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ORIGINAL ARTICLE

Association study of genetic polymorphisms of drug transporters, *SLCO1B1*, *SLCO1B3* and *ABCC2*, in African-Americans, Hispanics and Caucasians and olmesartan exposure

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It has been reported that organic anion-transporting polypeptide (OATP) 1B1, OATP1B3 and multidrug resistance-associated protein 2 are involved in the hepatobiliary transport of olmesartan. We investigated the association of *SLCO1B1*, *SLCO1B3* and *ABCC2* polymorphisms with the pharmacokinetics of olmesartan. We sequenced all exons, exon–intron junctions and the 5′ and 3′ flanking regions of the three genes in 115 individuals from African-American, Hispanic and Caucasian populations who had participated in our clinical studies. A total of 348 single-nucleotide polymorphisms (SNPs) were identified with a minor allele frequency of ⩾0.01 in at least one population; 132 SNPs were detected in *SLCO1B1*, 130 in *SLCO1B3* and 86 in *ABCC2*. We characterized the linkage disequilibrium (LD) and haplotypes shared across the populations and then evaluated the association between the haplotypes and the pharmacokinetics of olmesartan. Seven inter-ethnic LD blocks were observed in *SLCO1B1*, while three in *SLCO1B3* and four in *ABCC2*. Although extensive variability in the sequences of *SLCO1B1*, *SLCO1B3* and *ABCC2* existed across the three populations, there was no remarkable difference in any pharmacokinetic parameters of olmesartan between subjects with and without any major haplotypes in the three transporter genes we tested.
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INTRODUCTION

Olmesartan medoxomil, a potent angiotensin II type 1 receptor antagonist, is orally administered as a prodrug and completely hydrolyzed into the active metabolite olmesartan during absorption from the gastrointestinal tract. Olmesartan is excreted into both bile and urine without undergoing metabolism.[1] Some studies have suggested that organic anion-transporting polypeptide 1B1 (gene name, *SLCO1B1*) and organic anion-transporting polypeptide 1B3 (*SLCO1B3*) are involved in hepatic uptake and that the ATP-binding cassette, sub-family C member 2 (multidrug resistance-associated protein (MRP) 2, *ABCC2*), is involved in the biliary excretion of olmesartan.[2,3]

Membrane transporters have important roles in the uptake, distribution and excretion of endogenous compounds and xenobiotics. Polymorphisms in genes encoding transporters have been investigated extensively and appear to be associated with altered transporter activity. It has become clear that genetic polymorphisms have an impact on the inter-individual variability of the pharmacokinetics and pharmacodynamics of drugs. Indeed, the 521T>C (V174A) variant of *SLCO1B1* is associated with changes in the transporter activity of estrone sulfate, 17β-D-glucuronide and pravastatin *in vitro*.[4–7] Moreover, the 521C/C genotype has been associated with increased plasma concentrations of statins and glinides in human studies.[8–10] In *SLCO1B3*, several single-nucleotide polymorphisms (SNPs) have been identified in coding and noncoding regions. At least three nonsynonymous SNPs have been found so far, with 334T>G (S112A) and 699G>A (M233I) increasing transporter activity *in vitro*.[11] With regard to *ABCC2*, several mutations and deletions have been identified in patients with Dubin–Johnson syndrome, an autosomal recessive disorder, each of which impairs either the expression or function of MRP2 protein.[12–14] Beside mutations in Dubin–Johnson syndrome, the extensive genetic variation identified so far may have a potential effect on drug disposition.[15,16] In fact, the T allele of −24C>T has been

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associated with lower mRNA levels in normal renal tissues, leading to reduced transporter activity.[17] In addition, the synonymous mutation 1446C>G was associated with increased hepatic mRNA expression resulting in low C_{max} and area under the plasma concentration time curve (AUC) values for pravastatin.[18]

A haplotype-based approach to identifying the genetic variation underlying drug response and disposition as well as common diseases has been proposed.[19–22] The International HapMap Project has characterized the pattern of haplotype structure and linkage disequilibrium (LD) across the human genome to facilitate genome-wide association studies.[23,24] It is well established that, in high LD regions, only a limited number of haplotypes is observed and common haplotypes can be efficiently labeled with a small number of common SNPs, haplotype-tagging SNPs. These can maintain most of the information for the detection of other variants, while reducing the amount of genotyping. The use of haplotypes in association studies may have advantages over the use of individual SNPs. For example, if the causal allele is dependent on *cis* interactions with the alleles of other SNPs, the association may not be revealed unless the haplotype is evaluated.[25,26] Furthermore, haplotypes in a genomic region of interest can serve as genetic markers to detect an association with the phenotype, whether or not the markers themselves have a causal effect.

In this study, we investigated the distribution of SNPs of *SLCO1B1*, *SLCO1B3* and *ABCC2* involved in the hepatobiliary transport of olmesartan and estimated common LD blocks and common haplotypes across three ethnic/racial populations. We used a haplotype-based approach to assess the influence of haplotypes of these transporters on the pharmacokinetics of olmesartan.

MATERIALS AND METHODS

Subjects

There were 120 subjects who had participated in two of our studies on AZOR (combination tablet formulation of olmesartan medoxomil and amlodipine besylate). Their characteristics are listed in Table 1. Ages ranged from 18 to 45 years, and 42 subjects were female. Ethnicity was classified based on a self-description. In all, 40 of the subjects classified themselves as African-American, 17 as Caucasian, 61 as Hispanic and 2 as other. Owing to low DNA yields from 5 subjects, a total of 115 subjects were used. The health status of each individual was confirmed based on their medical history, a physical examination, laboratory reports including hematology and serum chemistry, and a 12-lead electrocardiogram. Clinical studies were conducted at MDS Pharma Services (Nepture, NZ and Phoenix, AZ, USA). The protocols were approved by the Institutional Review Boards of the study center and all the subjects gave written informed consent before admission into the studies. The protocols were conducted in accordance with the guidelines on Good Clinical Practice and with ethical standards for human experimentation established by the Declaration of Helsinki Principles.

Study design

Study 1 was a phase I bioavailability study with parallel-group, open-label, randomized and crossover designs. Two cohorts (cohort 1 and cohort 2) of 30 subjects each were enrolled in sequential order, with the first 30 subjects assigned to cohort 1 and the second 30 subjects to cohort 2. The subjects in cohort 1 were randomized to receive single doses of treatment A (AZOR: combination tablet formulation of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg) or treatment B (olmesartan medoxomil 10 mg co-administered with amlodipine besylate 5 mg) in one of two sequences (AB or BA). In cohort 2, the subjects were randomized to receive single doses of treatment C (AZOR: combination tablet formulation of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) or treatment D (olmesartan medoxomil 40 mg co-administered with amlodipine besylate 10 mg) in one of two sequences (CD or DC). A 21-day-washout period followed the dosing for each period.

Table 1 Characteristics of study subjects ($n=120$)

	Study 1		*Study 2*	
	Cohort 1 (n = 30)	*Cohort 2* (n = 30)	*Cohort 1* (n = 30)	*Cohort 2* (n = 30)
Age (years)	32.2 ± 6.20	30.2 ± 7.60	33.0 ± 6.70	30.2 ± 7.10
Body weight (kg)	78.6 ± 11.9	80.2 ± 13.0	73.5 ± 11.4	70.7 ± 13.5
Scr (mg dl^{-1})	1.01 ± 0.15	1.04 ± 0.17	0.70 ± 0.15	0.63 ± 0.17
BMI	26.5 ± 3.70	26.1 ± 3.40	26.1 ± 2.90	26.1 ± 2.80
Gender				
Male	23	26	19	10
Female	7	4	11	20
Ethnicity				
African-Americans	17	22	0	1
Hispanics	7	2	27	25
Caucasians	6	4	3	4
Others	0	2	0	0

Abbreviations: BMI, body mass index; Scr, serum creatinine.
Each value represents the mean ± s.d.

Study 2 was a phase I study with parallel-group, open-label, randomized, single-dose and 3-period crossover designs. Again two cohorts were established. The subjects in cohort 1 were randomized to receive single doses of treatment A (AZOR: combination tablet formulation of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg), treatment B (AZOR: combination tablet formulation of olmesartan medoxomil 20 mg and amlodipine besylate 5 mg) or treatment C (AZOR: combination tablet formulation of olmesartan medoxomil 10 mg and amlodipine besylate 10 mg) in one of six possible treatment sequences. In cohort 2, the subjects were randomized to receive single doses of treatment D (AZOR: combination tablet formulation of olmesartan medoxomil 40 mg and amlodipine besylate 5 mg), treatment E (AZOR: combination tablet formulation of olmesartan medoxomil 20 mg and amlodipine besylate 10 mg) or treatment F (AZOR: combination tablet formulation of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg) in one of six possible treatment sequences. A 21-day-washout period followed the dosing for each period.

