*, 2006 for detail]. Strong linkages were observed between *1A8* and *1A10*, among *1A9*, *1A7* and *1A6*, and between *1A3* and *1A1*. Thus, the region from *1A8* to common exons was divided into five LD blocks: Block 8/10 (*1A8* and *1A10*), Block 9/6 (*1A9*, *1A7* and *1A6*), Block 4 (*1A4*), Block 3/1 (*1A3* and *1A1*), and Block C (common exons 2-5). This block partitioning was similar to that of Thomas *et al.* [2006] in Asians except that they further divided the blocks at region *1A7*. LD profiles were considerably different between Caucasians and Asians: close linkage was observed among *UGT1A6*, *1A5*, *1A4*, *1A3* and *1A1*, forming one LD block in Caucasians [Thomas *et al.*, 2006]. Furthermore, a recent report showed that the LD profile across *UGT1A1*, *1A6* and *1A9* in African-Americans was clearly different from those of Caucasians and Asians [Maitland *et al.*, 2006].

Block haplotyping was only reported in Japanese [see Saeki *et al.*, 2006 for detail]. As for Block 8/10 consisting of two segments *1A8* and *1A10*, 14 haplotypes were inferred, and the 4 haplotypes with frequencies ≥5% accounted for 93.8% of the total haplotypes. It is noteworthy that the low-activity *1A10* haplotype **3* (containing 605C>T, T202I, now renamed to *UGT1A10*6*) [Jinno *et al.*, 2003b] was completely linked with the *1A8*1* haplotype (wild-type). Regarding Block 9/6 (*1A9-1A7-1A6*), 22 haplotypes were inferred, and the 3 haplotypes with frequencies ≥5% accounted for 85.2% of the total haplotypes. Notably, most of the high-activity segment haplotype *1A9*22* (with -126_-118 T_9>T_{10}, now renamed to be **1b* allele) [Yamanaka *et al.* 2004] was linked with *1A7*1* (wild-type) and *1A6*1* (wild-type). The

Table 9. Allelic Frequencies of *UGT1A1*6* (211G>A, G71R) in Different Ethnic Populations

Population	Allele Frequency	Number of Subjects	Reference
Caucasians			
German[¶]	ND	50	Akaba *et al.* 1998
Caucasian[¶]	ND	132	Innocenti *et al.* 2005
	0.007	150	Kaniwa *et al.* 2005
	ND	92	Thomas *et al.* 2006
Africans			
African-American[¶]	ND	150	Kaniwa *et al.* 2005
Asians			
Japanese	0.130	101	Akaba *et al.* 1998
	0.157	150	Kaniwa *et al.* 2005
	0.177	116	Kanai *et al.* 2005
	0.153	301	Saeki *et al.* 2006
Korean[¶]	0.230	50	Akaba *et al.* 1998
	0.213	324	Ki *et al.* 2003
	0.241	81	Han *et al.* 2006
Chinese	0.230	50	Akaba *et al.* 1998
Taiwanese	0.156	218	Huang *et al.* 2002
Thai	0.104	96	Boyd *et al.* 2006
Malay[¶]	0.030	50	Yusoff *et al.* 2006
	0.014	36	Sutomo *et al.* 2004
Indonesian (Javanese)[¶]	0.015	68	Sutomo *et al.* 2004
Asians (mostly East-Asians)*	0.130	150	Innocenti *et al.* 2005

ND: not detected.

[¶]Significant differences ($P<0.01$, chi-square test or Fisher's exact test) in allele frequencies between the Japanese population and each ethnic population. When plural studies were undertaken for each ethnic population, combined data were used for comparison. The multiple comparison was corrected by Bonferroni's method.

*Not statistically analyzed because of mixed populations.

Table 10. Allelic Frequencies of *UGT1A1*60* (-3279T>G) in Different Ethnic Populations

Population	Allele Frequency	Number of Subjects	Reference
Caucasians			
Caucasian[¶]	0.473	55	Innocenti *et al.* 2002
	0.550	150	Kaniwa *et al.* 2005
	0.439	132	Innocenti *et al.* 2005
German	0.351	57	Kanai *et al.* 2005
Africans			
African-American[¶]	0.851	37	Innocenti *et al.* 2002
	0.847	150	Kaniwa *et al.* 2005
Asians			
Japanese	0.167	27	Sugatani *et al.* 2002
	0.257	150	Kaniwa *et al.* 2005
	0.261	157	Kanai *et al.* 2005
	0.262	301	Saeki *et al.* 2006

(Table 10. Contd....)

Population	Allele Frequency	Number of Subjects	Reference
Korean	0.327 0.267 0.235	55 324 81	Kanai *et al.* 2005 Ki *et al.* 2003 Han *et al.* 2006
Chinese	0.300	50	Kanai *et al.* 2005
Asians (mostly East-Asians)*	0.340	150	Innocenti *et al.* 2005

¶Significant differences ($P<0.01$, chi-square test) in allele frequencies between the Japanese population and each ethnic population. When plural studies were undertaken for each ethnic population, combined data were used for comparison. The multiple comparison was corrected by Bonferroni's method.

*Not statistically analyzed because of mixed populations.

1A7 low-activity haplotype **3* (containing –57T>G, 387T>G, 391C>A, 392G>A, and 622T>C, resulting in N129K, R131K, and W208R) [Guillemette *et al.* 2000b, Villeneuve *et al.* 2003] was mostly linked with *1A6* high-activity haplotype **2* (containing 19T>G, 541A>G, and 552A>C, resulting in S7A, T181A, and R184S, respectively) [Krishnaswamy *et al.*, 2005]. The single *UGT1A4* segment is Block 4 [Saeki *et al.*, 2005]. Using 19 genetic polymorphisms, 16 haplotypes were inferred. Regarding Block 3/1 (*1A3-1A1*), 16 haplotypes were inferred, and the 5 haplotypes with frequencies ≥5% accounted for 89.5% of the total haplotypes. It is noteworthy that the high-activity segment haplotype *1A3*2* (containing 31T>C and 140T>C, resulting in W11R and V47A respectively, previous haplotype *1A3*11R47A*) [Iwai *et al.* 2004] was completely linked with the low-activity haplotype *1A1*28*. The low-activity haplotype *1A1*6* was linked with the *1A3*1* haplotype (wild-type) or *1A3*4* haplotype (containing 133C>T, R45W, previous haplotype *1A3*45W*). The *1A3*3* haplotype (containing 31T>C, W11R, previous haplotype *1A3*11R*) was perfectly linked with the low-activity *1A1*60* haplotype. As for common exons 2-5 (Block C), 14 haplotypes were inferred using 13 polymorphisms [Sai *et al.*, 2004].

Then, block-haplotype combinations (whole complex haplotypes) among Block 9/6, Block 4, and Block 3/1 were also estimated for Japanese [see Saeki *et al.*, 2006 for detail]. Block 8/10 and Block C (common exons 2 to 5) were excluded due to a high degree of recombination. We found several functionally important linkages across the blocks. The haplotype *UGT1A9*1-1A7*2-1A6*4* (containing *UGT1A7* N129K and R131K, and *UGT1A6* S7A and R184S, low activity in 1A7) [Guillemette *et al.*, 2000b] and *1A3*2-1A1*28c* (containing *UGT1A3* W11R and V47A, and UGT1A1 –3279T>G, A(TA)$_7$TAA and P229Q, high activity in 1A3 and low in 1A1) were perfectly linked. Most of the *UGT1A1*6*-containing haplotypes (G71R, low activity) were associated with *UGT1A7*3-1A6*2* (containing *UGT1A7* N129K, R131K and W208R, and *UGT1A6* S7A, T181A and R184S, low activity in 1A7 and high in 1A6). Inversely, most of *UGT1A7*3-1A6*2* haplotypes were associated with the *1A3*2-1A1*28b* (having -3279T>G and A(TA)$_7$TAA, low activity in 1A1) haplotypes (26% of *UGT1A7*3-1A6*2* haplotype) or *UGT1A1*6*-containing haplotypes (67%). The *UGT1A7*2* (low activity), *1A4*3* (containing 142T>G, L48V, activity changes depending on the substrates) [Ehmer *et al.*, 2004, Mori *et al.* 2005] and *1A1*60* (-3279T>G, low

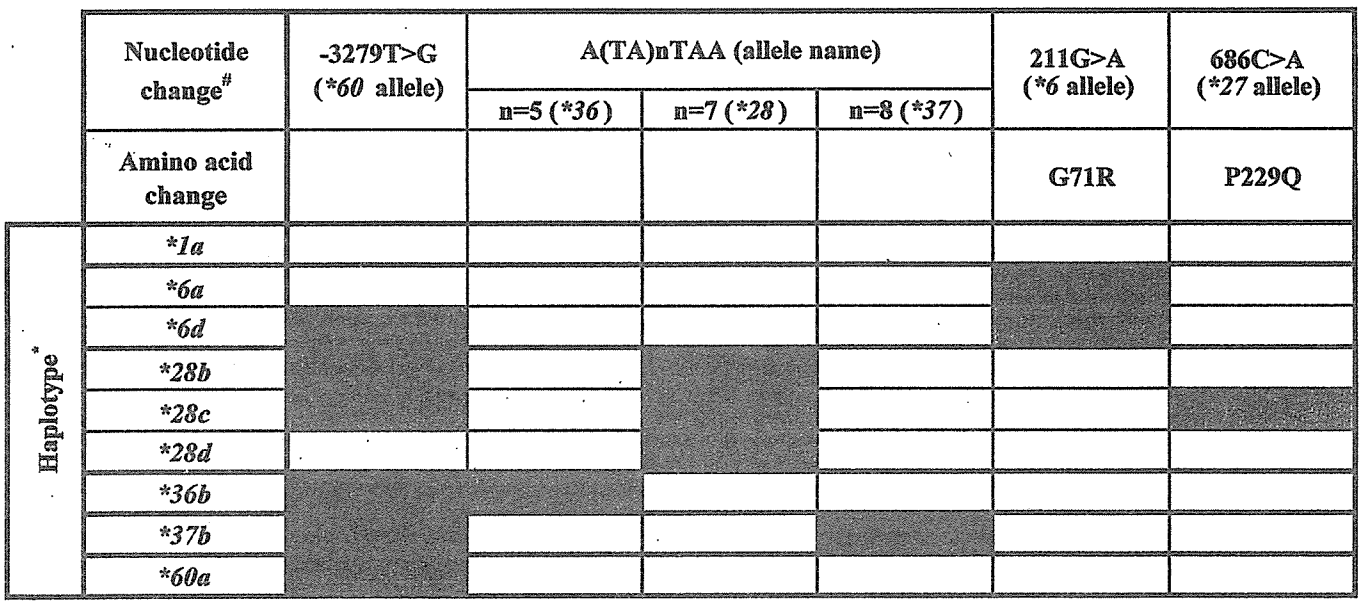

Fig. (4). Haplotype structure of *UGT1A1*. #A of the translational initiation codon is numbered +1 according to the reference sequence AF297093.1. *Major allele, white; minor allele, gray.

Table 11. Haplotype Frequencies of *UGT1A1* in Different Ethnic Populations

Population	*1a	*6		*28			*36b	*37b	*60a	Number of Subjects	Reference
		*6a	*6d	*28b	*28c	*28d					
Caucasian	0.53	-*	-*	0.36	-*	ND	0.01	0.01	0.09	55	Innocenti *et al.* 2002
	0.451	ND	ND	0.389	ND	ND	0.017	0.007	0.135	147	Kaniwa *et al.* 2005
	0.558	ND	ND	0.340	ND	ND	-**	ND	0.102	132	Innocenti *et al.* 2005
African-American	0.15	-*	-*	0.35	-*	ND	0.04	0.12	0.33	37	Innocenti *et al.* 2002
	0.150	ND	ND	0.446	ND	ND	0.044	0.065	0.296	149	Kaniwa *et al.* 2005
Asian	0.526	0.130	ND	0.076	0.034	ND	ND	ND	0.233	150	Innocenti *et al.* 2005
Japanese	0.582	0.151	ND	0.121	0.005	0.005	ND	ND	0.136	195	Sai *et al.* 2004
	0.610	0.141	0.003	0.097	0.003	ND	ND	ND	0.145	150	Kaniwa *et al.* 2005
Korean	0.518	0.235	ND	0.061	-***	0.012	ND	ND	0.172	81	Han *et al.* 2006

ND: Not detected.

