

Supplemental Material: CPIC guideline for *SLCO1B1* and simvastatin-induced myopathy

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Rationale:

The field of pharmacogenomics is advancing rapidly. To date, CPIC has published guidelines for several drug-gene-outcome relationships relevant to cardiovascular disease and many more guidelines are being constructed. For drugs with narrow therapeutic indices (e.g., anticoagulants and antiarrhythmics), inherited (or acquired) variability in pharmacokinetic (PK) processes can have devastating clinical effects. HMG-CoA reductase inhibitors (statins), however, have a relatively wide therapeutic index, raising the question “why use *SLCO1B1* genotype to optimize prescribing in the context of simvastatin therapy?”

Statins are the most commonly prescribed class of drugs in the industrialized world. While the *relative* rate of serious ADRs is extremely low for statins, their frequent use leads to a high *absolute* number of ADRs. As a result, any reduction in statin-related ADRs has the potential to improve public health.

Our recommendations are based upon ten important principles: **(A)** clinical indication for the use of a statin is extremely common (i.e., coronary heart disease is the most common cause of death in the industrialized world), **(B)** the drug is highly efficacious in the primary and secondary prevention of coronary heart disease (1-4), **(C)** statins are among the most commonly prescribed drugs, **(D)** at present, simvastatin is the most commonly prescribed statin, **(E)** severe adverse drug reactions (myopathy and rhabdomyolysis) are potentially fatal (5-20), **(F)** mild adverse drug reactions (myalgias) occur rather frequently (i.e., more than 1% of subjects exposed) (21-23), **(G)** the association between rs4149056 in *SLCO1B1* and muscle toxicity has a large effect size for simvastatin (odds ratio from 2.0 to 20.0,

depending upon drug dose, gene dose, and the definition of intolerance) (24), **(H)** rs4149056 in *SLCO1B1* is quite common within the general population (25-27), **(I)** simvastatin intolerance often leads to nonadherence (28), and **(J)** the public health implications of nonadherence are disastrous (an increase in the overall burden of coronary heart disease). Our dosing guideline therefore leverages rs4149056 to optimize simvastatin therapy, in the context of recent FDA recommendations (Supplemental Table 1).

All CPIC guidelines are simultaneously published and updated on-line at www.pharmgkb.org.

Literature Review:

We searched the PubMed database (1966 to May 2010) and Ovid MEDLINE (1950 to May 2010) using several keyword strategies: *SLCO1B1*, *SLCO1B1* x myopathy (26, 27, 29-48), *SLCO1B1* x statin myopathy (26, 27, 29-48), *SLCO1B1* x simvastatin (26, 27, 29, 32, 34, 35, 38, 49-52) (45, 48, 53-58), *SLCO1B1* x LDL lowering (30, 31, 49, 55, 56, 59-64), *SLCO1B1* x statin efficacy (30, 31, 36-38, 41, 46, 55-57, 59-68), *SLCO1B1* x statin kinetics x human x polymorphism (26, 27, 33, 34, 36, 38, 50, 51, 57, 60, 65, 68-80), *SLCO1B1* x cardiovascular (7, 27, 29, 32, 36, 38, 47, 49, 51, 55-57, 59, 81), and *SLCO1B1* x statin uptake x hepatocyte (51, 54, 75, 82-88). The results of our search have been summarized within the body of the main guideline manuscript, and all references have been included in this Supplement.

SLCO1B1 nomenclature is summarized in Supplemental Table 2. For rs4149056, the racial distribution has been summarized in Supplemental Table 3 with details by geographic locale in Supplemental Table 4.

To construct tables showing *SLCO1B1* minor allele frequency based on ancestry, the PubMed database was further searched using the following criteria: *SLCO1B1*, *OATP1B1*, population, rs4149056, *SLCO1B1**5, *SLCO1B1**15. Studies were included if: **(A)** the race of the population was clearly indicated, **(B)** allele frequencies or minor allele percentages for *SLCO1B1* haplotypes were reported, **(C)** the method by which *SLCO1B1* was genotyped was reliable, **(D)** the sample size was at least 20 subjects.

Because the pharmacokinetic effect of the C allele at rs4149056 appears to be larger for simvastatin than any other statin, we present a detailed list of published findings drug-by-drug in Supplemental Table 5.

Available Genetic Test Options

Commercially available genetic testing options change over time. Several current options are listed at <http://www.pharmgkb.org>. Many of our contributing institutions already conduct *SLCO1B1* genotyping.

