Continued.

Country (Population)		Allele frequency[a] 211G>A G71R	Number of subjects[b]	Reference
	Enzyme activity	Decreased		
	Malaysia	0.030	50	171)
		0.014	36	190)
	Singapore			
	(Chinese)[d]	0.150	90	191)
	(Malay)	0.047	85	191)
	(Indian)[d]	0.032	94	191)
	Indonesia (Javanese)	0.015	68	190)
Europe		**0.006**	**268**	
	Germany	ND	50	188)
		0.007	218	174)
Caucasians		**0.003**	**374**	
	Caucasian	ND	132	183)
		0.007	150	159)
		ND	92	192)
Africans				
	African-American	ND	150	159)

ND: not detected.
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).
[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 7. Frequencies of *NAT2* haplotypes in different ethnic populations

Country (Population)	Allele frequency[a] *5 341T>C I114T (481C>T)	*6 590G>A R197Q	*7 857G>A G286E	Checked *12, *14	481C>T was used for *5 genotyping (*)	Number of subjects[b]	Reference
Enzyme activity	Decreased	Decreased	Decreased				
Asia							
Eastern	**0.024**	**0.217**	**0.121**			**2,924**	
Japan	**0.014**	**0.205**	**0.088**			**731**	
	0.024	0.193	0.097		*	145	200)
	0.018	0.211	0.082		*	194	201)
	0.016	0.283	0.113	*12, *14		48	202)
	0.005	0.198	0.088	*12, *14		200	203)
	0.007	0.191	0.076	*12, *14		144	196)

Continued on next page.

Continued.

Country (Population)		Allele frequency[a] *5 341T>C I114T (481C>T)	*6 590G>A R197Q	*7 857G>A G286E	Checked *12, *14	481C>T was used for *5 genotyping (*)	Number of subjects[b]	Reference
	Enzyme activity	Decreased	Decreased	Decreased				
	Korea	**0.015**	**0.206**	**0.119**			**1,288**	
		0.016	0.201	0.115	*12		1,000	204)
		0.012	0.224	0.132	*12, *14		288	205)
	China	**0.043**	**0.227**	**0.130**			**506**	
		0.071	0.268	0.054		*	84	206)
	(Han)	0.046	0.188	0.142		*	120	207)
	(Han)	0.022	0.205	0.170	*12, *14		112	208)
	(Han)	0.033	0.213	0.117			120	209)
	(Hong Kong)	0.057	0.307	0.157	*14	*	70	210)
	Taiwan	0.025	0.310	0.150	*14		100	210)
		0.050	0.241	0.184	*14	*	299	211)
South-Eastern		**0.076**	**0.339**	**0.146**			**840**	
	Thailand	0.114	0.386	0.193	*12, *14		44	196)
		0.038	0.326	0.205		*	235	212)
	Vietname	0.028	0.176	ND	*12, *14		71	213)
	Filipine (Filipino in US)	0.065	0.360	0.180	*14	*	100	210)
	Cambodia (Khmer)	0.156	0.297	0.063		?	32	214)
	Malaysia							
	(Malay)	0.116	0.380	0.092		*	146	215)
	(Indian)[c]	0.198	0.320	0.047		*	139	215)
	Singapole (Chinese)[c]	0.075	0.318	0.102		*	187	216)
	Indonesia	0.089	0.368	0.153	*12, *14		212	217)
Southern		**0.296**	**0.284**	**0.038**			**464**	
	India (North)	0.248	0.194	0.075		*	147	218)
	Iran	0.330	0.187	0.057			88	219)
		0.314	0.380	0.007	*14	*	229	220)
Central		**0.203**	**0.271**	**0.118**			**340**	
	Kyrgyz Republic	0.193	0.266	0.118	*12		290	221)
	Turkmenistan	0.260	0.300	0.120	*12, *14		50	196)
Western		**0.402**	**0.325**	**0.052**			**398**	
	Oman	0.353	0.389	0.074	*12, *14		95	222)
	Turkey	0.417	0.305	0.045	*12, *14		303	196)

Continued on next page.

Continued.