*211G>A and 686C>A were not genotyped.

**$A(TA)_5TAA$ was detected in an extra subject but excluded from the haplotype analysis.

***686C>A was not genotyped.

activity) were very closely linked with each other. In addition, we found that *UGT1A10*3* (now **6*, having T202I, low activity) was strongly linked with these *1A7*2*, *1A4*3*, and *1A1*60* (80% of *UGT1A10*3*). These linkages across the segments were also reported in other populations. Kohle *et al.* reported close linkages among *1A1*28* ($A(TA)_7TAA$), *1A6*2* (T181A/R184S) and *1A7*3* (N129K/R131K/W208R) in Caucasians and Egyptians [Kohle *et al.*, 2003]. Linkage between *1A1*6* and *1A7*3* alleles was also suggested in Taiwanese [Huang *et al.*, 2005]. Note that different profiles for the linkage of *1A7*3* with the *1A1* polymorphisms between the Caucasians and East Asians reflect the facts that the frequency of the *1A1*6* haplotype in the East Asian populations was relatively high, and that the *1A1*28* and **6* alleles were mutually exclusive [Sai *et al.*, 2004]. Innocenti *et al.* reported the linkage between *UGT1A9* and *1A1* haplotypes, and the most common three *1A9-1A1* haplotype combinations were *1A9*22* (now **1b*, with -126_-118 $T_9>T_{10}$)-*1A1*1* (frequency: 36.4%), *1A9*1-1A1*28b* (28.0%) and *1A9*1-1A1*1* (18.6%) for Caucasians, and *1A9*22* (**1b*)-*1A1*1* (45.3%), *1A9*1-1A1*60* (22.3%) and *1A9*1-1A1*6* (12.7%) for Asians (mostly from East Asians) [Innocenti *et al.*, 2005]. For Japanese, *1A9*22* (**1b*)-*1A1*1*, *1A9*1-1A1*60*, and *1A9*1-1A1*6* (58.5%, 11.9%, and 13.3%, respectively) were also the three most common combinations, and most of the *1A1*1* haplotype (98%) was linked with *1A9*22* (**1b*), and 87% of *1A1*6*, 100% of *1A1*28c*, and 93% of *1A1*60* were associated with *1A9*1* [Saeki *et al.*, 2006]. A recently published report also showed that *1A9*22* (**1b*)-*1A1*1*, *1A9*1-1A1*60*, and *1A9*1-1A1*6* (48.1%, 16.0%, and 20.4%, respectively) were also the most common three combinations in Koreans [Han *et al.*, 2006]. Collectively, haplotype combinations are suggested to be different between Caucasians and East Asians.

These linkages might be crucial for the metabolism of a certain drug in which two or more UGT1A isoforms are significantly involved. In fact, multiple UGT isoforms contribute to glucuronidation of several compounds. For example, UGT1A1, 1A9 and 1A7 have glucuronidation activity to SN-38 [Ciotti *et al.*, 1999; Gagne *et al.*, 2002]. The *1A1*60*, **28*, and **6* haplotypes are associated with reduced *UGT1A1* activity [Beutler *et al.*, 1998; Sugatani *et al.*, 2002; Jinno *et al.*, 2003a]. The *1A7*3*, but not **2*, haplotype has a reduced (by 60%) glucuronidation activity to SN-38 [Gagne *et al.*, 2002]. As described in the above haplotype analyses, most *1A7*3*-containing haplotypes were estimated to be linked with *1A1*28* in Caucasians or with either *1A1*6* or *1A1*28* in East Asians. Thus, it is often difficult to distinguish the contributions of low-activity *1A1* and *1A7* haplotypes *in vivo*.

Since plural UGT isoforms are often involved in the glucuronidation of "one" compound, co-occurrence of the functionally less active haplotypes in the entire *UGT1A* gene complex needs careful consideration in studies on the association of genetic polymorphisms with pharmacokinetic parameters and both clinical and epidemiological data.

CONCLUDING REMARKS

In this review, we described the influence of genetic polymorphisms/haplotypes on drug metabolism and drug response. However, it should be noted that the genetic polymorphisms/haplotypes are just one of the important factors that contribute to the ethnic and interindividual differences in drug response. For example, the contribution of genetic polymorphisms/haplotypes (mainly *CYP2C9* and *VKORC1* encoding a target enzyme of warfarin) were estimated to be 25 to 44% to the anti-coagulant warfarin dose requirements in 4 different Asian populations [Lee *et al.*, 2006b; Obayashi *et al.*, 2006]. Other non-genetic factors such as age, gender, co-medications, and diagnosis are also important determinants for the dosage. Epigenetic factors may also be important to determine the expression levels of drug metabolizing enzymes. As for CYP3A4, Hirota *et al.* [2004] reported

skewed expression of CYP3A4 mRNA between two alleles, and the allelic expression ratio (less expressed mRNA/more expressed mRNA) varied from 0.3 to 1. This allelic expression ratio correlated well with CYP3A4 mRNA levels as well as testosterone 6β-hydroxylation activity. In addition, DNA methylation was also suggested to influence the CYP3As' expression in HepG2 cells [Dannenberg and Edenberg 2006].

Although depending on the genes, expression of CYPs and UGT1As were also regulated by nuclear receptors such as PXR/SXR and VDR as discussed in the CYP3A4 section [Drocourt *et al.*, 2002; Handschin and Meyer, 2003]. Since many xenobiotics are ligands for PXR/SXR [Handschin and Meyer 2003], co-medications, supplements and/or food ingredients are thought to be the influencing factors for PXR/SXR activation, thereby enhancing target gene expression. Since vitamin D also enhances the expression of CYP3A4 and CYP2C9 through binding to VDR [Drocourt *et al.*, 2002], it is possible that supplements and/or food ingredients could change the expression of these genes. Therefore, these environmental factors may also affect the enzymatic activity and thus the drug response.

However, under certain combinations of enzyme and drug, genetic polymorphisms could explain interindividual or interethnic diversities of pharmacokinetic and/or pharmacodynamic parameters. For example, pharmacogenetic studies in Caucasians have shown close associations of *UGT1A1*28* with reduced glucuronidation of SN-38 and incidence of severe neutropenia [Marsh and McLeod, 2004; Ando and Hasegawa, 2005]. Accordingly, the Food and Drug Administration in the United States has approved an amendment of the label for Camptosar (irinotecan HCl), to which was added a warning to consider a reduction in the starting dose of irinotecan for **28* homozygous patients (NDA 20-571). However, in East Asians, the influence of *UGT1A1*6* on irinotecan toxicities could be also substantial as suggested by *in vitro* and *in vivo* studies [Gagne *et al.*, 2002; Jinno *et al.*, 2003a; Sai *et al.*, 2004; Han *et al.*, 2006]. Thus, ethnic profiles of polymorphisms and haplotypes should be determined prior to clinical applications of genetic polymorphisms. Detailed haplotype data for drug metabolizing enzymes, transporters and receptors would be useful for further pharmacogenetic studies.

ACKNOWLEDGEMENTS

The authors thank all collaborators for participating in our studies addressed in this review. We also thank Ms. Chie Sudo for her secretarial assistance. Our studies described in this review were supported in part by the program for the Promotion of Fundamental Studies in Health Sciences, by the Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, and by the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology in Japan.

ABBREVIATIONS

AUC = Area under the plasma concentration-time curve

CYP = Cytochrome P450

EM = Extensive metabolizer

htSNP = Haplotype-tagging SNPs

IVS = Intervening sequence

LD = Linkage disequilibrium

PM = Poor metabolizer

PXR/SXR = Pregnane/steroid X receptor

SNP = Single nucleotide polymorphism

UGT = Uridinediphosphoglucuronate glucuronosyltransferase

VDR = Vitamin D receptor

XREM = Xenobiotic-responsive enhancer module

REFERENCES

Ahmadi, K. R.; Weale, M. E.; Xue, Z. Y.; Soranzo, N.; Yarnall, D. P.; Briley, J. D.; Maruyama, Y.; Kobayashi, M.; Wood, N. W.; Spurr, N. K.; Burns, D. K.; Roses, A. D.; Saunders, A. M. and Goldstein, D. B. (2005) A single-nucleotide polymorphism tagging set for human drug metabolism and transport. *Nat. Genet.* **37**, 84-89.

Akaba, K.; Kimuram, T.; Sasaki, A.; Tanabe, S.; Ikegami, T.; Hashimoto, M.; Umeda, H.; Yoshida, H.; Umetsu, K.; Chiba, H.; Yuasa, I. and Hayasaka, K. (1998) Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. *Biochem. Mol. Biol. Int.* **46**, 21-26.

Allabi, A. C.; Gala, J. L.; Horsmans, Y.; Babaoglu, M. O.; Bozkurt, A.; Heusterspreute, M. and Yasar, U. (2004) Functional impact of CYP2C9*5, CYP2C9*6, CYP2C9*8, and CYP2C9*11 *in vivo* among black Africans. *Clin. Pharmacol. Ther.* **76**, 113-118.

Allabi, A. C.; Gala, J. L. and Horsmans, Y. (2005) CYP2C9, CYP2C19, ABCB1 (MDR1) genetic polymorphisms and phenytoin metabolism in a Black Beninese population. *Pharmacogenet. Genomics* **15**, 779-786.

Andersson, T.; Regardh, C. G.; Dahl-Puustinen, M. L. and Bertilsson, L. (1990) Slow omeprazole metabolizers are also poor S-mephenytoin hydroxylators. *Ther. Drug Monit.* **12**, 415-416.

Ando, Y.; Saka, H.; Ando, M.; Sawa, T.; Muro, K.; Ueoka, H.; Yokoyama, A.; Saitoh, S.; Shimokata, K. and Hasegawa, Y. (2000) Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res.* **60**, 6921-6926.

Ando, Y. and Hasegawa, Y. (2005) Clinical pharmacogenetics of irinotecan (CPT-11). *Drug Metab. Rev.* **37**, 565-574.

Aono, S.; Adachi, Y.; Uyama, E.; Yamada, Y.; Keino, H.; Nanno, T.; Koiwai, O. and Sato, H. (1995) Analysis of genes for bilirubin UDP-glucuronosyltransferase in Gilbert's syndrome. *Lancet* **345**, 958-959.

Bajpai, M.; Roskos, L. K.; Shen, D. D. and Levy, R. H. (1996) Roles of cytochrome P4502C9 and cytochrome P4502C19 in the stereoselective metabolism of phenytoin to its major metabolite. *Drug Metab. Dispos.* **24**, 1401-1403.

Ball, S. E.; Scatina, J.; Kao, J.; Ferron, G. M.; Fruncillo, R.; Mayer, P.; Weinryb, I.; Guida, M.; Hopkins, P. J.; Warner, N. and Hall, J. (1999) Population distribution and effects on drug metabolism of a genetic variant in the 5' promoter region of CYP3A4. *Clin. Pharmacol. Ther.* **66**, 288-294.

Balram, C.; Sabapathy, K.; Fei, G.; Khoo, K. S. and Lee, E. J. (2002) Genetic polymorphisms of UDP-glucuronosyltransferase in Asians: UGT1A1*28 is a common allele in Indians. *Pharmacogenetics* **12**, 81-83.

Balram, C.; Zhou, Q.; Cheung, Y. B. and Lee, E. J. (2003) CYP3A5*3 and *6 single nucleotide polymorphisms in three distinct Asian populations. *Eur. J. Clin. Pharmacol.* **59**, 123-126.

Basu, N. K.; Ciotti, M.; Hwang, M. S.; Kole, L.; Mitra, P. S.; Cho, J. W. and Owens, I. S. (2004) Differential and special properties of the major human UGT1-encoded gastrointestinal UDP-glucuronosyltransferases enhance potential to control chemical uptake. *J. Biol. Chem.* **279**, 1429-1441.

Beutler, E.; Gelbart, T. and Demina, A. (1998) Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc. Natl. Acad. Sci. USA* **95**, 8170-8174.

