**Supplemental Material**

**The Clinical Pharmacogenetics Implementation Consortium**

**(CPIC) guideline for *SLCO1B1, ABCG2*, and *CYP2C9* and statin-associated musculoskeletal symptoms**

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# CPIC Updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on [www.cpicpgx.org](http://www.cpicpgx.org). Information will be reviewed and updated periodically on that website.

# Literature Review

We searched the PubMed database (1966 to July 2021) using the following keyword strategies: ***SLCO1B1***: (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (SLCO1B1 OR OATP1B1) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR Rhabdomyolysis OR Myositis OR “Statin associated muscle symptoms” OR withdrawal OR intolerance OR hepatocyte uptake OR response OR reaction) NOT ("review"[Publication Type]) AND English[lang] AND ("2014/01/01"[PDAT] : "2021/07/20"[PDAT])

***ABCG2:*** (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (ABCG2 OR BCRP) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR “Statin associated muscle symptoms” OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT ("review"[Publication Type]) AND English[lang]

***CYP2C9:*** (fluvastatin) AND (CYP2C9)

***HMGCR:*** (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (HMGCR) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR “Statin associated muscle symptoms” OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT ("review"[Publication Type]) AND English[lang]

***CYP3A4/5:*** (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (CYP3A4 OR CYP3A5) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR “Statin associated muscle symptoms” OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT ("review"[Publication Type]) AND English[lang]

Using these search terms, 1023 publications were identified. Study inclusion criteria included publications that incorporated analyses for the association between *SLCO1B1, ABCG2, CYP2C9, HMGCR, or CYP3A4/5* genotypes and statins pharmacokinetic parameters as well as clinical outcomes. Non-English manuscripts and reviews were excluded. Following the application of these inclusion and exclusion criteria, 197 publications were reviewed and included in the evidence table (**Table S1 to S5**).

# Available Genetic Test Options

Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members ([1](#_ENREF_1)). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables (see **Allele Definition Table**, **Allele Functionality Table** and **Allele Frequency Table** (<https://cpicpgx.org/guidelines/cpic-guideline-for-statins/>) adhere to these allele nomenclature standards ([1](#_ENREF_1)). Moreover, the **Allele Definition Table**, **Allele** **Functionality Table**, and **Allele** **Frequency Table** may be used to assemble lists of known functional and actionable pharmacogenetic variants and their population frequencies, which may inform decisions as to whether tests are adequately comprehensive in interrogations of alleles.

Commercially available genetic testing options change over time. Additional updated information can be found at the Genetic Testing Registry (GTR). The GTR provides a central location for voluntary submission of genetic test information by providers and is available at <http://www.ncbi.nlm.nih.gov/gtr/>.

# Linking genetic variability to variability in drug-related phenotypes

***SLCO1B1***. Both SLCO1B1 decreased and poor function phenotypes are associated with increased exposure for most statins, with greater effects of poor function phenotypes. Effects on exposure also vary by statin type (**Figure S1**). Therefore, the risk of SAMS varies based on statin type and statin dose. For simvastatin, the evidence linking SAMS to *SLCO1B1* rs4149056 (c.521T>C) is of high quality, and this association has been reproduced in retrospective studies of randomized trials and clinical practice-based cohorts (**Table S1**). This variant is present in several *SLCO1B1* star alleles including the relatively common *SLCO1B1\*5* and *\*15* alleles. Although the association of rs4149056 with myopathy varies by statin, there is evidence supporting the role of *SLCO1B1* variants in the clearance of all statins ([2](#_ENREF_2)) (**Table S1**). Pasanen *et al*. determined that homozygous carriers of the C allele at rs4149056 (CC genotype) had substantiality greater exposure to the active simvastatin acid (AUC0-12) than subjects homozygous for the ancestral T allele ([3](#_ENREF_3)). In single-dose studies (**Figure S1**), the observed plasma AUCs of active simvastatin acid, pitavastatin, atorvastatin, pravastatin and rosuvastatin have been 221%, 162-191%, 144%, 57-130% and 62-117% higher respectively in rs4149056 CC homozygotes than in rs4149056 TT homozygotes (**Figure S1**). Thus, the recommendations in this guideline (for *SLCO1B1*, *ABCG2* and *CYP2C9*) are based on both pharmacokinetic evidence and when available clinical evidence supporting increased risk of SAMS (see **Supplemental Material** for further detail). Further, we make note in this guideline when therapeutic recommendations are based solely on the basis of pharmacokinetic data due to the absence of clinical toxicity data related to SAMS (**Figure 1**).

Genotype at rs4149056 may also alter the desired lipid-lowering efficacy of statins (**Table S1**). Because rs4149056 influences hepatic uptake of statins, the C allele (e.g., *SLCO1B1\*5* and *\*15*) has opposite effects on toxicity and efficacy as the presence of the minor allele attenuates the LDL-cholesterol lowering effect (because hepatic HMGCR is the rate limiting step for *de novo* cholesterol biosynthesis). Carriers of the rs4149056 C allele experience lesser LDL-cholesterol reduction when taking simvastatin ([4-7](#_ENREF_4)). As anticipated from the pharmacokinetic data, the effect of rs4149056 on efficacy is minimal for pravastatin ([8-10](#_ENREF_8)), rosuvastatin ([11](#_ENREF_11), [12](#_ENREF_12)), and pitavastatin ([13-17](#_ENREF_13)). Even for simvastatin, however, the change in LDL-cholesterol level due to rs4149056 is small (<10 mg/dl) ([4](#_ENREF_4)), and there is no evidence that this variant impacts vascular events ([18](#_ENREF_18)). As such, our recommendations are primarily based on this variant’s effects on PK and SAMS, rather than the relationship between rs4149056 and efficacy on lowering LDL or risk of cardiovascular events.

***ABCG2.*** *ABCG2* decreased and poor function phenotypes are associated with increased exposure to rosuvastatin, with greater exposure for the poor function phenotypes (**Table S2**). In particular, rosuvastatin levels (AUC and Cmax) may be doubled in individuals with poor function phenotypes ([19](#_ENREF_19)). Based on the observed increase in exposure, the risk for myopathy would also be expected to be increased ([20](#_ENREF_20)). Nonetheless, there is only a single study directly assessing myopathy due to rosuvastatin use in individuals with decreased or poor function phenotypes which did not show any significant effect on myopathy ([21](#_ENREF_21)). However, for efficacy, the JUPITER Trial showed an increase in lipid lowering effects of rosuvastatin in individuals with decreased and poor function phenotypes ([22](#_ENREF_22)). Dosing based on genotype for rosuvastatin must necessarily include other considerations such as liver or renal function and ancestry (**Table 3**). The higher levels of rosuvastatin observed in individuals of Asian ancestry have been attributed to higher allele frequencies of the reduced function *ABCG2* polymorphism, c.421G>A (rs2231142) ([23](#_ENREF_23)); however, other factors may contribute to higher rosuvastatin levels in Asians ([24](#_ENREF_24)). The effect of the *ABCG2* polymorphism, rs2231142 (c.421C>A), has also been studied for its association with pharmacokinetic, toxicity or efficacy with other statins, such as atorvastatin, pitavastatin, fluvastatin and lovastatin (**Table S2**). Except for fluvastatin, in which a single study showed a clear association of rs2231142 with exposure, the evidence for association of *ABCG2* genetic variants with exposure, response or toxicity to other statins is considered weak to moderate primarily because of small sample sizes or variation in results among studies (**Table S2**).