Sample treatments and pharmacokinetic data analysis

Blood samples were collected into EDTA blood collection tubes and plasma was separated by centrifugation. Two aliquots of at least 0.7 ml of plasma each were removed, placed in screw-cap polypropylene tubes and immediately stored at −20 °C or below until the analysis. Blood samples were collected before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 h following each dose. The plasma concentrations of olmesartan were determined by a validated method of high-performance liquid chromatography with fluorescence detection. The lower limit of quantification for olmesartan was 1 ng ml^{-1}.[27] The pharmacokinetic parameters were calculated from the individual plasma concentrations of olmesartan by non-compartmental methods using WinNonlin Professional, version 4.0.1 (Pharsight, St Louis, MO, USA).

Identification of SNPs and genotyping

For genotyping, blood samples were collected into polypropylene EDTA evacuated tubes before the first treatment in each study. Genomic DNA was isolated from leukocytes. All of the exons, exon–intron junctions and 2 kb of the 5′ and 3′ flanking regions of *SLCO1B1*, *SLCO1B3* and *ABCC2* in the DNA from 115 subjects were amplified for the sequencing. Figure 1 illustrates the regions of each gene sequenced. The primers are summarized in Tables 1–3 (Supplementary data). PCR was performed in a GeneAmp PCR System 9700

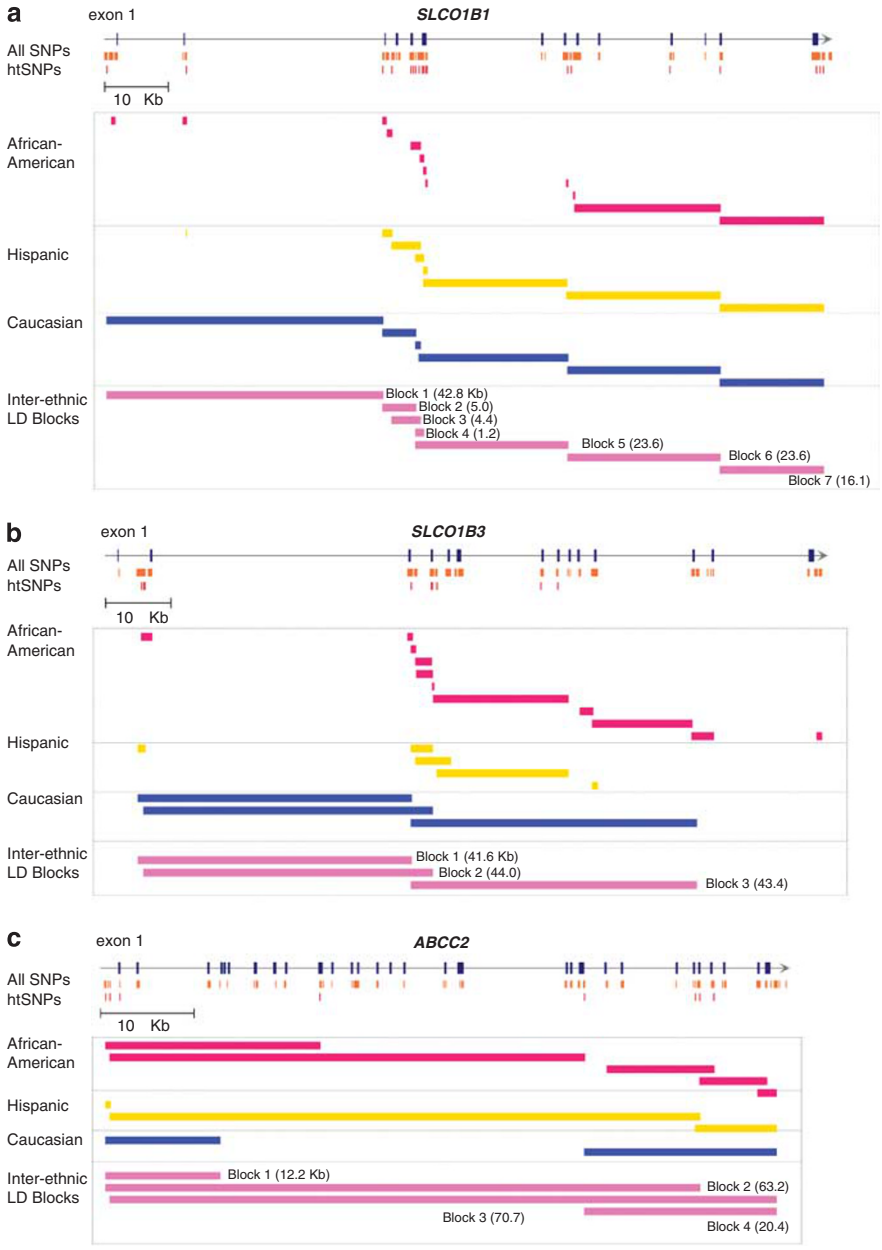

Figure 1 SNPs and LD blocks of *SLCO1B1* (**a**), *SLCO1B3* (**b**) and *ABCC2* (**c**).The horizontal line depicts the genomic region and the blue boxes show the exons of the transporter genes. Below the line, all the identified SNPs and haplotype tagged SNPs (htSNPs) are indicated in orange and red, respectively. For LD structure, SNPs with MAF $\geqslant$0.1 were used in each population. Red, yellow and blue bars indicate the LD blocks of the African-American, Hispanic and Caucasian populations, respectively. Inter-ethnic LD blocks are presented in pink at the bottom of the figures.

(Applied Biosystems, Carlsbad, CA, USA). All the amplicons were purified, diluted and used in standard Big-Dye terminator sequence reactions under standard procedures (Applied Biosystems), and the sequence was determined on an ABI 3730xL automated sequencer (Applied Biosystems). Each chromatogram was assembled in the NCBI human genome reference sequences NT_009714.16 for *SLCO1B1* and *SLCO1B3* and NT_030059.12 for *ABCC2* using the Phred/Phrap/Consed[28–30] software suite. Only putative SNPs were detected in the sequenced regions by the PolyPhred, version 4.0.[31] In contrast, insertion/deletion (indel) variations were not selected as candidate loci to construct an LD block, because the indel search function of PolyPhred version 4.0 was still under development and identified only sequences that appeared to be heterozygous for an indel. The positions of the SNPs were given in relation to the NCBI references NM_006446.2 for *SLCO1B1*, NM_019844.1 for *SLCO1B3* and NM_000392.1 for *ABCC2*.

Statistical analysis

Deviations from the Hardy–Weinberg equilibrium were tested with the SNP-HWE software[32] using an exact test. LD for each pair of SNPs was quantified by *D*' values and LD block structures were determined using the program QTLHAPLO.[33] Estimation of haplotype frequencies and identifying haplotype-tagging SNPs were performed by the same program. Haplotype marker-trait associations were tested with a mixed model using nlm package in R[34] to handle unbalanced and correlated observations arising from repeated measures on an individual who was administered with olmesartan at various dosages, 10, 20 and 40 mg. The model contained subjects as a random effect, diplotype as the predictor of main interest and other fixed effects including doses of olmesartan medoxomil and creatinine clearance values that were calculated with the Cockcroft-Gault formula.[35] However, ethnicity was not included in the final model, as a result of the prior evaluation using the model selection

criterion Akaike's information criterion. The pharmacokinetic data, AUC_{0-t} and C_{max} were log-transformed for the statistical analysis. The significance level for the association tests was set at $P<0.05$ after multiple testing correction by the Benjamini and Hochberg method[36] in each genetic inheritance mode (trend, genotype, dominant or recessive).

RESULTS

Allele frequencies of SNPs

A total of 348 SNPs were identified; a SNP was defined as a genotype success rate exceeding 80% and with a minor allele frequency (MAF) of $\geqslant 0.01$ in at least one population group. There was no evidence of deviation from the Hardy–Weinberg equilibrium within each population. The allele frequencies, locations and identifier codes for SNPs are shown in Table 2a–c. A total of 132 SNPs were detected in *SLCO1B1*, 130 in *SLCO1B3* and 86 in *ABCC2*. The rates of newly detected SNPs within these were ~0.1%, 0.07% and 0.3%, respectively. The majority of the SNPs were located in introns; with only 54 detected in coding regions, including 33 nonsynonymous SNPs.

The allele frequencies of some SNPs varied among populations (Table 2). A total of 149 population-specific SNPs were observed (149/348). African-Americans had the highest number of population-specific SNPs, 131, while Hispanics had 10 and Caucasians 8. Meanwhile, some SNPs were detected across the three populations with MAF$\geqslant$0.05; 36 SNPs in *SLCO1B1*, 48 in *SLCO1B3* and 12 in *ABCC2*.