Blaisdell, J.; Mohrenweiser, H.; Jackson, J.; Ferguson, S.; Coulter, S.; Chanas, B.; Xi, T.; Ghanayem, B. and Goldstein, J. A. (2002) Identification and functional characterization of new potentially defective alleles of human CYP2C19. *Pharmacogenetics* **12**, 703-711.

Blaisdell, J.; Jorge-Nebert, L. F.; Coulter, S.; Ferguson, S. S.; Lee, S. J.; Chanas, B.; Xi, T.; Mohrenweiser, H.; Ghanayem, B. and Goldstein, J. A. (2004) Discovery of new potentially defective alleles of human CYP2C9. *Pharmacogenetics* **14**, 527-537.

Blann, A.; Hewitt, J.; Siddiqui, F. and Bareford, D. (1999) Racial background is a determinant of average warfarin dose required to maintain the INR between 2.0 and 3.0. *Br. J. Haematol.* **107**, 207-209.

Bosma, P. J.; Chowdhury, J. R.; Bakker, C.; Gantla, S.; de Boer, A.; Oostra, B. A.; Lindhout, D.; Tytgat, G. N.; Jansen, P. L. and Oude Elferink, R. P. (1995) The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N. Engl. J. Med.* **333**, 1171-1175.

Boyd, M. A.; Srasuebkul, P.; Ruxrungtham, K.; Mackenzie, P. I.; Uchaipichat, V.; Stek, M. Jr.; Lange, J. M.; Phanuphak, P.; Cooper, D. A.; Udomuksorn, W.; Miners, J. O. (2006) Relationship between hyperbilirubinaemia and UDP-glucuronosyltransferase 1A1 (UGT1A1) polymorphism in adult HIV-infected Thai patients treated with indinavir. *Pharmacogenet. Genomics* **16**, 321-329.

Bradford, L. D. (2002) CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics* **3**, 229-243.

Bravo-Villalta, H. V.; Yamamoto, K.; Nakamura, K.; Baya, A.; Okada, Y. and Horiuchi, R. (2005) Genetic polymorphism of CYP2C9 and CYP2C19 in a Bolivian population: an investigative and comparative study. *Eur. J. Clin. Pharmacol.* **61**, 179-184.

Broly, F. and Meyer, U. A. (1993) Debrisoquine oxidation polymorphism: phenotypic consequences of a 3-base-pair deletion in exon 5 of the CYP2D6 gene. *Pharmacogenetics* **3**, 123-130.

Cavaco, I.; Gil, J. P.; Gil-Berglund, E. and Ribeiro, V. (2003) CYP3A4 and MDR1 alleles in a Portuguese population. *Clin. Chem. Lab. Med.* **41**, 1345-1350.

Chern, H. D.; Ueng, T. H.; Fu, Y. P. and Cheng, C. W. (2006) CYP2C9 polymorphism and warfarin sensitivity in Taiwan Chinese. *Clin. Chim. Acta.* **367**, 108-113.

Chida, M.; Yokoi, T.; Nemoto, N.; Inaba, M.; Kinoshita, M. and Kamataki, T. (1999a) A new variant CYP2D6 allele (CYP2D6*21) with a single base insertion in exon 5 in a Japanese population associated with a poor metabolizer phenotype. *Pharmacogenetics* **9**, 287-293.

Chida, M.; Yokoi, T.; Kosaka, Y.; Chiba, K.; Nakamura, H.; Ishizaki, T.; Yokota, J.; Kinoshita, M.; Sato, K.; Inaba, M.; Aoki, Y.; Gonzalez, F. J. and Kamataki, T. (1999b) Genetic polymorphism of CYP2D6 in the Japanese population. *Pharmacogenetics* **9**, 601-605.

Chida, M.; Ariyoshi, N.; Yokoi, T.; Nemoto, N.; Inaba, M.; Kinoshita, M. and Kamataki, T. (2002) New allelic arrangement CYP2D6*36 x 2 found in a Japanese poor metabolizer of debrisoquine. *Pharmacogenetics* **12**, 659-662.

Chowbay, B.; Cumaraswamy, S.; Cheung, Y. B.; Zhou, Q. and Lee, E. J. (2003) Genetic polymorphisms in MDR1 and CYP3A4 genes in Asians and the influence of MDR1 haplotypes on cyclosporin disposition in heart transplant recipients. *Pharmacogenetics* **13**, 89-95.

Chowbay, B.; Zhou, S. and Lee, E. J. (2005) An interethnic comparison of polymorphisms of the genes encoding drug-metabolizing enzymes and drug transporters: experience in Singapore. *Drug Metab. Rev.* **37**, 327-378.

Ciotti, M.; Basu, N.; Brangi, M. and Owens, I. S. (1999) Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38) by the human UDP-glucuronosyltransferases encoded at the UGT1 locus. *Biochem. Biophys. Res. Commun.* **260**, 199-202.

Congiu, M.; Mashford, M. L.; Slavin, J. L. and Desmond, P. V. (2002) UDP glucuronosyltransferase mRNA levels in human liver disease. *Drug Metab. Dispos.* **30**, 129-134.

Cubeddu, L. X.; Aranda, J.; Singh, B.; Klein, M.; Brachfeld, J.; Freis, E.; Roman, J. and Eades, T. A. (1986) comparison of verapamil and propranolol for the initial treatment of hypertension. Racial differences in response. *JAMA* **256**, 2214-2221.

Dahl, M. -L.; Yue, Q. -Y.; Roh, H. -K.; Johansson, I.; Sawe, J.; Sjoqvist, F. and Bertilsson, L. (1995) Genetic analysis of the CYP2D locus in relation to debrisoquine hydroxylation capacity in Korean, Japanese and Chinese subjects. *Pharmacogenetics* **5**, 159-165.

Dai, D.; Tang, J.; Rose, R.; Hodgson, E.; Bienstock, R. J.; Mohrenweiser, H. W. and Goldstein, J. A. (2001) Identification of variants of CYP3A4 and characterization of their abilities to metabolize testosterone and chlorpyrifos. *J. Pharmacol. Exp. Ther.* **299**, 825-831.

Dannenberg, L. O. and Edenberg, H. J. (2006) Epigenetics of gene expression in human hepatoma cells: expression profiling the response to inhibition of DNA methylation and histone deacetylation. *BMC Genomics* **19**, 181.

DeLozier, T. C.; Lee, S. C.; Coulter, S. J.; Goh, B. C. and Goldstein, J. A. (2005) Functional characterization of novel allelic variants of CYP2C9 recently discovered in southeast Asians. *J. Pharmacol. Exp. Ther.* **315**, 1085-1090.

De Morais, S. M.; Wilkinson, G. R.; Blaisdell, J.; Nakamura, K.; Meyer, U. A. and Goldstein, J. A. (1994a) The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. *J. Biol. Chem.* **269**, 15419-15422.

De Morais, S. M.; Wilkinson, G. R.; Blaisdell, J.; Meyer, U. A.; Nakamura, K. and Goldstein, J. A. (1994b) Identification of a new genetic defect responsible for the polymorphism of (S)-mephenytoin metabolism in Japanese. *Mol. Pharmacol.* **46**, 594-598.

Desta, Z.; Zhao, X.; Shin, J. -G. and Flockhart, D. A. (2002) Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin. Pharmacokinet.* **41**, 913-958.

Dickmann, L. J.; Rettie, A. E.; Kneller, M. B.; Kim, R. B.; Wood, A. J.; Stein, C. M.; Wilkinson, G. R. and Schwarz, U. I. (2001) Identification and functional characterization of a new CYP2C9 variant (CYP2C9*5) expressed among African Americans. *Mol. Pharmacol.* **60**, 382-387.

Drocourt, L.; Ourlin, J. C.; Pascussi, J. M.; Maurel, P. and Vilarem, M. J. (2002) Expression of CYP3A4, CYP2B6, and CYP2C9 is regulated by the vitamin D receptor pathway in primary human hepatocytes. *J. Biol. Chem.* **277**, 25125-25132.

Droll, K.; Bruce-Mensah, K.; Otton, S. V.; Gaedigk, A.; Sellers, E. M. and Tyndale, R. F. (1998) Comparison of three CYP2D6 probe substrates and genotype in Ghanaians, Chinese and Caucasians. *Pharmacogenetics* **8**, 325-333.

Ebisawa, A.; Hiratsuka, M.; Sakuyama, K.; Konno, Y.; Sasaki, T. and Mizugaki, M. (2005) Two novel single nucleotide polymorphisms (SNPs) of the CYP2D6 gene in Japanese individuals. *Drug Metab. Pharmacokinet.* **20**, 294-299.

Ehmer, U.; Vogel, A.; Schutte, J. K.; Krone, B.; Manns, M. P. and Strassburg, C. P. (2004) Variation of hepatic glucuronidation: Novel functional polymorphisms of the UDP-glucuronosyltransferase UGT1A4. *Hepatology* **39**, 970-977.

Eiselt, R.; Domanski, T. L.; Zibat, A.; Mueller, R.; Presecan-Siedel, E.; Hustert, E.; Zanger, U. M.; Brockmoller, J.; Klenk, H. P.; Meyer, U. A.; Khan, K. K.; He, Y. A.; Halpert, J. R. and Wojnowski, L. (2001) Identification and functional characterization of eight CYP3A4 protein variants. *Pharmacogenetics* **11**, 447-458.

Evans, W. E. and Relling, M. V. (1999) Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* **286**, 487-491.

Ferguson, R. J.; De Morais, S. M.; Benhamou, S.; Bouchardy, C.; Blaisdell, J.; Ibeanu, G.; Wilkinson, G. R.; Sarich, T. C.; Wright, J. M.; Dayer, P. and Goldstein, J. A. (1998) A new genetic defect in human CYP2C19: mutation of the initiation codon is responsible for poor metabolism of S-mephenytoin. *J. Pharmacol. Exp. Ther.* **284**, 356-361.

Fertrin, K. Y.; Goncalves, M. S.; Saad, S. T. and Costa, F. F. (2002) Frequencies of UDP-glucuronosyltransferase 1 (UGT1A1) gene promoter polymorphisms among distinct ethnic groups from Brazil. *Am. J. Med. Genet.* **108**, 117-119.

Finel, M.; Li, X.; Gardner-Stephen, D.; Bratton, S.; Mackenzie, P. I. and Radominska-Pandya, A. (2005) Human UDP-glucuronosyltransferase 1A5: identification, expression, and activity. *J. Pharmacol. Exp. Ther.* **315**, 1143-1149.

Fukuda, T.; Nishida, Y.; Imaoka, S.; Hiroi, T.; Naohara, M.; Funae, Y. and Azuma, J. (2000) The decreased *in vivo* clearance of CYP2D6 substrates by CYP2D6*10 might be caused not only by the low-expression but also by low affinity of CYP2D6. *Arch. Biochem. Biophys.* **380**, 303-308.

Fukuda, T.; Maune, H.; Ikenaga, Y.; Naohara, M.; Fukuda, K. and Azuma, J. (2005) Novel structure of the CYP2D6 gene that confuses geno-

typing for the CYP2D6*5 allele. *Drug Metab. Pharmacokinet.* **20**, 345-350.

Fukuen, S.; Fukuda, T.; Maune, H.; Ikenaga, Y.; Yamamoto, I.; Inaba, T. and Azuma, J. (2002) Novel detection assay by PCR-RFLP and frequency of the CYP3A5 SNPs, CYP3A5*3 and *6, in a Japanese population. *Pharmacogenetics* **12**, 331-334.

Fukushima-Uesaka, H.; Saito, Y.; Watanabe, H.; Shiseki, K.; Saeki, M.; Nakamura, T.; Kurose, K.; Sai, K.; Komamura, K.; Ueno, K.; Kamakura, S.; Kitakaze, M.; Hanai, S.; Nakajima, T.; Matsumoto, K.; Saito, H.; Goto, Y.; Kimura, H.; Katoh, M.; Sugai, K.; Minami, N.; Shirao, K.; Tamura ,T.; Yamamoto, N.; Minami, H.; Ohtsu, A.; Yoshida, T.; Saijo, N.; Kitamura, Y.; Kamatani, N.; Ozawa, S. and Sawada, J. (2004) Haplotypes of CYP3A4 and their close linkage with CYP3A5 haplotypes in a Japanese population. *Hum. Mutat.* **23**, 100.