At present, Vanderbilt University genotypes *SLCO1B1* on the Illumina ADME array in a CLIA approved environment, and actively moves the genotypes into their medical record at the point of prescribing. The Pharmaceutical Sciences Department at St. Jude Children's Research Hospital genotypes *SLCO1B1* through routine application of the DMET™ Plus Affymetrix array in a CLIA approved environment.

Several additional CLIA-approved labs offer genotyping via the Illumina VeraCode ADME array or the DMET™ Plus Affymetrix array, without direct links to medical records. Examples of readily available CLIA-approved ADME genotyping include Illumina Clinical Services Laboratory (San Diego, CA) and BioReliance (Rockville, MD). Examples of readily available CLIA-approved DMET™ genotyping include SeqWright DNA Technology Services (Houston, TX), Beckman Coulter Genomics (Morrisville, NC), Coriell Institute for Medical Research (Camden, NJ) and Expression Analysis (Durham, NC).

Single SNP genotyping is available through QPS, LLC (Quality Performance Service), a full-service CLIA-compliant contract research organization providing testing services to support preclinical and clinical research and development (in Newark, DE, Groningen, the Netherlands, and Taipei, Taiwan). QPS uses a Taqman assay to genotype rs4149056 (and rs2306283), and therefore provides results for the *1A, *1B, *5, *15 haplotypes. *SLCO1B1**5 genotyping (rs4149056 alone) is also available for clinical use at Uppsala University Hospital, in Sweden (www.genotyping.se) and at HUSLAB in Finland (www.huslab.fi). Uppsala University uses a method based upon Applied Biosystems real-time PCR (Life Technologies, Carlsbad, CA) and HUSLAB uses an accredited method based on cyclic minisequencing.

Levels of Evidence

The evidence summarized within the main guideline manuscript has been graded using the three-tiered system required by the Clinical Pharmacogenetics Implementation Consortium (Relling MV, Klein TE. Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clinical Pharmacology Therapeutics* 2011 89(3):464-7.), as modified slightly from Valdes *et al.* (2010).

HIGH: Evidence includes consistent results from well-designed, well-conducted studies.

MODERATE: Evidence is sufficient to determine the effects, but the strength of evidence is limited by the number, quality, or consistency of the individual studies, by the inability to generalize to routine practice, or by the indirect nature of the evidence.

LOW: Evidence is insufficient to assess the effects on health outcomes because of the limited number of studies, insufficient power of the studies, important flaws in their design or in the way they were conducted, gaps in the chain of evidence, or lack of information.

Strength of Recommendations

Multiple rating schemes were evaluated. Ultimately, we (CPIC) chose to use a slight modification of a transparent and simple system for just three categories for recommendations: strong, where “the evidence is high quality and the desirable effects clearly outweigh the undesirable effects”; moderate, in which “there is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, for recommendations in-between strong and weak where there is room for differences in opinion as to the need for the recommended course of action.

CPIC’s dosing recommendations weigh the evidence from a combination of preclinical and clinical data. Some of the factors that are taken into account include *in vivo* clinical outcome data for statins, *in vivo* pharmacodynamic data for statins, and *in vivo* pharmacokinetic data for statins, in individuals who vary by *SLCO1B1* genotype. We also consider *in vitro* pharmacodynamic and pharmacokinetic data for statins.

The dosing recommendations are simplified to allow rapid interpretation by clinicians, as adapted from the rating scale for evidence-based therapeutic recommendations on the use of retroviral agents (Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. DHHS October 14, 2011; 1–167. Guideline available on-line at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> . Accessed [January 15, 2012]).

- Strong recommendation for the statement
- Moderate recommendation for the statement
- Optional recommendation for the statement

Current Models for Implementation

Model #1: Genotyping “just in time.” Duke University’s Center for Personalized Medicine genotypes individuals with prior statin intolerance for *5 (rs4149056 alone) and provides patient and providers with genotype specific education and guidance. Duke also offers *SLCO1B1**5 genetic testing to assist primary care physicians (via test results and interpretation via the EMR) in reinitiating statin therapy for patients who are nonadherent to statin therapy. Patients found to be carriers of the *5 allele are provided with their genotype, and steered toward an alternate drug with lower risk for kinetic changes; e.g., rosuvastatin (if high potency is desired), pravastatin (if low potency is acceptable), or fluvastatin (to minimize drug-drug interaction). Noncarriers are advised to consider restarting their prior statin and monitor CK level.

