FULL TITLE:

Candidate-gene study of functional polymorphisms in *SLCO1B1* and *CYP3A4/5* and the cholesterol-lowering response to simvastatin

SHORT TITLE:

SLCO1B1, *CYP3A4/5* and simvastatin response

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ABSTRACT

Cholesterol-lowering response to 40mg simvastatin daily for 6 weeks was examined for associations with common genetic polymorphisms in key genes affecting simvastatin metabolism (*CYP3A4* and *CYP3A5*) and transport (*SLCO1B1*). In Whites (*n* = 608), *SLCO1B1* 521C was associated with lesser reductions of total and low-density lipoprotein cholesterol. Associations between *SLCO1B1* 521C and cholesterol response were not detected in African-Americans (*n* = 333). Associations between *CYP3A4**22 or *CYP3A5**3 and cholesterol response were not detected in either race, and no significant race-gene or gene-gene interactions were detected. As several of the analyses may have been underpowered (especially the analyses in the African American cohort), the findings not suggesting an association should not be considered conclusive and warrant further investigation. The finding regarding *SLCO1B1* 521C in Whites was consistent with several previous reports. *SLCO1B1* 521C resulted in a diminished cholesterol-lowering response, but a marginal effect size limits utility for predicting simvastatin response.

INTRODUCTION

Statins remain among the most prescribed classes of medication in the United States and are indicated for the prevention of cardiovascular disease [1]. By inhibiting HMG CoA (3-hydroxy-3-methylglutaryl-coenzyme A) Reductase, statins decrease intrahepatic cholesterol synthesis, up-regulate hepatocyte surface low-density lipoprotein cholesterol (LDL-C) receptors, increase hepatic LDL-C uptake and ultimately decrease blood concentrations of LDL-C. Reduction in LDL-C concentration is common proxy measure of statin efficacy, with an estimated reduction in risk of major cardiovascular events of nearly 20% per mmol/L (38 mg/dL) reduction in LDL-C [2]. However, not all patients respond favorably to statins. A substantial proportion of patients do not achieve cholesterol goals, and some experience adverse effects such as statin-induced myopathy (SIM) [3]. Clinical outcomes and cholesterol-lowering response to simvastatin have demonstrated associations with clinical factors including age, race, gender, smoking, diet, comorbidities and use of concomitant medications [4]. Genetic variation also appears to contribute to inter-individual variability in response to statins [5]. In recent decades, a plethora of candidate-gene studies and genome wide association studies (GWAS) have focused on genetic polymorphisms and patient response to statins. Polymorphisms in several genes (*e.g., ABCB1*, *ABCG2*, SLCO1B1, *UGT1A1*, *UGT1A3*, *UGT2B7*, *CYP2C9*, *CYP2C19*, *CYP2C8, CYP2D6, CYP3A4 and CYP3A5*) have been associated with statin blood concentrations, and polymorphisms in several additional genes (*e.g.*, *APOE*, *CETP*, *CLMN*, *CYP7A1*, *HMGCR, LDLR, LPA)* have been associated with response to statins or incidences of SIM [6].

For simvastatin, one of the most commonly prescribed statins [1], investigations have largely focused on *SLCO1B1* - the gene encoding the organic anion transporting polypeptide 1B1