***CYP2C9***. Genetic variations in *CYP2C9* are associated with increased exposure to fluvastatin (**Table S3**), but the pharmacokinetics or pharmacodynamics of other statins are not affected. To date, studies have focused on two alleles, *CYP2C9\*2* (decreased function) and *CYP2C9\*3* (no function). Hirvensalo *et al.* showed that for fluvastatin the AUC was 25% and 75% greater per copy of the *CYP2C9\*2* and *CYP2C9\*3* variant allele, respectively. Additionally, *CYP2C9\*2* and *CYP2C9\*3* alleles are associated with increased risk of fluvastatin-induced adverse effects, including liver toxicity and SAMS. However, the evidence supporting increased risk of myopathy in carriers of decreased or poor function alleles of *CYP2C9* is of moderate quality and mainly based on the pharmacokinetic evidence. Genetic variation in *CYP2C9* has not been associated with fluvastatin lipid-lowering response.

***CYP3A4* and *CYP3A5***. To date, studies have focused on two alleles, *CYP3A4\*1B* (a promoter variant) and *CYP3A5\*3* (harboring a common intronic variant causing a splice defect which leads to truncated inactive CYP3A5 protein). While neither variant has been shown to predict myopathy while on atorvastatin, Wilke *et al.* describe an association for these variants with the severity of muscle damage in a small cohort of 68 patients who reported myalgias while taking atorvastatin ([25](#_ENREF_25)). Although significant, the effect size was modest. For patients with myalgias on atorvastatin, the median CK level was 321 units/L in carriers of the *CYP3A4\*1B* allele, vs 246 units/L in non-carriers (adjusted p = 0.059), and the median CK level was 318 units/L in carriers of the *CYP3A5\*3* allele, vs 246 units/L in non-carriers (adjusted p = 0.010).

*CYP3A4* and *CYP3A5* genes are located on chromosome 7, at a locus that also contains two pseudogenes, and *CYP3A7* which is predominantly expressed *in utero* ([26](#_ENREF_26)). Functionally, the CYP3A4 and CYP3A5 enzymes have a high degree of overlap in their substrate specificity (biological redundancy), and there is wide patient-to-patient variability (more than 10-fold variation) in their expression in adults. While *CYP3A4\*1B* and *CYP3A5\*3* are in strong linkage disequilibrium (D’ >0.8), the *CYP3A5\*3* allele is thought to be the causal variant driving the association between this locus and CK elevation during atorvastatin therapy. Because this variant only predicts the severity of how high the CK may go, it does not predict who will develop SAMS, and thus, the association may not be clinically actionable. There are additional published studies (see **Table S5**), but the overall strength of evidence for *CYP3A4/5* and statin response was rated as weak. Therefore, the current guideline does not make any recommendations regarding *CYP3A4/5* genotype at this time.

HMGCR. *HMGCR* encodes for HMG-CoA reductase, the target of statins. Variations in *HMGCR* (e.g., rs1724484A>T and rs17238540T>G) have been shown to be associated with LDL-c response (see **Table S4**) but with very limited and weak data to support. Thus, the current guideline does not make recommendation regarding *HMGCR* and statin lipid response.

# Levels of evidence

The evidence summarized in **Supplemental Table S1-S3** is graded using a scale modified slightly from Valdes et al. ([27](#_ENREF_27))

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

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

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

# Strength of dosing recommendations

CPIC’s dosing recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data (**Supplemental Tables S1-S3**) as well as on some existing disease-specific consensus guidances ([28](#_ENREF_28)). Some of the factors that are considered in evaluating the evidence supporting dosage recommendations include: *in vivo* clinical outcome data for statins, *in vivo* pharmacokinetic and pharmacodynamic data for statins, *in vitro* enzyme activity of expressed wild-type or variant-containing gene, *in vitro* enzyme activity from tissues isolated from individuals of known genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of protein stability.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just four categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents ([29](#_ENREF_29)):

**Strong** recommendation for the statement: “The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.”

**Moderate** recommendation for the statement: “There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.”

**Optional** recommendation for the statement: “The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.”

**No recommendation**: “There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.”

# Other Considerations

Drug-drug interactions. Between 1998 and 2001, more than forty cases of muscle toxicity associated with the use of cerivastatin were found to be fatal. Many of these occurred within the context of gemfibrozil, a drug that strongly inhibits the cytochrome P450 (CYP) 2C8-catalyzed biotransformation of cerivastatin and also inhibits membrane transport and phase II conjugation of statins ([30](#_ENREF_30), [31](#_ENREF_31)).

The biological disposition of each statin differs on a drug-by-drug basis. Some statins undergo extensive phase I oxidation (atorvastatin, fluvastatin, lovastatin, and simvastatin), others do not (pitavastatin, pravastatin, and rosuvastatin). CYP3A4 inhibitors (e.g., azole antifungals, protease inhibitors, amiodarone, and many calcium channel blockers) increase risk of myopathy for statins metabolized by CYP3A4/5 (e.g., simvastatin, lovastatin and atorvastatin) ([32](#_ENREF_32)).

Many statins also undergo additional modification through phase II conjugation by enzymes in the UDP-glucuronosyltransferase-1 (UGT1) family. This process can be altered by concomitant administration of fibric acids ([33](#_ENREF_33)). Gemfibrozil, a fibric acid derivative, alters pharmacokinetic parameters of a variety of statins. By inhibiting the glucuronidation and membrane transport of simvastatin hydroxy-acids, gemfibrozil increases systemic exposure to active simvastatin acid ([34](#_ENREF_34)) placing patients at increased risk for developing myopathy. Because of interactions such as these, the all the statin package labels recommend reducing the dose of statins in patients using concomitant medications known to alter its pharmacokinetics.