Country (Population)			Allele frequency[a] *5 341T>C I114T (481C>T)	*6 590G>A R197Q	*7 857G>A G286E	Checked *12, *14	481C>T was used for *5 genotyping (*)	Number of subjects[b]	Reference
		Enzyme activity	Decreased	Decreased	Decreased				
Europe									
	Northern		**0.498**	**0.264**	**0.024**			**633**	
		Denmark	0.473	0.250	0.023		*	242	223)
		UK	0.527	0.246	0.022	*12, *14		112	196)
			0.468	0.310	0.016		*	63	224)
		(Scots)	0.490	0.271	0.036		*	96	225)
		Sweden	0.590	0.280	0.020	*12, *14		50	196)
			0.507	0.278	0.021		*	70	225)
	Western		**0.468**	**0.277**	**0.013**			**904**	
		Germany	0.465	0.278	0.013	*12, *14		844	196)
		France	0.517	0.250	0.008	*12, *14		60	196)
	Southern		**0.449**	**0.268**	**0.013**			**2,216**	
		Italy (Sardinian)	0.551	0.245	0.000	*12, *14		49	196)
		Portugal	0.433	0.328	0.027	*12	*	128	226)
		Spain	0.391	0.261	0.014	*12, *14		243	197)
			0.441	0.259	0.012	*12, *14		504	198)
			0.461	0.268	0.012	*12, *14		1,292	199)
	Eastern		**0.425**	**0.295**	**0.026**			**1,615**	
		Poland	0.444	0.300	0.034	*12, *14		248	196)
			0.437	0.288	0.015	*12		311	227)
		Slovakia	0.429	0.288	0.015		*	274	228)
		Romania	0.400	0.286	0.014	*12		140	221)
		Russia	0.417	0.317	0.029	*12, *14		290	196)
			0.416	0.288	0.041	*12, *14		352	60)
Caucasians			**0.448**	**0.283**	**0.018**			**930**	
		Caucasian	0.442	0.320	ND		?	122	214)
		Caucasian-American	0.445	0.280	0.023	*14	*	372	229)
			0.408	0.344	0.020	*14	*	49	210)
			0.459	0.266	0.019	*12, *14		387	196)
Africans			**0.342**	**0.213**	**0.063**			**530**	
		African-American	0.305	0.223	0.016	*14	*	128	229)
			0.372	0.230	0.007	*14		74	230)

Continued on next page.

Continued.

Country (Population)		Allele frequency[a] *5 341T>C I114T (481C>T)	*6 590G>A R197Q	*7 857G>A G286E	Checked *12, *14	481C>T was used for *5 genotyping (*)	Number of subjects[b]	Reference
	Enzyme activity	Decreased	Decreased	Decreased				
		0.291	0.244	0.070	*14	*	86	210)
	Morocco	0.511	0.250	0.034	*12, *14		44	196)
	Senegal	0.361	0.170	0.067	*12, *14		97	196)
	Botswana	0.322	0.188	0.168	*12, *14		101	196)
Hispanics		**0.347**	**0.181**	**0.032**			**202**	
	Nicaragua	0.358	0.175	ND	*12, *14		137	196)
	Hispanic (in US)	0.323	0.192	0.100	*14	*	65	210)
Central America Indian		0.070	0.020	0.221	*12, *14		172	231)

ND: not detected.
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).
[b]The subtotal number in each population/region is simply the sum of the subject numbers.
[c]Excluded from total data in the South-Eastern Asia region.

was not analyzed. However, the AF of these **14* subtypes was very low, especially in Asian (0) and European populations (0–0.01), and therefore, this issue has only a minimal impact on the **5* and **6* frequencies.[196–199]

The **5* frequency in Eastern Asians (AF = 0.024) is lowest compared to South-Eastern (0.076), Southern (0.296), Central (0.203), and Western (0.402) Asians as well as Europeans, which range from 0.425 (Eastern) to 0.498 (Northern). Therefore, the AF difference between Eastern/South-Eastern Asians and Europeans is over 0.3. Less than 0.1 differences in **6* frequencies are observed between Eastern Asians and Europeans and between South-Eastern Asians and Europeans. However, the difference is >0.1 between Eastern Asians (AF = 0.217) and South-Eastern Asians (0.339). The **7* frequency is highest in South-Eastern Asians (0.146), followed by Eastern (0.121) and Central (0.118) Asians, and is very low in Europeans varying from 0.013 (Western/Southern) to 0.026 (Eastern). The largest AF differences among the 3 Eastern Asian populations, all between Japanese and Chinese, are 0.029 for **5*, 0.022 for **6*, and 0.042 for **7*, which is similar to those in the populations among the 4 Europe sub-regions (0.073 for **5*, 0.031 for **6*, and 0.013 for **7*). AFs are relatively different in populations between Eastern and South-Eastern Asian countries (0.052 for **5*, 0.122 for **6*, and 0.025 for **7*). In addition, AF differences in *NAT2*5*, **6*, and **7* in the populations among the three Eastern Asian countries are less than 0.1, and thus, the differences could be regarded as minimal.

c) *GSTM1* and *GSTT1*: Glutathione *S*-transferases (GSTs) are phase II metabolic enzymes that mediate conjugation of reduced glutathione (GSH) with a variety of electrophilic compounds including therapeutic drugs.[232] The human cytosolic GST family contains at least 17 genes subdivided into seven separate classes designated α, μ, π, σ, θ, ζ, and ω. The μ-class enzyme GSTM1 and θ-class enzyme GSTT1 are expressed in many tissues including liver, brain, and kidney.