Model #2: Genotyping “just in case.” This pre-emptive model, assumes that – at some point in the not too distant future – *SLCO1B1* genotype data will be available on a patient by patient basis, through electronic access to whole genome sequencing data within comprehensive electronic medical records. One such model was implemented at Vanderbilt University Medical Center in 2011, wherein an Illumina ADME assay is run in a CLIA approved environment, and stored behind each patient’s EMR. The data are brought forward, gene-by-gene, at the point of prescribing, when any physician attempts to prescribe a drug from within a pre-selected group determined by the hospital Pharmacy and Therapeutics Committee. This committee meets quarterly to review the dynamic list of drugs on this list. At present, this list is based upon published CPIC guidelines: clopidogrel, warfarin, and simvastatin (with decision support algorithms for thiopurines and codeine under construction and scheduled for implementation soon). The initiative, called PREDICT (Pharmacogenomics Resource for Enhanced Decisions in Clinical Care and Treatment) was activated in 3000 subjects undergoing percutaneous coronary intervention in 2011, and recently expanded to 10,000 high risk individuals served by the Vanderbilt University primary care clinics. When a provider attempts to prescribe simvastatin, the patient’s EMR is immediately populated with rs4149056 genotype in a chart section called drug-genome interactions (just below drug allergies). (Pulley, J.M. et al. Operational implementation of prospective genotyping for personalized medicine: The design of the Vanderbilt PREDICT project. *Clinical Pharmacology and Therapeutics* in press)

Incidental findings

Hepatic uptake of unconjugated bilirubin is mediated by *SLCO1B1* (67). Variation in *SLCO1B1* has been shown to alter total serum bilirubin levels (67, 89-92) and has been associated with hyperbilirubinemia in adult Asians (93). Variants in *SLCO1B1* are also associated with increased risk for gallstone disease (rs11045819) (94), as well as hypertension (rs4149014) (95) and coronary artery disease (rs4149013) (96).

The *SLCO1B1* gene product transports many drugs and biochemicals (reviewed in details by Niemi et al, 2011). The C allele at rs4149056 is related to impaired transport of many drugs *in vitro* and *in vivo*, including for example changes in irinotecan disposition (97, 98) and clearance of the antiretroviral drug lopinavir (99). Other variants have an impact as well. For example, *SLCO1B1* rs11045819 polymorphism (c.463C>A) is associated with lower rifampin exposure in adults with pulmonary tuberculosis (100).

The Role of Ancestry

Our guideline reflects recent recommendations from the U.S. FDA regarding the strong dose-dependence of muscle toxicity for simvastatin. For other statins, the FDA has further recommended limiting the dose based upon major continental race (FDA Public Health Advisory on rosuvastatin; Media release March 2, 2005). For rosuvastatin, specifically, the FDA recommends limiting patients of Asian ancestry to a 5 mg starting dose, based upon two clinical observations: first, that patients of Asian ancestry exhibit a 2-fold increase in AUC for rosuvastatin, compared to patients of European ancestry, following single dose exposure (72) and second, that patients of Asian ancestry have greater lipid lowering efficacy at lower doses of rosuvastatin, compared to patients of European ancestry (72). As a result, the FDA has concluded that Asian Americans are one of three important groups with an elevated risk/benefit ratio (the others were patients on CSA/immune suppression and patients with severe kidney failure) (81, 83, 101-105).

Geographic differences in allele frequency for rs4149056 in *SLCO1B1* do not appear to contribute to this race discrepancy (72). For rosuvastatin, this difference appears to be at least partly attributable to variability in efflux transporters such as *ABCG2*, as well as gene-gene and gene-environment interactions not yet defined (Feng et al. Genetic and non-genetic determinants of statin-induced muscle toxicity. *Pharmacogenomics* in press). For simvastatin, race-dependent differences in *SLCO1B1* variant frequency carry an undefined impact on outcome. Because there is great variability in the distribution of this variant by race (106), we present a summary in Supplemental Table 3 and details in Supplemental Table 4.

Other Limitations

The pharmacokinetic predictors of statin-induced myopathy are well understood (16, 29, 31-34, 51, 70, 76-78, 107-113). Pharmacodynamic predictors have been less well characterized. Although the cellular mechanism linking statins to skeletal muscle damage still remains somewhat obscured, the weight of the evidence suggests that statin-mediated reduction in the levels of critical cholesterol precursors (i.e., isoprenoids) can lead to mitochondrial dysfunction, and programmed cell death (12, 36, 114, 115). While inherited variability in the prenylation of key mitochondrial oxygen transport proteins may drive a subclinical form of myopathy that becomes overtly manifest after exposure to statin, there is only limited evidence supporting the clinical utility of genotyping pharmacodynamic variants.