The Role of Ancestry. 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 ([35](#_ENREF_35)) and second, that patients of Asian ancestry have greater lipid lowering efficacy at lower doses of rosuvastatin, compared to patients of European ancestry ([35](#_ENREF_35)). 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 cyclosporine (CSA)/immune suppression and patients with severe kidney failure) ([36-42](#_ENREF_36)).

Geographic differences in allele frequency for *SLCO1B1* rs4149056 (c.521T>C) do not appear to contribute to this ancestry discrepancy ([35](#_ENREF_35)). 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 ([43](#_ENREF_43)). For simvastatin, ancestry-dependent differences in *SLCO1B1* variant frequency carry an undefined impact on outcome.

Other Limitations. The pharmacokinetic predictors of SAMS are well understood ([4](#_ENREF_4), [34](#_ENREF_34), [44-59](#_ENREF_44)). 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 ([60-63](#_ENREF_60)). 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.

Because rs4149056 (c.521T>C) can be inherited in combination with other *SLCO1B1* variants that carry a protective effect, the C allele 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 is that rare and *de novo* variants are often not tested for within currently available genotyping tests, if discovered, it may be unclear how to act upon such results. Yet, rare exonic variants in *SLCO1B1* have been shown to have clinical impact (e.g., methotrexate clearance) ([64](#_ENREF_64)). Therefore, altered drug kinetics and increased risk for severe drug toxicity may still occur in the absence of a c.521 C allele, and a c.521TT genotype at rs4149056 does not necessarily imply the absence of other potentially function-altering variant(s) in *SLCO1B1*. Allele and variant function are available on PharmVar.org as well as CPIC’s ***SLCO1B1*Allele Functionality Table** ([65](#_ENREF_65), [66](#_ENREF_66)).

# Resources to Incorporate Pharmacogenetics into an EHR with CDS

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care ([67-71](#_ENREF_67)). See <https://cpicpgx.org/guidelines/cpic-guideline-for-statins/> for resources to support the adoption of CPIC guidelines within an EHR. Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of *SLCO1B1, ABCG2* and *CYP2C9* genotype results to guide statin use in an EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR ([72](#_ENREF_72), [73](#_ENREF_73)). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the “person level” rather than at the date-centric “encounter level”. Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS ([67](#_ENREF_67), [74](#_ENREF_74)).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems for genes relevant to the CPIC guideline (see<https://cpicpgx.org/guidelines/cpic-guideline-for-statins/>).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC provides gene-drug specific tables that offer guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for drugs relevant to the CPIC guideline (see <https://cpicpgx.org/guidelines/cpic-guideline-for-statins/>).

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Figure S1. 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: Pasanen *et al* ([3](#_ENREF_3)), Ieiri *et al* ([16](#_ENREF_16)), Lee *et al*. ([75](#_ENREF_75)), Niemi *et al* ([76](#_ENREF_76)), Pasanen *et al* ([77](#_ENREF_77)), Choi *et al* ([78](#_ENREF_78)), Deng *et al* ([15](#_ENREF_15)), Ho *et al* ([79](#_ENREF_79)).

Portions of this figure have been reproduced from reference ([80](#_ENREF_80)) (Niemi *et al*) with permission from the author (MN), the publisher, the American Society for Pharmacology and Experimental Therapeutics (ASPET), and *Pharmacological Reviews*.