GSTM1 and GSTT1 exhibit whole gene deletion polymorphisms, *GSTM1*0* and *GSTT1*0*, respectively.[232,233] A large number of association studies on the *GSTM1* and *GSTT1* null genotypes have been performed to determine inter-individual differences in efficacy and toxicity with various drugs. *GSTT1*0* was reported to be associated with a poorer response rate and shorter overall survival in oxaliplatin-based chemotherapy (FOLFOX).[234,235] Metastatic colorectal cancer patients with the *GSTM1*0/*0* genotype treated with FOLFOX had a higher frequency of grade 4 neutropenia.[236] In addition, the *GSTM1/GSTT1* double null (**0/*0*) genotype was linked to drug-induced liver injury.[237,238] Despite the possible gene-dose effect of these deletions, most reports have only focused on the null genotypes of *GSTM1* and/or *GSTT1*. Thus, the *GSTM1* and *GSTT1* null genotypes are compared.

For the *GSTM1*-null genotype (*GSTM1*0/*0*, **Table 8**), the GF of *GSTM1*0/*0* is similar between Eastern Asians (GF = 0.521) and Europeans (about 0.51–0.53). The largest GF difference among the 3 major Eastern Asians [0.034

between Japanese (0.501) and Chinese (0.535)] is slightly greater than that in the populations among the 4 European sub-regions [0.024 between Southern (0.509) and Northern (0.533)], but is less than 0.1. Among Asians, the GF in Eastern Asians (0.521) is similar to that in South-Eastern Asians (0.562), but is higher than that in Indians (0.281). For the *GSTT1*-null genotype (*GSTT1*0/*0*, **Table 9**), the GF of *GSTT1*0/*0* in Eastern Asians (0.476) is about 2.5-fold (>0.25 in frequency) higher than that in Europeans (about 0.17–0.19). The largest GF difference among the 3 major Eastern Asian populations [0.066 between Koreans (0.509) and Chinese (0.443)] is 2.2-fold greater than that in the populations among 4 European sub-regions [0.030 between Southern (0.195) and Northern (0.165)], but the value is less than 0.1. Among Asians, the GF in Eastern Asians (0.476) is >0.1 higher than that in South-Eastern Asians (0.351) and in Indians (0.147).

Drug Transporters

a) *OATP1B1*: Organic anion transporting polypeptide 1B1 (OATP1B1, also known as OATP-C) is a liver-specific transporter that mediates the uptake of various endogenous and exogenous compounds from the blood into hepatocytes, including several important drugs, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (such as pravastatin), anti-bacterials cefazolin and refampicin, anti-cancer drugs, an active metabolite of irinotecan SN-38 and methotrexate, and anti-hypertensive drugs olmesartan and valsartan.[298] The OATP1B1 protein is encoded by the *SLCO1B1* gene and is predicted to have 12 transmembrane domains (TMDs).[299]

The polymorphism 521T>C (V174A) is known to impair plasma membrane expression of the OATP1B1 protein and reduced transport activity *in vitro*.[298] This polymorphism includes the *SLCO1B1*5*, **15* and **17* haplotypes. Association of the **15* haplotype [harboring 388A>G (Asn130Asp) and 521T>C (Val174Ala)] with significant increases in AUC was reported for pravastatin and irinotecan and its metabolite SN-38. Recently, the *SLCO1B1*17* haplotype with 388A>G (Asn130Asp), 521T>C (Val174Ala), and −11187G>A was also shown to increase the AUC of pravastatin and likely reduces pravastatin efficacy for inhibition of cholesterol synthesis, although the effect of the −11187G>A substitution on transcriptional activity has not been clarified *in vitro*.[300,301]

As shown in **Table 10**, the AF of 521T>C in the populations of Eastern Asia is 0.135, which is similar to that in the South-Eastern Asia region (AF = 0.124) and in Turkey (0.122), more than 0.1 higher than that in India (0.014), and slightly lower than that in Europe (0.183). The largest AF difference among the 3 Eastern Asian populations is 0.012 [between Japanese (0.139) and Chinese (0.127), less than 0.1], which is smaller than those among European populations, although only a few reports have been published concerning the AF in European populations.

