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Review

Population Differences in Major Functional Polymorphisms of Pharmacokinetics/pharmacodynamics-related Genes in Eastern Asians and Europeans: Implications in the Clinical Trials for Novel Drug Development

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Full text of this paper is available at http://www.jstage.jst.go.jp/browse/dmpk

Summary: Drug lag, recently discussed extensively in Japan, can be divided into two phases: clinical development time and application review time. The former factor is still an important problem that might be improved by promoting multi-regional clinical trials and considering the results from other similar populations with Japanese, such as Koreans and Chinese. In this review, we compare the allelic or genotype frequencies of 30 relatively common functional alleles mainly between Eastern Asians and Europeans as well as among 3 major populations in Eastern Asian countries, Japan, Korea, and China, in 12 pharmacokinetics (PK)/pharmacodynamics (PD)-related genes; *CYP2C9* (**2* and **3*), *CYP2C19* (**2, *3* and **17*), 13 *CYP2D6* haplotypes including **4*, **5* and **10*, *CYP3A5* (**3*), *UGT1A1* (**28* and **6*), *NAT2* (**5, *6* and **7*), *GSTM1* and *GSTT1* null genotypes, *SLCO1B1* 521T>C, *ABCG2* 421C>A, and *HLA-A*31:01* and *HLA-B*58:01*. In this review, differences in allele frequencies (AFs) or genotype frequencies (GFs) less than 0.1 (in the cases of highest AF (GF) $\geq$0.1) or less than 0.05 (in the cases of lowest AF (GF) $<$0.1) were regarded as similar. Between Eastern Asians and Europeans, AFs (or GFs) are regarded as being different for many alleles such as *CYP2C9* (**2*), *CYP2C19* (**2, *3* and **17*), *CYP2D6* (**4* and **10*), *CYP3A5* (**3*), *UGT1A1* (**28* and **6*), *NAT2* (**5*7*), *GSTT1* null and *ABCG2* 421C>A. Among the 3 Eastern Asian populations, however, only AFs of *CYP2C19*3*, *CYP2D6*10*, *HLA-A*31:01* and *HLA-B*58:01* are regarded as dissimilar. For *CYP2C19*3*, the total functional impact on CYP2C19 could be small if the frequencies of the two null alleles *CYP2C19*2* and **3* are combined. Regarding *CYP2D6*10*, frequency difference over 0.1 is observed only between Japanese and Chinese (0.147). Although environmental factors should be considered for PK/PD differences, we could propose that among Japan, Korea, and China, genetic differences are very small for the analyzed common PK-related gene polymorphisms. On the other hand, AFs of the two *HLA* alleles important for cutaneous adverse drug reactions are diverse even among Eastern Asians and thus should be taken into account.

Keywords: Eastern Asians; Europeans; genetic polymorphisms; allele frequencies; population differences

Introduction

Drug lag is the time elapsed between first introduction of a drug into the market of a country and its approval in another country. This issue has been extensively discussed in Japan since the lag for drug approval in Japan was approximately 2.5 years longer than in the US in 2006.[1] Drug lag can be divided into two phases: the clinical development period and the application review period. For application reviewing at the Pharmaceutical and Devices Agency (PMDA), the regulatory agency of Japan, the review period has been gradually decreasing, probably because of

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several administrative measures including increased numbers of review staff and scientific consultations between applicants and the PMDA, establishment of target review times, and the application of a standardized review process with predefined milestones.[2,3] However, the time for the clinical development process with new molecular entities in 2008 and 2009 was longer than in previous years.[2]

Regarding new molecular entities, multi-regional (or global) clinical trials (MRCT) are widely performed, now especially at the phase III stage. If the start of MRCT in Japan is synchronized with other regions, drug applications to each regional regulatory agency could also be synchronized. Thus, promotion of MRCT is an important factor for helping to resolve drug lag. A drawback to MRCT is, however, the smaller number of patients for each participating country. If the data in closely related ethnic populations could be considered, the reviewers could more easily evaluate the clinical results and accelerate the drug approval process.

However, it is now widely recognized that vast ethnic and even population differences exist in the pharmacokinetics and pharmacodynamics (efficacy and toxicity) of medicinal drugs. In fact for approved drugs in Japan from 2001 to 2007, the approved standard doses in the US were more than 2 times higher for 32% of drugs than those in Japan.[4] These differences can at least partially be attributed to the genetic variations of drug metabolism and pharmacokinetics (DMPK)-related proteins such as cytochrome P450s (CYPs) as well as adverse drug reaction-related molecules such as human leukocyte antigens (HLAs). Single nucleotide polymorphisms and base(s) or whole gene deletions or insertions can alter protein expression levels and/or its functions. Many functionally-related genetic variations have been published for DMPK-related genes, and allele frequencies (AFs) of these genetic variations are known to vary among ethnic populations.[5]

Currently, the Japanese regulatory authority (Ministry of Health, Labor and Welfare, PMDA) strongly recommends that clinical trials be performed using Japanese subjects. In contrast, the European Medical Agency has treated clinical trial data in European Union (EU) countries just as EU data, and data from ethnic populations such as Germans and Italians are not considered separately. If clinical trial data obtained in neighboring Asian countries such as Korea and China could be considered as originating from "Japanese-like" subjects, approval of new molecular entities would be highly accelerated, which would help improve the drug lag. Similarly, if clinical data using Japanese subjects were taken into account in neighboring Asian countries, new molecular entities developed in Japan could be promptly approved in these countries.

In this review, we compare the AFs or genotype frequencies (GFs) of representative functionally-related genetic variations in 8 drug metabolizing enzymes, 2 transporters, and 2 HLAs, mainly between Eastern Asians and Europeans as well as among the 3 major populations in Eastern Asian countries, Japan, Korea, and China. If the AF ranges in the populations among the 3 Eastern Asian countries are similar to those among European countries, the impact of genetic factors on these analyzed genes could be regarded as minimal. In this study, AF (or GF) differences less than 0.1 (in the cases of highest AF or GF $\geq$0.1) or less than 0.05 (in the cases of lowest AF or GF <0.1) were arbitrarily regarded as similar and as having no major impact between countries/regions. We also categorize the population data by country in the Tables since AFs and GFs of several genes may differ for populations with the same racial background; for example, the *NAT2* and *GSTM1/GSTT1* alleles/genotypes in Chinese from mainland China could be different from those of Chinese in Singapore in some cases. However, population names (instead of country names) are used for comparison purposes in the text, since genetic background is largely dependent on race. Note that minority races were excluded from the total data in China or Russia. Countries were assigned to geographical regions on the basis of classifications from the Statistics Division of the United Nations (http://unstats.un.org/unsd/methods/m49/m49regin.htm).