Genotype at rs4149056 (PK variability) also alters statin efficacy (37, 56). Because rs4149056 influences hepatic uptake of statins, the minor allele has opposite effects on toxicity and efficacy; i.e., the presence of the minor allele attenuates the LDL-lowering effect (because the liver is the primary site for *de novo* cholesterol biosynthesis). Carriers of the rs4149056 C allele thus experience decreased efficacy with regard to LDL-lowering when taking simvastatin (31, 55, 116, 117) compared to other statins such as atorvastatin (61) or fluvastatin (59). As anticipated from the kinetic data, the effect of rs4149056 on efficacy is minimal for pravastatin (60, 69, 84), rosuvastatin (49, 118), and pitavastatin (62, 71, 82, 119, 120). Even for simvastatin, however, the change in LDL level due to rs4149056 is small (<10 mg/dl) (31), and there is no evidence that this variant impacts vascular events. As such, we do not make recommendations based upon the relationship between rs4149056 and efficacy.

We also do not make recommendations based upon gain of function alleles (30). Because rs4149056 can be inherited in combination with other *SLCO1B1* variants that carry a protective effect, the C allele at

rs4149056 should not be assumed to confer risk with 100% certainty. Like all drug-gene-outcome relationships reviewed by CPIC, it is anticipated that these guidelines will be updated as more variants (both common and rare) are increasingly characterized, e.g., through deep re-sequencing.

In the interim, a clear limitation inherent in our approach is that both rare and *de novo* variants are not determined within currently available genotyping tests. Yet, rare exonic variants in *SLCO1B1* have been shown to have clinical impact (e.g., methotrexate clearance) (121). Therefore, altered drug kinetics and increased risk for severe drug toxicity may still occur in the absence of a C allele at rs4149056, and a TT genotype at rs4149056 does not imply the absence of another potentially deleterious variant in *SLCO1B1*.

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Supplemental Figure 1.