# Table S1. Evidence linking SLCO1B1 genotype with Statin phenotype

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of experimental model (in vitro, in vivo preclinical, or clinical)** | **Major Findings** | **References** | **Level of Evidence** |
| **Atorvastatin** |
| *In vitro* | SLCO1B1 is the major atorvastatin uptake transporter. The average contribution to atorvastatin uptake was *SLCO1B1* > SLCO1B3 >> OATP2B1 > NTCP. | Vildhede, *et al.* (2014) ([81](#_ENREF_81)) | Weak |
| *In vitro*  | *SLCO1B1* rs4149056 (c.521T>C, \*5) reduces atorvastatin transport activity by decreasing OATP1B1 function due to sorting errors in transporter localization | Kameyama, *et al.* (2005) ([82](#_ENREF_82)) | Weak |
| Clinical | *SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased risk of atorvastatin-induced myopathy | Puccetti, *et al.* (2010) ([83](#_ENREF_83))Brunham, *et al.* (2012) ([84](#_ENREF_84))Santos, *et al.* (2012) ([85](#_ENREF_85))Hou, *et al.* (2015) ([86](#_ENREF_86))Hubacek, *et al.* (2015) ([87](#_ENREF_87))Mirosevic, *et al.* (2015) ([88](#_ENREF_88))Liu, *et al.* (2017) ([89](#_ENREF_89))Xiang, *et al.* (2018) ([90](#_ENREF_90))Du, *et al.* (2018) ([91](#_ENREF_91))Ramakumari, *et al.* (2018) ([92](#_ENREF_92))Mori, *et al.* (2019) ([93](#_ENREF_93))Linskey, *et al.* (2020) ([94](#_ENREF_94))Turner, *et al.* (2020) ([95](#_ENREF_95)) | Moderate |
| Clinical  | *SLCO1B1* rs4149056 (c.521T>C) C allele is not significantly associated with an increased risk of atorvastatin-induced liver tox | Fukunaga, *et al.* (2016) ([96](#_ENREF_96)) | Weak  |
| Clinical  | *SLCO1B1* rs4149056 (c.521T>C) C polymorphism affects the pharmacokinetics of atorvastatin (higher AUC and Cmax). | Pasanen, *et al.* (2007) ([77](#_ENREF_77))Lee, *et al.* (2010) ([97](#_ENREF_97))DeGorter, *et al.* (2013) ([20](#_ENREF_20))Daka, *et al.* (2015) ([98](#_ENREF_98))Birmingham, *et al.* (2015) ([99](#_ENREF_99))Leon-Cachon, *et al.* (2016) ([100](#_ENREF_100))Rajput, *et al.* (2017) ([101](#_ENREF_101))Wang, *et al.* (2017) ([102](#_ENREF_102))Woo, *et al.* (2017) ([103](#_ENREF_103))Lee, *et al.* (2019) ([104](#_ENREF_104))Mori, *et al.* (2019) ([93](#_ENREF_93))Turner, *et al.* (2020) ([95](#_ENREF_95)) | High  |
| Clinical  | Individuals with the *SLCO1B1* rs4149056 (c.521T>C) C allele showed an attenuated total-cholesterol-lowering effect compared with those homozygous for the c.521T allele.  | Tachibana-Iimori, *et al.* (2004) ([105](#_ENREF_105))Drogari, *et al.* (2014) ([106](#_ENREF_106))Giannakopoulou, *et al.* (2014) ([107](#_ENREF_107))Meyer, *et al.* (2015) ([108](#_ENREF_108)) Prado, et al. (2015) ([109](#_ENREF_109))Mladenovska, *et al.* (2017) ([110](#_ENREF_110))Du, *et al.* (2018) ([91](#_ENREF_91)) | Weak |
| Clinical  | The *SLCO1B1* rs4149056 (c.521T>C) is associated with higher likelihood of dose decrease or switching during statin therapy. | de Keyser, *et al.* (2014) ([111](#_ENREF_111)) | Moderate |
| In vitro  | *SLCO1B1* rs2306283 (c.388A>G, \*1b) did not alter the activity of OATP1B1 significantly. | Kameyama, *et al.* (2005) ([82](#_ENREF_82)) | Weak |
| Clinical | *SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with risk of myotoxicity in individuals that received atorvastatin | Liu, *et al.* (2017) ([89](#_ENREF_89)) Du, *et al.* (2018) ([91](#_ENREF_91)) | Moderate |
| Clinical | *SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with atorvastatin pharmacokinetics. | Birmingham, *et al.* (2015) ([99](#_ENREF_99))Lee, *et al.* (2019) ([104](#_ENREF_104)) | Moderate |
| Clinical | *SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with atorvastatin efficacy | Drogari, *et al.* (2014) ([106](#_ENREF_106))Prado, *et al.* (2015) ([109](#_ENREF_109))Kadam, *et al.* (2016) ([112](#_ENREF_112))Mladenovska, *et al.* (2017) ([110](#_ENREF_110))Du, *et al.* (2018) ([91](#_ENREF_91)) | Weak |
| **Fluvastatin** |
| Clinical | Presence of the *SLCO1B1\*14* allele is associated with enhanced lipid-lowering efficacy for fluvastatin. | Couvert, *et al.* (2008) ([113](#_ENREF_113)) | Moderate |
| Clinical | The *SLCO1B1* rs4149056 (c.521T>C) C variant is associated with decreased lipid- lowering response to fluvastatin | Couvert, *et al.* (2008) ([113](#_ENREF_113))Meyer, *et al.* (2015) ([108](#_ENREF_108))Xiang, *et al.* (2018) ([114](#_ENREF_114)) | Weak |
| In vitro | The uptake of fluvastatin was not influenced by *SLCO1B1* rs4149056 (c.521T>C) at concentrations >1 uM | Deng, *et al.* (2008) ([115](#_ENREF_115))Xiang, *et al.* (2020 ([116](#_ENREF_116)) | Moderate |
| In vitro | The *SLCO1B1* rs4149056 (c.521T>C) C variant is associated with reduced uptake of both fluvastatin enantiomers (3R,5S-fluvastatin and 3S,5R-fluvastatin). | Hirvensalo, *et al.* (2019) ([117](#_ENREF_117)) | Moderate |
| Clinical | Fluvastatin PK did not differ between subjects with different *SLCO1B1* rs4149056 (c.521T>C) genotypes | Niemi, *et al.* (2006) ([118](#_ENREF_118))Zhou, *et al.* (2012) ([119](#_ENREF_119))Hirvensalo, *et al.* (2019) ([117](#_ENREF_117))Mori, *et al.* (2019) ([93](#_ENREF_93)) Xiang, et al. (2020) ([116](#_ENREF_116)) | Weak  |
| Clinical  | *SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with lipid-lowering response to fluvastatin | Couvert, *et al.* (2008) ([113](#_ENREF_113))Xiang, *et al.* (2018) ([114](#_ENREF_114)) | Weak  |
| **Lovastatin** |
| Clinical | *SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased concentration of lovastatin acid but have no significant effect on lovastatin lactone. | Tornio, *et al.* (2015) ([120](#_ENREF_120))Zhao, *et al.* (2017) ([121](#_ENREF_121)) | Weak |
| Clinical | *SLCO1B1* rs2306283 (c.388A>G) is not associated with concentration of lovastatin acid and lovastatin lactone. | Tornio, *et al.* (2015) ([120](#_ENREF_120))Zhao, *et al.* (2017) ([121](#_ENREF_121)) | Weak |