that mediates intrahepatic transport of simvastatin [7]. Increased simvastatin concentrations and an increased risk of myopathy have been associated with *SLCO1B1* polymorphisms in several studies, prompting the Clinical Pharmacogenetics Implementation Consortium (CPIC) to establish formal prescribing recommendations for simvastatin based on *SLCO1B1* genotype-defined risk of SIM [7-10]. Although nearly 200 common variants in *SLCO1B1* have been described, *SLCO1B1* 521C (rs4149056) has the highest level of evidence. All of the haplotypes identified as having an increased risk of SIM (*5, *15, *17) in CPIC's *Recommended Dosing of Simvastatin Based on SLCO1B1 Phenotype* contain the *SLCO1B1* 521C polymorphism [10]. Myopathy risk is increased because the *SLCO1B1* 521C polymorphism results in increased systemic concentrations of simvastatin (secondary to decreased transport of simvastatin into hepatocytes), ultimately increasing the exposure of muscle to simvastatin [6, 7, 11]. Since the primary action of simvastatin occurs within hepatocytes, *SLCO1B1* 521C reduces also the cholesterol-lowering response to simvastatin. This association has been demonstrated in several clinical studies. Sortica *et al.* reported the percent reduction of LDL-C in a study of 216 Brazilian patients that received 20 mg simvastatin daily for 6 months was 38.6 ± 8.0, 39.9 ± 8.6, and 42.1 ± 15.8 for homozygous *SLCO1B1* 521C carriers, heterozygous *SLCO1B1* 521C carriers and wildtype, respectively [12]. Fu *et al.* reported the percent reduction of LDL-C in a study of 174 patients of Chinese ancestry that received 20 mg simvastatin daily for 4 months was 27.2 ± 5.4, 28.9 ± 5.9, and 30.8 ± 5.4 for homozygous *SLCO1B1* 521C carriers, heterozygous *SLCO1B1* 521C carriers and wildtype, respectively [13]. As these reported findings were only suggestive trends, Dou *et al*. performed a meta-analysis of these studies and determined that the association between *SLCO1B1* 521C and cholesterol reductions was statistically significant [14]. Hopewell *et al*. reported similar findings in the Heart Protection Study of 18,705 patients that received 40 mg simvastatin daily for 4-6 weeks: the percent reduction of LDL-C was 42.4 ± 0.2, 43.6 ± 0.4, and 44.7± 0.4 for homozygous *SLCO1B1* 521C carriers, heterozygous *SLCO1B1* 521C carriers and wildtype, respectively [15]. Although the relationship between

SLCO1B1 521C and cholesterol response has been reported in several independent studies, its marginal effect size substantially reduces its potential for clinical utility.

As simvastatin is metabolized primarily by the cytochrome P450, family 3, subfamily A, polypeptides 4 and 5 enzymes (CYP3A4 and CYP3A5, respectively), associations have been reported between simvastatin pharmacokinetics/dynamics and functional polymorphisms in *CYP3A4* and *CYP3A5*. Specifically, the decrease-of-function (DOF) *CYP3A4**22 (rs35599367) and the loss-of-function (LOF) *CYP3A5*3* (rs776746) polymorphisms have been associated with increased simvastatin concentrations [6, 16-18] and increased cholesterol-lowering response [19-22]. In fact, we reported significant associations between these polymorphisms and simvastatin concentrations in this cohort [17, 18]. Reports of associations between these polymorphisms and simvastatin response have also been published. Kivistö *et al.* reported that the mean percent reduction in total cholesterol was higher (31% vs. 17%, $p = 0.026$) in *CYP3A5**3 homozygotes compared to *CYP3A5**1/*3 or *CYP3A5**1 homozygotes in a study of 69 Caucasians that received lovastatin, simvastatin, or atorvastatin (all primarily metabolized by CYP3A) [19]. However, the percent reduction in LDL-C was not statistically different in *CYP3A5**3 homozygotes compared to *CYP3A5**1/*3 or *CYP3A5**1 homozygotes (31% vs. 46%, $p = 0.083$). No associations between *CYP3A5**3 and LDL-C lowering were detected in the following reports: Fiegenbaum *et al.*'s analysis of 99 Europeans that received 20 mg simvastatin daily for 6 months [23], Hu *et al.*'s analysis of 229 Chinese that received 40 mg simvastatin daily for 6 weeks [21], Bailey *et al.*'s analysis of 291 Europeans of the Genetic Effects On STATins (GEOSTAT-1) that received 40 mg simvastatin daily for 3 months [24] and Hopewell *et al.*'s analysis of 18,705 Europeans of the Heart Protection Study (HPS) that received 40 mg simvastatin daily for 4-6 weeks [15]. These findings collectively do not suggest that *CYP3A5**3 alters cholesterol-lowering response to simvastatin, at least not in the patient populations studied.