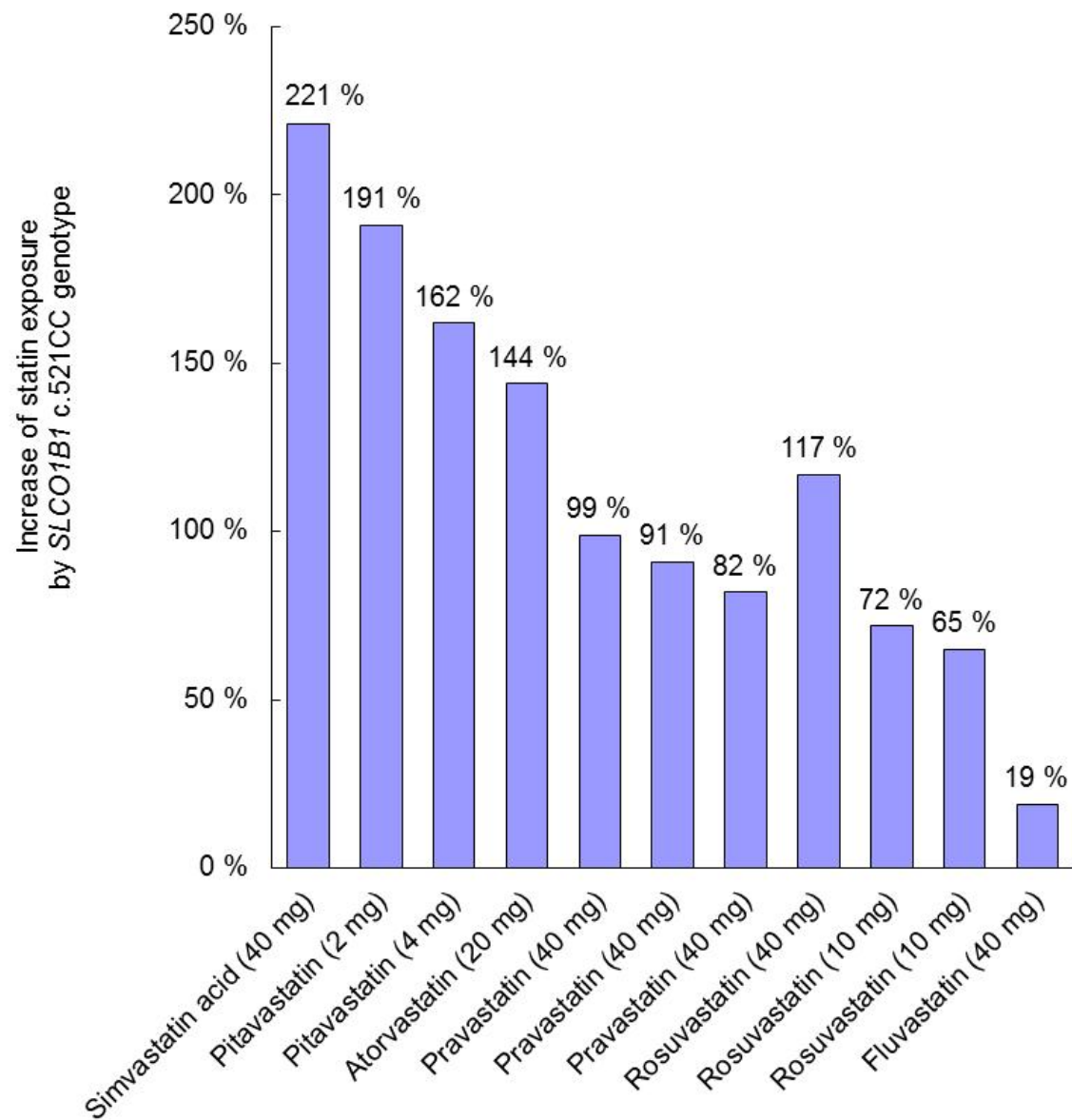


FIGURE LEGEND

Supplemental Figure 1. Pharmacokinetic impact of rs4149056 genotype for several statins.

Effect of the *SLCO1B1* c.521T>C variant (rs4149056) on plasma exposure (i.e., area under the concentration-time curve) for different statins, CC vs TT. This summary figure represents a composite of single-dose data from the following references: 66 (Pasanen et al), 71 (Ieiri et al), 72 (Lee et al), 75 (Niemi et al), 77 (Pasanen et al), 118 (Choi et al), 120 (Deng et al), 122 (Ho et al).

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Supplemental Table 1. FDA Dosing Recommendations for Simvastatin, posted in 2011.

Warning(s) Regarding 80 mg Simvastatin	Simvastatin Contraindicated	Maximum Simvastatin Dose	
		Max 10 mg daily (i.e., 20 mg dose contraindicated)	Max 20 mg daily (i.e., 40 mg dose contraindicated)
<ul style="list-style-type: none"> • simvastatin 80 mg should not be started in new patients • it is acceptable to continue simvastatin 80 mg daily in patients who have been taking it for 12 months or more without side effects • switch patients requiring on a drug that interacts with simvastatin to an alternative statin with less potential for drug-drug interaction 	<ul style="list-style-type: none"> • itraconazole, Ketoconazole, Posaconazole • erythromycin, Clarithromycin, Telithromycin • IV Protease inhibitors • efavirenz • emtricitabine • cyclosporine • ranitidine 	<ul style="list-style-type: none"> • diltiazem • verapamil 	<ul style="list-style-type: none"> • nifedipine • amlodipine • diltiazem

Supplemental Table 2. Genotypes that constitute the * alleles for <i>SLCO1B1</i>	
Allele	Constituted by genotypes at:
*1A	Wild-type at all loci
*1B	rs2306283 G allele (A ancestral) (c.388A>G, p.N130D)
*2	rs56101265 C allele (T ancestral) (c.217T>C, p.F73L)
*3	rs56061388 C allele (T ancestral) (c.245T>C, p.V82A)
*4	rs11045819 A allele (C ancestral) (c.463C>A, p.P155T)
*5	rs4149056 C allele (T ancestral) (c.521T>C, p.V174A)
*6	rs55901008 C allele (T ancestral) (c.1058T>C, p.I353T)
*7	rs56387224 G allele (A ancestral) (c.1294A>G, p.N432D)
*8	rs72559748 G allele (A ancestral) (c.1385A>G, p.D462G)
*9	rs59502379 C allele (G ancestral) (c.1463G>C, p.G488A)
*10	rs56199088 G allele (A ancestral) (c.1964A>G, p.D655G)
*11	rs55737008 G allele (A ancestral) (c.2000A>G, p.E667G)
*12	rs56101265 C allele (T ancestral); rs56199088 G allele (A ancestral)
*13	rs56061388 C allele (T ancestral); rs55737008 G allele (A ancestral); rs72559745 G allele (A ancestral)
*14	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral)
*15	rs2306283 G allele (A ancestral); rs4149056 C allele (T ancestral)
*16	rs59710386 C allele (A ancestral; g.-10499A>C); rs2306283 G allele (A ancestral); rs4149056 C allele (T ancestral)
*17	rs4149015 A allele (G ancestral; g.-11187G>A); rs2306283 G allele (A ancestral); rs4149056 C allele (T ancestral)
*22	rs34671512 C allele (A ancestral; c.1929A>C, p.L643F)
*23	hg19 chr12:21325710 A allele (G ancestral; c.211G>A, p.G71R)
*24	rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral; c.733 A>G, p.I245V)
*25	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral); rs11045852 G allele (A ancestral); rs11045853 A allele (G ancestral; c.758 G>A, p.R253Q)
*26	rs142965323 A allele (G ancestral; c.1309G>A, p.G437R)
*27	rs2306283 G allele (A ancestral); rs59113707 G allele (C ancestral; c.1200C>G, p.F400L)
*28	rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral); rs11045853 A allele (G ancestral)
*29	rs2306283 G allele (A ancestral); rs140790673 T allele (C ancestral, c.2045C>T, p.S682F)
*30	rs2306283 G allele (A ancestral); rs79135870 G allele (A ancestral, c.664 A>G, p.I222V)
*31	rs2306283 G allele (A ancestral); rs59502379 C allele (G ancestral)
*32	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral); rs11045852 G allele (A ancestral)
*33	rs139257324 G allele (C ancestral; c.169 C>G, p.R57W); rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral); rs11045853 A allele (G ancestral)
*34	hg19 chr12:21392079 T allele (C ancestral; c.2032 C>T, p.H678Y)
*35	rs2306283 G allele (A ancestral); rs34671512 C allele (A ancestral)
*36	hg19 chr12:21355487 G allele (T ancestral; c.1198 T>G, p.F400V)