Cytochrome P450s

Most clinical drugs are metabolized by cytochrome P450s (CYPs), the most important phase I enzymes that catalyze the mono-oxygenation of drugs to produce metabolites with altered activity and increased hydrophilicity. It is well known that most of the CYP enzymes have genetic polymorphisms, some of which affect enzyme activity and their transcriptional level and, consequently, may affect drug efficacy or cause adverse drug reactions. In this section, we review population/ethnic differences in functionally established and clinically important genetic polymorphisms of CYPs, CYP2C9, 2C19, 2D6, and 3A5. Nucleotide position numbering and "star allele" nomenclature is utilized according to the home page of the Human Cytochrome P450 Allele Nomenclature Committee (http://www.cypalleles.ki.se).

a) *CYP2C9*: CYP2C9 is involved in the metabolism of many clinically important drugs including phenytoin, oral anticoagulants (*S*-warfarin and *S*-acenocoumarol), antidiabetics (tolbutamide, glibenclamide, glipizide, glyburide, and glimepiride), angiotensin II receptor antagonists (losartan and candesartan), and many nonsteroidal anti-inflammatory drugs (*S*-ibuprofen, diclofenac, tenoxicam, flurbiprofen, and celecoxib).[6] More than 40 allelic polymorphisms of *CYP2C9* have been identified that are associated with decreased enzyme activity (http://www.cypalleles.ki.se/cyp2c9.htm). *CYP2C9*2* (430C>T, Arg144Cys) and *CYP2C9*3* (1075A>C, Ile359Leu), the most common of these polymorphisms, exhibit largely reduced catalytic activity with substrate-dependent manner.[6]

As shown in **Table 1**, the **2* allele is almost absent (AF < 0.001) in Eastern Asians (found only 2 alleles in

Table 1. Frequencies of *CYP2C9* polymorphism in different ethnic populations

Country (Population)			Allele frequency[a] *2 430C>T R144C	Allele frequency[a] *3 1075A>C I359L	Number of subjects[b]	Reference
		Enzyme activity	Decreased	Decreased		
Asia						
	Eastern		**<0.001**	**0.033**	**6,642**	
		Japan	**ND**	**0.029**	**2,559**	
			ND	0.033	724	7)
			ND	0.034	500	8)
			ND	0.021	341	9)
			ND	0.021	259	9)
			ND	0.021	218	10)
			ND	0.018	140	11)
			ND	0.048	105	12)
			ND	0.035	100	12)
			ND	0.033	90	13)
			ND	0.012	82	12)
		Korea	**ND**	**0.036**	**1,527**	
			ND	0.011	574	14)
			ND	0.060	358	15)
			ND	0.051	295	16)
			ND	0.045	200	8)
			ND	0.035	100	12)
		China	**0.001**	**0.037**	**1,979**	
			NT	0.038	711	17)
		(Han)	0.001	0.041	398	8)
		(Han)	0.001	0.036	394	18)
			NT	0.033	376	17)
			ND	0.025	100	12)
		(Inner Mongolia)[c]	ND	0.036	280	19)
		Taiwan	**ND**	**0.027**	**297**	
			ND	0.019	104	20)
			ND	0.026	98	21)
			ND	0.037	95	20)
	South-Eastern		**0.007**	**0.025**	**1,124**	
		Thailand	ND	0.025	242	22)
			ND	0.028	89	23)
		Vietnam (Kinh)	ND	0.022	157	24)
		Malaysia (Malay)	0.013	0.023	304	25)
		(Malay)	0.019	0.024	210	26)
		(Chinese)[d]	ND	0.038	261	25)
		(Chinese)[d]	ND	0.033	165	26)
		(Indian)[d]	0.021	0.097	165	26)
		Indonesia	ND	0.037	122	27)
	Southern		**0.085**	**0.072**	**1,279**	
		India (South)	0.040	0.080	481	28)
		(North)	0.049	0.039	102	29)
		Pakistan	0.008	0.075	120	30)
			0.051	0.154	68	31)
		Iran	0.128	ND	200	32)
			0.109	0.097	160	33)
			0.253	0.098	148	34)
	Western		**0.120**	**0.094**	**891**	
		Lebanon	0.154	0.078	231	35)
			0.112	0.096	161	36)
		Turkey	0.106	0.100	499	37)
Europe						
	Northern		**0.112**	**0.064**	**3,103**	
		Denmark	0.121	0.053	276	38)

Continued on next page.

Continued.

Country (Population)			Allele frequency[a] *2 430C>T R144C	Allele frequency[a] *3 1075A>C I359L	Number of subjects[b]	Reference
		Enzyme activity	Decreased	Decreased		
	Faroe Island		0.088	0.053	311	39)
	Norway		0.099	0.065	309	38)
	Lithuania		0.145	0.048	83	40)
	Sweden		0.110	0.066	1,464	41)
			0.107	0.074	430	42)
	UK		0.157	0.072	230	43)
Western			**0.127**	**0.072**	**839**	
	Germany		0.140	0.051	118	44)
	Austria/Germany		0.119	0.081	165	45)
	Netherlands		0.127	0.069	284	46)
	French		0.149	0.079	151	18)
	Belgium		0.100	0.074	121	47)
Southern			**0.143**	**0.086**	**3,167**	
	Greece		0.129	0.081	283	48)
	Italy		0.125	0.097	360	49)
			0.133	0.080	218	50)
			0.112	0.092	157	51)
			0.170	0.092	147	52)
	Portugal		NT	0.080	129	53)
			0.132	NT	125	53)[f]
	Spain		0.157	0.078	1,092	54)
			0.120	0.062	200	55)
			0.143	0.160	150	56)
			0.156	0.098	102	57)
	Croatia		0.165	0.095	200	58)
	Slovenia		0.120	0.062	129	59)
Eastern			**0.122**	**0.065**	**872**	
	Russia (Russian in European part)		0.119	0.050	352	60)
			0.105	0.067	290	61)
	(Russian in Siberia)		0.121	0.068	87	62)
	(Tuvinian in Siberia)[e]		0.011	0.051	88	62)
	(Buryat in Siberia)[e]		0.023	0.017	88	62)
	(Altaian in Siberia)[e]		0.057	0.092	87	62)
	(Yakut in Siberia)[e]		0.011	0.006	88	62)
	Hungary		0.164	0.094	143	63)
Caucasians			**0.140**	**0.064**	**1,742**	
	Caucasian		0.159	0.057	454	8)
			0.128	0.063	292	64)
			0.151	0.057	212	65)
			0.133	0.056	142	12)
			0.132	0.043	140	66)
	Ashkenazi Jewish		0.128	0.083	502	65)
Africans			**0.022**	**0.018**	**688**	
	African-American		0.028	0.020	300	65)
			0.013	0.019	268	64)
			0.025	0.013	120	66)

ND: not detected. NT: not tested.
The base A in the initiation codon ATG is denoted +1.
[a]The total allele frequency in each population/region is calculated by dividing the sum of the each allele number by the total allele number in the population/region (including ND but not NT).
[b]The subtotal number in each population/region is simply the sum of the subject numbers.
[c]Excluded from the total population data in China.
[d]Excluded from total data in the South-Eastern Asia region.
[e]Excluded from total data in the Eastern Europe region.
[f]Same subjects contained in above 129 subjects were analyzed, and thus excluded from the total number of subjects in Southern Europe.