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. and Sawada, J. (2005) Genetic variations and haplotypes of CYP2C19 in a Japanese population. *Drug Metab. Pharmacokinet.* **20**, 300-307.

Furuta, T.; Shirai, N.; Sugimoto, M.; Nakamura, A.; Hishida, A. and Ishizaki, T. (2005) Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab. Pharmacokinet.* **20**, 153-167.

Gaedigk, A.; Bradford, L. D.; Alander, S. W. and Leeder, J. S. (2006) CYP2D6*36 gene arrangements within the CYP2D6 locus: association of CYP2D6*36 with poor metabolizer status. *Drug Metab. Dispos.* **34**, 563-569.

Gagne, J. F.; Montminy, V.; Belanger, P.; Journault, K.; Gaucher, G. and Guillemette, C. (2002) Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). *Mol. Pharmacol.* **62**, 608-617.

Garcia-Barcelo, M.; Chow, L. Y.; Kum Chiu, H. F.; Wing, Y. K.; Shing Lee, D. T.; Lam, K. L. and Waye, M. M. (1999) Frequencies of defective CYP2C19 alleles in a Hong Kong Chinese population: detection of the rare allele CYP2C19*4. *Clin. Chem.* **45**, 2273-2274.

Garcia-Barcelo, M.; Chow, L. Y.; Chiu, H. F.; Wing, Y. K.; Lee, D. T.; Lam, K. L. and Waye, M. M. (2000a) Genetic analysis of the CYP2D6 locus in a Hong Kong Chinese population. *Clin. Chem.* **46**, 18-23.

Garcia-Barcelo, M.; Chow, L. Y.; Lam, K. L.; Chiu, H. F.; Wing, Y. K. and Waye, M. M. (2000b) Occurrence of CYP2D6 gene duplication in Hong Kong Chinese. *Clin. Chem.* **46**, 1411-1413.

Garcia-Martin, E.; Martinez, C.; Ladero, J. M. and Agundez, J. A. (2006) Interethnic and intraethnic variability of CYP2C8 and CYP2C9 polymorphisms in healthy individuals. *Mol. Diagn. Ther.* **10**, 29-40.

Garsa, A. A.; McLeod, H. L. and Marsh, S. (2005) CYP3A4 and CYP3A5 genotyping by Pyrosequencing. *BMC Med. Genet.* **6**, 19.

Gellner, K.; Eiselt, R.; Hustert, E.; Arnold, H.; Koch, I.; Haberl, M.; Deglmann, C. J.; Burk, O.; Buntefuss, D.; Escher, S.; Bishop, C.; Koebe, H. G.; Brinkmann, U.; Klenk, H. P.; Kleine, K.; Meyer, U. A. and Wojnowski, L. (2001) Genomic organization of the human CYP3A locus: identification of a new, inducible CYP3A gene. *Pharmacogenetics* **11**, 111-121.

Goldstein, J. A. and de Morais, S. M. (1994) Biochemistry and molecular biology of the human CYP2C subfamily. *Pharmacogenetics* **4**, 285-299.

Goodwin, B.; Hodgson, E. and Liddle, C. (1999) The orphan human pregnane X receptor mediates the transcriptional activation of CYP3A4 by rifampicin through a distal enhancer module. *Mol. Pharmacol.* **56**, 1329-1339.

Goodwin, B.; Hodgson, E.; D'Costa, D. J.; Robertson, G. R. and Liddle, C. (2002) Transcriptional regulation of the human CYP3A4 gene by the constitutive androstane receptor. *Mol. Pharmacol.* **62**, 359-365.

Grant D. M. (2005) Technologies for the analysis of single nucleotide polymorphisms-an overview. In *Pharmacogenomics: Second Edition*; Kalow, W.; Meyer, U. A.; Tyndale, R. F.; Eds.; Taylor and Francis Group: Boca Raton, FL, pp. 305-312.

Griese, E. -U.; Zanger, U. M.; Brudermanns, U; Gaedigk, A.; Mikus, G.; Morike, K.; Stuven, T. and Eichelbaum, M. (1998) Assessment of the predictive power of genotypes for the in-vivo catalytic function of CYP2D6 in a German population. *Pharmacogenetics* **8**, 5-26.

Guengerich, F. P. (1999) Cytochrome P-450 3A4: regulation and role in drug metabolism. *Annu. Rev. Pharmacol. Toxicol.* **39**, 1-17.

Guillemette, C.; Millikan, R. C.; Newman, B. and Housman, D. E. (2000a) Genetic polymorphisms in uridine diphospho-glucuronosyltransferase 1A1 and association with breast cancer among African Americans. *Cancer Res.* **60**, 950-956.

Guillemette, C.; Ritter, J. K.; Auyeung, D. J.; Kessler, F. K. and Housman, D. E. (2000b) Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human UGT1A7 gene. *Pharmacogenetics* **10**, 629-644.

Guillemette, C. (2003) Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. *Pharmacogenomics J.* **3**, 136-158.

Guo, Y.; Zhang, Y.; Wang, Y.; Chen, X.; Si, D.; Zhong, D.; Fawcett, J. P. and Zhou, H. (2005a) Role of CYP2C9 and its variants (CYP2C9*3 and CYP2C9*13) in the metabolism of lornoxicam in humans. *Drug Metab. Dispos.* **33**, 749-753.

Guo, Y.; Wang, Y.; Si, D.; Fawcett, P. J.; Zhong, D. and Zhou, H. (2005b) Catalytic activities of human cytochrome P450 2C9*1, 2C9*3 and 2C9*13. *Xenobiotica* **35**, 853-861.

Hall, D.; Ybazeta, G.; Destro-Bisol, G.; Petzl-Erler, M. L. and Di Rienzo, A. (1999) Variability at the uridine diphosphate glucuronosyltransferase 1A1 promoter in human populations and primates. *Pharmacogenetics* **9**, 591-599.

Han, J. Y.; Lim, H. S.; Shin, E. S.; Yoo, Y. K.; Park, Y. H.; Lee, J. E.; Jang, I. J.; Lee, D. H. and Lee, J. S. (2006) Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. *J. Clin. Oncol.* **24**, 2237-2244.

Handschin, C. and Meyer, U. A. (2003) Induction of drug metabolism: the role of nuclear receptors. *Pharmacol. Rev.* **55**, 649-673.

Hanioka, N.; Okumura, Y.; Saito, Y.; Hichiya, H.; Soyama, A.; Saito, K.; Ueno, K.; Sawada, J. and Narimatsu, S. (2006). Catalytic roles of CYP2D6.10 and CYP2D6.36 enzymes in mexiletine metabolism: *in vitro* functional analysis of recombinant proteins expressed in *Saccharomyces cerevisiae*. *Biochem. Pharmacol.* **71**, 1386-1395.

Herman, D.; Peternel, P.; Stegnar, M.; Breskvar, K. and Dolzan, V. (2006) A novel sequence variant in exon 7 of CYP2C9 gene (CYP2C9*24) in a patient on warfarin therapy. *Thromb. Haemost.* **95**, 192-194.

Hersberger, M.; Marti-Jaun, J.; Rentsh, K. and Hanseler, 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.* **46**, 1072-1077.

Hesselink, D. A.; van Gelder, T.; van Schaik, R. H.; Balk, A. H.; van der Heiden, I. P.; van Dam, T.; van der Werf, M.; Weimar, W. and Mathot, R. A. (2004) Population pharmacokinetics of cyclosporine in kidney and heart transplant recipients and the influence of ethnicity and genetic polymorphisms in the MDR-1, CYP3A4, and CYP3A5 genes. *Clin. Pharmacol. Ther.* **76**, 545-556.

Higashi, M. K.; Veenstra, D. L.; Kondo, L. M.; Wittkowsky, A. K.; Srinouanprachanh, S. L.; Farin, F. M. and Rettie, A. E. (2002) Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA* **287**, 1690-1698.

Hiratsuka, M.; Takekuma, Y.; Endo, N.; Narahara, K.; Hamdy, S. I.; Kishikawa, Y.; Matsuura, M.; Agatsuma, Y.; Inoue, T. and Mizugaki, M. (2002) Allele and genotype frequencies of CYP2B6 and CYP3A5 in the Japanese population. *Eur. J. Clin. Pharmacol.* **58**, 417-421.

Hirota, T.; Ieiri, I.; Takane, H.; Maegawa, S.; Hosokawa, M.; Kobayashi, K.; Chiba, K.; Nanba, E.; Oshimura, M.; Sato, T.; Higuchi, S. and Otsubo, K. (2004) Allelic expression imbalance of the human CYP3A4 gene and individual phenotypic status. *Hum. Mol. Genet.* **13**, 2959-2969.

Hsieh, K. P.; Lin, Y. Y.; Cheng, C. L.; Lai, M. L.; Lin, M. S.; Siest, J. P. and Huang, J. D. (2001) Novel mutations of CYP3A4 in Chinese. *Drug Metab. Dispos.* **29**, 268-273.

Huang, C. S.; Chang, P. F.; Huang, M. J.; Chen, E. S.; Hung, K. L. and Tsou, K. I. (2002) Relationship between bilirubin UDP-glucuronosyl transferase 1A1 gene and neonatal hyperbilirubinemia. *Pediatr. Res.* **52**, 601-605.

Huang, M. J.; Yang, S. S.; Lin, M. S. and Huang, C. S. (2005) Polymorphisms of uridine-diphosphoglucuronosyltransferase 1A7 gene in Taiwan Chinese. *World J. Gastroenterol.* **11**, 797-802.

Hustert, E.; Haberl, M.; Burk, O.; Wolbold, R.; He, Y. Q.; Klein, K.; Nuessler, A. C.; Neuhaus, P.; Klattig, J.; Eiselt, R.; Koch, I.; Zibat, A.; Brockmoller, J.; Halpert, J. R.; Zanger, U. M. and Wojnowski,

L. (2001) The genetic determinants of the CYP3A5 polymorphism. *Pharmacogenetics* **11**, 773-779.

Ibeanu, G. C.; Goldstein, J. A.; Meyer, U.; Benhamou, S.; Bouchardy, C.; Dayer, P.; Ghanayem, B. I. and Blaisdell, J. (1998) Identification of new human CYP2C19 alleles (CYP2C19*6 and CYP2C19*2B) in a Caucasian poor metabolizer of mephenytoin. *J. Pharmacol. Exp. Ther.* **286**, 1490-1495.

Ibeanu, G. C.; Blaisdell, J.; Ferguson, R. J.; Ghanayem, B. I.; Brosen, K.; Benhamou, S.; Bouchardy, C.; Wilkinson, G. R.; Dayer, P. and Goldstein, J. A. (1999) A novel transversion in the intron 5 donor splice junction of CYP2C19 and a sequence polymorphism in exon 3 contribute to the poor metabolizer phenotype for the anticonvulsant drug S-mephenytoin. *J. Pharmacol. Exp. Ther.* **290**, 635-640.

Ieiri, I.; Tainaka, H.; Morita, T.; Hadama, A.; Mamiya, K.; Hayashibara, M.; Ninomiya, H.; Ohmori, S.; Kitada, M.; Tashiro, N.; Higuchi, S. and Otsubo, K. (2000) Catalytic activity of three variants (Ile, Leu, and Thr) at amino acid residue 359 in human CYP2C9 gene and simultaneous detection using single-strand conformation polymorphism analysis. *Ther. Drug Monit.* **22**, 237-244.

Ikenaga, Y.; Fukuda, T.; Fukuda, K.; Nishida, Y.; Naohara, M.; Maune, H. and Azuma, J. (2005) The frequency of candidate alleles for CYP2D6 genotyping in the Japanese population with an additional respect to the -1584C to G substitution. *Drug Metab. Pharmacokinet.* **20**, 113-116.

Imai, J.; Ieiri, I.; Mamiya, K.; Miyahara, S.; Furuumi, H.; Nanba, E.; Yamane, M.; Fukumaki, Y.; Ninomiya, H.; Tashiro, N.; Otsubo, K. and Higuchi, S. (2000) Polymorphism of the cytochrome P450 (CYP) 2C9 gene in Japanese epileptic patients: genetic analysis of the CYP2C9 locus. *Pharmacogenetics* **10**, 85-89.

Ingelman-Sundberg, M. (2005) Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J.* **5**, 6-13.