We evaluated LD using SNPs with a MAF$\geqslant$0.1 in each population by QTLHAPLO. We defined an LD block as a consecutive region with $D'>0.9$ and extended an edge of the LD block by using an adjacent SNP while the cumulative frequency of major haplotype with a frequency$>$0.1 exceeded 0.9. In *SLCO1B1*, 12 LD blocks were inferred from 38 SNPs in African-Americans, 8 were inferred from 36 SNPs in Hispanics and 6 were inferred from 29 SNPs in Caucasians (Figure 1). In *SLCO1B3*, 11 LD blocks were inferred from 57 SNPs in African-Americans, 5 were inferred from 47 SNPs in Hispanics and 3 were inferred from 19 SNPs in Caucasians. In *ABCC2*, 5 LD blocks were inferred from 18 SNPs in African-Americans, 3 were inferred from 12 SNPs in Hispanics and 2 were inferred from 9 SNPs in Caucasians. The number of LD blocks differed across the three populations, with the African-American population having a larger number and shorter stretches of LD in *SLCO1B1* and *SLCO1B3*.

Inter-ethnic LD blocks and haplotypes based on tag SNPs

In an attempt to define the inter-ethnic LD blocks across the populations, we examined two population-based (Hispanics and Caucasians) LD blocks by QTLHAPLO. Block structure was assessed using SNPs with a MAF$\geqslant$0.1 and any overlapping pairs were joined.[19] Borders were characterized by the SNPs at the terminal ends of the block in any one population. We did not adapt the LD block structure of African-Americans, due to the small block size compared to the other populations. Figure 1 also illustrates the inter-ethnic LD blocks of the three genes. Eight inter-ethnic LD blocks were observed in *SLCO1B1*; block 1 (SNP ID 574~485), block 2 (485~514), block 3 (493~521), block 4 (514~525), block 5 (514~546), block 6 (546~592) and block 7 (592~616). In *SLCO1B3*, three inter-ethnic LD blocks were observed; block 1 (633~666), block 2 (646~684) and block 3 (666~765). *ABCC2* contained four inter-ethnic LD blocks; block 1 (792~796), block 2 (792~867), block 3 (795~891) and block 4 (848~891).

The haplotypes in the inter-ethnic LD blocks were estimated using SNPs with a MAF$\geqslant$0.05. The tagged SNPs were selected from the Hispanic and Caucasian population-based LD blocks. We merged the haplotype tagged SNPs from any one population as the inter-ethnic tagged SNPs, after identifying the haplotype tagged SNPs in each population using QTLHAPLO. The most frequent haplotypes in each block for the three genes are summarized in Table 3. In general, African-Americans tended to have greater diversity than the Hispanic and Caucasian populations. The most frequent haplotypes in each block were almost the same for Hispanics and Caucasians, but different for African-Americans.

Association study

Table 4 shows the results of the association study between *SLCO1B1*, *SLCO1B3* and *ABCC2* haplotypes and the pharmacokinetics of olmesartan. The mean and s.d. of pharmacokinetic parameters of olmesartan for 2-copy carriers, 1-copy carriers and noncarriers for the major haplotypes in *SLCO1B1*, *SLCO1B3* and *ABCC2* are shown in Table 4 to 6 (Supplementary data). However, the pharmacokinetic data of treatment B and D in cohort 1 were not used because of the difference of the formulation. After statistical analysis, some haplotypes showed association with pharmacokinetic parameters in *SLCO1B1* and *SLCO1B3*. In *SLCO1B1*, allele dosage effects ($P=0.0042$, 0.0093) in all dose groups in two haplotypes (AGAAA and ACCTTC) were shown. In *SLCO1B3*, the smallest *P*-value ($P=0.0153$) was shown in the GACCT haplotype in block 3. However, none of these results pass the significance threshold after multiple test correction. On the other hand, there was no haplotype-trait association in the *ABCC2* gene.

DISCUSSION

The difference of the length of LD blocks is observed across ethnic groups. Hispanics and African-Americans are also known as racially admixed populations. We therefore thought that the genetic backgrounds of our Hispanic and African-American samples might be different from those of the HapMap MXL and ASW. In this study, we attempted to discover SNPs and define putative LD blocks in three ethnic populations, African-American, Hispanic and Caucasian, considering the nature of the LD across *SLCO1B1*, *SLCO1B3* or *ABCC2* genes to identify inter-ethnic LD blocks. Among 348 SNPs we identified in our study, 149 SNPs (42.8%) were population-specific SNPs; 131 for African-Americans, 10 for Hispanics and 8 for Caucasians, indicating that large intra-ethnic diversity in frequency of SNPs in African-Americans. In contrast, 133 SNPs (38.2%) were detected across the three populations; 49 SNPs (37.1%, 49/132 in total) for *SLCO1B1*, 63 (48.5%) for *SLCO1B3* and 21 (24.4%) for *ABCC2*, suggesting that large inter-ethnic differences in frequency of SNPs in *ABCC2* among the three genes we investigated.

In *SLCO1B1*, we defined 12 major haplotypes in 7 common LD blocks. Carriers with AGAAA haplotype in block 2 or GAAT haplotype in block 3 tended to show higher AUC values than noncarriers. Both AGAAA and GAAT haplotypes include SNP 505 (underlined), registered in dbSNP as rs2306283 and located in exon 5, which was reported as the functionally important SNP 388A$>$G (N130D).[37,38] Two human studies on the pharmacokinetic profile of pravastatin reported that 388A$>$G was associated with increased transport activity of organic anion-transporting polypeptide 1B1, leading to lower AUC of pravastatin in subjects having G allele position at 505.[37,38] Higher AUC values in subjects with A allele may be due to SNP 388A$>$G; however, these trends were not statistically significant. Another functionally important SNP is 521T$>$C (rs4149056; V174A), SNP 524 in block 4.[8] In our study, SNP 524

Table 2 SNPs identified in (a) SLCO1B1 (b) SLCO1B3 (c) ABCC2

							Allele 1 frequency			
SNP ID	*Physical position*	*Allele 1*	*Allele 2*	*Amino acid 1*	*Amino acid 2*	*dbSNP ID*	*African-American*	*Hispanic*	*Caucasian*	*Gene structure*
(a)										
570	21282270	A	C			rs79241114	0.926	0.983	1.000	5_FLNK
572	21282410	A	G			rs4149013	1.000	0.975	0.938	5_FLNK
573	21282474	A	G			rs58208020	0.972	1.000	1.000	5_FLNK
574	21282570	T	C			rs17328763	0.986	0.924	0.781	5_FLNK
575	21282938	A	T			rs76775514	0.931	0.992	1.000	5_FLNK
576	21282953	G	T			rs4149014	0.056	0.034	0.000	5_FLNK
577	21282958	G	T				0.986	1.000	1.000	5_FLNK
578	21282972	C	G			rs55747526	0.014	0.000	0.000	5_FLNK
579	21283054	C	T			rs187349737	0.986	1.000	1.000	5_FLNK
580	21283108	A	C				0.014	0.000	0.000	5_FLNK
581	21283250	A	G			rs59310111	0.875	1.000	1.000	5_FLNK
582	21283322	A	G			rs4149015	0.000	0.025	0.063	5_FLNK
583	21283340	C	T				0.014	0.000	0.000	5_FLNK
584	21283520	A	G			rs73598368	0.014	0.000	0.000	5_FLNK
586	21283819	C	T			rs11835045	0.181	0.034	0.000	5_FLNK
587	21284010	A	C			rs59710386	1.000	0.975	1.000	5_FLNK
588	21284114	A	G			rs184715914	0.986	1.000	1.000	5_FLNK
480	21294293	G	T			rs2010668	0.864	0.958	1.000	Intron 1
481	21294329	C	T			rs11045784	0.056	0.000	0.000	Intron 1
483	21294795	A	T			rs12812795	0.939	0.858	0.938	Intron 2
484	21294840	A	G			rs12303784	0.864	0.858	0.938	Intron 2
485	21325347	A	G			rs7295464	0.847	0.845	0.813	Intron 2
487	21325798	A	G				0.986	1.000	1.000	Intron 3
488	21325814	G	T			rs2291073	0.500	0.051	0.063	Intron 3
489	21325949	A	G			rs2291074	0.833	0.814	1.000	Intron 3
490	21326094	C	T			rs115335582	0.028	0.000	0.000	Intron 3
491	21326226	G	T				0.014	0.000	0.000	Intron 3
492	21326728	A	G			rs60318946	0.806	0.871	0.875	Intron 3
493	21326756	G	T			rs10770789	0.653	0.672	0.813	Intron 3
494	21326810	G	T			rs10770790	0.833	0.847	0.813	Intron 3
495	21326846	C	T				0.014	0.000	0.000	Intron 3
496	21326848	C	T				0.014	0.000	0.000	Intron 3
497	21326957	C	G			rs141947394	0.972	1.000	1.000	Intron 3
498	21327026	A	G				0.014	0.000	0.000	Intron 3
499	21327104	G	T			rs138953877	0.014	0.000	0.000	Intron 3
500	21327349	A	T				0.986	1.000	1.000	Intron 3
501	21327798	A	G			rs146177262	1.000	0.981	1.000	Intron 4
502	21327842	A	G			rs10466794	0.972	1.000	1.000	Intron 4
503	21327906	A	G			rs71581981	0.000	0.000	0.063	Intron 4
505	21329738	A	G	N	D	rs2306283	0.270	0.585	0.688	Exon 5
506	21329761	A	G	S	S	rs11045818	0.014	0.051	0.100	Exon 5
507	21329813	A	C	T	P	rs11045819	0.042	0.051	0.100	Exon 5
508	21329991	C	T			rs11045820	0.986	0.949	0.900	Intron 5
509	21329996	A	T			rs4149044	0.500	0.822	0.833	Intron 5
511	21330020	A	G			rs4149045	0.485	0.178	0.167	Intron 5
512	21330022	A	G			rs4149046	0.152	0.432	0.500	Intron 5
513	21330338	C	T			rs4149047	0.986	1.000	1.000	Intron 5
514	21330351	A	G			rs4149048	0.500	0.822	0.833	Intron 5
515	21330687	A	G			rs4149049	0.865	0.814	1.000	Intron 5
516	21330988	C	T			rs4149050	0.516	0.212	0.250	Intron 5
517	21331003	A	G				0.016	0.000	0.000	Intron 5
518	21331057	A	G			rs4149051	0.500	0.793	0.750	Intron 5
519	21331059	A	G			rs4149052	0.514	0.793	0.750	Intron 5
520	21331135	G	T			rs4149053	0.547	0.788	0.750	Intron 5
521	21331179	A	G			rs4149054	0.394	0.212	0.250	Intron 5