| Clinical | *SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased risk of statin-induced myopathy + rhabdomyolysis. | Lu, *et al*. (2021)([122](#_ENREF_122)) | Moderate |
| **Pitavastatin** |
| Clinical | *SLCO1B1* SNP rs4149056 (c.521T>C) did not affect the lipid-lowering efficacy of pitavastatin. | Yang, *et al.* (2010) ([123](#_ENREF_123)) | Moderate |
| Clinical | *SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased AUC and decreased clearance of pitavastatin. | Chung, *et al.* (2005) ([124](#_ENREF_124))Ieiri, *et al.* (2007) ([125](#_ENREF_125))Deng, *et al.* (2008) ([115](#_ENREF_115))Oh, *et al.* (2013) ([126](#_ENREF_126))Zhou, *et al.* (2013) ([127](#_ENREF_127))Mori, *et al.* (2019) ([93](#_ENREF_93)) | High  |
| Clinical | *SLCO1B1* SNP rs2306283 (c.388A>G) did not affect the lipid-lowering efficacy of pitavastatin. | Yang, *et al.* (2010) ([123](#_ENREF_123)) | Moderate |
| Clinical | Pitavastatin AUC and Cmax increased for carriers of the *SLCO1B1* rs2306283 (c.388A>G) polymorphism. | Wen, *et al.* (2010) ([128](#_ENREF_128)) | Weak |
| **Simvastatin** |
| In vitro | *SLCO1B1* rs4149056 (c.521T>C) is the key SNP determining the functional properties of *SLCO1B1*\*5, \*15 allelic proteins and that decreased activities of these variant proteins are mainly caused by a sorting error produced by this SNP. Reduced transport function for *SLCO1B1*\*15 as compared with \*1a. | Iwai, *et al.* (2004) ([129](#_ENREF_129))Kameyama, *et al.* (2005) ([82](#_ENREF_82)) Ho, *et al.* (2006) ([130](#_ENREF_130)) | Moderate |
| Clinical | *SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased risk of simvastatin-induced myopathy | Link, *et al.* (2008) ([131](#_ENREF_131))Brunham, *et al.* (2012) ([84](#_ENREF_84))Hubacek, *et al.* (2015) ([87](#_ENREF_87))Liu, *et al.* (2017) ([89](#_ENREF_89))Shek, *et al.* (2017) ([132](#_ENREF_132))Bakar, *et al.* (2018) ([133](#_ENREF_133))Flores-Unzueta, *et al.* (2018) ([134](#_ENREF_134))Xiang, *et al.* (2018) ([90](#_ENREF_90))Carr, *et al.* (2019) ([135](#_ENREF_135))C. Thambiah, *et al.* (2019) ([136](#_ENREF_136)) | High |
| Clinical | *SLCO1B1*\*17 is associated with an increased risk of simvastatin-induced myopathy | Chan, *et al.* (2019) ([137](#_ENREF_137))  | Weak |
| Clinical | *SLCO1B1* rs4149056 C (c.521T>C) polymorphism markedly affects the pharmacokinetics of active simvastatin acid, but has no significant effect on parent simvastatin | Pasanen, *et al.* (2006) ([3](#_ENREF_3))Zhou, *et al.* (2013) ([138](#_ENREF_138))Tsamandouras, *et al.* (2014) ([139](#_ENREF_139))Birmingham, *et al.* (2015) ([99](#_ENREF_99))Choi, *et al.* (2015) ([140](#_ENREF_140)) Luzum, *et al.* (2015) ([141](#_ENREF_141))Hasunuma, *et al.* (2016) ([142](#_ENREF_142))Jiang, *et al.* (2017) ([143](#_ENREF_143))Wagner, *et al.* (2018) ([144](#_ENREF_144))Ogungbenro, *et al.* (2019) ([145](#_ENREF_145)) | High |
| Clinical | Individuals with the *SLCO1B1* rs4149056 (c.521T>C) C allele showed an attenuated lipid-lowering effect compared with those homozygous for the 521T allele. The effect size may be small. | Tachibana-Iimori, *et al.* (2004) ([105](#_ENREF_105))Bailey, *et al.* (2010) ([146](#_ENREF_146))Hopewell, *et al.* (2013) ([147](#_ENREF_147))Giannakopoulou, *et al.* (2014) ([107](#_ENREF_107))Dou, *et al.* (2015) ([148](#_ENREF_148))Li, *et al.* (2015) ([149](#_ENREF_149))Meyer, *et al.* (2015) ([108](#_ENREF_108))Kitzmiller, *et al.* (2017) ([150](#_ENREF_150))Oni-Orisan, *et al.* (2018) ([151](#_ENREF_151))Kaewboonlert, *et al.* (2018) ([152](#_ENREF_152))Wu, *et al.* (2018) ([153](#_ENREF_153)) | High |
| Clinical | Individuals with the rs4149056 C (c.521C) allele may be more likely to have dose decrease or switch. | De Keyser, *et al.* (2014) ([111](#_ENREF_111)) | Weak |
| Clinical | *SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with risk of myotoxicity in individuals that received atorvastatin, simvastatin | Liu, *et al.* (2017) ([89](#_ENREF_89)) | Weak |
| Clinical | *SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with simvastatin or simvastatin acid pharmacokinetics. | Birmingham, *et al.* (2015) ([99](#_ENREF_99)) | Weak |
| Clinical | *SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with the lipid-lowering effect of simvastatin. | Kaewboonlert, *et al.* (2018) ([152](#_ENREF_152))Wu, *et al.* (2018) ([153](#_ENREF_153)) | Weak |
| **Statin** |
| Clinical  | *SLCO1B1* rs2900478 is associated with a statistically significant though clinically negligible, lipid-lowering effect of statin | Postmus, *et al.* (2014) ([18](#_ENREF_18)) | Moderate |
| Clinical | *SLCO1B1*\*5 (rs4149056) (c.521C) C allele is associated with an increased risk of statin-induced myopathy | Voora, *et al.* (2009) ([154](#_ENREF_154))Hubacek, *et al.* (2015) ([87](#_ENREF_87))Khine, *et al.* (2016) ([155](#_ENREF_155))Bakar, *et al.* (2018) ([133](#_ENREF_133))C. Thambiah, *et al.* (2019) ([136](#_ENREF_136))Floyd, *et al.* (2019) ([156](#_ENREF_156)) | Weak |
| Clinical | Presence of the *SLCO1B1* rs4149056 (c.521T>C) C allele is associated with increased risk of composite adverse events when treated with statins (atorvastatin, pravastatin or simvastatin) in patients with hypercholesterolemia | Voora, *et al.* (2009) ([154](#_ENREF_154))Carr, *et al.* (2013) ([157](#_ENREF_157)) | Moderate |
| Clinical  | *SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased LDL-C levels in statin-treated patients | Li, *et al.* (2015) ([149](#_ENREF_149)) | Moderate |
| Clinical | *SLCO1B1* rs2306283 (c.388A>G) is not associated with an increased LDL-C levels in statin-treated patients | Li, *et al.* (2015) ([149](#_ENREF_149)) | Moderate |
| Clinical | Genetically guided statin therapy improves patients’ perceptions of statins, more statin prescriptions, and lower LDL-c. | Li, *et al.* (2014) ([158](#_ENREF_158))Peyser, *et al.* (2018) ([159](#_ENREF_159)) | Weak  |