Studies of *CYP3A4**22 and simvastatin response have been rare, and although associations have been reported, findings have been inconsistent. Elens *et al.* reported that the LDL-C reduction in *CYP3A4**22 carriers was 7% greater compared to non-carriers (41% vs. 48%; $p = 0.054$) in 80 incident simvastatin users of the Rotterdam Study after adjusting for age, sex, baseline cholesterol and simvastatin dose and duration [20]. The mean daily dose of simvastatin required for optimal cholesterol control was nearly 40% less for *CYP3A4**22 carriers compared to non-carriers in a study of 84 hyperlipidemia patients ($p = 0.042$) [22]. Conversely, no association was reported between *CYP3A4**22 and LDL-C lowering response in a study of 209 patients that received 10-40 mg simvastatin daily for 6 months [25]. It remains uncertain whether *CYP3A4**22 affects simvastatin cholesterol lowering.

Despite several reports of associations between increased simvastatin concentrations and the DOF *CYP3A4**22 polymorphism or the LOF *CYP3A5* polymorphism, associations between these polymorphisms and simvastatin cholesterol-lowering response have seldom been detected. The lack of genetic investigation of simvastatin response in African Americans and our recent reports of associations between these *CYP3A* polymorphisms and 12-hour simvastatin concentrations in this cohort provided the rationale for this follow-up candidate gene study. Herein, we present our study aimed at evaluating the associations of *CYP3A4**22, *CYP3A5**3 and *SLCO1B1* 521C alleles with the cholesterol response to 40 mg simvastatin daily for 6 weeks in White and African-American participants of the Cholesterol and Pharmacogenetics (CAP) clinical trial.

METHODS

Study participants

This candidate-gene analysis included 609 self-reported White and 335 self-reported African-American males and females aged ≥30 years that had a baseline total serum

cholesterol level between 160 and 400 mg/dL. The participants of CAP (ClinicalTrials.gov identifier NCT00451828) were recruited and enrolled at San Francisco General Hospital and the University of California, Los Angeles, School of Medicine, and collected baseline data included demographic, medical history, risk factors for coronary heart disease, physical examination, and clinical laboratory test results. They received 40 mg simvastatin daily for 6 weeks, clinic visits occurred at 2-week intervals during the 6-week study and exclusion criteria included the following: concomitant use of medications (prescription or over-the-counter) known to significantly alter patient cholesterol levels or simvastatin pharmacokinetics; known liver disease or elevated transaminase levels more than twice the upper limit of normal; uncontrolled hypertriglyceridemia, hypertension or diabetes mellitus; abnormal renal or thyroid function; current alcohol or drug abuse; and known statin intolerance. Compliance was determined by pill counts, and the CAP clinical trial was approved by institutional review boards at all clinical, laboratory and coordinating centers. Additional details of the clinical trial methodology were provided in the initial report of the CAP clinical trial [26].

Genotype analyses

SLCO1B1 T521C (rs4149056) was determined using the Cardio-MetaboChip (Illumina, San Diego, CA) genotyping platform, and *CYP3A4**22 (rs35599367) was determined using a TaqMan® genotyping assay (C_59013445_10; Life Technologies, NY). *CYP3A5**3 (rs776746) was determined using the Illumina Human Hap 300 or Human Hap 610-Quad genotyping platform (Illumina, San Diego, CA) for Whites and was determined using a TaqMan® genotyping assay (C_26201809_30; Life Technologies) for African Americans.

Ancestry and relatedness analysis

To assess relatedness between participants, the Cardio-MetaboChip was used to calculate pairwise identity-by-state (IBS) distances [27]. To meet the assumption of independent

observations, tests were performed to determine whether any participants were first cousins or more closely related (pi_hat > 0.125). One member of a pair of African-American participants with pi_hat = 0.1653 was excluded, and two additional subjects were excluded due to high degrees of relatedness (final n = 941). To assess genetic ancestry of the participants, the resulting matrix of IBS distances was used to perform multidimensional scaling (MDS) analysis in Plink [28]. In addition to self-reported race, the first three MDS components were used as covariates in order to account for background genetic ancestry.