Table 8. Frequencies of *GSTM1*-null genotype in different ethnic populations

Country (Population)			Null frequency[a] (Null activity)	Number of subjects[b]	Reference
Asia					
	Eastern		**0.521**	**8,931**	
		Japan	**0.501**	**2,215**	
			0.453	201	239)
			0.513	622	240)
			0.441	143	241)
			0.559	220	242)
			0.513	150	243)
			0.425	200	244)
			0.523	476	245)
			0.502	203	246)
		Korea	**0.527**	**3,704**	
			0.524	63	247)
			0.525	181	248)
			0.559	220	249)
			0.537	177	250)
			0.538	1,037	251)
			0.543	1,699	252)
			0.382	327	253)
		China	**0.535**	**2,467**	
			0.506	419	254)
			0.368	106	255)
			0.598	393	256)
		(Han)	0.520	763	257)
		(Han)	0.561	196	258)
		(Han)	0.556	590	259)
		(Uygur)[c]	0.532	154	258)
		Taiwan	0.527	184	260)
		Mongolia	0.464	207	261)
	South-Eastern		**0.562**	**1,666**	
		Vietnam	0.420	100	262)
		Philippines	0.517	60	263)
		Thailand	0.597	320	264)
			0.510	145	265)
			0.627	485	266)
		(North)	0.580	81	267)
		Indonesia	0.556	162	268)

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Continued.

Country (Population)			Null frequency[a] (Null activity)	Number of subjects[b]	Reference
		Malaysia			
		(Malay)	0.616	146	269)
		(Indian)[d]	0.331	139	269)
		Singapore			
		(Chinese)[d]	0.636	187	270)
		(Chinese)[d]	0.631	187	271)
		(Malay)	0.653	167	271)
		(Indian)[d]	0.316	152	271)
	Southern				
		India	**0.281**	**1,421**	
			0.240	450	272)
		(North)	0.330	370	273)
		(North)	0.365	200	274)
		(South)	0.267	146	275)
		(South)	0.224	255	276)
Europe					
	Northern		**0.533**	**3,686**	
		Norway	0.483	375	277)
			0.506	423	278)
		Sweden	0.512	203	279)
			0.559	544	278)
		Finland	0.469	482	278)
		Denmark	0.536	537	278)
		UK	0.578	1,122	278)
	Western		**0.515**	**6,486**	
		Netherlands	0.504	419	278)
		Germany	0.535	353	280)
			0.516	734	278)
			0.473	622	281)
			0.516	3,054	282)
		France	0.534	1,184	278)
		(Northwest)	0.491	120	283)
	Southern		**0.509**	**3,770**	
		Italy	0.488	127	284)
			0.494	810	278)
			0.527	254	285)
		Spain	0.497	312	278)
			0.504	1,132	286)

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Country (Population)			Null frequency[a] (Null activity)	Number of subjects[b]	Reference
			0.477	130	287)
		Portugal	0.524	84	288)
			0.583	501	278)
		Slovenia	0.520	102	278)
		Greece	0.520	171	289)
		(Northwest)	0.381	147	290)
	Eastern		**0.511**	**1,184**	
		Czech	0.567	67	291)
		Bulgaria	0.518	112	292)
		Poland	0.511	321	227)
		Slovakia	0.512	332	278)
		Russia	0.497	352	60)
Caucasians			**0.529**	**2,714**	
		Caucasian-Americans	0.543	1,751	278)
			0.474	290	293)
			0.520	369	294)
		Caucasian-Canadians	0.513	304	278)
Africans			**0.266**	**594**	
		African-Americans	0.261	120	293)
			0.322	87	295)
			0.278	259	294)
		South African Xhosa	0.211	128	296)

[a]The total genotype frequency in each population/region is calculated by dividing the sum of the each null genotype number by the total subject 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.

b) *ABCG2*: An ATP-binding cassette transporter G2 (ABCG2, also known as breast cancer resistance protein, BCRP) was originally identified as a multi-drug resistance transporter.[318] This transporter is normally expressed at high levels in the placenta, small intestine, colon, hepatic canalicular membrane, and blood vessels. Many anti-cancer drugs such as methotrexate, imatinib, and SN-38 and its glucuronide metabolite, as well as other drugs including glyburide and sulfasalazine have been demonstrated to be substrates for ABCG2.