All coordinates refer to GenBank SLCO1B1 mRNA sequence NM_006446.4 at http://www.ncbi.nlm.nih.gov/nuccore/NM_006446.4.

For detailed haplotype mapping information please see SLCO1B1 haplotype table at <http://www.pharmgkb.org/gene/PA134865839?tabType=tabHaplotypes#tabview=tab4&subtab=>.

All variants are annotated to the positive chromosomal strand.

PharmGKB will continue to update the list of * alleles on their website:

<http://www.pharmgkb.org/gene/PA134865839#tabview=tab4&subtab=33>.

Supplemental Table 4. Detailed distribution of *SLCO1B1* allele frequency by race.

Race group	Ethnicity	Haplotype frequency (%)				Total patients	alleles observed					Total alleles	Source
		*1A	*1B	*5	*15/*16/*17		*1A	*1B	*5	*15/*16/*17	other		
African	American	22%	76%	0%	1%	38	17	58	0	1	0	76	(69, 122)
African	North African	34%	48%	2%	16%	29	20	28	1	9	0	58	(106)
African	Sub-Saharan Africa	21%	77%	0%	2%	105	44	162	0	4	0	210	(106)
African	Ugandan	22%	70%	0%	3%	109	48	153	0	7	10	218	(123)
African	Tanzanian	13%	84%	0%	3%	366	97	614	0	21	0	732	(124)
Asian	Japanese	35%	54%	1%	10%	267	188	287	4	55	0	534	(125)
Asian	Japanese	33%	46%	0%	18%	120	78	110	0	44	8	240	(126)
Asian	Malays	17%	70%	0%	13%	35	12	49	0	9	0	70	(127)
Asian	Korean	31%	46%	0%	23%	24	15	22	0	11	0	48	(128)
Asian	Chinese	19%	71%	0%	11%	94	35	133	0	20	0	188	(129)
Asian	Malays	12%	79%	0%	9%	97	23	153	0	18	0	194	(129)
Asian	Korean	29%	60%	0%	12%	200	115	238	0	47	0	400	(130)
Asian	Korean	18%	62%	0%	18%	81	29	101	0	29	3	162	(97)
Asian	Chinese	26%	60%	0%	14%	111	58	133	0	31	0	222	(131)
Asian	Chinese	22%	69%	1%	8%	106	46	146	3	17	0	212	(132)
Asian	Korean	26%	60%	0%	14%	469	247	560	0	131	0	938	(132)
Asian	Vietnamese	21%	63%	0%	16%	104	44	130	0	34	0	208	(132)
Asian	East Asian	25%	63%	0%	12%	239	120	301	0	57	0	478	(106)
Asian	Japanese	36%	47%	0%	17%	177	128	166	0	60	0	354	(133)
Asian	Japanese	33%	49%	0%	18%	80	52	79	0	29	0	160	(134)
Asian	Chinese	25%	64%	0%	12%	96	47	122	0	23	0	192	(135)
Asian	Malays	19%	71%	0%	9%	96	37	137	0	18	0	192	(135)
Asian	Chinese	30%	59%	0%	11%	32	19	38	0	7	0	64	(136)
Asian	Chinese	33%	59%	0%	9%	35	23	41	0	6	0	70	(127)
Caucasian		47%	31%	1%	21%	36	34	22	1	15	0	72	(127)
Caucasian	German	49%	33%	1%	11%	250	245	165	5	55	30	500	(137)
Caucasian	Finnish	11%	2%	3%	17%	468	100	21	25	161	629	936	(138)
Caucasian	American	61%	25%	1%	14%	69	84	34	1	19	0	138	(122)
Caucasian	German	58%	25%	3%	15%	99	114	49	5	30	0	198	(139)
Caucasian	European	56%	26%	2%	16%	151	169	79	6	48	0	302	(106)
Caucasian	German	60%	9%	3%	12%	276	333	48	17	66	88	552	(123)
Caucasian	Turkish	52%	22%	1%	9%	78	82	34	2	15	24	156	(123)
Caucasian	French	53%	14%	2%	15%	185	196	52	8	56	58	370	(140)
Caucasian	Dutch	57%	27%	1%	15%	1885	2148	1022	27	572	0	3770	(141)
Caucasian	Canadian	50%	5%	0%	18%	41	41	4	0	15	22	82	(142)
Caucasian	German	56%	35%	3%	7%	236	263	163	12	34	0	472	(124)
Middle East		49%	31%	5%	15%	133	130	83	13	40	0	266	(106)
Oceanic		34%	66%	0%	0%	28	19	37	0	0	0	56	(106)
South/Central American		37%	39%	0%	24%	64	47	50	0	31	0	128	(106)
SW Asian	Indian	46%	47%	0%	7%	35	32	33	0	5	0	70	(127)
SW Asian	Indian	41%	56%	2%	2%	93	76	104	3	3	0	186	(129)
SW Asian	South/Central Asian	52%	39%	0%	9%	192	200	150	0	34	0	384	(106)
SW Asian	Indian	44%	50%	0%	6%	96	85	96	0	11	0	192	(135)