Statistical analysis

Baseline continuous variables were summarized by median and interquartile range and compared by race groups using the Wilcoxon rank sum test. Baseline categorical variables were summarized by counts and percentages and compared between race groups using the χ^2 test (or Fisher's exact where necessary). Monte Carlo estimates of the exact *p*-values for Hardy-Weinberg equilibrium within race groups were calculated using 10,000 permutations. Changes in cholesterol were determined by comparing measured concentrations of cholesterol in serum samples collected at baseline and at the 6-week post-treatment visit. Regression analyses were used to detect associations between genotypes (*CYP3A4**22, *CYP3A5**3 and *SLCO1B1* T521C) and changes in LDL and total cholesterol. Regression analyses were also used to test whether changes in LDL and total cholesterol were associated with 12-hour plasma concentrations of simvastatin. Based on previously reported findings regarding non-genetic influences on the cholesterol-lowering response to simvastatin in the CAP trial [26], we adjusted our models for covariates including race, smoking status, and age. Genetic ancestry (first 3 MDS components) was also included as a covariate. Differences in the cholesterol-lowering response by genotypes and race group were assessed in the race-combined cohort using a multiplicative interaction term (genotype*race). Race-specific differences in cholesterol-lowering response by genotypes were assessed in analyses stratified by race group. To assess whether the effects of

SLCO1B1 T521C on cholesterol-lowering response to simvastatin were dependent on *CYP3A4* and/or *CYP3A5* status, the following gene-gene interactions were tested by incorporating a multiplicative interaction term within unadjusted and adjusted regression models in both the race-combined and -stratified cohorts: *SLCO1B1*CYP3A4*, *SLCO1B1*CYP3A5*, *SLCO1B1*CYP3A4/5* (*CYP3A4* and *CYP3A5* combined by the number of decreased function alleles), and *SLCO1B1*CYP3A4/5* (*CYP3A4* and *CYP3A5* combined into extensive, intermediate, and poor metabolizers as previously described). Statistical analyses were performed using SAS version 9.3 (Cary, NC), and $p < 0.05$ was considered statistically significant. Adjustments for multiple comparisons were made using the Benjamini and Hochberg's linear step-up method [29], limiting the false discovery rate to 5%. We estimated 80% power to detect a 14% difference in LDL-C reduction by *CYP3A4**22 genotype, a 5% difference by *CYP3A5**3 genotype and an 8% difference by *SLCO1B1* T521C genotype in unadjusted models.

RESULTS

Baseline characteristics of the 941 CAP participants included in this analysis are presented in Table 1. Genotypes at all three loci were within Hardy-Weinberg equilibrium for both race groups, and minor allele frequencies of *SLCO1B1* 521C, *CYP3A4**22 and *CYP3A5**3 were consistent with those reported in other cohorts [21, 22, 29, 30]. Statistical analyses of the associations between cholesterol-lowering response to simvastatin and *CYP3A4**22, *CYP3A5**3 and *SLCO1B1* 521C genotypes are presented in Table 2.

Results from the race-combined and -stratified analyses reveled that *SLCO1B1* 521C was the only genetic variable that was significantly associated with cholesterol-lowering response to simvastatin 40 mg daily for 6 weeks, and this relationship occurred only in Whites: reduction of LDL-C was 44±25, 55±19 and 57±22 mg/dL in Whites of C/C, T/C and T/T genotype, respectively ($p = 0.038$ without correction for multiple hypotheses), and reduction