Innocenti, F.; Grimsley, C.; Das, S.; Ramirez, J.; Cheng, C.; Kuttab-Boulos, H.; Ratain, M. J. and Di Rienzo, A. (2002) Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups. *Pharmacogenetics* **12**, 725-733.

Innocenti, F.; Liu, W.; Chen, P.; Desai, A. A.; Das, S. and Ratain, M. J. (2005) Haplotypes of variants in the UDP-glucuronosyltransferase1A9 and 1A1 genes. *Pharmacogenet. Genomics* **15**, 295-301.

Inomata, S.; Nagashima, A.; Itagaki, F.; Homma, M.; Nishimura, M.; Osaka, Y.; Okuyama, K.; Tanaka, E.; Nakamura, T.; Kohda, Y.; Naito, S.; Miyabe, M. and Toyooka, H. (2005) CYP2C19 genotype affects diazepam pharmacokinetics and emergence from general anesthesia. *Clin. Pharmacol. Ther.* **78**, 647-655.

Inoue, K.; Yamazaki, H.; Imiya, K.; Akasaka, S.; Guengerich, F. P. and Shimada, T. (1997) Relationship between CYP2C9 and 2C19 genotypes and tolbutamide methyl hydroxylation and S-mephenytoin 4'-hydroxylation activities in livers of Japanese and Caucasian populations. *Pharmacogenetics* **7**, 103-113.

Ishiguro, A.; Kubota, T.; Sasaki, H.; Yamada, Y. and Iga, T. (2003) Common mutant alleles of CYP2D6 causing the defect of CYP2D6 enzyme activity in a Japanese population. *Br. J. Clin. Pharmacol.* **55**, 414-415.

Ishiguro, A.; Kubota, T.; Ishikawa, H. and Iga, T. (2004a) Metabolic activity of dextromethorphan O-demethylation in healthy Japanese volunteers carrying duplicated CYP2D6 genes: duplicated allele of CYP2D6*10 does not increase CYP2D6 metabolic activity. *Clin. Chim. Acta* **344**, 201-204.

Ishiguro, A.; Kubota, T.; Sasaki, H. and Iga, T. (2004b) A long PCR assay to distinguish CYP2D6*5 and a novel CYP2D6 mutant allele associated with an 11-kb EcoRI haplotype. *Clin. Chim. Acta* **347**, 217-221.

Iwai, M.; Maruo, Y.; Ito, M.; Yamamoto, K.; Sato, H. and Takeuchi, Y. (2004) Six novel UDP-glucuronosyltransferase (UGT1A3) polymorphisms with varying activity. *J. Hum. Genet.* **49**, 123-128.

Ji, L.; Pan, S.; Marti-Jaun, J.; Hanseler, E.; Rentsch, K. and Hersberger, M. (2002a) Single-step assays to analyze CYP2D6 gene polymorphisms in Asians: allele frequencies and a novel *14B allele in mainland Chinese. *Clin. Chem.* **48**, 983-988.

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

Jinno, H.; Tanaka-Kagawa, T.; Hanioka, N.; Saeki, M.; Ishida, S.; Nishimura, T.; Ando, M.; Saito, Y.; Ozawa, S. and Sawada, J. (2003a) Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite of irinotecan (CPT-11), by human UGT1A1 variants, G71R, P229Q, and Y486D. *Drug Metab. Dispos.* **31**, 108-113.

Jinno, H.; Saeki, M.; Tanaka-Kagawa, T.; Hanioka, N.; Saito, Y.; Ozawa, S.; Ando, M.; Shirao, K.; Minami, H.; Ohtsu, A.; Yoshida, T.; Saijo, N. and Sawada, J. (2003b) Functional characterization of wild-type and variant (T202I and M591) human UDP-glucuronosyltransferase 1A10. *Drug Metab. Dispos.* **31**, 528-532.

Johansson, I.; Oscarson, M.; Yue, Q. Y.; Bertilsson, L.; Sjoqvist, F. and Ingelman-Sundberg, M. (1994) Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation. *Mol. Pharmacol.* **46**, 452-459.

Judson, R.; Stephens, J. C. and Windemuth, A. (2000) The predictive power of haplotypes in clinical response. *Pharmacogenomics* **1**, 15-26.

Kagimoto, M.; Heim, M.; Kagimoto, K.; Zeugin, T. and Meyer, U. A. (1990) Multiple mutations of the human cytochrome P450IID6 gene (CYP2D6) in poor metabolizers of debrisoquine. Study of the functional significance of individual mutations by expression of chimeric genes. *J. Biol. Chem.* **265**, 17209-17214.

Kanai, M.; Kijima, K.; Shirahata, E.; Sasaki, A.; Akaba, K.; Umetsu, K.; Tezuka, N.; Kurachi, H.; Aikawa, S. and Hayasaka, K. (2005) Neonatal hyperbilirubinemia and the bilirubin uridine diphosphate-glucuronosyltransferase gene: the common -3263T > G mutation of phenobarbital response enhancer module is not associated with the neonatal hyperbilirubinemia in Japanese. *Pediatr. Int.* **47**, 137-141.

Kaniwa, N.; Kurose, K.; Jinno, H.; Tanaka-Kagawa, T.; Saito, Y.; Saeki, M.; Sawada, J.; Tohkin, M. and Hasegawa, R. (2005) Racial variability in haplotype frequencies of UGT1A1 and glucuronidation activity of a novel single nucleotide polymorphism 686C> T (P229L) found in an African-American. *Drug Metab. Dispos.* **33**, 458-465.

Ki, C. S.; Lee, K. A.; Lee, S. Y.; Kim, H. J.; Cho, S. S.; Park, J. H.; Cho, S.; Sohn, K. M. and Kim, J. W. (2003) Haplotype structure of the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene and its relationship to serum total bilirubin concentration in a male Korean population. *Clin. Chem.* **49**, 2078-2081.

Kidd, R. S.; Curry, T. B.; Gallagher, S.; Edeki, T.; Blaisdell, J. and Goldstein, J. A. (2001) Identification of a null allele of CYP2C9 in an African-American exhibiting toxicity to phenytoin. *Pharmacogenetics* **11**, 803-808.

King, B. P.; Khan, T. I.; Aithal, G. P.; Kamali, F. and Daly, A. K. (2004) Upstream and coding region CYP2C9 polymorphisms: correlation with warfarin dose and metabolism. *Pharmacogenetics* **14**, 813-822.

Kirchheiner, J.; Nickchen, K.; Bauer, M.; Wong, M. L.; Licinio, J.; Roots, I. and Brockmoller, J. (2004) Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol. Psychiatry* **9**, 442-473.

Kirchheiner, J. and Brockmoller, J. (2005) Clinical consequences of cytochrome P450 2C9 polymorphisms. *Clin. Pharmacol. Ther.* **77**, 1-16.

Kittles, R. A.; Chen, W.; Panguluri, R. K.; Ahaghotu, C.; Jackson, A.; Adebamowo, C. A.; Griffin, R.; Williams, T.; Ukoli, F.; Adams-Campbell, L.; Kwagyan, J.; Isaacs, W.; Freeman, V. and Dunston, G. M. (2002) CYP3A4-V and prostate cancer in African Americans: causal or confounding association because of population stratification? *Hum. Genet.* **110**, 553-560.

Kohle, C.; Mohrle, B.; Munzel, P. A.; Schwab, M.; Wernet, D.; Badary, O. A. and Bock, K. W. (2003) Frequent co-occurrence of the TATA box mutation associated with Gilbert's syndrome (UGT1A1*28) with other polymorphisms of the UDP-glucuronosyltransferase-1 locus (UGT1A6*2 and UGT1A7*3) in Caucasians and Egyptians. *Biochem. Pharmacol.* **65**, 1521-1527.

Krishna, D. R. and Shekar, M. S. (2005) Cytochrome P450 3A: genetic polymorphisms and inter-ethnic differences. *Methods Find. Exp. Clin. Pharmacol.* **27**, 559-567.

Krishnaswamy, S.; Hao, Q.; Al-Rohaimi, A.; Hesse, L. M.; von Moltke, L. L.; Greenblatt, D. J. and Court, M. H. (2005) UDP glucuronosyltransferase (UGT) 1A6 pharmacogenetics: II. Functional impact of the three most common nonsynonymous UGT1A6 polymorphisms (S7A, T181A, and R184S). *J. Pharmacol. Exp. Ther.* **313**, 1340-1346.

Kubota, T; Yamaura, Y.; Ohkawa, N.; Hara, H. and Chiba, K. (2000) Frequencies of CYP2D6 mutant alleles in a normal Japanese popula-

tion and metabolic activity of dextromethorphan O-demethylation in different CYP2D6 genotypes. *Br. J. Clin. Pharmacol.* **50**, 31-34.

Kuehl, P.; Zhang, J.; Lin, Y.; Lamba, J.; Assem, M.; Schuetz, J.; Watkins, P. B.; Daly, A.; Wrighton, S. A.; Hall, S. D.; Maurel, P.; Relling, M.; Brimer, C.; Yasuda, K.; Venkataramanan, R.; Strom, S.; Thummel, K.; Boguski, M. S. and Schuetz, E. (2001) Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat. Genet.* **27**, 383-391.

Lamba, J. K.; Lin, Y. S.; Thummel, K.; Daly, A.; Watkins, P. B.; Strom, S.; Zhang, J. and Schuetz, E. G. (2002) Common allelic variants of cytochrome P4503A4 and their prevalence in different populations. *Pharmacogenetics* **12**, 121-132.

Lampe, J. W.; Bigler, J.; Horner, N. K. and Potter, J. D. (1999) UDP-glucuronosyltransferase (UGT1A1*28 and UGT1A6*2) polymorphisms in Caucasians and Asians: relationships to serum bilirubin concentrations. *Pharmacogenetics* **9**, 341-349.

Lee, C. R.; Goldstein, J. A. and Pieper, J. A. (2002) Cytochrome P450 2C9 polymorphisms: a comprehensive review of the *in-vitro* and human data. *Pharmacogenetics* **12**, 251-263.

Lee, S. J. and Goldstein, J. A. (2005) Functionally defective or altered CYP3A4 and CYP3A5 single nucleotide polymorphisms and their detection with genotyping tests. *Pharmacogenomics* **6**, 357-371.

Lee, S. J.; Bell, D. A.; Coulter, S. J.; Ghanayem, B. and Goldstein, J. A. (2005) Recombinant CYP3A4*17 is defective in metabolizing the hypertensive drug nifedipine, and the CYP3A4*17 allele may occur on the same chromosome as CYP3A5*3, representing a new putative defective CYP3A haplotype. *J. Pharmacol. Exp. Ther.* **313**, 302-309.

Lee, S. -Y.; Sohn, K. M.; Ryu, J. Y.; Yoon, Y. R.; Shin, J. G. and Kim, J. -W. (2006a) Sequence-based *CYP2D6* genotyping in the Korean population. *Ther. Drug Monit.* **28**, 382-387.

Lee, S. C.; Ng, S. S.; Oldenburg, J.; Chong, P. Y.; Rost, S.; Guo, J. Y.; Yap, H. L.; Rankin, S. C.; Khor, H. B.; Yeo, T. C.; Ng, K. S.; Soong, R. and Goh, B. C. (2006b) Interethnic variability of warfarin maintenance requirement is explained by VKORC1 genotype in an Asian population. *Clin. Pharmacol. Ther.* **79**, 197-205.

Le Meur, Y.; Djebli, N.; Szelag, J. C.; Hoizey, G.; Toupance, O.; Rerolle, J. P. and Marquet, P. (2006) CYP3A5*3 influences sirolimus oral clearance in *de novo* and stable renal transplant recipients. *Clin. Pharmacol. Ther.* **80**, 51-60.

Lewis, D. F.; Dickins, M.; Weaver, R. J.; Eddershaw, P. J.; Goldfarb, P. S. and Tarbit, M. H. (1998) Molecular modelling of human CYP2C subfamily enzymes CYP2C9 and CYP2C19: rationalization of substrate specificity and site-directed mutagenesis experiments in the CYP2C subfamily. *Xenobiotica* **28**, 235-268.