Supplemental Table 5. Impact of rs4149056 (V174A) on the pharmacokinetics of various statins

Study	Patients	Treatment	Primary Endpoint(s)	Additional Finding(s)
(143)	N=23 healthy Japanese volunteers	Pravastatin 10 mg	Patients with the compound N130D + V174A variant had reduced total and non-renal pravastatin clearance, as compared with patients with the N130D variant.	<i>SLCO1B1</i> , including V174A, are likely associated with altered pravastatin pharmacokinetics (PK).
(108)	N=30 healthy white males	Pravastatin 40 mg	Pravastatin AUC and C_{max} increased for V174A carriers compared to WT or N130D carriers.	<i>SLCO1B1</i> variant haplotypes alter pravastatin disposition. Whereas V174A expression delayed hepatocellular uptake of pravastatin, N130D expression seemed to accelerate <i>SLCO1B1</i> -dependent uptake of the drug.
(76)	N=41 healthy Finnish volunteers	Pravastatin 40 mg	Pravastatin AUC increased with V174A and -11187G>A variant alleles compared to WT.	Carriers of the compound N130D + V174A variants, as well as carriers of the compound N130D + V174A + -1187G>A, also had higher pravastatin AUC compared with WT.
(82)	N=24 healthy Korean volunteers	Pitavastatin 1-8 mg	Pitavastatin AUC and C_{max} increased for carriers of the compound N130D + V174A variant versus patients with WT or N130D alleles alone.	No significant differences were found according to genotype in terms of dose-normalized AUC or C_{max} values of pitavastatin lactone
(72)	N=36 white, 36 Chinese, 35 Malay, and 35 Asian-Indian subjects living in Singapore, Singapore	Rosuvastatin 40 mg	Rosuvastatin AUC's were 2.36, 2.00, and 1.68 times higher in Chinese, Malay, and Asian-Indian subjects; respectively, compared with White subjects.	<i>SLCO1B1</i> genotypes did not account for the observed PK differences between Asians and White subjects.
(60)	N=16 healthy volunteers, including 8 carriers of an <i>SLCO1B1</i> variant haplotype and 8 control subjects	Pravastatin 40 mg orally daily for three weeks	Pravastatin AUC and C_{max} were significantly higher in patients with V174A alleles compared to controls. Patients with the compound N130D + V174A variant, and patients with the triplotype -11187G>A + N130D + V174A, also had higher pravastatin AUC and C_{max}	Despite considerably higher plasma pravastatin concentrations in carriers of an <i>SLCO1B1</i> variant haplotype, there was no significant difference in the lipid-lowering efficacy of pravastatin between the variant haplotype and control groups.
(75)	N=32 healthy Finnish volunteers	Pravastatin 40 mg and fluvastatin 40 mg	Pravastatin AUC, C_{max} increased for men homozygous for V174A compared to men who were carriers for V174A or WT. Women who were WT had significantly higher Pravastatin AUC, C_{max} than men who were WT. Fluvastatin PK did not differ between subjects with different <i>SLCO1B1</i> genotypes or between the sexes.	<i>SLCO1B1</i> polymorphism alters PK of pravastatin but not fluvastatin, which suggests that fluvastatin does not rely on <i>SLCO1B1</i> for hepatic uptake. Patient gender may affect pravastatin PK.
(66)	N=4 healthy Caucasian volunteers	Simvastatin 40 mg	Simvastatin acid AUC and C_{max} increased for V174A carriers vs. WT	The V174A variant may increase risk for myopathy as well as reduce lipid-lowering effects due to decreased hepatic uptake.
(69)	N=107 healthy volunteers (69 European-American and 38 African-Americans)	Pravastatin 40 mg	Pravastatin AUC, C_{max} increased in heterozygous carriers of the compound N130D + V174A variant and in N130D + V174A homozygotes	European-Americans had significantly higher pravastatin AUC and C_{max} than African-Americans.