of total cholesterol was 43±27, 57±21 and 60±24 mg/dL in Whites of C/C, T/C and T/T genotype, respectively (p = 0.008 without correction for multiple hypotheses). Although the race-combined analysis of *SLCO1B1* 521 C and LDL-C reduction resulted in a significant p-value, data in the African-American cohort demonstrated a relationship (non-significant p-value) with direction both opposing biological plausibility and opposite that in the White cohort and in the previously-reported analyses. Neither *CYP3A4**22 nor *CYP3A5**3 were associated with differences in cholesterol-lowering responses in either race or in the combined-race cohort. Race-gene and gene-gene interactions for each genotype (*SLCO1B1* 521C, *CYP3A4**22 and *CYP3A5**3) were not statistically significant (interaction terms and p-values not shown). Simvastatin cholesterol-lowering response was not associated with 12-hour post-dose simvastatin concentrations in the race-combined and –stratified cohorts of CAP.

DISCUSSION

Our study findings regarding *SLCO1B1* 521C were consistent with those observed in HPS [15] and in the meta-analysis reported by Duo *et al*. [14]: *SLCO1B1* 521C was associated with a diminished cholesterol-lowering response. The consistencies regarding the magnitude and direction of this effect not only support the validity of our study but also provide addition evidence supporting the central role of SLCO1B1 in the pharmacology of simvastatin. Although readily observed in clinical studies, the effect is marginal and unlikely to provide prescribing guidance beyond its established role in CPIC's recommendations regarding simvastatin myopathy [9, 10].

Although associations between simvastatin pharmacokinetics and the functional polymorphisms *CYP3A4**22 and *CYP3A*5*3 have been reported in several cohorts [6, 16-18]

including our recent reports of analyses conducted in this cohort [17, 18], reports of their association with the cholesterol-lowering response to simvastatin have been rare. In fact, associations have been detected in only a single cohort each (Kivistö *et al.* for *CYP3A5**3 and Elens *et al*. for C*YP3A4**22) [19, 20]. Those cohorts were relatively small (*n* = 69 and *n* = 80 for the reports by Kivistö *et al.* and Elens *et al*., respectively), and the reported associations failed to replicated in subsequent analyses of other larger cohorts and in this analysis of CAP. Specifically, *CYP3A4**22 was not associated with change in LDL-C in the report by Ragia *et al*. (*n* = 209) [25], and *CYP3A5**3 was not associated with changes in LDL-C in the studies reported by Hu *et al*. (*n* = 229) [21], Fiegenbaum *et al.* (*n* = 99) [23], Bailey *et al.* (*n* = 291) and Hopewell *et al*. (*n* = 18,705) [15].

This study had several advantages. The cohort size was relatively large (*n* = 941) and included a significant number of African-Americans (*n* = 333), providing novel opportunity for genetic investigation in an understudied patient population. The availability of genotyping chip data was another advantage, allowing genetic-ancestry adjustment and the exclusion of related subjects. Another advantage was comprehensive data collection, allowing adjustments for several clinical variables (age, gender, smoking status). The eligibility criteria of the CAP clinical trial helped minimize confounding factors including comorbidities, diet and concomitant prescription and over-the-counter medications.

Nevertheless, there were several limitations to this study: other genes reported to play a role (albeit a minor role compared with *SLCO1B1* and *CYP3A4/5*) in simvastatin pharmacokinetics (e.g., *ABCB1*, *ABCG2*, *UGT1A1*, *UGT1A3*, *UGT2B7*, *CYP2C9*, *CYP2C19*, *CYP2C8* and *CYP2D6*) or statin cholesterol-lowering response (e.g., *APOE*, *CETP*, *CLMN*, *CYP7A1*, *HMGCR, LDLR, LPA)* were not included [3-6]. Likewise, not all polymorphisms of *CYP3A4*, *CYP3A5* and *SLCO1B1* were included in this candidate-gene study, and epistatic and epigenetic factors were not investigated. Despite the associations between 12-hour

post-dose simvastatin concentrations and *CYP3A4**22, *CYP3A5**3 and *SLCO1B1* 521C in CAP that we reported previously, regression analyses did not reveal associations (results not shown) between cholesterol-lowering response and simvastatin concentration in the race-combined and –stratified cohorts of CAP. This was not entirely unexpected because the pharmacokinetic data was limited (*i.e.,* significant discordance likely exists between 12-hour concentrations in plasma and daily systemic exposure in hepatocytes) [17,18]. Several of our analyses, especially the race-stratified analyses in the African American cohort, were underpowered. In fact, the analyses of *SLCO1B1* 521C in African Americans included only 14 heterozygotes and did not include any 521C homozygotes. The lack of observable associations in this population should not be considered definitive, and further investigation is warranted.