Chinese). Similarly, the frequency of *2 is very low (0.007) in South-Eastern Asians. In contrast, the frequency of the *2 allele in Europeans ranges from 0.112 (Northern) to 0.143 (Southern), which is more than 0.1 higher than that in Eastern/South-Eastern Asians. The frequency of *3 in Eastern Asians is 0.033, which is similar to that in South-Eastern Asians (0.025). Europeans have a slightly higher *3 frequency (from 0.064 in Northern to 0.086 in Southern) than Eastern/South-Eastern Asians. The frequencies of *2 and *3 in Southern and Western Asians are quite similar to those in Europeans. Differences of *3 frequency in the populations among the 3 major Eastern Asian countries (Japan, Korea, China) are very small (AF $\leq$ 0.01) and are lower than that among the 4 European sub-regions (AF $\leq$ 0.022).

b) *CYP2C19*: CYP2C19, another member of the CYP2C subfamily, metabolizes many commonly used drugs, including anticonvulsants such as *S*-mephenytoin, proton-pump inhibitors such as omeprazole, the antiplatelet clopidogrel, and the anxiolytic diazepam.[67,68] More than 30 allelic polymorphisms have been identified that are associated with decreased, increased, or unaltered enzymatic activity (http://www.cypalleles.ki.se/cyp2c19.htm). About 15 to 25% of the Eastern Asian populations are poor metabolizers (PMs) of *S*-mephenytoin, whereas the PM frequency in Caucasians is less than 5%.[8] The PM phenotype is caused by the *CYP2C19*2* (681G>A, splicing defect) and *CYP2C19*3* (636G>A, W212X, premature stop codon) polymorphisms. *CYP2C19*17*, on the other hand, was reported to be associated with increased gene transcription linked to −806C>T causing ultra-rapid activity.[89] However, the magnitude of this effect seems to be considerably smaller than that of the *2 and *3 alleles.[69]

As shown in **Table 2**, the frequency of *2 in Eastern Asians (AF = 0.286), which ranges from 0.275 (Korean) to 0.293 (Japanese), is more than 0.1 higher than in Europeans, which ranges from 0.122 (Eastern) to 0.161 (Northern). Thus, the largest difference in *2 frequency (0.018, Japanese vs. Korean) in the populations among the 3 major Eastern Asian countries (Japan, Korea, China) is less than that among the 4 European sub-regions (0.039, Eastern vs. Northern). The *2 frequencies in South-Eastern (0.289) and Southern Asians (0.298) are almost identical to that in Eastern Asians, but are >0.1 higher than that in Western Asians (0.124), which is rather similar to that in Europeans. The AF of *3 in Eastern Asians (0.088) is >0.05 higher than that in Europeans (~0.001). In addition, the *3 allele varies in frequency among Eastern Asian populations, with the frequency in Chinese (0.042) differing by over 0.05 compared to that in Japanese (0.124). Thus, *CYP2C19*3* could be important for population differences in CYP2C19-catalyzed drugs among Eastern Asian countries. However, combining the two null *2 and *3 frequencies, the largest AF difference is 0.083 between Chinese (0.334) and Japanese (0.417), which is within our current criteria for significance (less than 0.1 in the case of $\geq$0.1 AF). The *3 frequency in South-Eastern Asians (0.041) is similar to that in Chinese (0.042). The frequencies of *3 gradually decrease from Southern (0.028) to Western (0.012) Asians and reach rarity in Europeans, at most 0.002 in Eastern Europeans. The frequencies of *17 in Europeans, which range from 0.190 (Northern) to 0.272 (Eastern), is more than 0.1 higher than that in Eastern Asians (0.011). Only a slight difference in frequency ($\leq$0.002) is observed among Eastern Asians.

c) *CYP2D6*: CYP2D6 metabolizes a large number of clinically important drugs such as anti-arrythmics (propafenone and mexiletine), psychiatrics (risperidone and haloperidol), anti-histamines (promethazine and chlorpheniramine), and anti-depressants (nortriptyline and clomipramine).[98,99] The *CYP2D6* gene is extremely polymorphic, with more than 130 different alleles having been reported (http://www.cypalleles.ki.se/cyp2d6.htm). Some of these alleles are associated with increased, decreased, or the absence of enzyme activity. According to the combination of *CYP2D6* alleles, subjects can be categorized into poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra-extensive (ultra-rapid) metabolizers (UMs) of CYP2D6 drugs. The PM phenotype results from two nonfunctional alleles including *3, *4 and *5, whereas the EM phenotype generally results from one or two alleles with normal function including *1 and *2. The IM phenotype is usually observed in persons having one null allele and one defective allele with impaired expression and/or function such as *10, or two defective alleles. The UM phenotype is explained by having duplication or multiplication of the active *CYP2D6* gene.[98,99] Approximately 7 to 10% of European Caucasians and 1% of Eastern Asians have been reported to be PMs.[99]

As shown in **Table 3**, the *2 allele varies in frequency among Asian sub-regional populations (Eastern/South-Eastern vs. Southern/Western) and between Eastern/South-Eastern Asians and Northern/Western Europeans with differences more than 0.2, but it seems to have no impact on PK/PD because *2 exhibits wild-type function. The *CYP2D6*3* allele is not detected in populations from the Eastern to Southern Asian regions, but is present in Europeans with frequencies ranging from 0.009 (Eastern) to 0.017 (Western). The frequency of the *4 allele is also rare (AF = 0.003) in Eastern Asians, ranging from 0.002 (China) to 0.004 (Korea); however, it gradually increases from South-Eastern (0.014), Southern (0.071) and Western (0.119) Asians, to reach greater than 0.15 in Europeans, which range from 0.160 (Southern) to 0.236 (Northern). Thus, more than a 0.1 difference in *4 frequency is observed between Eastern/South-Eastern Asians and Europeans. The null allele *CYP2D6*5* is detected at almost the same frequencies within Eastern Asians (0.059, ranging from 0.058 to 0.060) as well as within the 4 European sub-regional populations [ranging from 0.021 (Southern) to 0.037 (Northern)]. The frequency in Southern (0.017) and