# Table S2. Evidence linking ABCG2 genotype with Statin phenotype

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of experimental model (in vitro, in vivo preclinical, or clinical)** | **Major Findings** | **References**  | **Level of Evidence** |
| Clinical | *ABCG2* rs2231142 (c.421C>A) CA genotype is found to be more frequent in statin-intolerant cases. | Shek, *et al.* (2017) ([132](#_ENREF_132)) | Weak |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is associated with simvastatin-induced liver symptoms | Shek, *et al.* (2018) ([160](#_ENREF_160)) | Moderate  |
| Clinical | *ABCG2* rs2231142 (c.421C>A) may be associated with statin-induced muscle symptoms. | Chan, *et al.* (2019) ([137](#_ENREF_137)) | Weak |
| Clinical | *ABCG2* rs2231142 (c.421C>A) A allele carriers had higher AUC(0-t) and Cmax of simvastatin acid as compared with those carrying the CC genotype. It did not affect simvastatin lactone concentration. | Keskitalo, *et al.* (2009) ([161](#_ENREF_161))Birmingham, *et al.* (2015) ([99](#_ENREF_99))Choi, *et al.* (2015) ([140](#_ENREF_140)) | Weak |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is not significantly associated with the lipid-lowering effect of simvastatin | Bailey, *et al.* (2010) ([146](#_ENREF_146)) | High  |
| In vitro | Rosuvastatin is a substrate of SLCO1B1, SLCO1B3, and SLCO2B1 in sinusoidal uptake and of MRP2, MDR1, and ABCG2 in biliary excretion. SLCO1B1 as well as NTCP plays an important role in rosuvastatin uptake into human hepatocytes. | Kitamura, *et al.* (2018) ([162](#_ENREF_162)) | Moderate |
| In vitro | Rosuvastatin is transported efficiently by ABCG2 and suggest that ABCG2 plays a significant role in the disposition of rosuvastatin. | Huang, *et al.* (2006) ([163](#_ENREF_163)) | High  |
| Clinical  | *ABCG2* rs2231142 (c.421C>A) is not significantly associated with high SIM risk | Sreter, *et al.* (2017) ([164](#_ENREF_164))Bai, *et al.* (2019) ([21](#_ENREF_21)) | Moderate  |
| Clinical  | *ABCG2* rs2231142 (c.421C>A) is associated with greater LDL response to rosuvastatin | Tomlinson, *et al.* (2010) ([165](#_ENREF_165))Lee, *et al.* (2013) ([166](#_ENREF_166))Kim, *et al.* (2017) ([167](#_ENREF_167))Kim, *et al.* (2019) ([168](#_ENREF_168)) | Moderate |
| Clinical | *ABCG2* SNP rs2199936 is significantly associated with absolute LDL-C reduction. (rs2231142 (421C>A) is in LD with rs2199936 in the HapMap (CEU, r2=0.81). | Chasman, *et al*. (2012) ([169](#_ENREF_169)) | High  |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is significantly associated with rosuvastatin exposure. Genotypes AC + AA are associated with increased exposure to rosuvastatin compared to CC. | Zhang, *et al.* (2006) ([170](#_ENREF_170))Keskitalo, *et al.* (2009) ([19](#_ENREF_19))Zhou, *et al.* (2013) ([171](#_ENREF_171))DeGorter, *et al.* (2013) ([20](#_ENREF_20))Lee, *et al.* (2013) ([166](#_ENREF_166))Birmingham, *et al.* (2015) ([172](#_ENREF_172))Birmingham, *et al*. (2015) ([99](#_ENREF_99))Wan, *et al.* (2015) ([173](#_ENREF_173))Kim, *et al.* (2019) ([168](#_ENREF_168))Liu, *et al.* (2016) ([174](#_ENREF_174))Kashihara, *et al.* (2017) ([175](#_ENREF_175))Bai, *et al.* (2019) ([21](#_ENREF_21))Soko, *et al.* (2019) ([176](#_ENREF_176))Zhang, *et al.* (2020) ([177](#_ENREF_177)) | High |
| Clinical | *ABCG2* rs2231142 (c.421C>A) A allele is not significantly associated with an increased risk of atorvastatin-induced liver tox | Fukunaga, *et al.* (2016) ([96](#_ENREF_96)) | Weak |
| Clinical | *ABCG2* rs2231142 (c.421C>A) A allele is significantly associated with an increased risk of atorvastatin-induced adverse events. | Mirosevic Skvrce, *et al.* (2015) ([88](#_ENREF_88)) | Moderate |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is significantly associated with atorvastatin exposure | Keskitalo, *et al.* (2009) ([19](#_ENREF_19))DeGorter, *et al.* (2013) ([20](#_ENREF_20))Birmingham, *et al*. (2015) ([99](#_ENREF_99))Tsamandouras, *et al.* (2017) ([178](#_ENREF_178))Lee, *et al.* (2019) ([104](#_ENREF_104)) | Weak |
| Clinical | In vitro study showed that *ABCG2* affect atorvastatin transport | Keskitalo, *et al.* (2009) ([19](#_ENREF_19)) | High  |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is not associated with atorvastatin response. | Prado, *et al.* (2018) ([179](#_ENREF_179)) | Moderate |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is not associated with decreased clearance of pravastatin. | Ho, *et al.* (2007) ([180](#_ENREF_180))Keskitalo, *et al.* (2009) ([161](#_ENREF_161))Lu, *et al.* (2016) ([181](#_ENREF_181)) | Moderate |
| In vitro | Pitavastatin acid is a substrate of *ABCG2*, whereas the lactone form is not. *ABCG2* is involved in the biliary excretion of pitavastatin | Fujino, *et al.* (2005) ([182](#_ENREF_182))Hirano, *et al.* (2005) ([183](#_ENREF_183)) | Moderate |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is not significantly associated with concentration of pitavastatin. | Ieiri, *et al.* (2007) ([125](#_ENREF_125))Oh, *et al.* (2013) ([126](#_ENREF_126)) | Moderate |
| Clinical | *ABCG2* rs2231142 (c.421C>A) AA genotype is associated with higher fluvastatin AUC. | Keskitalo, *et al*. (2009) ([161](#_ENREF_161)) | High |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is associated with greater odds of developing fluvastatin-induced adverse effects (liver and muscle toxicity). | Mirosevic, *et al.* (2013) ([184](#_ENREF_184)) | Moderate |
| Clinical | *ABCG2* rs2231142 (c.421C>A) is not associated with concentration of lovastatin acid and lovastatin lactone. | Zhao, *et al.* (2017) ([121](#_ENREF_121)) | Weak |

# Table S3. Evidence linking CYP2C9 genotype with Statin phenotype

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of experimental model (in vitro, in vivo preclinical, or clinical)** | **Major Findings** | **References**  | **Level of Evidence** |
| In vitro | Fluvastatin is metabolized in human liver by several enzymes, with CYP2C9 being the most important, followed by CYP3A4 and CYP2C8. | Fischer, *et al.* (1999) ([185](#_ENREF_185))Toda, *et al.* (2009) ([186](#_ENREF_186))Hirvensalo, *et al.* (2019) ([117](#_ENREF_117)) | High |
| In vitro | Fluvastatin is a potent inhibitor of *CYP2C9*. | Transon, *et al.* (1996) ([187](#_ENREF_187))Cohen, *et al.* (2000) ([188](#_ENREF_188)) | Moderate |
| In vitro | *CYP2C9\*2, \*3* were associated with reduced clearance of fluvastatin enantiomers in vitro. | Hirvensalo, *et al.* (2019) ([117](#_ENREF_117)) | Moderate |
| In vitro | Fluvastatin and lovastatin increased *CYP2C9* protein level in endothelial cells | Bertrand-Thiebault, *et al.* (2007) ([189](#_ENREF_189)) | Weak |
| Clinical | *CYP2C9\*2, \*3* are not significantly associated with lipid-lowering response to fluvastatin | Kirschheiner, *et al.* (2003) ([190](#_ENREF_190))Xiang, *et al.* (2018) ([114](#_ENREF_114)) | Weak |
| Clinical | *CYP2C9\*3* affected the pharmacokinetics of both fluvastatin enantiomers. *CYP2C9*\*3 associated with significantly increased area under the plasma concentration-time curve (AUC) of both 3R,5S-fluvastatin and 3S,5R-fluvastatin. | Kirschheiner, *et al.* (2003) ([190](#_ENREF_190))Toda, *et al.* (2009) ([186](#_ENREF_186))Zhou, *et al.* (2012) ([119](#_ENREF_119))Hirvensalo, *et al.* (2019) ([117](#_ENREF_117))Xiang, *et al.* (2020) ([116](#_ENREF_116)) | High |
| Clinical | *CYP2C9\*2* influences the pharmacokinetics of the fluvastatin (affect the AUC of both fluvastatin enantiomers). | Fischer, *et al.* (1999) ([185](#_ENREF_185))Kirschheiner, *et al.* (2003) ([190](#_ENREF_190))Hirvensalo, *et al.* (2019) ([117](#_ENREF_117)) | Moderate |
| Clinical | *CYP2C9\*2* or *\*3* allele is associated with greater odds of developing fluvastatin-induced adverse effects (liver and muscle toxicity). | Mirosevic, *et al.* (2013) ([184](#_ENREF_184)) | Moderate |
| Unknown | Statins, *CYP2C9* genotypes are not significantly associated with muscle tox or lipid response to statins (simvastatin, fluvastatin, rosuvastatin). | Zuccaro, *et al.* (2007) ([191](#_ENREF_191)) | Weak |
| Clinical | A case with liver cirrhosis who experienced fluvastatin-induced fatal rhabdomyolysis. This patient had been treated with simvastatin (20 mg/day) for coronary artery disease and was switched to fluvastatin (20 mg/day) 10 days before admission. | Baek, *et al.* (2011) ([192](#_ENREF_192)) | Weak |
| Clinical | *CYP2C9\*3* is not associated with LDL response to rosuvastatin | Bailey, *et al.* (2010) ([146](#_ENREF_146)) | Moderate  |
| Clinical | *CYP2C9\*3* allele is associated with an increased concentration of pitavastatin. | Zhou, *et al.* (2013) ([127](#_ENREF_127)) | Weak |