With proven efficacy and relatively few adverse effects, statins remain among the most commonly prescribed medication classes in the United States. Although most patients benefit, some are unable to attain cholesterol-reduction goals, some experience atherosclerotic events despite therapy, and some experience adverse events. Despite the completion of hundreds of candidate gene studies and numerous GWAS, a clinically relevant pharmacogenetic test to predict statin efficacy has not yet emerged. Our finding regarding *SLCO1B1* 521C in Whites confirmed the findings from several other studies: *SLCO1B1* 521C results in a diminished cholesterol-lowering response, but its marginal effect size limits utility for predicting simvastatin response. Although these common variants result in altered simvastatin metabolism (*CYP3A4**22, *CYP3A5**3) and transport (SLCO1B1 521C), their clinical utility for predicting inter-individual cholesterol-lowering response is not well supported. Future approaches utilizing multi-gene genetic-score approaches may prove superior for investigating the potential utility of these polymorphisms collectively to predict the cholesterol-lowering response or the efficacy (prevention of cardiovascular events) of simvastatin.

STUDY HIGHLIGHTS:

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Common functional variants in key genes involved in simvastatin metabolism (*CYP3A4**22, *CYP3A5**3) and transport (*SLCO1B1* 521C) have been associated with altered simvastatin concentrations in several studies. A marginal effect (diminished cholesterol reduction) of *SLCO1B1* 521C on simvastatin response has been reported in several studies, but results from studies of *CYP3A4**22 or *CYP3A5**3 and simvastatin response have had inconsistent results.

WHAT QUESTION DID THIS STUDY ADDRESS?

*This candidate-gene analysis examined the association of common genetic polymorphisms affecting simvastatin metabolism (CYP3A4*22 and CYP3A5*3) and transport (SLCO1B1 T521C) with the cholesterol-lowering effect of simvastatin in 333 African Americans and 608 Whites that received 40 mg simvastatin daily for 6 weeks.*

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

This analysis provided a unique opportunity to examine the relationships among simvastatin response and these polymorphisms (*CYP3A4**22, *CYP3A5**3 and *SLCO1B1* T521C) in a sizeable African American population. Furthermore, we previously reported that these polymorphisms significantly affected simvastatin concentrations in this cohort, providing an opportunity to examine the influence of these polymorphisms on both the pharmacokinetics and pharmacodynamics of simvastatin.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Individually, common genetic polymorphisms affecting simvastatin metabolism (*CYP3A4**22 and *CYP3A5**3) and transport (*SLCO1B1* T521C) appear to have negligible/marginal influence on cholesterol response to simvastatin. Collectively, however, effect may be clinically relevant, and future studies involving genetic score approaches may be more successful.

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CONFLICTS OF INTEREST/DISCLOSURE:

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS:

J.P.K., J.A.L., and M.W.M. wrote the manuscript; J.P.K., M.W.M., and R.M.K. designed the research; J.P.K., J.A.L., R.K., and M.W.M. performed the research; J.A.L. and A.D. analyzed the data.