Table 2 (Continued)

SNP ID	Physical position	Allele 1	Allele 2	Amino acid 1	Amino acid 2	dbSNP ID	Allele 1 frequency			Gene structure
							African-American	Hispanic	Caucasian	
522	21331238	A	G			rs141555703	0.016	0.017	0.000	Intron 5
523	21331499	C	T			rs74541382	0.015	0.000	0.000	Intron 5
524	21331549	C	T	A	V	rs4149056	0.045	0.161	0.188	Exon 6
525	21331599	C	T	L	L	rs4149057	0.258	0.449	0.567	Exon 6
526	21331625	C	T	F	F	rs2291075	0.484	0.737	0.625	Exon 6
527	21331987	C	T			rs2291076	0.879	0.602	0.563	Intron 7
528	21332147	A	T			rs138232245	0.000	0.017	0.000	Intron 7
529	21332221	A	T			rs2291077	0.583	0.457	0.393	Intron 7
531	21349885	A	G	I	V	rs11045852	0.946	1.000	1.000	Exon 8
532	21349910	A	G	Q	R	rs11045853	0.014	0.000	0.000	Exon 8
533	21350034	A	G	L	L	rs11045854	0.054	0.000	0.000	Exon 8
534	21350396	C	T			rs7957274	0.030	0.069	0.094	Intron 8
535	21350401	A	T			rs11045855	0.946	1.000	1.000	Intron 8
536	21353317	G	T			rs12312746	0.042	0.000	0.000	Intron 8
537	21353330	A	G			rs12305699	0.014	0.000	0.000	Intron 8
538	21353557	C	T	Y	Y	rs57040246	0.944	1.000	1.000	Exon 9
539	21353629	A	G			rs78755070	0.014	0.056	0.000	Intron 9
540	21353648	A	C			rs12319213	0.903	1.000	1.000	Intron 9
541	21353672	A	G			rs12305884	0.097	0.000	0.000	Intron 9
542	21353782	G	T				0.986	1.000	1.000	Intron 9
543	21353788	C	T			rs12305852	0.958	1.000	1.000	Intron 9
544	21353826	A	G			rs12319308	0.903	1.000	1.000	Intron 9
545	21353872	A	G			rs4149066	0.700	0.864	1.000	Intron 9
546	21353911	C	G			rs4149067	0.515	0.678	0.833	Intron 9
547	21354340	C	T			rs144180550	0.986	1.000	1.000	Intron 9
548	21354368	C	T			rs114419265	0.986	0.990	1.000	Intron 9
549	21354399	C	T			rs192850908	0.014	0.000	0.000	Intron 9
550	21354419	A	G			rs116568444	0.015	0.000	0.000	Intron 9
551	21354470	A	G			rs1564365	0.912	0.966	0.933	Intron 9
552	21354494	C	T			rs1564364	0.162	0.534	0.567	Intron 9
553	21354797	A	T			rs12314902	0.043	0.000	0.000	Intron 9
554	21354938	A	G			rs12307943	0.103	0.000	0.000	Intron 9
555	21355085	C	T			rs7955751	0.278	0.139	0.000	Intron 9
556	21355115	A	G			rs143523167	0.044	0.000	0.000	Intron 9
557	21355167	G	T			rs77076549	0.971	1.000	1.000	Intron 9
558	21355489	C	G	F	L	rs59113707	0.958	1.000	1.000	Exon 10
559	21355537	A	G	V	V	rs11045859	0.097	0.000	0.000	Exon 10
560	21355597	C	T	A	A	rs139049237	0.986	1.000	1.000	Exon 10
561	21355827	A	G				0.014	0.000	0.000	Intron 10
562	21355938	C	G			rs76076366	0.943	1.000	1.000	Intron 10
563	21358783	C	G			rs75563002	0.956	1.000	1.000	Intron 10
564	21358933	C	G	A	G	rs59502379	0.985	0.991	1.000	Exon 11
565	21369785	A	G			rs191168976	0.014	0.000	0.000	Intron 11
566	21369883	C	G			rs4149070	0.622	0.856	0.900	Intron 11
567	21369964	C	T			rs4149071	0.324	0.144	0.100	Intron 11
568	21369985	A	G			rs4149072	0.189	0.134	0.033	Intron 11
569	21370275	C	G			rs77112190	0.014	0.000	0.000	Intron 12
590	21375307	A	G			rs71577817	1.000	0.991	0.933	Intron 13
591	21377497	A	C			rs12814646	0.069	0.076	0.094	Intron 13
592	21377559	C	G			rs4149080	0.125	0.186	0.219	Intron 13
594	21377922	A	G			rs72655362	0.097	0.000	0.000	Intron 14
595	21391818	C	T			rs12815795	0.056	0.076	0.094	Intron 14
597	21391976	A	C	L	F	rs34671512	0.903	0.992	0.969	Exon 15
598	21392205	C	T			rs72655363	0.986	1.000	1.000	Exon 15
599	21392244	C	G			rs74064260	0.028	0.000	0.000	Exon 15
601	21392562	G	T			rs4149087	0.236	0.407	0.375	Exon 15

Table 2 (Continued)