Table 9. Frequencies of *GSTT1*-null genotype in different ethnic populations

Country (Population)			Null frequency[a] (Null activity)	Number of subjects[b]	Reference
Asia					
	Eastern		**0.476**	**7,875**	
		Japan	**0.496**	**1,518**	
			0.444	126	297)
			0.434	143	241)
			0.491	220	242)
			0.540	150	243)
			0.520	200	244)
			0.500	476	245)
			0.512	203	246)
		Korea	**0.509**	**3,641**	
			0.420	181	248)
			0.459	220	249)
			0.531	177	250)
			0.543	1,037	251)
			0.505	1,699	252)
			0.499	327	253)
		China	**0.443**	**2,355**	
			0.455	418	254)
			0.489	393	256)
		(Han)	0.387	763	257)
		(Han)	0.500	196	258)
		(Han)	0.460	585	259)
		(Uygur)[c]	0.266	154	258)
		Mongolia	0.256	207	261)
	South-Eastern		**0.351**	**890**	
		Vietnam	0.300	100	262)
		Philippines	0.333	60	263)
		Thailand	0.381	320	264)
		(North)	0.481	81	267)
		Indonesia	0.414	162	268)
		Singapore			
		(Chinese)[d]	0.545	187	270)
		(Chinese)[d]	0.583	187	271)
		(Malay)	0.383	167	271)
		(Indian)[d]	0.164	152	271)
	Southern				
		India	**0.147**	**1,421**	
			0.123	450	272)
		(North)	0.184	370	273)
		(North)	0.140	200	274)
		(South)	0.089	146	275)
		(South)	0.176	255	276)
Europe					
	Northern		**0.165**	**2,291**	
		Sweden	0.182	203	279)
			0.130	423	278)
		Finland	0.130	385	278)
		Denmark	0.129	358	278)
		UK	0.205	922	278)
	Western		**0.183**	**5,562**	
		Netherlands	0.229	419	278)
		Germany	0.188	353	280)
			0.195	487	278)
			0.185	622	281)
			0.173	3,054	282)
		France	0.168	512	278)
			0.261	115	283)
	Southern		**0.195**	**2,660**	
		Italy	0.163	553	278)
			0.224	254	285)
		Spain	0.205	312	278)
			0.221	1,121	286)
		Slovenia	0.255	102	278)
		Greece	0.099	171	289)
		(Northwest)	0.109	147	290)
	Eastern		**0.188**	**1,169**	
		Czech Republic	0.224	67	291)
		Bulgaria	0.161	112	292)
		Poland	0.193	316	227)
		Slovakia	0.180	322	278)
		Russia	0.193	352	60)
Caucasians			**0.197**	**1,223**	
		Caucasian-Americans	0.276	286	278)
			0.186	290	293)
			0.164	373	294)

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Country (Population)		Null frequency[a] (Null activity)	Number of subjects[b]	Reference
	Caucasian-Canadians	0.172	274	278)
Africans		**0.231**	**594**	
	South African Xhosa	0.406	128	296)
	African-Americans	0.220	120	293)
		0.184	87	295)
		0.166	259	294)

[a]The total genotype frequency in each population/region is calculated by dividing the sum of the each null genotype number by the total subject 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.

Many functionally-related polymorphisms/mutations have been reported for the *ABCG2* gene. Of these, 421C>A (Q141K) was reported to be associated with reduced protein expression levels in both transfected cells and human tissues due to increased lysosomal and proteasomal degradation.[318] The variant protein with K141 is associated with increased AUCs for diflomotecan, sulfasalazine, and rosuvastatin (but not for pitavastatin or imatinib), and also with increased frequencies of diarrhea by higher plasma concentrations of gefitinib.[319,320] A recent study showed that this polymorphism was also involved in the enhanced diarrhea risk with primary rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) therapy.[321] On the other hand, the functional effect of another frequent polymorphism, 34G>A (Val12Met), has been controversial.[319] Thus, we selected the 421C>A (Gln141Lys) substitution for purposes of comparison.

The AF in Eastern Asians (AF = 0.301) is close to that in South-Eastern Asians (0.295), but is about 3-fold (>0.25 in

Table 10. Frequencies of *SLCO1B1* 521T>C in different ethnic populations

Country (Population)			Allele frequency[a] 521T>C, V174A Transporter activity	Allele frequency[a] 521T>C, V174A Decreased	Number of subjects[b]	Reference
Asia						
	Eastern			**0.135**	**2,548**	
		Japan		**0.139**	**1,064**	
				0.110	267	302)
				0.158	120	303)
				0.137	500	8)
				0.175	177	304)
		Korea		**0.136**	**869**	
				0.140	469	305)
				0.118	200	306)
				0.144	200	8)
		China		**0.127**	**615**	
			(Han)	0.094	106	305)
			(Han)	0.140	111	307)
			(Han)	0.132	398	8)
	South-Eastern			**0.124**	**335**	
		Vietnam		0.163	104	305)
		Singapore				
			(Chinese)[c]	0.130	100	308)
			(Chinese)[c]	0.086	35	309)

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Continued.