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Table 1. Baseline Characteristics

	Overall (n = 941)	**Whites (n = 608, 65%)**	**African Americans (n = 333, 35%)**	***p-value***
†Age, yr	53 ± 17	54 ± 16	52 ± 18	0.843
†BMI, kg/m^2	28 ± 7	27 ± 7	29 ± 7	**<0.001**
†Compliance, %	98 ± 5	98 ± 5	98 ± 6	**0.027**
‡Male gender	484 (51%)	322 (53%)	162 (49%)	0.206
‡Smoker	187 (20%)	84 (14%)	103 (31%)	**<0.001**
*CYP3A4**22 allele frequency	0.03	0.04	0.01	**0.003**
*CYP3A5**3 allele frequency	0.73	0.93	0.35	**<0.001**
SLC01B1 521 C allele frequency	0.10	0.14	0.02	**<0.001**

BMI = body mass index. *CYP3A4* = the gene encoding cytochrome P450, family 3, subfamily A, polypeptide 4. *CYP3A5* = the gene encoding cytochrome P450, family 3, subfamily A, polypeptide 5. *SLCO1B1* = the gene encoding solute carrier organic anion transporter family member 1B1. †Continuous variables are represented as median ± interquartile range and compared using the Wilcoxon rank sum test. ‡Categorical variables are represented as count (%) and compared using the χ^2 test or Fisher's exact where necessary. Bolded *p*-values were significantly associated with LDL-C lowering response to simvastatin in the Cholesterol and Pharmacogenetics (CAP) clinical trial.

Table 2. Associations of *CYP3A4**22, *CYP3A5**3 and *SLCO1B1* 521C with changes in cholesterol levels after 40mg simvastatin daily for 6 weeks

	Overall			Whites			African Americans		
	n	**Δ LDL-C (mg/dL)**	**Δ TC (mg/dL)**	**n**	**Δ LDL-C (mg/dL)**	**Δ TC (mg/dL)**	**N**	**Δ LDL-C (mg/dL)**	**Δ TC (mg/dL)**
CYP3A4									
*1/*1	864	-54 ± 22	-57 ± 24	561	-56 ± 21	-59 ± 23	303	-51 ± 24	-53 ± 25
*1/*22	54	-56 ± 23	-60 ± 26	46	-58 ± 21	-62 ± 23	8	-44 ± 29	-50 ± 38
†*p*-value		0.816	0.444		0.489	0.307		0.376	0.742
‡*p*-value		0.898	0.726		0.901	0.783		0.820	0.963
CYP3A5									
*1/*1	125	-49 ± 25	-51 ± 24	6	-56 ± 17	-57 ± 16	119	-48 ± 25	-51 ± 25
*1/*3	216	-53 ± 22	-55 ± 24	73	-56 ± 20	-58 ± 22	143	-51 ± 24	-53 ± 25
*3/*3	537	-57 ± 21	-59 ± 23	507	-57 ± 21	-59 ± 23	30	-53 ± 21	-57 ± 25
†*p*-value		0.464	0.328		0.507	0.414		0.832	0.683
‡*p*-value		0.726	0.669		0.901	0.828		0.972	0.963
SLCO1B1									
C/C	14	-44 ± 25	-43 ± 27	14	-44 ± 25	-43 ± 27	0	-	-
C/T	151	-55 ± 19	-58 ± 21	137	-55 ± 19	-57 ± 21	14	-57 ± 20	-60 ± 23
T/T	718	-55 ± 22	-58 ± 24	441	-57 ± 22	-60 ± 24	277	-51 ± 23	-54 ± 25
†*p*-value		0.103	**0.028**		**0.038**	**0.008**		0.310	0.305
‡*p*-value		0.495	0.204		0.366	0.107		0.783	0.783

Δ LDL-C = change in low-density lipoprotein cholesterol. Δ TC = change in total cholesterol. *CYP3A4* = the gene encoding cytochrome P450, family 3, subfamily A, polypeptide 4. *CYP3A5* = the gene encoding cytochrome P450, family 3, subfamily A, polypeptide 5. *SLCO1B1* = the gene encoding solute carrier organic anion transporter family member 1B1. †Adjusted for age, smoking status, genetic ancestry (first 3 multi-dimensional scaling components) and self-reported race (when applicable); ‡also corrected for multiple comparisons with a false discovery rate of 5%. Values are presented as mean ± standard deviation. Only *p*-values < 0.05 are bolded.