SNP ID	Physical position	Allele 1	Allele 2	Amino acid 1	Amino acid 2	dbSNP ID	Allele 1 frequency			Gene structure
							African-American	Hispanic	Caucasian	
602	21392572	A	C			rs11045891	0.972	0.924	0.906	Exon 15
603	21392586	A	G			rs4149088	0.764	0.593	0.625	Exon 15
604	21392698	A	G			rs61760249	0.014	0.008	0.031	Exon 15
605	21392794	A	G			rs11045892	0.944	0.924	0.906	3_FLNK
606	21392819	C	T			rs11045893	0.056	0.076	0.100	3_FLNK
607	21392867	C	T			rs146311058	1.000	1.000	0.969	3_FLNK
608	21393018	G	T			rs12372157	0.229	0.414	0.367	3_FLNK
611	21393419	G	T			rs76497895	0.986	0.983	1.000	3_FLNK
612	21393469	C	T			rs11045895	0.069	0.000	0.000	3_FLNK
613	21393480	C	T			rs77757956	0.958	0.862	1.000	3_FLNK
615	21393586	A	G			rs12370842	0.044	0.069	0.077	3_FLNK
616	21393651	A	C			rs11045896	0.819	0.669	0.719	3_FLNK
617	21393726	A	G			rs111273303	0.986	1.000	1.000	3_FLNK
618	21393729	A	C			rs115431317	0.903	1.000	1.000	3_FLNK
619	21393753	A	G			rs111436442	0.986	1.000	1.000	3_FLNK
620	21393815	A	C				0.000	0.000	0.031	3_FLNK
621	21393829	A	T			rs12372593	0.056	0.070	0.094	3_FLNK
622	21393830	A	T			rs12367506	0.944	0.930	0.906	3_FLNK
624	21394544	G	A			rs11045897	0.972	0.931	0.906	3_FLNK
625	21394558	T	C			rs1080411	1.000	0.991	0.969	3_FLNK
626	21394679	C	A			rs74064264	0.972	1.000	1.000	3_FLNK
(b)										
628	20963734	A	C			rs140417865	0.014	0.000	0.000	Intron 1
629	20966590	A	G			rs12810377	0.980	0.943	0.967	Intron 1
631	20966681	A	T			rs12812137	0.015	0.060	0.031	Intron 1
633	20966722	C	T			rs1356149	0.029	0.134	0.219	Intron 1
634	20966929	A	G				1.000	1.000	0.967	Intron 1
635	20966945	A	C			rs77714247	1.000	0.982	0.967	Intron 1
636	20966962	A	G			rs76036462	0.984	1.000	1.000	Intron 1
637	20966995	G	T			rs10841654	0.000	0.045	0.000	Intron 1
638	20967110	C	T			rs138383488	0.985	1.000	1.000	Intron 1
639	20967215	C	G			rs4149107	0.074	0.198	0.250	Intron 1
640	20967283	A	G			rs2138334	0.875	0.353	0.313	Intron 1
641	20967345	A	G			rs115521203	0.929	0.991	1.000	Intron 1
642	20967361	A	G			rs182634947	0.000	0.036	0.000	Intron 1
643	20967546	C	T			rs143939336	0.029	0.036	0.000	Intron 1
644	20967591	A	G			rs150240058	0.014	0.000	0.000	Intron 1
645	20967604	C	T				1.000	0.982	1.000	Intron 1
646	20967617	A	G			rs3942320	0.676	0.813	0.750	Intron 1
647	20967627	A	C			rs11608908	0.986	0.946	0.969	Intron 1
649	20967673	C	A			rs2417947	0.210	0.009	0.000	Intron 1
650	20967682	G	A			rs2417946	0.468	0.264	0.250	Intron 1
651	20967685	C	T			rs142364021	0.986	1.000	1.000	Intron 1
652	20967743	A	G			rs7309718	0.943	0.870	0.781	Intron 1
653	20968219	C	T			rs189898653	0.014	0.000	0.000	Intron 1
655	20968515	G	T			rs151186495	0.986	1.000	1.000	Intron 1
658	20968828	C	T			rs10734710	0.371	0.070	0.000	Intron 2
659	21007718	G	A			rs4149108	0.857	0.948	1.000	Intron 2
660	21007868	G	A			rs142620717	0.971	1.000	1.000	Intron 2
661	21007985	C	G	F	L	rs79042365	0.912	1.000	1.000	Exon 3
664	21008143	A	C			rs7302920	0.941	1.000	1.000	Intron 3
666	21008356	T	G			rs4149109	0.563	0.214	0.125	Intron 3
668	21008432	C	G			rs4149110	0.578	0.214	0.094	Intron 3
670	21008846	C	G			rs77638597	1.000	0.991	0.933	Intron 3
671	21008908	A	T			rs74067318	0.833	0.905	0.967	Intron 3

Table 2 (Continued)

SNP ID	Physical position	Allele 1	Allele 2	Amino acid 1	Amino acid 2	dbSNP ID	Allele 1 frequency			Gene structure
							African-American	Hispanic	Caucasian	
672	21009049	A	T			rs10841672	0.609	0.207	0.100	Intron 3
674	21009080	G	A				0.984	1.000	1.000	Intron 3
675	21009149	A	T			rs187606474	0.891	1.000	1.000	Intron 3
676	21009213	A	G			rs10841673	0.606	0.202	0.100	Intron 3
678	21011235	C	T			rs4149114	0.439	0.819	0.906	Intron 3
679	21011253	A	G			rs141618120	0.985	1.000	1.000	Intron 3
680	21011296	A	G			rs4149115	0.576	0.188	0.094	Intron 3
681	21011310	C	T			rs4149116	0.412	0.813	0.906	Intron 3
683	21011480	G	T	A	S	rs4149117	0.443	0.805	0.906	Exon 4
684	21011581	A	G			rs4149118	0.236	0.578	0.700	Intron 4
685	21011753	A	T			rs12579674	0.889	0.814	0.938	Intron 4
687	21011792	A	G			rs12579677	0.903	0.814	0.938	Intron 4
688	21011813	C	T			rs4762683	0.557	0.178	0.094	Intron 4
689	21012105	A	G			rs73233619	0.941	1.000	1.000	Intron 4
690	21012137	G	T			rs12582527	0.914	0.828	1.000	Intron 4
691	21012253	G	A			rs6487160	0.571	0.181	0.094	Intron 4
692	21012273	G	A			rs6487161	0.529	0.172	0.094	Intron 4
693	21012291	A	C			rs1910188	0.557	0.184	0.100	Intron 4
694	21012341	C	T			rs147571794	1.000	0.983	1.000	Intron 4
696	21013631	C	T			rs2417943	0.568	0.203	0.094	Intron 4
698	21013678	A	G			rs2900473	0.569	0.203	0.094	Intron 4
700	21013821	A	G			rs71539433	0.014	0.000	0.000	Intron 4
703	21013948	C	T			rs3764009	0.568	0.203	0.094	Intron 4
704	21014030	A	G	T	A	rs57585902	0.973	1.000	1.000	Exon 5
705	21014125	C	T			rs145180166	0.946	1.000	1.000	Intron 5
706	21014126	A	G			rs111795682	0.000	0.000	0.031	Intron 5
707	21014139	C	G			rs3764008	0.568	0.203	0.094	Intron 5
708	21014163	A	T			rs3764007	0.431	0.797	0.906	Intron 5
709	21014178	A	G			rs7306033	0.892	0.924	0.813	Intron 5
710	21014269	A	G			rs4149119	0.432	0.797	0.906	Intron 5
712	21014343	C	T			rs4762798	0.621	0.182	0.067	Intron 5
713	21015075	G	T			rs4149122	0.571	0.128	0.067	Intron 5
714	21015119	A	G			rs79578494	0.028	0.086	0.031	Intron 5
715	21015139	G	T			rs1017385	0.574	0.193	0.094	Intron 5
716	21015205	A	C			rs1017386	0.429	0.813	0.906	Intron 5
717	21015243	C	G			rs2017737	0.569	0.184	0.094	Intron 5
719	21015526	C	T			rs74067337	0.903	1.000	1.000	Intron 6
720	21015610	A	G			rs1036261	0.569	0.203	0.094	Intron 6
721	21015760	A	G	I	M	rs7311358	0.429	0.824	0.906	Exon 7
722	21015815	T	G			rs16923270	0.914	0.912	0.969	Intron 7
723	21015818	T	C			rs80224189	0.900	0.982	1.000	Intron 7
725	21015864	C	G			rs71583718	0.971	0.905	0.969	Intron 7
726	21015906	C	G			rs17680137	0.986	0.931	0.813	Intron 7
727	21015960	T	C			rs75186825	0.972	1.000	1.000	Intron 7
728	21016194	G	A			rs186453342	0.986	0.991	0.969	Intron 7
729	21016195	G	A			rs189315032	0.986	0.991	0.969	Intron 7
730	21028093	C	T			rs3829311	0.338	0.712	0.875	Intron 7
731	21028135	G	T			rs114404671	0.041	0.008	0.000	Intron 7
732	21028200	A	T	R	R	rs61736830	0.014	0.000	0.000	Exon 8
733	21028208	C	G	A	G	rs60140950	0.014	0.076	0.188	Exon 8
734	21028338	A	G	L	L		0.014	0.000	0.000	Exon 8
735	21028432	A	G			rs117522823	0.000	0.025	0.000	Intron 8
736	21030476	A	T			rs140143437	0.014	0.000	0.000	Intron 8
737	21030486	G	T				0.014	0.000	0.000	Intron 8
738	21030582	A	G			rs4149135	0.446	0.797	0.906	Intron 8
739	21030584	A	G			rs4149136	0.097	0.085	0.031	Intron 8

Table 2 (Continued)