Country (Population)		Transporter activity	Allele frequency[a] 521T>C, V174A Decreased	Number of subjects[b]	Reference
		(Chinese)[c]	0.120	96	310)
		(Malay)	0.110	100	308)
		(Malay)	0.129	35	309)
		(Malay)	0.094	96	310)
		(Indian)[c]	0.065	100	308)
		(Indian)[c]	0.071	35	309)
		(Indian)[c]	0.057	96	310)
	Southern				
		India (North)	0.014	173	311)
	Western				
		Turkey	0.122	94	312)
Europe			**0.183**	**950**	
	Northern				
		Finland	0.202	468	313)
	Western				
		Germany	0.150	300	312)
		France	0.177	45	314)
	Southern				
		Italy	0.153	49	314)
		(Tuscany)	0.216	88	HapMap[d]
Caucasians			**0.161**	**830**	
		Caucasians	0.222	36	309)
			0.120	250	315)
		Caucasian-Americans	0.179	454	8)
		Eupopean-Americans	0.143	49	316)
		Caucasian-Canadian	0.183	41	317)
Africans			**0.048**	**387**	
		Uganda	0.039	115	312)
		African-Americans	0.023	22	316)
			0.053	250	8)

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 total data in the South-Eastern Asia region.
[d]http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=4149056

AF) higher than that in Europeans (0.103) (**Table 11**). The highest AF difference among populations of the 3 Eastern Asian countries is 0.031 [between Korea (0.284) and China (0.315)], which is less than 0.1, and is similar to that among the European national populations, although only a few reports of the AFs of these polymorphisms in European populations have been published.

HLAs

HLA molecules are essential for the presentation of foreign antigens to the immune system.[338] *HLA* genes are highly polymorphic to enable presentation of a wide variety of antigenic peptides to T cells for initiation of the immune response. There are two classes of HLA molecule that are divided by structure and function. Class I HLA molecules (*e.g.*, HLA-A, HLA-B and HLA-Cw) are expressed in all nucleated cells and are involved in the presentation of antigens to cytotoxic $CD8^+$ T cells capable of recognizing and lysing target cells.[338] Class II HLA molecules (*e.g.*, HLA-DR, HLA-DQ, and HLA-DP) are expressed in a more limited population of immune cells (dendritic cells, macrophages, and B cells) that present antigens to $CD4^+$ helper T cells involved in modulating antibody and T-cytotoxic immune responses.[338] Recently, strong associations between some *HLA* alleles and incidence of severe cutaneous drug adverse reactions (cADRs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DIHS) and maculopapular eruption (MPE) have been reported, but the associations are dependent on ethnic group and causative drug.[339] These cADRs are thought to be independent of drug PK profiles, and thus are considered as idiosyncratic.

a) *HLA-A*31:01*: *HLA-A*31:01* is associated with carbamazepine (CBZ)-induced cADRs. In the Han-Chinese population, *HLA-A*31:01* was reported to be associated with MPE (odds ratio = 17.5).[340] In the Japanese population, 60.7% (37/61) of the patients with CBZ-induced cADRs (SJS/TEN, DIHS and others) had the *HLA-A*31:01* allele (odds ratio = 10.8).[341] In addition, *HLA-A*31:01* is significantly associated with CBZ-induced cADRs including hypersensitivity, SJS/TEN, and MPE in Northern European populations.[342]

As shown in **Table 12**, the AF of *HLA-A*31:01* in Eastern Asians (0.044) was higher than that of South-Eastern Asians (0.008) and Jordanians (0.017), but similar to that of Southern Asians (0.046). In Eastern Asians, the AF in Japanese (0.087) is 1.7- and 4.0-fold higher than that in Koreans (0.050) and Chinese (0.022), respectively. The frequency difference (0.065) between Japanese and Chinese is more than 0.05. In Europe, the AFs are very similar, ranging from 0.022 (Northern) to 0.032 (Southern), which are close to the overall AFs in Eastern Asians.

b) *HLA-B*58:01*: *HLA-B*58:01* is strongly associated with allopurinol-induced cADRs in Han Chinese in Taiwan and Thai. One hundred percent of 51 Han Chinese patients with severe cADRs to allopurinol were reported to be *HLA-B*58:01* positive (odds ratio = 580.3).[343] Subsequently, all of the 27 (100%) allopurinol-induced SJS/TEN Thai patients carried the *HLA-B*58:01* allele (odds ratio = 348.3).[344] A moderate but statistically significant association with *HLA-B*58:01* was observed in Japanese SJS/TEN patients administered allopurinol, where 4 out of 10 patients carried the *HLA-B*58:01* allele (odds ratio = 40.8).[345] Furthermore, in a European origin study, a moderate association of *HLA-B*58:01* with allopurinol-induced SJS/TEN was also observed (odds ratio = 80).[346]

As shown in **Table 12**, the AF of *HLA-B*58:01* in Japanese is rare (0.004) compared with Koreans (0.061) and Chinese (0.074) in which the frequency is 15.3- (0.057 in AF difference) and 18.5-fold (0.070 in AF difference) higher than in Japanese, respectively. The AF difference between Japanese and Koreans/Chinese is more than 0.05. The overall AF in Eastern Asians (0.060) is similar to that in South-Eastern Asians (0.066), but is higher than that in Jordanians (0.014). The AFs are very low in Europeans, ranging from 0.005 (Northern/Southern) to 0.012 (Eastern), which differ at borderline (~0.05) from the overall AFs in Eastern/South-Eastern Asians.