Liu, C. H.; Peck, K.; Huang, J. D.; Lin, M. S.; Wang, C. H.; Hsu, W. P.; Wang, H. W.; Lee, H. L. and Lai, M. L. (2005) Screening CYP3A single nucleotide polymorphisms in a Han Chinese population with a genotyping chip. *Pharmacogenomics* **6**, 731-747.

Luo, H. R.; Gaedigk, A.; Aloumanis, V. and Wan, Y. J. (2005) Identification of CYP2D6 impaired functional alleles in Mexican Americans. *Eur. J. Clin. Pharmacol.* **61**, 797-802.

Mackenzie, P. I.; Walter Bock, K.; Burchell, B.; Guillemette, C.; Ikushiro, S.; Iyanagi, T.; Miners, J. O.; Owens, I. S. and Nebert, D. W. (2005) Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily. *Pharmacogenet. Genomics* **15**, 677-685.

Maekawa, K.; Fukushima-Uesaka, H.; Tohkin, M.; Hasegawa, R.; Kajio, H.; Kuzuya, N.; Yasuda, K.; Kawamoto, M.; Kamatani, N.; Suzuki, K.; Yanagawa, T.; Saito, Y. and Sawada, J. (2006) Four novel defective alleles and comprehensive haplotype analysis of CYP2C9 in Japanese. *Pharmacogenet. Genomics* **16**, 497-514.

Maitland, M. L.; Grimsley, C.; Kuttab-Boulos, H.; Witonsky, D.; Kasza, K. E.; Yang, L.; Roe, B. A. and Di Rienzo, A. (2006) Comparative genomics analysis of human sequence variation in the UGT1A gene cluster. *Pharmacogenomics J.* **6**, 52-62.

Mamiya, K.; Ieiri, I.; Miyahara, S.; Imai, J.; Furuumi, H.; Fukumaki, Y.; Ninomiya, H.; Tashiro, N.; Yamada, H. and Higuchi, S. (1998) Association of polymorphisms in the cytochrome P450 (CYP) 2C19 and 2C18 genes in Japanese epileptic patients. *Pharmacogenetics* **8**, 87-90.

Marcucci, K. A.; Pearce, R. E.; Crespi, C.; Steimel, D. T.; Leeder, J. S. and Gaedigk, A. (2002) Characterization of cytochrome P450 2D6.1 (CYP2D6.1), CYP2D6.2, and CYP2D6.17 activities toward model CYP2D6 substrates dextromethorphan, bufuralol, and debrisoquine. *Drug Metab. Dispos.* **30**, 595-601.

Marez, D.; Legrand, M.; Sabbagh, N.; Guidice, J. M.; Spire, C.; Lafitte, J. J.; Meyer, U. A. and Broly, F. (1997) Polymorphism of the cytochrome P450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies and evolution. *Pharmacogenetics* **7**, 193-202.

Marsh, S. and McLeod, H. L. (2004) Pharmacogenetics of irinotecan toxicity. *Pharmacogenomics* **5**, 835-843.

Masimirembwa, C.; Persson, I.; Bertilsson, L.; Hasler, J. and Ingelman-Sundberg, M. (1996) A novel mutant variant of the CYP2D6 gene (CYP2D6*17) common in a black African population: association with diminished debrisoquine hydxylase activity. *Br. J. Clin. Pharmacol.* **42**, 713-719.

Matsumura, K.; Saito, T.; Takahashi, Y.; Ozeki, T.; Kiyotani, K.; Fujieda, M.; Yamazaki, H.; Kunitoh, H. and Kamataki, T. (2004) Identification of a novel polymorphic enhancer of the human CYP3A4 gene. *Mol. Pharmacol.* **65**, 326-334.

Mitsunaga,Y.; Kubota, T.; Ishiguro, A.; Yamada, Y.; Sasaki, H.; Chiba, K. and Iga, T. (2002) Frequent occurrence of CYP2D6*10 duplication allele in a Japanese population. *Mutat. Res.* **505**, 83-85.

Monaghan, G.; Ryan, M.; Seddon, R.; Hume, R. and Burchell, B. (1996) Genetic variation in bilirubin UPD-glucuronosyltransferase gene promoter and Gilbert's syndrome. *Lancet* **347**, 578-581.

Mori, A.; Maruo, Y.; Iwai, M.; Sato, H. and Takeuchi, Y. (2005) UDP-glucuronosyltransferase 1A4 polymorphisms in a Japanese population and kinetics of clozapine glucuronidation. *Drug Metab. Dispos.* **33**, 672-675.

Morin, S.; Bodin, L.; Loriot, M. A.; Thijssen, H. H.; Robert, A.; Strabach, S.; Verstuyft, C.; Tregouet, D. A.; Dubert, L.; Laurent-Puig, P.; Funck-Brentano, C.; Jaillon, P.; Beaune, P. H. and Becquemont, L. (2004) Pharmacogenetics of acenocoumarol pharmacodynamics. *Clin. Pharmacol. Ther.* **75**, 403-414.

Morita, J.; Kobayashi, K.; Wanibuchi, A.; Kimura, M.; Irie, S.; Ishizaki, T. and Chiba, K. (2004) A novel single nucleotide polymorphism (SNP) of the CYP2C19 gene in a Japanese subject with lowered capacity of mephobarbital 4'-hydroxylation. *Drug Metab. Pharmacokinet.* **19**, 236-238.

Murayama, N.; Nakamura, T.; Saeki, M.; Soyama, A.; Saito, Y.; Sai, K.; Ishida, S.; Nakajima, O.; Itoda, M.; Ohno, Y.; Ozawa, S. and Sawada, J. (2002) CYP3A4 gene polymorphisms influence testosterone 6beta-hydroxylation. *Drug Metab. Pharmacokinet.* **17**, 150-156.

Nakajima, Y.; Yoshitani, T.; Fukushima-Uesaka, H.; Saito, Y.; Kaniwa, N.; Kurose, K.; Ozawa, S.; Aoyagi, N.; Kamatani, N.; Yamamoto, N.; Kunitoh, H.; Ohe, Y.; Tamura, T.; Yoshida, T.; Minami, H.; Saijo, N.; Katori, N. and Sawada, J. (2006) Impact of the haplotype CYP3A4*16B harboring the Thr185Ser substitution on paclitaxel metabolism in Japanese patients with cancer. *Clin. Pharmacol. Ther.* **80**, 179-191.

Naoe, T.; Takeyama, K.; Yokozawa, T.; Kiyoi, H.; Seto, M.; Uike, N.; Ino, T.; Utsunomiya, A.; Maruta, A.; Jin-nai, I.; Kamada, N.; Kubota, Y.; Nakamura, H.; Shimazaki, C.; Horiike, S.; Kodera, Y.; Saito, H.; Ueda, R.; Wiemels, J. and Ohno, R. (2000) Analysis of genetic polymorphism in NQO1, GST-M1, GST-T1, and CYP3A4 in 469 Japanese patients with therapy-related leukemia/ myelodysplastic syndrome and *de novo* acute myeloid leukemia. *Clin. Cancer Res.* **6**, 4091-4095.

Nasu, K.; Kubota, T. and Ishizaki, T. (1997) Genetic analysis of CYP2C9 polymorphism in a Japanese population. *Pharmacogenetics* **7**, 405-409.

Nishida, Y.; Fukuda, T.; Yamamoto, I. and Azuma, J. (2000) CYP2D6 genotypes in a Japanese population: low frequencies of CYP2D6 gene duplication but high frequency of CYP2D6*10. *Pharmacogenetics* **10**, 567-570.

Obayashi, K.; Nakamura, K.; Kawana, J.; Ogata, H.; Hanada, K.; Kurabayashi, M.; Hasegawa, A.; Yamamoto, K. and Horiuchi, R. (2006) VKORC1 gene variations are the major contributors of variation in warfarin dose in Japanese patients. *Clin. Pharmacol. Ther.* **80**, 169-178.

Ozdemir, V.; Kalowa, W.; Tang, B. K.; Paterson, A. D.; Walker, S. E.; Endrenyi, L. and Kashuba, A. D. (2000) Evaluation of the genetic component of variability in CYP3A4 activity: a repeated drug administration method. *Pharmacogenetics* **10**, 373-388.

Pang, C. P.; Zhang, J.; Woo, J.; Chan, D.; Law, L. K.; Tong, S. F.; Kwok, T. and Kay, R. (1998) Rarity of debrisoquine hydroxylase gene polymorphism in Chinese patients with Parkinson's disease. *Mov. Disord.* **13**, 529-532.

Park, J. Y.; Kim, K. A.; Park, P. W.; Lee, O. J.; Kang, D. K.; Shon, J. H.; Liu, K. H. and Shin, J. G. (2006) Effect of CYP3A5*3 genotype on the pharmacokinetics and pharmacodynamics of alprazolam in healthy subjects. *Clin. Pharmacol. Ther.* **79**, 590-599.

Plummer, S. J.; Conti, D. V.; Paris, P. L.; Curran, A. P.; Casey, G. and Witte, J. S. (2003) CYP3A4 and CYP3A5 genotypes, haplotypes, and risk of prostate cancer. *Cancer Epidemiol. Biomarkers Prev.* **12**, 928-932.

Premawardhena, A.; Fisher, C. A.; Liu, Y. T.; Verma, I. C.; de Silva, S.; Arambepola, M.; Clegg, J. B. and Weatherall, D. J. (2003) The global distribution of length polymorphisms of the promoters of the glucuronosyltransferase 1 gene (UGT1A1): hematologic and evolutionary implications. *Blood Cells Mol. Dis.* **31**, 98-101.

Radominska-Pandya, A.; Czernik, P. J.; Little, J. M.; Battaglia, E. and Mackenzie, P. I. (1999) Structural and functional studies of UDP-glucuronosyltransferases. *Drug Metab. Rev.* **31**, 817-899.

Raimundo, S.; Fischer, J.; Eichelbaum, M.; Griese, E. U.; Schwab, M. and Zanger, U. M. (2000) Elucidation of the genetic basis of the common 'intermediate metabolizer' phenotype for drug oxidation by CYP2D6. *Pharmacogenetics* **10**, 577-581.

Raimundo, S.; Toscano, C.; Klein, K.; Fischer, J.; Griese, E. U.; Eichelbaum, M.; Schwab, M. and Zanger, U. M. (2004) A novel intronic mutation, 2988G>A, with high predictivity for impaired function of cytochrome P450 2D6 in white subjects. *Clin. Pharmacol. Ther.* **76**, 128-138.

Rebbeck, T. R.; Jaffe, J. M.; Walker, A. H.; Wein, A. J. and Malkowicz, S. B. (1998) Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4. *J. Natl. Cancer Inst.* **90**, 1225-1229.

Rettie, A. E. and Jones, J. P. (2005) Clinical and toxicological relevance of CYP2C9: Drug-drug interactions and pharmacogenetics. *Annu. Rev. Pharmacol. Toxicol.* **45**, 477-494.

Reyes-Hernandez, O. D.; Arteaga-Illan, G. and Elizondo, G. (2004) Detection of CYP3A4*1B and CYP3A4*2 polymorphisms by RFLP. Distribution frequencies in a Mexican population. *Clin. Genet.* **66**, 166-168.

Ritter, J. K.; Kessler, F. K.; Thompson, M. T.; Grove, A. D.; Auyeung, D. J. and Fisher, R. A. (1999) Expression and inducibility of the human bilirubin UDP-glucuronosyltransferase UGT1A1 in liver and cultured primary hepatocytes: evidence for both genetic and environmental influences. *Hepatology* **30**, 476-484.

Rodriguez-Antona, C.; Sayi, J. G.; Gustafsson, L. L.; Bertilsson, L. and Ingelman-Sundberg, M. (2005) Phenotype-genotype variability in the human CYP3A locus as assessed by the probe drug quinine and analyses of variant CYP3A4 alleles. *Biochem. Biophys. Res. Commun.* **338**, 299-305.

Roh, H. K.; Dahl, M. L.; Johansson, I.; Ingelman-Sundberg, M.; Cha, Y. N. and Bertilsson, L. (1996) Debrisoquine and S-mephenytoin hydroxylation phenotypes and genotypes in a Korean population. *Pharmacogenetics* **6**, 441-447.

Roy, J. N.; Lajoie, J.; Zijenah, L. S.; Barama, A.; Poirier, C.; Ward, B. J. and Roger, M. (2005) CYP3A5 genetic polymorphisms in different ethnic populations. *Drug Metab. Dispos.* **33**, 884-887.