SNP ID	Physical position	Allele 1	Allele 2	Amino acid 1	Amino acid 2	dbSNP ID	Allele 1 frequency			Gene structure
							African-American	Hispanic	Caucasian	
740	21030590	C	T			rs4149137	0.770	0.364	0.313	Intron 8
741	21030672	A	T			rs4149139	0.959	0.932	1.000	Intron 8
742	21032242	G	T			rs4149142	0.431	0.797	0.906	Intron 9
745	21033929	A	C	Y	S		0.014	0.000	0.000	Exon 11
746	21034017	A	T			rs4149144	0.770	0.864	0.969	Intron 11
747	21035814	A	G				0.986	1.000	1.000	Intron 11
748	21035930	A	T			rs4482080	0.125	0.000	0.000	Intron 11
749	21035943	A	G			rs4332570	0.569	0.203	0.094	Intron 11
750	21035981	A	G			rs4149149	0.569	0.203	0.094	Intron 11
751	21035982	A	G			rs4149150	0.431	0.797	0.906	Intron 11
752	21036102	A	G			rs2053095	0.569	0.203	0.094	Intron 11
753	21036168	C	T			rs2053096	0.414	0.797	0.906	Intron 11
754	21036270	G	T			rs2053097	0.431	0.797	0.906	Intron 11
755	21036300	C	T			rs77784280	1.000	0.992	0.969	Intron 11
756	21036326	G	T			rs4149151	0.958	0.958	1.000	Intron 11
757	21036411	A	G	A	A	rs2053098	0.569	0.203	0.094	Exon 12
758	21036468	C	T	V	V	rs77851390	0.014	0.000	0.000	Exon 12
759	21036533	C	T	A	V	rs12299012	0.014	0.000	0.000	Exon 12
760	21036683	A	C			rs2053099	0.569	0.203	0.094	Intron 12
761	21051169	G	T			rs74065710	0.108	0.008	0.000	Intron 12
763	21051399	C	G	A	G	rs76963574	1.000	0.983	1.000	Exon 13
764	21051489	C	T			rs4149153	0.459	0.220	0.094	Intron 13
765	21051769	A	T			rs7973653	0.014	0.076	0.188	Intron 13
767	21052196	C	T			rs73233632	0.878	1.000	1.000	Intron 13
768	21053480	C	T			rs74722169	0.958	1.000	1.000	Intron 13
769	21054046	A	C			rs4149155	0.042	0.068	0.000	Intron 13
772	21068848	C	T			rs12822208	1.000	1.000	0.969	Intron 14
773	21068915	C	T			rs78862986	0.986	0.975	1.000	Intron 14
774	21069049	A	G	S	S	rs60571683	0.000	0.042	0.125	Exon 15
775	21069808	A	G			rs79132805	0.097	0.000	0.000	3_FLNK
776	21069823	A	G			rs77957556	0.014	0.000	0.000	3_FLNK
778	21070135	C	T			rs74805787	1.000	0.975	0.969	3_FLNK
779	21070137	A	T			rs10841707	0.542	0.915	1.000	3_FLNK
780	21070188	C	G				0.014	0.000	0.000	3_FLNK
781	21070243	A	C			rs145796483	0.041	0.000	0.000	3_FLNK
782	21070488	C	T				1.000	0.992	0.969	3_FLNK
783	21070519	A	G			rs34734909	0.986	0.975	1.000	3_FLNK
785	21070683	C	T			rs12581998	0.847	0.788	0.875	3_FLNK
787	21070814	A	G			rs11831588	0.986	1.000	1.000	3_FLNK
788	21070887	A	C			rs138529107	0.986	1.000	1.000	3_FLNK
789	21070922	C	G			rs919840	0.542	0.915	1.000	3_FLNK
(c)										
790	101540955	C	T			rs17222660	0.014	0.000	0.000	5_FLNK
791	101541039	A	G			rs17222653	0.014	0.000	0.000	5_FLNK
792	101541053	A	G			rs1885301	0.417	0.447	0.375	5_FLNK
794	101541579	A	G			rs7910642	0.153	0.110	0.125	5_FLNK
795	101541583	A	G			rs2804402	0.667	0.585	0.625	5_FLNK
796	101542578	C	T			rs717620	0.931	0.853	0.906	Exon 1
797	101542579	A	G			rs17216156	0.014	0.000	0.000	Exon 1
798	101544357	A	G			rs17222610	0.028	0.000	0.000	Intron 1
799	101544447	A	T	Y	F	rs927344	0.014	0.000	0.000	Exon 2
801	101544646	A	G				0.014	0.000	0.000	Intron 2
802	101551902	C	T			rs2756108	0.014	0.000	0.000	Intron 2
803	101552099	C	G	L	V		0.986	1.000	1.000	Exon 3
805	101553259	C	T			rs2804400	0.697	0.588	0.625	Intron 3
806	101553995	A	G			rs11818057	0.944	0.983	1.000	Intron 5

Table 2 (Continued)

SNP ID	Physical position	Allele 1	Allele 2	Amino acid 1	Amino acid 2	dbSNP ID	Allele 1 frequency			Gene structure
							African-American	Hispanic	Caucasian	
807	101556824	G	T			rs17222751	0.986	0.982	1.000	Intron 6
811	101557182	C	T				0.986	1.000	1.000	Intron 7
812	101559158	A	C				0.986	0.982	1.000	Intron 8
813	101560106	A	C			rs79174032	0.014	0.017	0.000	Intron 8
814	101560169	A	G	H	R	rs7080681	0.014	0.000	0.000	Exon 9
815	101560218	C	T	T	T		0.014	0.000	0.000	Exon 9
816	101563815	A	G	I	V	rs2273697	0.257	0.178	0.094	Exon 10
817	101563978	G	T	G	V		0.014	0.000	0.000	Exon 10
818	101564169	C	T				1.000	0.992	0.969	Intron 10
820	101567255	A	G	I	V		0.014	0.000	0.000	Exon 12
821	101567501	A	C			rs57420310	0.056	0.018	0.000	Intron 12
822	101567620	A	C			rs60123852	0.944	0.983	1.000	Intron 12
823	101567672	A	G			rs60190212	0.056	0.017	0.000	Intron 12
824	101567786	A	T			rs76594618	0.986	1.000	1.000	Intron 12
825	101567857	G	T	L	F	rs17216233	0.014	0.000	0.000	Exon 13
827	101568013	C	G			rs8187674	0.944	0.983	1.000	Intron 13
828	101569917	A	G	E	E		0.014	0.000	0.000	Exon 14
829	101569997	C	T			rs17222639	0.000	0.034	0.125	Intron 14
831	101572816	C	T	T	I	rs17222632	0.027	0.000	0.000	Exon 16
832	101577018	A	G			rs56874013	0.056	0.025	0.000	Intron 16
834	101577035	A	T			rs79956128	0.028	0.008	0.000	Intron 16
835	101577277	G	T			rs17216268	0.986	1.000	1.000	Intron 17
836	101578683	C	T	A	V		0.014	0.000	0.000	Exon 18
838	101579082	C	T			rs77153111	0.056	0.009	0.000	Intron 19
839	101589925	A	G			rs4148395	0.250	0.175	0.094	Intron 19
840	101590020	A	G			rs11597282	0.000	0.033	0.031	Intron 19
841	101590460	G	T			rs17222737	0.014	0.000	0.000	Intron 20
842	101590486	A	G	S	G	rs41318029	0.014	0.000	0.000	Exon 21
843	101590619	C	T			rs41318031	0.944	0.975	0.938	Intron 21
844	101591334	G	T			rs76672487	0.973	0.992	1.000	Intron 21
846	101591439	A	G	A	A		0.014	0.000	0.000	Exon 22
847	101591866	A	G	Q	R		0.000	0.000	0.031	Exon 23
848	101591944	C	T			rs4148396	0.716	0.619	0.656	Intron 23
849	101592002	C	T				0.986	1.000	1.000	Intron 23
850	101594274	C	T	I	I	rs17216345	0.000	0.000	0.031	Exon 24
851	101594409	G	T			rs4581377	0.882	0.983	1.000	Intron 24
852	101594436	C	T			rs4611137	0.069	0.000	0.000	Intron 24
856	101595975	G	T	R	L	rs8187692	0.931	1.000	1.000	Exon 25
857	101595996	A	T	E	V	rs17222723	0.042	0.025	0.063	Exon 25
858	101596098	C	T				0.014	0.000	0.000	Intron 25
859	101596112	A	G				0.014	0.008	0.000	Intron 25
860	101601664	C	T			rs75004679	0.129	0.017	0.000	Intron 25
861	101603522	C	T			rs17216177	0.171	0.042	0.063	Intron 26
862	101603523	A	G				0.986	1.000	1.000	Intron 26
863	101603713	C	T				0.986	1.000	1.000	Intron 27
864	101603781	C	G			rs3740067	0.833	0.644	0.625	Intron 27
865	101604006	A	G			rs34456559	0.958	0.975	0.938	Intron 27
866	101604107	C	T	P	L	rs17216317	0.986	0.992	1.000	Exon 28
867	101604207	C	T	I	I	rs3740066	0.764	0.627	0.625	Exon 28
869	101605455	C	T	A	A	rs17216275	0.957	0.983	1.000	Exon 29
870	101605503	C	T	L	L	rs7899457	0.871	0.983	1.000	Exon 29
871	101605550	C	G			rs17216282	0.044	0.026	0.067	Intron 29
872	101605607	C	T				0.971	1.000	1.000	Intron 29
873	101605633	C	G				0.985	1.000	1.000	Intron 29
874	101605693	A	G			rs3740065	0.750	0.888	0.933	Intron 29
875	101606683	A	G			rs3740064	0.229	0.095	0.000	Intron 29