Conclusion

In this review, we compared the AFs or GFs of relatively common functional polymorphisms/haplotypes in PK/PD-related genes mainly between Eastern Asians and Europeans as well as among the 3 major populations in Eastern Asian countries, Japan, Korea, and China. Based on our arbitrary criteria that AF or GF differences 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) are regarded as similar, AFs (or GFs) that deviated from our criteria can be regarded as different for many alleles including *CYP2C9*2*, *CYP2C19*2*, **3* and **17*, *CYP2D6*4* and **10*, *CYP3A5*3*, *UGT1A1*28* and **6*, *NAT2*5* and **7*, *GSTT1* null genotype, and *ABCG2* 421C>A between Eastern Asians and Europeans. No deviation from the criteria was observed for all genetic polymorphisms/haplotypes among populations of 4 European regions. Among the 3 Eastern Asian populations, 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 at 0.147 is observed only between Japanese and Chinese. We also compared these differences with the 4 European sub-regions and found that the differences among the 3 Eastern Asian populations were, in general, close to those among the European populations. Based on these analyses, genetic differences are suggested to be very small among Japanese, Koreans, and Chinese for common PK-related gene polymorphisms.

Table 11. Frequencies of *ABCG2* 421C>A in different ethnic populations

Country (Population)			Allele frequency[a] 421C>A, Q141K	Number of subjects[b]	Reference
		Transporter activity	Decreased		
Asia					
	Eastern		**0.301**	**1,602**	
		Japan	**0.313**	**411**	
			0.350	10	322)
			0.355	100	323)
			0.266	124	324)
			0.319	177	325)
		Korea	**0.284**	**670**	
			0.278	250	326)
			0.280	275	327)
			0.300	145	328)
		China	**0.315**	**521**	
			0.291	191	327)
		(Han)	0.342	95	329)
		(Han)	0.323	235	330)
	South-Eastern		**0.295**	**237**	
		Vietnam	0.311	140	327)
		Singapore			
		(Chinese)[c]	0.277	94	191)
		(Malay)	0.273	97	191)
		(Indian)[c]	0.154	94	191)
Europe			**0.103**	**1,611**	
	Northern				
		Sweden	0.100	60	331)
	Western		**0.107**	**1,314**	
		Netherlands[d]	0.120	100	332)
		Germany	0.100	349	333)
			0.108	865	334)
	Southern				
		Italy (Tuscany)	0.062	88	HapMap[e]
	Eastern				
		Hungary	0.094	149	335)
Caucasians			**0.105**	**479**	

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Country (Population)		Allele frequency[a] 421C>A, Q141K	Number of subjects[b]	Reference
	Transporter activity	Decreased		
	European-Caucasians	0.107	84	329)
	Caucasians	0.087	150	336)
		0.142	88	322)
	European-Americans	0.080	69	337)
	Caucasian-Americans	0.119	88	329)
Africans		**0.027**	**1,094**	
	Africans (sub-Saharan)	0.009	938	329)
	African-Americans	0.053	94	329)
		0.000	24	322)
		0.039	38	337)

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 total data in the South-Eastern Asia region.
[d]The population included 1 African, 1 Asian and 5 mixed ethnic subjects (*i.e.*, Caucasians were 93%).
[e]http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=2231142

Table 12. Frequencies of *HLA-A*31:01* and *B*58:01* in different ethnic populations

Country (Population)		Allele frequency[a] *A*31:01*	Number of subjects	Allele frequency[a] *B*58:01*	Number of subjects[b]	Reference
Asia						
Eastern		**0.044**	**6,011**	**0.060**	**6,117**	
	Japan	**0.087**	**1,506**	**0.004**	**1,506**	
		0.091	1,018	0.005	1,018	347)
		0.071	371	0.004	371	348)
		0.093	117	ND	117	349)
	Korea	**0.050**	**959**	**0.061**	**959**	
		0.054	485	0.065	485	350)
		0.045	474	0.057	474	351)
	China	**0.022**	**1,496**	**0.074**	**1,602**	
	(North Han)	0.019	618	0.060	618	352)
	(North Han)	0.071	105	0.029	105	353)
	(South Han, Canton Guangzhou)	NT		0.047	106	354)
	(South Han, Canton Meizhou)	ND	100	0.170	100	355)
	(Southwest Han, Yunnan)	0.035	101	0.074	101	356)
	(Hong Kong)	0.018	572	0.073	572	357)
	(Tibetan)[c]	0.092	158	0.016	158	358)
	(Mongolian, Inner Mongolia)[c]	0.054	102	0.088	102	359)