# Table S4. Evidence linking HMGCR genotype with Statin phenotype

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of experimental model (in vitro, in vivo preclinical, or clinical)** | **Major Findings** | **References**  | **Level of Evidence** |
| Clinical  | Multiple cases of statin-related immune-mediated necrotizing myopathy (SINAM) were described. Many are positive for anti-HMGCR antibody, but there are exceptions. | Mygland, *et al.* (2014) ([193](#_ENREF_193))Ong, *et al.* (2017) ([194](#_ENREF_194))Karunaratne, *et al*. (2018) ([195](#_ENREF_195))Pitlick, *et al.* (2019) ([196](#_ENREF_196)) | Weak |
| Clinical  | *HMGCR* haplotypes H2 and H7 were associated with attenuated reduction of LDL cholesterol when treated with simvastatin. Tag SNP rs17238540 and rs17244841 were also associated with altered LDL-C response. | Krauss, *et al.* (2008) ([197](#_ENREF_197)) | Weak |
|  | Carriers of both *HMGCR* H2/H7 haplotype and LDLR L5 haplotype had significantly attenuated statin-mediated changes in LDLC and LDLR in comparison to either noncarriers or carriers of individual haplotypes. This effect is more evident in African-Americans than in European-Americans. | Mangravite, *et al.* (2010) ([198](#_ENREF_198)) | Weak |
|  | *HMGCR* ScrF I polymorphism is associated with vLDL-C lowering effect by simvastatin. | Ying, *et al.* (2007) ([199](#_ENREF_199)) | Weak |
| In vitro | *HMGCR* variant rs3846662 influenced *HMGCR* alternative splicing. Greater upregulation of *HMGCR*v\_1 in vitro was significantly correlated with reduced statin response (smaller reductions of plasma total and low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B). | Medina, *et al.* (2008) ([200](#_ENREF_200)) | Weak |
| Clinical | *HMGCR* variants rs17238540 and rs17244841 were significantly associated with a smaller reduction in total cholesterol and LDL cholesterol following pravastatin therapy. | Chasman, *et al.* (2004) ([201](#_ENREF_201))Polisecki, *et al.* (2008) ([202](#_ENREF_202)) | Weak |
| Clinical  | *HMGCR* variants rs17238540, rs17244841 were not associated with lipid response to fluvastatin. | Singer, *et al.* (2007) ([203](#_ENREF_203)) | Weak |
| Clinical  | Multiple cases of statin-related immune-mediated necrotizing myopathy (SINAM) were described. All are previously atorvastatin treated. All are positive for anti-*HMGCR* antibody. | Nichols, *et al.* (2015) ([204](#_ENREF_204))De Cock, *et al.* (2018) ([205](#_ENREF_205))Woolley, *et al.* (2018) ([206](#_ENREF_206))Sharma, *et al.* (2019) ([207](#_ENREF_207)) | Weak |
| In vitro | Atorvastatin had no significant effect on LRP or *HMGCR* mRNA levels in circulating mononuclear cells. | Pocathikorn, *et al.* (2010) ([208](#_ENREF_208)) | Weak |
| Clinical | *HMGCR* variants rs17238540 and rs17244841 were significantly associated with reduction in total cholesterol and LDL-c levels. | Thompson, *et al.* (2009) ([209](#_ENREF_209))Poduri, *et al.* (2010) ([210](#_ENREF_210))Kirac, *et al.* (2017) ([211](#_ENREF_211)) | Weak |
| Clinical | *HMGCR* variant rs17671591 is associated with greater plasma LDL-C reductions after therapy with atorvastatin. | Cuevas, *et al.* (2016) ([212](#_ENREF_212)) | Weak |
| Clinical | *HMGCR* rs3846662 was associated with LDL lowering response to atorvastatin. | Chung, *et al.* (2012) ([213](#_ENREF_213))Yue, *et al.* (2016) ([214](#_ENREF_214)) | Weak |
| Clinical | *HMGCR* variants (rs10474433, rs17671591, rs6453131) were associated with statin response by with smaller effect than the ApoE variants. | Thompson, *et al.* (2009) ([209](#_ENREF_209)) | Weak |
| In vitro  | Atorvastatin insensitivity is associated with upregulation of HMGCR and SCD. | Lettiero, *et al.* (2018) ([215](#_ENREF_215)) | Weak |