Table 2. Frequencies of *CYP2C19* polymorphism in different ethnic populations

Country (Population)			Allele frequency[a] *2 681G>A splicing defect	*3 636G>A W212X	*17 −806C>T Increased transcription	Number of subjects[b]	Reference
		Enzyme activity	None	None	Increased		
Asia							
	Eastern		**0.286**	**0.088**	**0.011**	**4,627**	
		Japan	**0.293**	**0.124**	**0.011**	**1,944**	
			0.303	0.131	NT	500	8)
			0.279	0.128	0.013	265	70)
			0.274	0.108	NT	217	71)
			0.287	0.132	NT	186	72)
			0.350	0.111	NT	140	11)
			0.276	0.119	NT	134	73)
			0.256	0.139	NT	119	73)
			0.262	0.100	0.010	105	12)
			0.345	0.090	0.005	100	12)
			0.271	0.156	NT	96	74)
			0.331	0.133	0.012	82	12)
		Korea	**0.275**	**0.088**	**0.012**	**1,202**	
			0.283	0.076	NT	377	75)
			0.284	0.101	0.015	271	76)
			0.286	0.074	NT	200	8)
			0.280	0.110	0.003	150	77)
			0.221	0.096	NT	104	78)
			0.250	0.080	0.015	100	12)
		China	**0.292**	**0.042**	**0.010**	**1,008**	
			0.455	0.045	NT	121	74)
			0.297	0.035	0.005	100	12)
		(Han)	0.249	0.034	0.012	384	79)
		(Han)	0.257	0.052	NT	202	80)
		(Han)	0.366	0.074	NT	101	80)
		(Han)	0.255	0.020	NT	100	81)
		(Inner Mongolia)[c]	0.243	0.043	NT	280	19)
		(Dai)[c]	0.303	0.034	NT	193	82)
	South-Eastern		**0.289**	**0.041**	**NT**	**1,480**	
		Thailand	0.29	0.03	NT	774	83)
			0.351	0.050	NT	121	74)
		Myanmer (Burmese)	0.30	0.04	NT	127	83)
		(Karen)	0.28	0.01	NT	131	83)
		Vietnam	0.264	0.049	NT	165	75)
		(including 3 Thai origin)	0.236	0.139	NT	90	74)

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Continued.

Country (Population)			Allele frequency[a] *2 681G>A splicing defect	*3 636G>A W212X	*17 −806C>T Increased transcription	Number of subjects[b]	Reference
		Enzyme activity	None	None	Increased		
			0.306	0.063	NT	72	84)
		Singapore (Han Chinese)[d]	0.307	0.045	NT	398	8)
	Southern		**0.298**	**0.028**	**NT**	**1,580**	
		India (South)	0.350	0.010	NT	453	28)
		(North)	0.262	0.040	NT	300	85)
		(North)	0.420	0.077	NT	300	85)
		(Tamilian)	0.379	0.022	NT	112	86)
		Pakistan	0.272	NT	NT	68	31)
		Iran	0.140	ND	NT	200	32)
			0.126	0.007	NT	147	34)
	Western		**0.124**	**0.012**	**NT**	**565**	
		Lebanon	0.130	0.031	NT	161	87)
		Turkey	0.121	0.004	NT	404	88)
Europe							
	Northern		**0.161**	**ND**	**0.190**	**1,625**	
		Denmark	0.150	NT	0.201	276	38)
		Norway	0.152	NT	0.220	309	38)
		Faroe Island	0.187	ND	0.154	311	39)
		Sweden	NT	NT	0.180	314	89)
			0.16	ND	0.20	185	77)
		UK	0.152	NT	NT	230	43)
	Western		**0.140**	**0.001**	**0.257**	**1,637**	
		Germany	0.159	0.002	NT	328	88)
			0.152	ND	0.255	237	90)
			0.152	ND	0.257	186	90)
		Netherlands	0.133	0.002	NT	765	91)
		Belgium	0.091	ND	NT	121	47)
	Southern		**0.128**	**<0.001**	**0.196**	**1,599**	
		Greece	0.1307	ND	NT	283	48)
			NT	NT	0.1961	283	92)
		Italy	0.111	ND	NT	360	49)
			0.106	ND	NT	218	50)
		Portugal	0.140	NT	NT	126	53)
		Croatia	0.15	ND	NT	200	58)

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Continued.

Country (Population)		Allele frequency[a] *2 681G>A splicing defect	*3 636G>A W212X	*17 −806C>T Increased transcription	Number of subjects[b]	Reference
	Enzyme activity	None	None	Increased		
	Slovenia	0.159	0.004	NT	129	59)
Eastern		**0.122**	**0.002**	**0.272**	**854**	
	Russia (Russian in European part)	0.131	NT	NT	352	60)
	(Russian in European part)	0.114	0.003	NT	290	61)
	(Russian in Siberia)	0.122	ND	NT	87	62)
	(Tuvinian in Siberia)[c]	0.148	0.023	NT	88	62)
	(Buryat in Siberia)[c]	0.210	0.068	NT	88	62)
	(Yakut in Siberia)[c]	0.233	0.046	NT	88	62)
	(Altaian in Siberia)[c]	0.149	0.04	NT	87	62)
	Poland	0.116	ND	0.272	125	93)
Caucasians		**0.145**	**<0.001**	**0.188**	**5,529**	
	Caucasian	0.142	ND	NT	3,938	94)
		0.169	NT	0.180	615	95)
		0.15	0.001	NT	454	8)
		0.127	0.009	NT	273	96)
		0.136	ND	0.201	142	12)
		NT	NT	0.22	107	97)
Africans		**0.185**	**0.004**	**0.235**	**927**	
	African-American	0.183	0.001	NT	478	94)
		0.182	0.008	NT	236	96)
		NT	NT	0.21	114	97)
	African-Brazilian	0.202	NT	0.263	99	95)

ND: not detected. NT: not tested.
The base A in the initiation codon ATG is denoted +1 and the base before A is numbered −1.
[a]The total allele frequency in each population/region is calculated by dividing the sum of the allele number by the total allele number in the population/region (including ND but not NT).
[b]The subtotal number in each population/region is simply the sum of the subject numbers.
[c]Excluded from the total population data in China.
[d]Excluded from total data in the South-Eastern Asia region.
[e]Excluded from total data in the Eastern Europe region.

Western (0.015) Asians is rather similar to that in Europeans. In contrast to **4*, the frequency of the **10* allele is high in Eastern Asians (0.443) ranging from 0.379 (Japanese) to 0.526 (Chinese) and also in South-Eastern Asians (0.521); however, it gradually decreases in Southern (0.121) and Western (0.061) Asians, and reaches a much lower level in Europeans (0.015 in Germany and 0.042 in Russia). Therefore, over a 0.3 difference in frequency is present between Eastern/South-Eastern Asians and Europeans. Among the 3 major Eastern Asian populations, only *CYP2D6*10* has over a 0.1 frequency difference between Japanese and Chinese (0.147, 1.39-fold difference), and thus, attention whould be paid to the *CYP2D6*10*-associated IM phenotype. It is noteworthy that the differences in **10* frequencies are less than 0.1 between Japanese and Koreans (0.076) as well as between Koreans and Chinese (0.071).

d) *CYP3A5*: CYP3A5 metabolizes a broad range of structurally diverse therapeutic compounds, including calcium channel blockers (*e.g.*, amlodipine), benzodiazepines (*e.g.*, midazolam), and calcineurin inhibitors (*e.g.*, tacroli-