Table 2 (Continued)

SNP ID	Physical position	Allele 1	Allele 2	Amino acid 1	Amino acid 2	dbSNP ID	Allele 1 frequency: African-American	Allele 1 frequency: Hispanic	Allele 1 frequency: Caucasian	Gene structure
876	101606861	G	T	V	V	rs1137968	0.957	0.974	0.933	Exon 30
877	101606976	A	G				1.000	0.983	1.000	Intron 30
881	101610455	A	G	E	E	rs8187706	0.136	0.017	0.000	Exon 31
882	101610533	C	T	H	H	rs8187707	0.970	0.975	0.964	Exon 31
883	101610540	A	G	M	V		0.985	1.000	1.000	Exon 31
884	101610565	A	G			rs17216212	0.045	0.025	0.036	Intron 31
885	101610627	C	T			rs77106298	1.000	0.983	0.964	Intron 31
886	101611250	C	T				0.014	0.000	0.000	Intron 31
887	101611294	A	G	Y	C	rs8187710	0.181	0.042	0.063	Exon 32
888	101611798	G	T			rs12251995	0.056	0.000	0.000	3_FLNK
889	101612164	A	T				0.000	0.008	0.063	3_FLNK
890	101612267	C	T				0.056	0.000	0.000	3_FLNK
891	101612320	C	T			rs12826	0.833	0.653	0.625	3_FLNK
892	101612416	A	G				0.014	0.000	0.000	3_FLNK
893	101612466	A	T				0.958	1.000	1.000	3_FLNK
896	101613384	G	T				0.986	1.000	1.000	3_FLNK

Abbreviation: SNP, single-nucleotide polymorphism.
SNP IDs were private IDs. Physical positions were based on the NCBI human reference genome (build 37.3).

Table 3 Major haplotypes in the inter-ethnic LD blocks of three genes in three populations

Gene	Block	SNP ID (htSNP)	Haplotype	Frequency: African-Americans	Frequency: Hispanics	Frequency: Caucasians
SLCO1B1	1	574, 483, 484, 485	TAAA	0.78	0.74	0.62
	2	492, 493, 505, 509, 512	AGAAA	0.14	0.43	0.50
			AGGTG	0.31	0.05	0.03
	3	493, 505, 512, 516	GAAT	0.14	0.40	0.44
			GGGC	0.51	0.18	0.19
	4	514, 516, 524, 525	ATTC	0.23	0.45	0.56
			GCTT	0.48	0.05	0.06
	5	514, 525, 526, 527, 529, 546	ACCTTC	0.12	0.39	0.44
			GTTCAG	0.33	0.14	0.13
	6	546, 552, 566, 591, 592	CCCCG	0.14	0.53	0.62
			GTGCG	0.33	0.14	–
	7	592, 601, 608, 616	GTTA	0.79	0.61	0.65
SLCO1B3	1	639, 640, 646, 650, 666	GAAAT	0.38	0.04	–
			GGAAG	0.10	0.61	0.69
	2	650, 666, 683, 684	AGGA	0.15	0.53	0.69
			ATTG	0.36	0.07	–
	3	666, 684, 693, 730, 740	TGATC	0.57	0.19	0.10
			GACCT	0.23	0.58	0.70
ABCC2	1	792, 794, 795, 796	GGAC	0.43	0.46	0.50
	2	792, 794, 796, 816, 867	GGCAC	0.26	0.17	0.06
			GGCGC	0.19	0.28	0.34
	3	795, 796, 816, 867, 874	ACACA	0.26	0.17	0.06
			ACGCA	0.22	0.33	0.47
	4	848, 864, 867, 874	CCCA	0.53	0.51	0.53

Abbreviations: LD, linkage disequilibrium; htSNP, haplotype tagged SNPs; SNP, single-nucleotide polymorphism.
Gray columns indicate the most frequent haplotypes in each ethnic group in each LD block.

Table 4 Result of association study of SLCO1B1, SLCO1B3 and ABCC2 haplotypes with the pharmacokinetics of olmesartan