# Table S5. Evidence linking CYP3A4/5 genotype with Statin phenotype

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of experimental model (in vitro, in vivo preclinical, or clinical)** | **Major Findings** | **References**  | **Level of Evidence** |
| Clinical | *CYP3A5\*3/\*3* genotype (6986A>G) is associated with simvastatin-induced muscle symptoms. | Shek, *et al.* (2017) ([132](#_ENREF_132))Liu, *et al.* (2017) ([89](#_ENREF_89)) | Weak |
| Clinical  | *CYP3A5\*3/\*3* genotype (6986A>G) is more frequent in statin-intolerant cases. | Shek, *et al.* (2018) ([160](#_ENREF_160)) | Weak |
| Clinical | *CYP3A5\*3/\*3* genotype (6986A>G) is associated with simvastatin-induced liver symptoms | Shek, *et al.* (2017) ([132](#_ENREF_132)) | Weak |
| Clinical | When simvastatin-intolerant patients were switched to rosuvastatin, serious side effect were not observed and many of them carry *CYP3A5\*3/\*3* | Shek, *et al.* (2018) ([160](#_ENREF_160)) | Weak |
| Clinical  | *CYP3A4* rs2740574 (G>A) G allele is associated with smaller risk of a dose decrease or switch to another drug during simvastatin and atorvastatin therapy. | Becker, *et al.* (2010) ([216](#_ENREF_216)) | Weak |
| Clinical  | *CYP3A4\*22* is associated with lower statin dose (atorvastatin, simvastatin, or lovastatin) | Wang, *et al.* (2011) ([217](#_ENREF_217)) | Weak |
| Clinical  | *CYP3A5\*3* is associated with cholesterol response to simvastatin. | Kivisto, *et al.* (2004) ([218](#_ENREF_218))Fiegenbaum, *et al.* (2005) ([219](#_ENREF_219))Hu, *et al.* (2013) ([220](#_ENREF_220))Kolovou, *et al.* (2014) ([221](#_ENREF_221))Kitzmiller, *et al.* (2017) ([150](#_ENREF_150)) | Weak |
| Clinical  | *CYP3A4\*22* is associated with cholesterol response to simvastatin. | Elens, *et al.* (2011) ([222](#_ENREF_222))Ragia, *et al.* (2015) ([223](#_ENREF_223))Kitzmiller, *et al.* (2017) ([150](#_ENREF_150)) | Weak |
| Clinical  | *CYP3A4\*1G* is not associated with cholesterol response to simvastatin. | Gao, *et al.* (2008) ([224](#_ENREF_224))Hu, *et al.* (2013) ([220](#_ENREF_220)) | Weak |
| Clinical  | *CYP3A4\*1B* is not associated with cholesterol response to simvastatin. | Fiegenbaum, *et al.* (2005) ([219](#_ENREF_219)) | Weak |
| Clinical  | *CYP3A4\*4* is not associated with LDL lowering response to simvastatin but may affect percentage reductions in total cholesterol and triglycerides. | Wang, *et al.* (2005) ([225](#_ENREF_225)) | Weak |
| Clinical  | *CYP3A5\*3* may be associated with higher simvastatin concentration | Kim, *et al.* (2007) ([226](#_ENREF_226))Kitzmiller, *et al.* (2014) ([227](#_ENREF_227))Choi, *et al.* (2015) ([140](#_ENREF_140))Luzum, *et al.* (2015) ([141](#_ENREF_141)) | Weak |
| Clinical  | *CYP3A4\*22* is associated with higher plasma simvastatin concentration compared to *CYP3A4*\*1/\*1. | Kitzmiller, *et al.* (2014) ([227](#_ENREF_227))Luzum, *et al.* (2015) ([141](#_ENREF_141)) | Weak |
| Clinical  | *CYP3A5\*3* is not significantly associated with risk of myotoxicity in individuals that received rosuvastatin | Liu, *et al.* (2017) ([89](#_ENREF_89))Ramakumari, *et al.* (2018) ([92](#_ENREF_92)) | Weak |
| Clinical | Patients with *CYP3A5\*1* allele achieved LDL cholesterol target more frequently as compared to patients with *CYP3A5*\*3/\*3 when treated with rosuvastatin. | Bailey, *et al.* (2010) ([146](#_ENREF_146)) | Weak |
| Clinical  | *CYP3A5\*3* is not significantly associated with risk of myotoxicity in individuals that received atorvastatin, however it may affect the severity of myotoxicity (magnitude of serum CK elevation). | Wilke, *et al.* (2005) ([25](#_ENREF_25))Liu, *et al*. (2017) ([89](#_ENREF_89))Ramakumari, *et al.* (2018) ([92](#_ENREF_92)) | Weak |
| Clinical  | *CYP3A4\*22* is not significantly associated with adverse events in individuals that received atorvastatin. | Mirosevic, *et al.* (2015) ([88](#_ENREF_88)) | Weak |
| Clinical  | *CYP3A5\*3* is significantly associated with atorvastatin efficacy | Kivisto, *et al.* (2004) ([218](#_ENREF_218))Thompson, *et al.* (2005) ([228](#_ENREF_228))Willrich, *et al.* (2008) ([229](#_ENREF_229))Rosales, *et al.* (2012) ([230](#_ENREF_230))Drogari, *et al.* (2014) ([106](#_ENREF_106))Wei, *et al.* (2015) ([231](#_ENREF_231)) | Weak |
| Clinical  | *CYP3A4\*22* is not significantly associated with atorvastatin efficacy | Drogari, *et al. (*2014) ([106](#_ENREF_106))Ragia, *et al.* (2015) ([223](#_ENREF_223)) | Weak |
| Clinical  | *CYP3A4* rs2740574 G allele may be associated with a greater reduction in serum total cholesterol and LDL-c.as compared to AA when treated with atorvastatin. | Kajinami, *et al.* (2004) ([232](#_ENREF_232))Rosales, *et al.* (2012) ([230](#_ENREF_230)) | Weak |
| Clinical  | *CYP3A4* rs2242480 is associated with lipid-lowering efficacy of atorvastatin. | Gao, *et al.* (2008) ([224](#_ENREF_224))Peng, *et al.* (2018) ([233](#_ENREF_233)) | Weak |
| Clinical  | *CYP3A4* rs2242480 is associated with lower AUC and greater clearance when treated with atorvastatin | He, *et al.* (2014) ([234](#_ENREF_234)) | Weak  |
| Clinical  | *CYP3A5* genotype has minimal effects on the pharmacokinetic parameters of atorvastatin. | Shin, *et al.* (2011) ([235](#_ENREF_235)) | Weak |
| Clinical  | *CYP3A5*\*3 is associated with enhanced lovastatin lipid lowering efficacy | Kivisto, *et al.* (2004) ([218](#_ENREF_218)) | Weak |
| Clinical  | *CYP3A5*\*3 is not significantly associated with lipid lowering efficacy to fluvastatin | Kivisto, *et al.* (2004) ([218](#_ENREF_218)) | Weak  |
| Clinical  | *CYP3A5*\*3 is not significantly associated with lipid lowering efficacy to pravastatin | Kivisto, *et al.* (2004) ([218](#_ENREF_218)) | Weak |

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