Table 3. Frequencies of *CYP2D6* polymorphism in different ethnic populations

Country (Population)			Enzyme activity	Allele frequency[a] *2 major SNPs/alterations: 2850C>T 4180G>C R296C S486T; Normal	*3 2549delA 259 Frame shift; None	*4 1846G>A splicing defect; None	*5 *CYP2D6* deleted; None	*6 1707delT 118 Frame shift; None	*10 100C>T P34S; Decreased	*14 1758G>A G169R; Decreased	*21 2573_2574 insC 267 Frame shift; None	*36 Gene conversion to *CYP2D7* in exon 9; None	(*1) × 2[b] Duplication;	*2 × 2 Duplication; Increased	*4 × 2 Duplication; None	*10 × 2 Duplication; Decreased	Number of subjects[c]	Reference
Asia																			
	Eastern			**0.110**	**ND**	**0.003**	**0.059**	**<0.001**	**0.443**	**0.006**	**0.004**	**0.010**	**0.004**	**0.006**	**ND**	**0.005**	**4,089**	
		Japan		**0.111**	**ND**	**0.003**	**0.058**	**ND**	**0.379**	**0.003**	**0.006**	**0.010**	**0.005**	**0.005**	**ND**	**0.008**	**1,600**	
				0.100	ND	0.001	0.051	ND	0.378	0.001	0.006	NT	NT	NT	NT	NT	500	8)
				0.128	NT	0.004	0.057	NT	0.341[d]	0.003	0.005	0.004[f]	0.005	0.004	NT	0.005	455	100)
				0.129	ND	ND	0.062	NT	0.386	0.022	NT	NT	NT	NT	NT	NT	162	101)
				NT	ND	0.005	0.071	ND	0.433	ND	ND	ND	0.005	ND	ND	0.010	105	12)
				NT	ND	0.005	0.070	ND	0.435	0.005	0.005	ND	0.005	0.01	ND	0.015	100	12)
				0.077	NT	0.005	0.071	NT	0.413[e]	NT	0.010	NT	0.005	NT	NT	0.005	98	102)
				0.092	NT	0.005	0.061	NT	0.408	NT	0.010	NT	NT	NT	NT	NT	98	103)
				NT	ND	ND	0.048	ND	0.373	ND	ND	0.012	ND	0.012	ND	0.012	82	12)
		Korea		**0.104**	**ND**	**0.004**	**0.060**	**ND**	**0.455**	**0.006**	**0.003**	**0.020**	**0.001**	**0.008**	**ND**	**0.004**	**1,458**	
				0.101	NT	NT	0.056	NT	0.456	0.003	0.003	NT	0.001	0.010	NT	0.004	758	104)
				0.101	ND	0.003	0.061	ND	0.450	0.005	0.003	NT	0.001	0.005	ND	0.005	400	105)
				0.121	ND	0.008	0.062	ND	0.441	0.005	0.005	NT	NT	NT	NT	NT	200	8)
				NT	ND	0.005	0.075	ND	0.505	0.030	ND	0.020	0.005	0.005	ND	ND	100	12)
		China		**0.095**	**ND**	**0.002**	**0.060**	**<0.001**	**0.526**	**0.013**	**0.003**	**0.005**	**0.006**	**0.004**	**ND**	**0.004**	**1,031**	
				0.080	NT	ND	0.046	NT	0.647	ND	NT	NT	NT	NT	NT	NT	119	106)
				NT	ND	ND	0.064	ND	0.530	0.005	0.005	ND	0.005	ND	ND	0.005	100	12)
			(Han)	0.111	ND	0.001	0.047	ND	0.525	0.013	ND	NT	0.006	0.004	NT	0.004	400	107)
			(Han)	NT	ND	0.002	0.072	ND	0.513	0.020	NT	NT	0.011	NT	NT	0.002	223	108)
			(Han)	0.014	NT	0.010	0.070	0.005	0.490	0.015	0.005	0.010	NT	0.005	NT	NT	100	81)
			(Han)	0.135	NT	NT	0.096	NT	0.438	0.011	0.011	NT	ND	ND	NT	ND	89	109)
	South-Eastern			**0.078**	**NT**	**0.014**	**0.070**	**NT**	**0.521**	**0.012**	**ND**	**NT**	**ND**	**ND**	**NT**	**ND**	**194**	
		Vietnam (Kinh)		0.078	NT	NT	0.061	NT	0.570	0.012	ND	NT	ND	ND	NT	ND	122	109)

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Country (Population)			Allele frequency[a]														
			*2	*3	*4	*5	*6	*10	*14	*21	*36	(*1) × 2[b]	*2 × 2	*4 × 2	*10 × 2		
			major SNPs/alterations responsible for the phenotype of the corresponding allele													Number of subjects[c]	Reference
			2850C>T 4180G>C R296C S486T	2549delA 259 Frame shift	1846G>A splicing defect	*CYP2D6* deleted	1707delT 118 Frame shift	100C>T P34S	1758G>A G169R	2573_2574 insC 267 Frame shift	Gene conversion to *CYP2D7* in exon 9	Duplication	Duplication	Duplication	Duplication		
		Enzyme activity	Normal	None	None	None	None	Decreased	Decreased	None	None		Increased	None	Decreased		
		(including 3 Thai origin)	NT	NT	0.014	0.080	NT	0.435	NT	NT	NT	NT	NT	NT	NT	72	84)
		Singapore (Han Chinese)[g]	0.110	ND	0.011	0.061	ND	0.484	0.011	0.003	NT	NT	NT	NT	NT	398	8)
	Southern		**0.348**	**ND**	**0.071**	**0.017**	**NT**	**0.121**	**ND**	**NT**	**NT**	**NT**	**NT**	**NT**	**NT**	**553**	
		India (South)	0.348	ND	0.073	0.019	NT	0.102	ND	NT	NT	NT	NT	NT	NT	447	110)
		(Tamilian)	NT	ND	0.066	0.009	NT	0.203	NT	NT	NT	NT	NT	NT	NT	106	111)
	Western		**0.353**	**0.006**	**0.119**	**0.015**	**0.007**	**0.061**	**ND**	**NT**	**NT**	**0.036**	**0.020**	**0.003**	**NT**	**544**	
		Turkey	0.353	ND	0.113	0.015	0.007	0.061	ND	NT	NT	0.036	0.020	0.003	NT	404	88)
			NT	0.025	0.139	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	140	112)
Europe																	
	Northern		**0.312**	**0.014**	**0.236**	**0.037**	**0.008**	**NT**	**NT**	**NT**	**NT**	**0.007**	**0.011**	**0.008**	**NT**	**1,511**	
		Denmark	NT	0.013	0.219	0.038	0.006	NT	NT	NT	NT	0.015	NT	NT	NT	228	113)
		Faroe Island	NT	0.002	0.334	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	309	39)
		Norway	NT	0.003	0.205	0.023	0.003	NT	NT	NT	NT	NT	0.017	NT	NT	151	114)
			NT	ND	0.211	0.060	0.018	NT	NT	NT	NT	NT	NT	NT	NT	83	115)
		Sweden	0.324	0.014	0.244	0.043	0.009	NT	NT	NT	NT	NT	NT	NT	NT	281	116)
			0.297	0.031	0.185	0.031	0.008	NT	NT	NT	NT	0.001	0.018	0.006	NT	254	117)
			0.315	0.024	0.193	0.039	0.007	NT	NT	NT	NT	0.005	ND	0.010	NT	205	117)
	Western		**0.324**	**0.017**	**0.193**	**0.022**	**0.011**	**0.015**	**ND**	**NT**	**NT**	**0.005**	**0.013**	**0.001**	**NT**	**1,677**	
		Germany	0.324	0.020	0.207	0.020	0.009	0.015	ND	NT	NT	0.005	0.013	0.001	NT	589	118)
			NT	0.009	0.186	0.026	0.031	NT	NT	NT	NT	NT	NT	NT	NT	323	119)
		Netherlands	NT	0.018	0.184	NT	0.004	NT	NT	NT	NT	NT	NT	NT	NT	765	91)
	Southern		**0.040**	**0.015**	**0.160**	**0.021**	**0.013**	**NT**	**NT**	**NT**	**NT**	**NT**	**NT**	**NT**	**NT**	**1,450**	
		Greece	NT	0.023	0.1784	NT	0.019	NT	NT	NT	NT	NT	NT	NT	NT	283	48)