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

Saeki, M.; Saito, Y.; Nakamura, T.; Murayama, N.; Kim, S. R.; Ozawa, S.; Komamura, K.; Ueno, K.; Kamakura, S.; Nakajima, T.; Saito, H.; Kitamura, Y.; Kamatani, N. and Sawada, J. (2003) Single nucleotide polymorphisms and haplotype frequencies of CYP3A5 in a Japanese population. *Hum. Mutat.* **21**, 653.

Saeki, M.; Saito, Y.; Jinno, H.; Sai, K.; Hachisuka, A.; Kaniwa, N.; Ozawa, S.; Kawamoto, M.; Kamatani, N.; Shirao, K.; Minami, H.; Ohtsu, A.; Yoshida, T.; Saijo, N.; Komamura, K.; Kotake, T.; Morishita, H.; Kamakura, S.; Kitakaze, M.; Tomoike, H. and Sawada, J. (2005) Genetic variations and haplotypes of UGT1A4 in a Japanese population. *Drug Metab. Pharmacokinet.* **20**, 144-151.

Saeki, M.; Saito, Y.; Jinno, H.; Sai, K.; Ozawa, S.; Kurose, K.; Kaniwa, N.; Komamura, K.; Kotake, T.; Morishita, H.; Kamakura, S.; Kitakaze, M.; Tomoike, H.; Shirao, K.; Tamura, T.; Yamamoto, N.; Kunitoh, H.; Hamaguchi, T.; Yoshida, T.; Kubota, K.; Ohtsu, A.; Muto, M.; Minami, H.; Saijo, N.; Kamatani, N. and Sawada, J. (2006) Haplotype structures of the UGT1A gene complex in a Japanese population. *Pharmacogenomics J.* **6**, 63-75.

Sai, K.; Saeki, M.; Saito, Y.; Ozawa, S.; Katori, N.; Jinno, H.; Hasegawa, R.; Kaniwa, N.; Sawada, J.; Komamura, K.; Ueno, K.; Kamakura, S.; Kitakaze, M.; Kitamura, Y.; Kamatani, N.; Minami, H.; Ohtsu, A.; Shirao, K.; Yoshida, T. and Saijo, N. (2004) UGT1A1 haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administered Japanese patients with cancer. *Clin. Pharmacol. Ther.* **75**, 501-515.

Sata, F.; Sapone, A.; Elizondo, G.; Stocker, P.; Miller, V. P.; Zheng, W.; Raunio, H.; Crespi, C. L. and Gonzalez, F. J. (2000) CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: evidence for an allelic variant with altered catalytic activity. *Clin. Pharmacol. Ther.* **67**, 48-56.

Saxena, R.; Shaw, G. L.; Relling, M. V.; Frame, J. N.; Moir, D. T.; Evans, W. E.; Caporaso, N. and Weiffenbach, B. (1994) Idetification of a new variant CYP2D6 allele with a single base deletion in exon 3 and its association with the poor metabolizer phenotype. *Hum. Mol. Genet.* **3**, 923-926.

Schirmer, M.; Toliat, M. R.; Haberl, M.; Suk, A.; Kamdem, L. K.; Klein, K.; Brockmoller, J.; Nurnberg, P.; Zanger, U. M. and Wojnowski, L. (2006) Genetic signature consistent with selection against the CYP3A4*1B allele in non-African populations. *Pharmacogenet. Genomics* **16**, 59-71.

Schwarz, U. I. (2003) Clinical relevance of genetic polymorphisms in the human CYP2C9 gene. *Eur. J. Clin. Invest.* **33**, 23-30.

Scordo, M. G.; Aklillu, E.; Yasar, U.; Dahl, M. L.; Spina, E. and 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.

Scott, J. and Poffenbarger, P. L. (1979) Pharmacogenetics of tolbutamide metabolism in humans. *Diabetes* **28**, 41-51.

Shimada, T.; Yamazaki, H.; Mimura, M.; Inui, Y. and Guengerich, F. P. (1994) Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J. Pharmacol. Exp. Ther.* **270**, 414-423.

Shintani, M.; Ieiri, I.; Inoue, K.; Mamiya, K.; Ninomiya, H.; Tashiro, N.; Higuchi, S. and Otsubo, K. (2001) Genetic polymorphisms and functional characterization of the 5'-flanking region of the human CYP2C9 gene: *in vitro* and *in vivo* studies. *Clin. Pharmacol. Ther.* **70**, 175-182.

Si, D.; Guo, Y.; Zhang, Y.; Yang, L.; Zhou, H. and Zhong, D. (2004) Identification of a novel variant CYP2C9 allele in Chinese. *Pharmacogenetics* **14**, 465-469.

Sim, S. C.; Risinger, C.; Dahl, M. L.; Aklillu, E.; Christensen, M.; Bertilsson, L. and Ingelman-Sundberg, M. (2006) A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin. Pharmacol. Ther.* **79**, 103-113.

Soyama, A.; Saito, Y.; Komamura, K.; Ueno, K.; Kamakura, S.; Ozawa, S. and Sawada, J. (2002) Novel single nucleotide polymorphisms in the CYP2D6 gene associated with CYP2D6*2 and/or CYP2D6*10 alleles. *Drug Metab. Pharmacokinet.* **17**, 475-478.

Soyama, A.; Kubo, T.; Miyajima, A.; Saito, Y.; Shiseki, K.; Komamura, K.; Ueno, K.; Kamakura, S.; Kitakaze, M.; Tomoike, H.; Ozawa; S. and Sawada, J. (2004) Novel nonsynonymous single nucleotide polymorphisms in the CYP2D6 gene. *Drug Metab. Pharmacokinet.* **19**, 313-319.

Soyama, A.; Saito, Y.; Kubo, T.; Miyajima, A.; Ohno, Y.; Komamura, K.; Ueno, K.; Kamakura, S.; Kitakaze, M.; Tomoike, H.; Ozawa, S. and Sawada, J. (2006a) Sequence-based analysis of the CYP2D6*36-CYP2D6*10 tandem-type arrangement, a major CYP2D6*10 haplotype in the Japanese population. *Drug Metab. Pharmacokinet.* **21**, 208-216.

Soyama, A.; Saito, Y.; Ohno, Y.; Komamura, K.; Kamakura, S.; Kitakaze, M.; Tomoike, H.; Ozawa, S. and Sawada, J. (2006b) A novel defective CYP2D6 haplotype harboring single-type *36 and chimeric CYP-REP7/6 and CYP-REP7/6 diversity in Japanese. *Drug Metab. Pharmacokinet.* **21**, 395-405.

Steen, V. M.; Molven, A.; Aarskog, N. K. and Gulbrandsen, A. K. (1995) Homologous unequal cross-over involving a 2.8 kb direct repeat as a mechanism for the generation of allelic variants of human cytochrome P450 CYP2D6 gene. *Hum. Mol. Genet.* **4**, 2251-2257.

Sugatani, J.; Yamakawa, K.; Yoshinari, K.; Machida, T.; Takagi, H.; Mori, M.; Kakizaki, S.; Sueyoshi, T.; Negishi, M. and Miwa, M. (2002) Identification of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia. *Biochem. Biophys. Res. Commun.* **292**, 492-497.

Sutomo, R.; Talib, N. A.; Yusoff, N. M.; Van Rostenberghe, H.; Sadewa, A. H.; Sunarti Sofro, A. S.; Yokoyama, N.; Lee, M. J.; Matsuo, M. and Nishio, H. (2004) Screening for G71R mutation of the UGT1A1 gene in the Javanese-Indonesian and Malay-Malaysian populations. *Pediatr. Int.* **46**, 565-569.

Tai, G.; Farin, F.; Rieder, M. J.; Dreisbach, A. W.; Veenstra, D. L.; Verlinde, C. L. and Rettie, A. E. (2005) *In-vitro* and *in-vivo* effects of the CYP2C9*11 polymorphism on warfarin metabolism and dose. *Pharmacogenet. Genomics* **15**, 475-481.

Takanashi, K.; Tainaka, H.; Kobayashi, K.; Yasumori, T.; Hosakawa, M. and Chiba, K. (2000) CYP2C9 Ile359 and Leu359 variants: enzyme kinetic study with seven substrates. *Pharmacogenetics* **10**, 95-104.

Takahashi, H.; Wilkinson, G. R.; Caraco, Y.; Muszkat, M.; Kim, R. B.; Kashima, T.; Kimura, S. and Echizen, H. (2003) Population differences in S-warfarin metabolism between CYP2C9 genotype-matched Caucasian and Japanese patients. *Clin. Pharmacol. Ther.* **73**, 253-263.

Takahashi, H.; Wilkinson, G. R.; Nutescu, E. A.; Morita, T.; Ritchie, M. D.; Scordo, M. G.; Pengo, V.; Barban, M.; Padrini, R.; Ieiri, I.; Otsubo, K.; Kashima, T.; Kimura, S.; Kijima, S. and Echizen, H. (2006) Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population differences in maintenance dose of warfarin in Japanese, Caucasians and African-Americans. *Pharmacogenet. Genomics* **16**, 101-110.

Tate, S. K. and Goldstein, D. B. (2004) Will tomorrow's medicines work for everyone? *Nat. Genet.* **36**, S34-42.

Tateishi, T.; Chida, M.; Ariyoshi, N.; Mizorogi, Y.; Kamataki, T. and Kobayashi, S. (1999) Analysis of the CYP2D6 gene in relation to dextromethorphan O-demethylation capacity in a Japanese population. *Clin. Pharmacol. Ther.* **65**, 570-575.

Tayeb, M. T.; Clark, C.; Ameyaw, M. M.; Haites, N. E.; Evans, D. A.; Tariq, M.; Mobarek, A.; Ofori-Adjei, D. and McLeod, H. L. (2000) CYP3A4 promoter variant in Saudi, Ghanaian and Scottish Caucasian populations. *Pharmacogenetics* **10**, 753-756.

Teh, L. K.; Ismail, R.; Yusoff, R.; Hussein, A.; Isa, M. N. and Rahman, A. R. (2001) Heterogeneity of the CYP2D6 gene among Malays in Malaysia. *J. Clin. Pharm. Ther.* **26**, 205-211.

Thomas, S. S.; Li, S. S.; Lampe, J. W.; Potter, J. D. and Bigler, J. (2006) Genetic variability, haplotypes, and htSNPs for exons 1 at the human UGT1A locus. *Hum. Mutat.* **27**, 717.

Thompson, E. E.; Kuttab-Boulos, H.; Witonsky, D.; Yang, L.; Roe, B. A. and Di Rienzo, A. (2004) CYP3A variation and the evolution of salt-sensitivity variants. *Am. J. Hum. Genet.* **75**, 1059-1069.

Thompson, E. E.; Kuttab-Boulos, H.; Yang, L.; Roe, B. A. and Di Rienzo, A. (2006) Sequence diversity and haplotype structure at the human CYP3A cluster. *Pharmacogenomics J.* **6**, 105-114.

Thummel, K. E. and Wilkinson, G. R. (1998) *In vitro* and *in vivo* drug interactions involving human CYP3A. *Annu. Rev. Pharmacol. Toxicol.* **38**, 389-430.

Tirona, R. G.; Lee, W.; Leake, B. F.; Lan, L. B.; Cline, C. B.; Lamba, V.; Parviz, F.; Duncan, S. A.; Inoue, Y.; Gonzalez, F. J.; Schuetz, E. G. and Kim, R. B. (2003) The orphan nuclear receptor HNF4alpha determines PXR- and CAR-mediated xenobiotic induction of CYP3A4. *Nat. Med.* **9**, 220-224.

Toscano, C.; Klein, K.; Blievernicht, J.; Schaeffeler, E.; Saussele, T.; Raimundo, S.; Eichelbaum, M.; Schwab, M. and Zanger, U. M. (2006) Impaired expression of CYP2D6 in intermediate metabolizers carrying the *41 allele caused by the intronic SNP 2988G>A: evidence for modulation of splicing events. *Pharmacogenet. Genomics* **16**, 755-766.