				Trend			*Genotype*			*Dominant*			*Recessive*		
Gene	*Block*	*Haplotype*	*Parameter*	*Coefficient*	*s.e.*	P-*value*	*Coefficient*	*s.e.*	P-*value*	*Coefficient*	*s.e.*	P-*value*	*Coefficient*	*s.e.*	P-*value*
SLCO1B1	1	TAAA	AUC_{0-t}	0.0306	0.0738	0.6794	0.0074	0.1943	0.9696	0.0272	0.1873	0.8848	0.0386	0.0894	0.6663
			C_{max}	0.0262	0.0652	0.6888	0.1129	0.1726	0.5142	0.1128	0.1663	0.4992	0.0130	0.0787	0.8695
	2	AGAAA	AUC_{0-t}	0.1868	0.0638	0.0042	0.1997	0.0954	0.0388	0.2387	0.0901	0.0093	0.2601	0.1296	0.0473
			C_{max}	0.1298	0.0571	0.0251	0.1296	0.0860	0.1348	0.1606	0.0811	0.0502	0.1908	0.1141	0.0974
		AGGTG	AUC_{0-t}	−0.0891	0.1009	0.3791	−0.0884	0.1077	0.4134	−0.0914	0.1062	0.3912	−0.1530	0.4892	0.7550
			C_{max}	−0.0929	0.0905	0.3069	−0.0634	0.0961	0.5107	−0.0779	0.0953	0.4156	−0.5379	0.4433	0.2277
	3	GAAT	AUC_{0-t}	0.1825	0.0652	0.0061	0.1612	0.0941	0.0897	0.2085	0.0896	0.0218	0.3048	0.1385	0.0298
			C_{max}	0.1310	0.0578	0.0254	0.0896	0.0837	0.2871	0.1345	0.0798	0.0948	0.2533	0.1202	0.0375
		GGGC	AUC_{0-t}	−0.1334	0.0707	0.0618	−0.1728	0.0931	0.0663	−0.1774	0.0891	0.0491	−0.1194	0.1671	0.4764
			C_{max}	−0.0697	0.0636	0.2754	−0.1075	0.0830	0.1980	−0.1027	0.0795	0.1993	−0.0232	0.1515	0.8787
	4	ATTC	AUC_{0-t}	0.1458	0.0636	0.0240	0.1554	0.1006	0.1257	0.1918	0.0943	0.0445	0.2014	0.1204	0.0975
			C_{max}	0.1055	0.0567	0.0656	0.1165	0.0899	0.1978	0.1414	0.0841	0.0958	0.1413	0.1063	0.1868
		GCTT	AUC_{0-t}	−0.1263	0.0858	0.1443	−0.1688	0.1096	0.1267	−0.1672	0.1043	0.1121	−0.0940	0.2283	0.6814
			C_{max}	−0.0578	0.0777	0.4586	−0.0964	0.0987	0.3310	−0.0871	0.0941	0.3568	0.0104	0.2080	0.9602
	5	ACCTTC	AUC_{0-t}	0.1788	0.0675	0.0093	0.1817	0.0964	0.0623	0.2170	0.0914	0.0194	0.2657	0.1458	0.0713
			C_{max}	0.1284	0.0599	0.0343	0.1187	0.0859	0.1699	0.1492	0.0814	0.0697	0.2071	0.1272	0.1066
		GTTCAG	AUC_{0-t}	−0.0840	0.0824	0.3104	−0.1140	0.0984	0.2494	−0.1089	0.0949	0.2541	−0.0197	0.2511	0.9376
			C_{max}	−0.0179	0.0737	0.8090	−0.0471	0.0874	0.5911	−0.0361	0.0845	0.6702	0.0915	0.2276	0.6884
	6	CCCCG	AUC_{0-t}	0.1390	0.0622	0.0276	0.1593	0.1020	0.1215	0.1934	0.0953	0.0448	0.1801	0.1130	0.1140
			C_{max}	0.0832	0.0557	0.1382	0.1019	0.0922	0.2717	0.1204	0.0858	0.1633	0.1022	0.0994	0.3064
		GTGCG	AUC_{0-t}	−0.1400	0.0822	0.0915	−0.1773	0.1001	0.0793	−0.1752	0.0959	0.0704	−0.1027	0.2483	0.6800
			C_{max}	−0.1238	0.0736	0.0955	−0.1219	0.0890	0.1737	−0.1352	0.0856	0.1172	−0.2163	0.2253	0.3391
	7	GTTA	AUC_{0-t}	0.0437	0.0630	0.4890	0.2211	0.1351	0.1048	0.1883	0.1255	0.1363	−0.0061	0.0895	0.9454
			C_{max}	0.0503	0.0555	0.3666	0.2216	0.1187	0.0646	0.1940	0.1102	0.0812	0.0040	0.0789	0.9592
SLCO1B3	1	GAAAT	AUC_{0-t}	−0.1481	0.0866	0.0906	−0.0665	0.1312	0.6133	−0.1493	0.1178	0.2080	−0.3801	0.2072	0.0696
			C_{max}	−0.0710	0.0796	0.3745	0.0230	0.1191	0.8471	−0.0463	0.1072	0.6665	−0.2644	0.1914	0.1703
		GGAAG	AUC_{0-t}	0.0273	0.0643	0.6723	0.0889	0.1192	0.4577	0.0763	0.1092	0.4862	0.0023	0.1054	0.9826
			C_{max}	−0.0005	0.0576	0.9934	0.0387	0.1074	0.7192	0.0237	0.0984	0.8102	−0.0227	0.0936	0.8092
	2	AGGA	AUC_{0-t}	0.1203	0.0584	0.0421	0.1630	0.1122	0.1492	0.1970	0.0982	0.0476	0.1564	0.1039	0.1353
			C_{max}	0.0661	0.0526	0.2114	0.0460	0.1014	0.6513	0.0861	0.0890	0.3356	0.1102	0.0921	0.2345
		ATTG	AUC_{0-t}	−0.1062	0.0854	0.2168	−0.0326	0.1249	0.7945	−0.0966	0.1134	0.3967	−0.3058	0.2087	0.1460
			C_{max}	−0.0536	0.0777	0.4924	−0.0230	0.1125	0.8388	−0.0511	0.1021	0.6175	−0.1461	0.1924	0.4494
	3	TGATC	AUC_{0-t}	−0.1229	0.0679	0.0729	−0.0839	0.0973	0.3904	−0.1259	0.0921	0.1743	−0.2452	0.1457	0.0954
			C_{max}	−0.0631	0.0610	0.3032	−0.0482	0.0863	0.5776	−0.0670	0.0814	0.4120	−0.1195	0.1332	0.3716
		GACCT	AUC_{0-t}	0.1391	0.0564	0.0153	0.1961	0.1069	0.0694	0.2317	0.0955	0.0169	0.1697	0.0979	0.0860
			C_{max}	0.0747	0.0507	0.1433	0.0818	0.0963	0.3975	0.1116	0.0862	0.1985	0.1039	0.0864	0.2318
ABCC2	1	GGAC	AUC_{0-t}	0.0674	0.0685	0.3273	0.0011	0.1064	0.9915	0.0362	0.1028	0.7252	0.1499	0.1169	0.2024
			C_{max}	0.0630	0.0607	0.3017	0.0829	0.0947	0.3832	0.0919	0.0908	0.3133	0.0637	0.1041	0.5418
	2	GGCAC	AUC_{0-t}	0.0118	0.0837	0.8879	0.0548	0.0963	0.5708	0.0371	0.0937	0.6934	−0.2050	0.2842	0.4722
			C_{max}	0.0610	0.0738	0.4108	0.0995	0.0842	0.2398	0.0871	0.0820	0.2906	−0.1139	0.2579	0.6597
		GGCGC	AUC_{0-t}	0.0216	0.0791	0.7851	0.0489	0.0911	0.5921	0.0402	0.0890	0.6524	−0.0988	0.2479	0.6910
			C_{max}	−0.0074	0.0701	0.9164	0.0280	0.0799	0.7264	0.0143	0.0785	0.8555	−0.1935	0.2239	0.3896
	3	ACACA	AUC_{0-t}	0.0048	0.0816	0.9530	0.0387	0.0990	0.6970	0.0240	0.0951	0.8016	−0.1150	0.2442	0.6387
			C_{max}	0.0557	0.0718	0.4396	0.0804	0.0868	0.3566	0.0749	0.0833	0.3707	0.0012	0.2181	0.9956
		ACGCA	AUC_{0-t}	0.0104	0.0719	0.8856	0.0563	0.0945	0.5531	0.0396	0.0905	0.6624	−0.0813	0.1696	0.6324
			C_{max}	−0.0007	0.0637	0.9914	0.0233	0.0833	0.7807	0.0138	0.0798	0.8630	−0.0537	0.1515	0.7235
	4	CCCA	AUC_{0-t}	0.0029	0.0672	0.9652	−0.0713	0.1165	0.5422	−0.0501	0.1114	0.6537	0.0508	0.1040	0.6265
			C_{max}	0.0257	0.0592	0.6645	−0.0355	0.1027	0.7305	−0.0110	0.0983	0.9107	0.0713	0.0914	0.4373

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration.
The units of AUC and C_{max} are ng h ml^{-1} and ng ml^{-1}, respectively.

was not associated with changes in any pharmacokinetic parameters. In addition to this, the SLCO1B1*1A (388A–521C), *1B (388G–521T), *5 (388A–521C) and *15 (388G–521C) haplotypes,[4] which were formed through these two SNPs, did not show any statistical significant associations (data not shown).

With regard to *SLCO1B3*, we defined six major haplotypes. Although GACCT haplotype in block 3 was associated with changes in the pharmacokinetics of olmesartan, there was no significant association after multiple test correction. TGATC haplotype in block 3 showed allele dosage trends in all dose groups. As the frequency of

TGATC haplotype in African-Americans was the highest (0.59 vs 0.19 and 0.10) in the three populations, lower AUC values are expected in this population even when the same dosage is administered. All SNPs, 666, 684, 693, 730 and 740, composing both haplotype were located in intron regions. Thus, reasons to why this haplotype is associated with changes in pharmacokinetics of olmesartan are not cleared. However, interestingly, there were 32 SNPs that showed a high LD ($r^2 > 0.8$ in all populations) relationship with SNP 693, including the cSNPs at 683 (334T>G, S112A, rs4149117 in exon 4), 721 (699G>A, M233I, rs7311358 in exon 7) and 757 (1557A>G, A519A, rs2053098 in exon 12) (data not shown).

In our study, SNPs 683 and 721 also showed a strong LD ($r^2 = 0.94$, 0.81 and 1.0 in African-Americans, Hispanics and Caucasians, respectively). Studies on the pharmacogenomics of *SLCO1B3* are scant in comparison with those on *SLCO1B1*. The association between *SLCO1B3* polymorphisms and the pharmacokinetics of paclitaxel has been studied; however, the clearance of unbound paclitaxel was not significantly associated with the *SLCO1B3* 334T>G or 699G>A polymorphisms.[39] Functional impacts of these SNPs on substrate drugs are warranted to be cleared in humans.

In *ABCC2*, no haplotype showed significantly associations with any pharmacokinetics parameters of olmesartan. We defined four common LD blocks in this study. Block 1 is located in the 5′ flanking region of *ABCC2*, and SNP 796 in block 1, which corresponds to SNP –24C>T, has been shown to reduce mRNA expression.[17] Several studies have examined the functional meaning of the coding SNPs in *ABCC2*, but there was no obvious genetic link between the coding SNPs and the haplotype in our study.

The single-SNP-based analysis was also conducted for all haplotype tagged SNPs to discuss the effect of individual SNP on the olmesartan pharmacokinetics, but there was no significant result after multiple test correction (Table 7, Supplementary data).

It has been reported that olmesartan has a dual clearance pathway, with ~60% of a dose being excreted into feces via bile and the remaining 40% being excreted into the urine,[1,2] and that multiple transporters in multiple tissues were involved in the overall pharmacokinetics of olmesartan.[3] Therefore, the effect of genetic variations of single transporters on the pharmacokinetics of olmesartan is considered to be small.

In the association study using subjects in early phase clinical studies, the sample size of enrolled subjects is often insufficient. Based on a two-tailed *t*-test assuming dominant genetic model, the statistical power for the association between haplotype AGAAA of the *SLCO1B1* gene and AUC_{0-t} at 40 mg dose was calculated to be 0.21. In a 0.8 powered study, it is estimated that about five times the number of samples is needed to confirm the results. It is therefore critical to extend current findings to the analyses of large populations.

In conclusion, we characterized the LD structures and haplotypes of *SLCO1B1*, *SLCO1B3* and *ABCC2*. The LD structures were different among three ethnic populations, but the mean olmesartan plasma concentration vs time profiles were same among them. These results may contribute to the framework of a future study on those transporters relevant to the variation in the pharmacokinetics of drugs. Indeed, the effects of associated haplotypes on the pharmacokinetics of olmesartan and the functional consequences warrant further study.

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