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Country (Population)			Allele frequency[a]														
			*2	*3	*4	*5	*6	*10	*14	*21	*36	(*1) × 2[b]	*2 × 2	*4 × 2	*10 × 2		
			major SNPs/alterations responsible for the phenotype of the corresponding allele													Number of subjects[c]	Reference
			2850C>T 4180G>C R296C S486T	2549delA 259 Frame shift	1846G>A splicing defect	*CYP2D6* deleted	1707delT 118 Frame shift	100C>T P34S	1758G>A G169R	2573_2574 insC 267 Frame shift	Gene conversion to *CYP2D7* in exon 9	Duplication	Duplication	Duplication	Duplication		
		Enzyme activity	Normal	None	None	None	None	Decreased	Decreased	None	None		Increased	None	Decreased		
		Italy	NT	0.007	0.153	0.034	0.014	NT	NT	NT	NT	NT	NT	NT	NT	360	49)
			NT	0.009	0.161	0.018	0.009	NT	NT	NT	NT	NT	NT	NT	NT	218	50)
		Portugal	NT	0.014	0.133	0.028	0.018	NT	NT	NT	NT	NT	NT	NT	NT	100	120)
		Spain	NT	0.016	0.184	0.011	0.005	NT	NT	NT	NT	NT	NT	NT	NT	185	121)
		(La Alpujarra)	NT	0.010	0.159	0.014	ND	NT	NT	NT	NT	NT	NT	NT	NT	104	121)
		Croatia	0.040	0.0275	0.140	0.010	0.015	NT	NT	NT	NT	NT	NT	NT	NT	200	58)
	Eastern		**NT**	**0.009**	**0.175**	**0.024**	**0.012**	**0.042**	**NT**	**NT**	**NT**	**0.017**	**0.005**	**NT**	**NT**	**642**	
		Russia (European part)	NT	0.009	0.169	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	352	60)
		(European part)	NT	0.01	0.182	0.024	0.012	0.042	NT	NT	NT	0.017	0.005	NT	NT	290	61)
Caucasians			**0.176**	**0.018**	**0.205**	**0.025**	**0.011**	**0.018**	**ND**	**ND**	**<0.001**	**0.006**	**0.006**	**0.001**	**<0.001**	**4,579**	
			0.159	0.018	0.210	0.023	0.011	0.010	NT	NT	<0.001	0.007	0.005	0.001	<0.001	3,779	94)
			0.251	0.022	0.188	0.033	0.017	0.028	ND	ND	NT	NT	NT	NT	NT	454	8)
			0.330	0.010	0.179	0.039	0.010	0.020	ND	NT	NT	0.002	0.007	0.002	NT	204	122)
			NT	0.021	0.182	0.017	0.021	0.196	ND	ND	ND	ND	0.014	0.007	ND	142	12)
Africans			**0.160**	**0.002**	**0.057**	**0.033**	**0.002**	**0.042**	**ND**	**ND**	**0.006**	**0.009**	**0.014**	**0.017**	**ND**	**953**	
	African-American		0.060	0.002	0.055	0.028	0.002	0.038	NT	NT	0.006	0.008	0.012	0.024	ND	452	94)
			0.191	0.002	0.054	0.066	0.004	0.036	ND	NT	NT	0.012	0.016	0.003	NT	251	122)
			0.309	ND	0.061	0.010	ND	0.057	ND	ND	NT	NT	NT	NT	NT	250	8)

ND: not detected. NT: not tested.

The base A in the initiation codon ATG is denoted +1 and the base before A is numbered −1.

[a]The total allele frequency in each population/region is calculated by dividing the sum of the each allele number by the total allele number in the population/region (including ND but not NT).

[b]*(*1) × 2* denotes alleles not identified as the other duplicated alleles.

[c]The subtotal number in each population/region is simply the sum of the subject numbers.

[d]Including **10-*36* and **10-*36-*36* alleles.

[e]Including **10-*36* allele.

[f]Calculated from **36-*36* allele.

[g]Excluded from total data in the South-Eastern Asia region.

mus).[99] Many drugs metabolized by CYP3A5 are also substrates of CYP3A4, and distinguishing the relative contribution of each isoform in drug metabolism is difficult.[99] Therefore, the metabolic rates of CYP3A drugs measured *in vivo* are likely to reflect the combined activities of CYP3A4 and CYP3A5.[123] Many variant alleles have been identified in the *CYP3A4* (http://www.cypalleles.ki.se/cyp3a4.htm) and *CYP3A5* genes (http://www.cypalleles.ki.se/cyp3a5.htm), although functional alleles are relatively infrequent except for *CYP3A5*3*, which produces a truncated protein without catalytic activity.[99,123]

As shown in **Table 4**, the frequencies of *CYP3A5*3* in Eastern Asians (AF = 0.761), which range from 0.737 (Chinese) to 0.762 (Japanese), are lower (more than 0.2 in frequency) than those in Europeans, which range from 0.922 (Northern) to 0.932 (Eastern). The AF difference (0.025) in populations among the 3 major Eastern Asian countries (Japan, Korea, China) was higher than that (0.010) among the 4 European sub-regions, but is less than 0.1. The **3* frequencies in South-Eastern (0.657) and Southern (0.648) Asians are more than 0.1 and 0.25 lower than those in Eastern Asians and Europeans, respectively.

Other Drug Metabolizing Enzymes

a) *UGT1A1*: Glucuronidation, catalyzed by UDP-glucuronosyltransferases (UGTs), is one of the critical steps in the detoxification and elimination of various endogenous and exogenous compounds.[153] Glucuronidation accounts for about 35% of phase II drug metabolism.[154] Of the 9 active UGT1As, UGT1A1 is known to be the principal isoform for glucuronidation of bilirubin, SN-38, an active metabolite of the anti-cancer drug irinotecan,[155] the HIV enzyme inhibitor raltegravir, the anti-osteoporosis drug bazedoxifene, and the thrombopoietin receptor agonist eltrombopag.