(71)	N=38 healthy Japanese volunteers	Pitavastatin 2 mg	Pitavastatin AUC, C _{max} increased for N130D or compound N130D+ V174A heterozygotes, and for compound N130D+ V174A homozygotes	Pitavastatin lactone PK parameters were not altered by <i>SLCO1B1</i> genotype.
(77)	N=32 healthy volunteers	Atorvastatin 20 mg and rosuvastatin 10 mg	AUC and C _{max} for atorvastatin, 2-hydroxyatorvastatin, and rosuvastatin were increased in patients with the V174A variant.	Unexpectedly, <i>SLCO1B1</i> polymorphism has a larger effect on the PK of atorvastatin than rosuvastatin.
(118)	N=30 Korean volunteers	Rosuvastatin 10 mg	Rosuvastatin AUC increased for compound N130D + V174A homozygotes, compound N130D + V174A carriers, and N130D carriers compared with WT. C _{max} increased for compound N130D + V174A homozygotes compared to other groups.	Rosuvastatin-lactone PK were similar among the three groups.
(120)	N=11 healthy Korean volunteers	Pravastatin 40 mg or Pitavastatin 4 mg	Pitavastatin AUC and C _{max} increased more than pravastatin for compound N130D + V174A homozygotes compared with WT	Uptake into oocytes overexpressing the compound N130D + V174A allele was decreased for pitavastatin more so than pravastatin. Fluvastatin was unaffected.
(78)	N=10 healthy Japanese volunteers	Pravastatin 10 mg (+ olmesartan 10 mg)	Pravastatin PK not significantly affected for N130D homozygotes, versus carriers of the compound N130D + V174A variant and/or versus N130D + V174A homozygotes	Co-administration of olmesartan + pravastatin did not affect PK based on <i>SLCO1B1</i> genotype.
(107)	N=16 healthy Chinese volunteers	Atorvastatin 40 mg (+ rifampicin 600 mg)	When combined with concomitant rifampicin, Atorvastatin AUC increased among V174A carriers and WT patients compared to V174A homozygotes	Rifampicin PK not affected by variation in <i>SLCO1B1</i> genotype.
(70)	N=57 healthy Japanese male volunteers	Pravastatin	Relative bioavailability F _(rel) increased for pravastatin in carriers of the compound N130D + V174A variant, and in homozygotes, versus WT.	Since compound N130D + V174A genotype alters F _(rel) , <i>SLCO1B1</i> is one of the determinants of systemic exposure to pravastatin.
(119)	N=18 healthy Chinese volunteers	Pitavastatin 2 mg	Pitavastatin AUC, C _{max} increased with N130D carriers compared to wild type (WT).	Pitavastatin CL was reduced in N130D carriers. No differences according to genotype were observed in T _{1/2} and T _{max} .
(144)	N=290 Korean volunteers	Atorvastatin 20 mg	Mean AUC of atorvastatin and 2-hydroxyatorvastatin was larger for compound N130D + V174A homozygotes (n = 3), than for N130D + V174A carriers (n = 8), and also larger than patients with WT. No PK difference with atorvastatin lactone was found.	This study showed the compound N130D + V174A variant may be associated with individual difference in the AUC of atorvastatin.
(7)	185 cases of rhabdomyolysis compared to 732 controls	Cerivastatin at various doses	Permutation test results suggested an association between cerivastatin-associated rhabdomyolysis and <i>SLCO1B1</i> variants (P=0.002), but not <i>CYP2C8</i> variants (P=0.073) or <i>UGTs</i> (P=0.523). The V174A allele was associated with risk of rhabdomyolysis (odds ratio: 1.89; 95% confidence interval: 1.40-2.56).	In transfected cells, V174A allele reduced cerivastatin transport by 40% compared with the reference transporter (P<0.001).