Tracy, T. S.; Hutzler, J. M.; Haining, R. L.; Rettie, A. E.; Hummel, M. A. and Dickmann, L. J. (2002) Polymorphic variants (CYP2C9*3 and CYP2C9*5) and the F114L active site mutation of CYP2C9: effect on atypical kinetic metabolism profiles. *Drug Metab. Dispos.* **30**, 385-390.

Tsuzuki, D.; Takemi, C.; Yamamoto, S.; Tamagake, K.; Imaoka, S.; Funae, Y.; Kataoka, H.; Shinoda, S. and Narimatsu, S. (2001) Functional evaluation of cytochrome P450 2D6 with Gly42Arg substitution expressed in *Saccharomyces cerevisiae*. *Pharmacogenetics* **11**, 709-718.

Tukey, R. H. and Strassburg, C. P. (2000) Human UDP-glucuronosyltransferases: metabolism, expression, and disease. *Annu. Rev. Pharmacol. Toxicol.* **40**, 581-616.

Tyndale, R.; Aoyama, T.; Broly, F.; Matsunaga, T.; Inaba, T.; Kalow, W.; Gelboin, H. V.; Meyer, U. A. and Gonzalez, F. J. (1991) Identification of a new variant CYP2D6 allele lacking the codon encoding Lys-281: possible association with the poor metabolizer phenotype. *Pharmacogenetics* **1**, 26-32.

van Schaik, R. H.; de Wildt, S. N.; van Iperen, N. M.; Uitterlinden, A. G.; van den Anker, J. N. and Lindemans, J. (2000) CYP3A4-V polymorphism detection by PCR-restriction fragment length polymorphism analysis and its allelic frequency among 199 Dutch Caucasians. *Clin. Chem.* **46**, 1834-1836.

van Schaik, R. H.; van der Heiden, I. P.; van den Anker, J. N. and Lindemans, J. (2002) CYP3A5 variant allele frequencies in Dutch Caucasians. *Clin. Chem.* **48**, 1668-1671.

Veenstra, D. L.; Blough, D. K.; Higashi, M. K.; Farin, F. M.; Srinouanprachan, S.; Rieder, M. J. and Rettie, A. E. (2005) CYP2C9 haplotype structure in European American warfarin patients and association with clinical outcomes. *Clin. Pharmacol. Ther.* **77**, 353-364.

Villeneuve, L.; Girard, H.; Fortier, L. C.; Gagne, J. F. and Guillemette, C. (2003) Novel functional polymorphisms in the UGT1A7 and UGT1A9 glucuronidating enzymes in Caucasian and African-American subjects and their impact on the metabolism of 7-ethyl-10-hydroxycamptothecin and flavopiridol anticancer drugs. *J. Pharmacol. Exp. Ther.* **307**, 117-128.

Walker, A. H.; Jaffe, J. M.; Gunasegaram, S.; Cummings, S. A.; Huang, C. S.; Chern, H. D.; Olopade, O. I.; Weber, B. L. and Rebbeck, T. R. (1998) Characterization of an allelic variant in the nifedipine-specific element of CYP3A4: ethnic distribution and implications for prostate cancer risk. *Hum. Mutat.* **12**, 289.

Walton, R.; Kimber, M.; Rockett, K.; Trafford, C.; Kwiatkowski, D. and Sirugo, G. (2005) Haplotype block structure of the cytochrome P450 CYP2C gene cluster on chromosome 10. *Nat. Genet.* **37**, 915-916.

Wandel, C.; Witte, J. S.; Hall, J. M.; Stein, C. M.; Wood, A. J. and Wilkinson, G. R. (2000) CYP3A activity in African American and European American men: population differences and functional effect of the CYP3A4*1B5'-promoter region polymorphism. *Clin. Pharmacol. Ther.* **68**, 82-91.

Wang, S. -L.; Huang, J. -d.; Lai, M. -D.; Liu, B. -H. and Lai, M. -L. (1993) Molecular basis of genetic variation in debrisoquin hydroxylation in Chinese subjects: Polymorphism in RFLP and DNA sequence of CYP2D6. *Clin. Pharmacol. Ther.* **53**, 410-418.

Wang, S. L.; Huang, J.; Lai, M. D. and Tsai, J. J. (1995) Detection of CYP2C9 polymorphism based on the polymerase chain reaction in Chinese. *Pharmacogenetics* **5**, 37-42.

Wang, A.; Yu, B. N.; Luo, C. H.; Tan, Z. R.; Zhou, G.; Wang, L. S.; Zhang, W.; Li, Z.; Liu, J. and Zhou, H. H. (2005) Ile118Val genetic polymorphism of CYP3A4 and its effects on lipid-lowering efficacy of simvastatin in Chinese hyperlipidemic patients. *Eur. J. Clin. Pharmacol.* **60**, 843-848.

Wen, S.; Wang, H.; Ding, Y.; Liang, H. and Wang, S. (2004) Screening of 12 SNPs of CYP3A4 in a Chinese population using oligonucleotide microarray. *Genet. Test* **8**, 411-416.

Wennerholm, A.; Johansson, I.; Hidestrand, M.; Bertilsson, L.; Gustafsson, L. L. and Ingelman-Sundberg, M. (2001) Characterization of the CYP2D6*29 allele commonly present in a black Tanzanian population causing reduced catalytic activity. *Pharmacogenetics* **11**, 417-427.

Wennerholm, A.; Dandara, C.; Sayi, J.; Svenson, J. -O.; Abdi, Y. A.; Ingelman-Sundberg, M.; Bertilsson, L.; Hasler, J. and Gustufsson, L. L. (2002) The African-specific CYP2D6*17 allele encodes an enzyme with changed substrate specificity. *Clin. Pharmacol. Ther.* **71**, 77-88.

Westlind, A.; Lofberg, L.; Tindberg, N.; Andersson, T. B. and Ingelman-Sundberg, M. (1999) Interindividual differences in hepatic expression of CYP3A4: relationship to genetic polymorphism in the 5'-upstream regulatory region. *Biochem. Biophys. Res. Commun.* **259**, 201-205.

Westlind-Johnsson, A.; Hermann, R.; Huennemeyer, A.; Hauns, B.; Lahu, G.; Nassr, N.; Zech, K.; Ingelman-Sundberg, M. and von Richter, O. (2006) Identification and characterization of CYP3A4*20, a

novel rare CYP3A4 allele without functional activity. *Clin. Pharmacol. Ther.* **79**, 339-349.

Wong, M.; Balleine, R. L.; Collins, M.; Liddle, C.; Clarke, C. L. and Gurney, H. (2004) CYP3A5 genotype and midazolam clearance in Australian patients receiving chemotherapy. *Clin. Pharmacol. Ther.* **75**, 529-538.

Wrighton, S. A.; VandenBranden, M. and Ring, B. J. (1996) The human drug metabolizing cytochromes P450. *J. Pharmacokinet. Biopharm.* **24**, 461-473.

Xiao, Z. S.; Goldstein, J. A.; Xie, H. G.; Blaisdell, J.; Wang, W.; Jiang, C. H.; Yan, F. X.; He, N.; Huang, S. L.; Xu, Z. H. and Zhou, H. H. (1997) Differences in the incidence of the CYP2C19 polymorphism affecting the S-mephenytoin phenotype in Chinese Han and Bai populations and identification of a new rare CYP2C19 mutant allele. *J. Pharmacol. Exp. Ther.* **281**, 604-609.

Yamanaka, H.; Nakajima, M.; Katoh, M.; Hara, Y.; Tachibana, O.; Yamashita, J.; McLeod, H. L. and Yokoi, T. (2004) A novel polymorphism in the promoter region of human UGT1A9 gene (UGT1A9*22) and its effects on the transcriptional activity. *Pharmacogenetics* **14**, 329-332.

Yamazaki, H.; Kiyotani, K.; Tsubuko, S.; Matsunaga, M.; Fujieda, M.; Saito, T.; Miura, J.; Kobayashi, S. and Kamataki, T. (2003) Two novel haplotypes of CYP2D6 gene in a Japanese population. *Drug Metab. Pharmacokinet.* **18**, 269-271.

Yasar, U.; Aklillu, E.; Canaparo, R.; Sandberg, M.; Sayi, J.; Roh, H. K. and Wennerholm, A. (2002a) Analysis of CYP2C9*5 in Caucasian, Oriental and black-African populations. *Eur. J. Clin. Pharmacol.* **58**, 555-558.

Yasar, U.; Lundgren, S.; Eliasson, E.; Bennet, A.; Wiman, B.; de Faire, U. and Rane, A. (2002b) Linkage between the CYP2C8 and CYP2C9 genetic polymorphisms. *Biochem. Biophys. Res. Commun.* **299**, 25-28.

Yokoi, T.; Kosaka, Y.; Chida, M.; Chiba, K.; Nakamura, H.; Ishizaki, T.; Kinoshita, M.; Sato, K.; Gonzalez, F. J. and Kamataki, T. (1996) A new CYP2D6 allele with a nine base insertion in exon 9 in a Japanese population associated with poor metabolizer phenotype. *Pharmacogenetics* **6**, 395-401.

Yokota, H.; Tamura, S.; Furuya, H.; Kimura, S.; Watanabe, M.; Kanazawa, I.; Kondo, I. and Gonzalez, F. J. (1993) Evidence for a new variant CYP2D6 allele CYP2D6J in a Japanese population associated with lower *in vivo* rates of sparteine metabolism. *Pharmacogenetics* **3**, 256-263.

Yoon, Y. -R.; Cha, I. -J.; Shon, J. -H.; Kim, K. -A.; Cha, Y. -N.; Jang, I. -J.; Park, C. -W.; Shin, S. -G.; Flockhart, D. A. and Shin, J. -G. (2000) Relationship of paroxetine disposition to metoprorol metabolic ratio and *CYP2D6*19* genotype of Korean subjects. *Clin. Pharmacol. Ther.* **67**, 567-576.

Yoon, Y. R.; Shon, J. H.; Kim, M. K.; Lim, Y. C.; Lee, H. R.; Park, J. Y.; Cha, I. J. and Shin, J. G. (2001) Frequency of cytochrome P450 2C9 mutant alleles in a Korean population. *Br. J. Clin. Pharmacol.* **51**, 277-280.

Yusoff, S.; Van Rostenberghe, H.; Yusoff, N. M.; Talib, N. A.; Ramli, N.; Ismail, N. Z.; Ismail, W. P.; Matsuo, M. and Nishio, H. (2006) Frequencies of A(TA)7TAA, G71R, and G493R mutations of the UGT1A1 gene in the Malaysian population. *Biol. Neonate* **89**, 171-176.

Zanger, U. M.; Fischer, J.; Raimundo, S.; Stuven, T.; Evert, B. O.; Schwab, M. and Eichelbaum, M. (2001) Comprehensive analysis of the genetic factors determining expression and function of hepatic CYP2D6. *Pharmacogenetics* **11**, 573-585.

Zeigler-Johnson, C. M.; Walker, A. H.; Mancke, B.; Spangler, E.; Jalloh, M.; McBride, S.; Deitz, A.; Malkowicz, S. B.; Ofori-Adjei, D.; Gueye, S. M. and Rebbeck, T. R. (2002) Ethnic differences in the frequency of prostate cancer susceptibility alleles at SRD5A2 and CYP3A4. *Hum. Hered.* **54**, 13-21.

Zeigler-Johnson, C.; Friebel, T.; Walker, A. H.; Wang, Y.; Spangler, E.; Panossian, S.; Patacsil, M.; Aplenc, R.; Wein, A. J.; Malkowicz, S. B. and Rebbeck, T. R. (2004) CYP3A4, CYP3A5, and CYP3A43 genotypes and haplotypes in the etiology and severity of prostate cancer. *Cancer Res.* **64**, 8461-8467.

Zhao, F.; Loke, C.; Rankin, S. C.; Guo, J. Y.; Lee, H. S.; Wu, T. S.; Tan, T.; Liu, T. C.; Lu, W. L.; Lim, Y. T.; Zhang, Q.; Goh, B. C. and Lee, S. C. (2004) Novel CYP2C9 genetic variants in Asian subjects and their influence on maintenance warfarin dose. *Clin. Pharmacol. Ther.* **76**, 210-219.

Received: 07 August, 2006 Revised: 30 October, 2006 Accepted: 01 November, 2006