Several genetic polymorphisms that are relatively common for *UGT1A1* are involved in altered drug metabolism. The A(TA)$_n$TAA 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; $n = 7$, **28*; $n = 8$, **37*). *In vitro* and *in vivo* studies have shown that increasing the TA repeat number leads to a decrease in the transcriptional activity of *UGT1A1*. Given the transcriptional activity of $n = 6$ is defined as 100%, the activities of $n = 5$, 7, and 8 are approximately 130%, 65%, and 50%, respectively.[156] Another *1A1* polymorphism 211G>A (G71R, **6* allele) in exon 1 has reduced metabolic activity for SN-38.[157] *UGT1A1*28* and/or **6* is known to be associated with an increased risk of SN-38 induced severe neutropenia.[158] Genotyping tests are now available for **28* in the US and **28* and **6* in Japan in order to reduce the occurrence of adverse reactions.[158] Because the allele frequencies of **36* and **37* have not been detected/reported in the populations of Asian countries (**Table 5**), we confine our review to **28* and **6* frequencies in this section.

For **28* (**Table 5**), the AFs in Eastern Asians (AF = 0.139) are very similar to those in South-Eastern Asians (0.140), but are lower than those in Southern (0.465) and Western (0.296) Asians as well as those in Europeans (*ca.*, 0.33). Thus, the AF difference between Eastern/South-Eastern Asians and Europeans is >0.15. The largest AF difference among the 3 Eastern Asian populations [between Japanese (0.110, lowest of Eastern Asians) and Chinese (0.127, highest)] is 0.017 (less than 0.1), which is smaller than that among European populations (0.026) [between Northern (0.318, lowest in Europeans) and Eastern (0.344, highest)]. For the **6* allele (**Table 6**), this polymorphism has been known to be almost specific for Asians, and its frequency is highest in Eastern Asians (0.183), followed by South-Eastern Asians (0.051) and is more than 0.15 lower in Europeans (0.003). The largest AF difference in the population among the 3 Eastern Asian countries [between Japanese (0.155, lowest) and Koreans (0.220, highest)] is 0.065. Thus, the largest AF differences of *UGT1A1*28* and **6* in the populations of the three Eastern Asian countries are less than 0.1 and thus, these differences could be regarded as minimal.

b) *NAT2*: In humans, the *NAT1* and *NAT2* genes, both located in chromosome 8p22, are responsible for *N*-acetyltransferase activities. The NAT2 enzyme catalyzes acetylation of numerous arylamine- and hydrazine-containing drugs including isoniazid and sulfamethoxazole.[193]

NAT2 is a highly polymorphic enzyme, and individuals can be divided into rapid, intermediate, and slow acetylator phenotypes based on the genetic polymorphisms of this gene. *NAT2*4* is defined as wild-type, and major variant halplotypes *NAT2*5*, **6*, and **7* bear 341T>C (I114T), 590G>A (R197Q) and 857G>A (G286E) substitutions, respectively.[193] Acetylation activities *in vitro* are ranked for several substrates as follows: *NAT2*4>NAT2*7>NAT2*6>NAT2*5*.[193,194] The I114T substitution in *NAT2*5* yields *ca.* a 90% reduction of acetylation activity for sulfamethazine.[195] In addition, **14* (with 191G>A, R64Q) is associated with reduced acetylation activities, but its frequency is relatively high only in Africans.[196]

Only the **5*, **6* and **7* alleles were analyzed in many older papers, and therefore, the frequencies of **5*, **6*, and **7* are compared for Asians and Europeans. In some very old papers marked in **Table 7**, **5* was genotyped by 481C>T, but this polymorphism is not included in *NAT2*5C-E* but is included in *NAT2*11* and **12C*. Although *NAT2*5C* is relatively frequent in Europeans (AF: 0–0.04), it has no major impact on the total **5* frequencies as shown in **Table 7** (less than 6% of the **5* frequencies).[196] No *NAT2*5C* was detected in South-Eastern or Eastern Asians.[196] In addition, the frequencies of the other *NAT2* alleles are very low (below 0.001).[196] *NAT2*14* subtypes **14C/*14F* and **14D* also have 341T>C (a tag for **5*) and 590G>A (a tag for **6*), respectively, and thus, the frequencies of **5* and **6* might be overestimated when **14*

Table 4. Frequencies of *CYP3A5* polymorphism in different ethnic populations

Country (Population)			Allele frequency[a] *3 6986A>G splicing defect	Number of subjects[b]	Reference
		Enzyme activity	None		
Asia					
	Eastern		**0.761**	**3,829**	
		Japan	**0.762**	**1,478**	
			0.787	402	124)
			0.720	402	124)
			0.768	200	125)
			0.759	187	126)
			0.810	105	12)
			0.780	100	12)
			0.741	82	12)
		Korea	**0.759**	**473**	
			0.765	194	127)
			0.740	104	78)
			0.755	100	12)
			0.826	46	128)
			0.690	29	129)
		China	**0.737**	**883**	
			0.778	302	130)
			0.724	203	131)
		(Han)	0.727	165	132)
		(Han)	0.673	113	133)
			0.723	100	12)
		(Tibetan)[c]	0.807	257	133)
		(Uygur)[c]	0.848	161	132)
		(Wa)[c]	0.563	142	133)
		(Bai)[c]	0.702	129	133)
		(Kazakh)[c]	0.845	110	133)
		(Kazakh)[c]	0.866	108	132)
		(Uygur)[c]	0.881	88	133)
	South-Eastern		**0.657**	**490**	
		Thailand	0.669	320	134)
		Vietnam (including 3 Thai origin)	0.667	72	84)
		Singapore (Malay)	0.61	98	135)
		(Chinese)[d]	0.76	108	135)
		(Indian)[d]	0.59	90	135)

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Country (Population)			Allele frequency[a] *3 6986A>G splicing defect	Number of subjects[b]	Reference
		Enzyme activity	None		
	Southern		**0.648**	**744**	
		India (South)	0.635	544	136)
			0.683	200	137)
Europe					
	Northern		**0.922**	**2,576**	
		Denmark	0.948	203	138)
		Finland	0.91	754	139)
			0.93	726	139)
		Sweden	0.919	663	140)
		UK	0.926	230	43)
	Western		**0.931**	**3,447**	
		Germany	0.942	1,084	141)
			0.928	782	142)
			0.938	428	142)
			0.928	237	90)
			0.889	186	90)
		Netherlands	0.917	500	143)
			0.928	124	144)
		France	0.948	106	145)
	Southern		**0.923**	**1,550**	
		Greece	0.9435	283	48)
		Italy	0.933	218	50)
		Portugal	0.875	132	53)
		Spain	0.921	574	146)
			0.914	204	147)
		Bosnia Herzegovina	0.932	139	148)
	Eastern		**0.932**	**287**	
		Russian (Siberia)	0.916	87	62)
		(Tuvinian in Siberia)[c]	0.856	88	62)
		(Buryat in Siberia)[c]	0.822	88	62)
		(Yakut in Siberia)[c]	0.926	88	62)
		(Altaian in Siberia)[c]	0.894	87	62)
		Poland	0.940	200	149)
Caucasians			**0.955**	**142**	

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Country (Population)		Allele frequency[a] *3 6986A>G splicing defect	Number of subjects[b]	Reference
	Enzyme activity	None		
	Caucasian	0.955	142	12)
Africans		**0.318**	**665**	
	South Africa	0.145	320	150)
	African-American	0.357	245	151)
	Zimbabwe	0.776	100	152)

The base A in the initiation codon ATG is denoted +1.
[a]The total allele frequency in each population/region is calculated by dividing the sum of the each allele number by the total allele number in the population/region.
[b]The subtotal number in each population/region is simply the sum of the subject numbers.
[c]Excluded from the total population data of China.
[d]Excluded from total data in the South-Eastern Asia region.
[e]Excluded from total data in the Eastern Europe region.