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Country (Population)		Allele frequency[a] *A*31:01*	Number of subjects	Allele frequency[a] *B*58:01*	Number of subjects[b]	Reference
	Taiwan	**0.018**	**1,790**	**0.101**	**1,790**	
		0.018	710	0.098	710	360)
		0.008	364	0.100	364	361)
		0.014	212	0.101	212	362)
	(Han)	0.028	504	0.106	504	363)
South-Eastern		**0.008**	**1,043**	**0.066**	**1,092**	
	Indonesia (Javanese, West Java)	<0.01	236	0.057	236	364)
	(Sundanese-Javanese, West Java)	ND	201	0.060	201	365)
	(Javanese, West Java)	ND	36	0.042	36	365)
	Thailand (Northeast)	0.013	400	0.079	400	366)
		NT		0.061	49	367)
	Vietnam (Kinh, Hanoi)	0.021	170	0.065	170	368)
Southern		**0.046**	**674**	**0.046**	**304**	
	India (North)	0.060	90	0.077	91	369)
	(North)	0.019	52	0.058	52	370)
	(Dravidian, South, Tamil Nadu)	0.189	61	ND	61	371)
	Pakistan (Pathan, North, NWFP)	0.015	100	/		372)
	(Sindhi, South, Sindh)	0.040	101	/		372)
	(Baloch, South Balochistan)	0.015	66	/		372)
	(Brahui, South Balochistan)	0.043	104	/		372)
	Iran (Baloch)	0.022	100	0.040	100	373)
Western						
	Jordan	0.017	146	0.014	146	374)
Europe						
Northern		**0.022**	**250**	**0.005**	**7,048**	
	UK (Wales)	/		0.005	1,798	375)
	(Northern Ireland)	/		0.003	5,000	376, 377)
	Ireland	0.022	250	0.004	250	378)
Western		**0.023**	**8,961**	**0.008**	**8,862**	
	Belgium	0.042	99	/		379)
	Germany	0.023	8,862	0.008	8,862	380)
Southern		**0.032**	**187**	**0.005**	**201**	
	Italy	NT		0.033	15	381)
	Spain (Basques, Gipuzkoa)	0.030	99	ND	99	382)
	(Catalans, Catalonia)	0.034	88	0.006	87	382)

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Country (Population)			Allele frequency[a] *A*31:01*	Number of subjects	Allele frequency[a] *B*58:01*	Number of subjects[b]	Reference
	Eastern		**0.027**	**255**	**0.012**	**255**	
		Bulgaria	0.018	55	0.018	55	383)
		Poland	0.030	200	0.010	200	384)
Africans			**0.010**	**1,388**	**0.061**	**1,206**	
	Northern		**0.017**	**173**	**0.029**	**173**	
		Morocco (Berber, Metalsa, Nador)	0.021	73	0.014	73	385)
		Tunisia	0.015	100	0.040	100	386)
	Eastern		**0.009**	**1,124**	**0.049**	**841**	
		Uganda (Kampara)	0.009	175	0.060	175	387)
			0.025	163	0.040	161	388)
		Kenya (Luo)	0.013	265	0.070	265	388)
		(Nandi)	0.004	241	0.100	240	388)
		Rwanda (women)	0.002	280	/		389)
	Middle						
		Cameroon (Yaounde)	0.011	91	0.054	92	390)
USA	**(American)**		**0.026**	**15,711**	**0.018**	**15,719**	
		European	0.024	7869	0.005	7,868	391)
		Eastern European	0.024	558	0.008	558	392)
		African	0.010	2,404	0.035	2,410	391)
		African	0.011	564	0.032	564	393)
		Asian and Pacific Islander	0.032	1,771	0.058	1,767	391)
		Hispanic	0.048	1,992	0.015	1,999	391)
		Mexican	0.059	553	0.009	553	394)

[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.

In contrast, AFs of two *HLA* alleles associated with cADRs, *HLA-A*31:01* and *HLA-B*58:01*, are regarded as different even among the 3 Eastern Asian populations, especially between Japanese and Chinese. It would be important to examine population differences in the incidence rate of adverse reactions other than cADRs and frequency differences within the Eastern Asian populations especially if the adverse reactions are related to *HLA* alleles.

It should be noted that the current criteria for judging the difference are our arbitrary ones to detect just the AF or GF differences of the polymorphisms/haplotypes for this review, and the real impact of the found frequency differences is dependent on the relevance of each drug to each gene product. It should also be noted that PK/PD is influenced by environmental factors such as foods, smoking, alcohol, climate, and medical and socioeconomic factors.

In conclusion, based on the current analyses, we could propose that among Japanese, Koreans, and Chinese, AFs/GFs in functional genetic polymorphisms of the analyzed PK-related genes are very similar. Rather, inter-individual differences based on genetic polymorphisms may have a large impact on clinical trial data. On the other hand, AFs of the two *HLA* alleles important for cADR are diverse even among Eastern Asians and thus would need to be taken into account.

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