Table 5. Frequencies of TATA box polymorphism of *UGT1A1* in different ethnic populations

Country (Population)	Allele frequency[a] *36 $A(TA)_5TAA$	*28 $A(TA)_7TAA$	*37 $A(TA)_8TAA$	Number of subjects[b]	Reference
	Increased transcription	Reduced transcription	Reduced transcription		
Enzyme activity	Increased	Decreased	Decreased		
Asia					
Eastern		**0.139**		**4,443**	
Japan		**0.110**		**634**	
	ND	0.097	ND	150	159)
	ND	0.086	ND	116	160)
	ND	0.090	ND	67	161)
	ND	0.130	ND	301	162)
Korea		**0.115**		**405**	
	ND	0.127	ND	324	163)
	ND	0.068	ND	81	164)
China		**0.127**		**1,378**	
(Han)	ND	0.118	ND	539	165)
(Han)	NT	0.134	NT	789	166)
(Hong Kong)	ND	0.130	ND	50	167)
(Dong)[c]	ND	0.153	ND	273	165)
(She)[c]	ND	0.078	ND	264	165)
(Uyghur)[c]	NT	0.168	NT	769	166)
(Kazak)[c]	NT	0.211	NT	502	166)

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Country (Population)		Allele frequency[a] *36 A(TA)$_5$TAA Increased transcription Increased	*28 A(TA)$_7$TAA Reduced transcription Decreased	*37 A(TA)$_8$TAA Reduced transcription Decreased	Number of subjects[b]	Reference
	Taiwan	ND	0.124	ND	218	168)
South-Eastern			**0.140**		**527**	
	Thailand	ND	0.156	ND	96	169)
		ND	0.118	ND	76	167)
	Vietnam	ND	0.084	ND	83	167)
	Philippines (in US)	ND	0.122	ND	37	170)
	Myanmar	ND	0.172	ND	32	167)
	Malaysia	ND	0.080	ND	50	171)
	Singapore					
	(Chinese)[d]	ND	0.157	ND	89	172)
	(Malay)	ND	0.188	ND	93	172)
	(Indian)[d]	ND	0.351	ND	84	172)
	Indonesia	ND	0.192	ND	60	167)
Southern			**0.465**		**374**	
	Bangladesh	ND	0.481	ND	26	167)
	India	ND	0.408	ND	119	167)
	Sri Lanka	ND	0.493	ND	229	167)
Western			**0.296**		**103**	
	Yemen	ND	0.254	ND	61	167)
	Lebanon	ND	0.357	ND	42	167)
Europe						
Northern			**0.318**		**376**	
	Iceland	ND	0.341	ND	69	167)
	UK	ND	0.271	ND	59	167)
	Sweden	ND	0.323	ND	248	173)
Western			**0.340**		**318**	
	Germany	ND	0.362	ND	218	174)
		NT	0.290	NT	100	175)
Southern			**0.330**		**687**	
	Italy	ND	0.362	ND	98	176)
	(Sardinian)	ND	0.257	ND	70	161)

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Continued.

Country (Population)		Allele frequency[a]			Number of subjects[b]	Reference
		*36	*28	*37		
		A(TA)$_5$TAA	A(TA)$_7$TAA	A(TA)$_8$TAA		
		Increased transcription	Reduced transcription	Reduced transcription		
	Enzyme activity	Increased	Decreased	Decreased		
	Portugal	ND	0.280	ND	98	177)
	Spain	NT	0.270	NT	115	178)
	(Basque)	ND	0.333	ND	27	167)
	(Catalan)	ND	0.380	ND	46	167)
	Greece	ND	0.401	ND	186	179)
	(Cypriot)	ND	0.287	ND	47	167)
Eastern			**0.344**		**183**	
	Czech	NT	0.392	NT	65	180)
	Russian	ND	0.318	ND	118	181)
Caucasians			**0.340**		**636**	
	Caucasian	ND	0.387	ND	71	156)
		0.009	0.366	0.009	56	182)
		0.017	0.388	0.007	147	159)
		0.004	0.338	ND	133	183)
	Caucasian-American	0.005	0.295	0.002	202	184)
	French-Canadian	ND	0.337	ND	254	185)
	Caucasian-Brazilian	0.007	0.324	0.007	71	186)
Africans			**0.401**		**882**	
	Central Africa (Pygmy Mbenzele)	0.036	0.560	0.071	42	161)
	Kenya	0.100	0.444	0.013	80	167)
	Ivory Coast	0.061	0.358	0.115	74	167)
	Malawi	0.092	0.368	0.046	76	167)
	Madagascar	0.023	0.205	ND	67	167)
	African-American	0.035	0.426	0.069	101	156)
		0.080	0.380	0.020	200	187)
		0.038	0.346	0.115	39	182)
		0.044	0.446	0.064	149	159)
	African-Brazilian	0.065	0.407	0.009	54	186)
Hispanic		0.011	0.375	ND	50	161)
Pacific Islanders			**0.045**		**146**	
	Papua New Guinea	ND	0.014	ND	105	167)

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Country (Population)	Allele frequency[a] *36 A(TA)5TAA Increased transcription	*28 A(TA)7TAA Reduced transcription	*37 A(TA)8TAA Reduced transcription	Number of subjects[b]	Reference
Enzyme activity	Increased	Decreased	Decreased		
Tonga	ND	0.122	ND	41	167)
Parakana Indian	ND	0.328	ND	32	186)

ND: not detected. NT: not tested.
[a]The total allele frequency in each population/region is calculated by dividing the sum of the each allele number by the total allele number in the population/region (including ND but not NT).
[b]The subtotal number in each population/region is simply the sum of the subject numbers.
[c]Excluded from the total population data of China.
[d]Excluded from total data in the South-Eastern Asia region.

Table 6. Allelic frequencies of *UGT1A1*6* in different ethnic populations

Country (Population)	Allele frequency[a] 211G>A G71R	Number of subjects[b]	Reference
Enzyme activity	Decreased		
Asia			
Eastern	**0.183**	**5085**	
Japan	**0.155**	**668**	
	0.134	101	188)
	0.157	150	159)
	0.177	116	160)
	0.153	301	162)
Korea	**0.220**	**455**	
	0.230	50	188)
	0.213	324	163)
	0.241	81	164)
China	**0.205**	**1936**	
(Han)	0.185	539	165)
(Han)	0.211	789	166)
(Han)	0.215	608	189)
(Dong)[c]	0.099	273	165)
(She)[c]	0.125	264	165)
(Uyghur)[c]	0.168	769	166)
(Kazak)[c]	0.211	502	166)
Taiwan	0.156	218	168)
South-Eastern	**0.051**	**335**	
Thailand	0.104	96	169)

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