

OPEN

Association Between SLCO1B1 Gene T521C Polymorphism and Statin-Related Myopathy Risk

A Meta-Analysis of Case–Control Studies

Qingtao Hou, MD, Sheyu Li, MD, Ling Li, PhD, Yun Li, MM, Xin Sun, PhD, and Haoming Tian, MM

Abstract: Statin-related myopathy is an important adverse effect of statin which is classically unpredictable. The evidence of association between solute carrier organic anion transporter 1B1 (SLCO1B1) gene T521C polymorphism and statin-related myopathy risk remained controversial. This study aimed to investigate this genetic association.

Databases of PubMed, EMBASE, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database, and Wanfang Data were searched till June 17, 2015. Case-control studies investigating the association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk were included. The Newcastle–Ottawa Scale (NOS) was used for assessing the quality of included studies. Data were pooled by odds ratios (ORs) and their 95% confidence intervals (CIs).

Nine studies with 1360 cases and 3082 controls were included. Cases of statin-related myopathy were found to be significantly associated with the variant C allele (TC + CC vs TT: OR = 2.09, 95% CI = 1.27–3.43, $P = 0.003$; C vs T: OR = 2.10, 95% CI = 1.43–3.09, $P < 0.001$), especially when statin-related myopathy was defined as an elevation of creatine kinase (CK) >10 times the upper limit of normal (ULN) or rhabdomyolysis (TC + CC vs TT: OR = 3.83, 95% CI = 1.41–10.39, $P = 0.008$; C vs T: OR = 2.94, 95% CI = 1.47–5.89, $P = 0.002$). When stratified by statin type, the association was

significant in individuals receiving simvastatin (TC + CC vs TT: OR = 3.09, 95% CI = 1.64–5.85, $P = 0.001$; C vs T: OR = 3.00, 95% CI = 1.38–6.49, $P = 0.005$), but not in those receiving atorvastatin (TC + CC vs TT: OR = 1.31, 95% CI = 0.74–2.30, $P = 0.35$; C vs T: OR = 1.33, 95% CI = 0.57–3.12, $P = 0.52$).

The available evidence suggests that SLCO1B1 gene T521C polymorphism is associated with an increased risk of statin-related myopathy, especially in individuals receiving simvastatin. Thus, a genetic test before initiation of statins may be meaningful for personalizing the treatment.

(*Medicine* 94(37):e1268)

Abbreviations: CBM = Chinese Biomedical Literature Database, CI = confidence interval, CK = creatine kinase, CNKI = China National Knowledge Infrastructure, HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A, HWE = Hardy–Weinberg equilibrium, MeSH = Medical Subject Heading, NOS = Newcastle–Ottawa Scale, OATP1B1 = organic anion transporter polypeptide 1B1, OATP1B3 = organic anion transporter polypeptide 1B3, OATP2B1 = organic anion transporter polypeptide 2B1, OATPs = organic anion transporter polypeptides, OR = odds ratio, SLCO1B1 = solute carrier organic anion transporter 1B1, SNP = single-nucleotide polymorphism, ULN = upper limit of normal.

Editor: Mirko Manchia.

Received: March 8, 2015; revised: June 22, 2015; accepted: July 9, 2015. From the Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, China (QH, SL, HT); Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, China (LL, XS); and Department of Endocrinology and Metabolism, The Third People's Hospital of Chengdu, Chengdu, China (YL).

Correspondence: Haoming Tian, Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, No. 37, Guoxue Road, Chengdu, Sichuan 610041, China (email: hmtian999@126.com).

Dr Ling Li, PhD, candidate and Prof Xin Sun, PhD, are both biostatisticians from the Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, China. Dr Ling Li fully participated all through the data analysis and statistical procedure, and Prof Xin Sun provided methodological guidance of this manuscript and reviewed the statistical analysis.

Author distribution: HT and XS conceived and designed the study. QH and SL performed data extraction and drafted the manuscript. XS and LL are both biostatisticians from the Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, China. XS provided methodological guidance of this manuscript as well as reviewed the statistics. LL fully participated all through the data analysis and statistical procedure. All authors actively discussed the results of the study.

QH and SL have contributed equally to this work.

This study was funded by the National Natural Science of China (Grant No. 81400811).

Supplemental Digital Content is available for this article.

The authors have no conflicts of interest to disclose.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution License 4.0, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001268

INTRODUCTION

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, also known as statins, are recommended as candidate drugs for the treatment of hypercholesterolemia and prevention of cardiovascular disease. Although their clinical benefits have been undoubted, a series of potential adverse events especially myopathy have been widely reported.^{1,2} However, there has been no consensus on the definition of statin-related myopathy and the clinical spectrum has ranged from the mild myalgia or asymptomatic creatine kinase (CK) elevation to the rare but fatal rhabdomyolysis.^{3,4}

The underlying pathogenesis of statin-related myopathy is still uncertain. Potential contributing risk factors include drug properties, concomitant interacting medications, individual demographic characteristics, co-morbidities, and genetic factors.⁵ Genetic factors play a crucial role in the development of statin-related myopathy. Recently, some studies have clarified the association between the polymorphisms of solute carrier organic anion transporter 1B1 (SLCO1B1) gene and statin-related myopathy risk. Among them, the T521C polymorphism has been the focus of much interest and debate.^{6–8}

Although a number of studies have reported the association of SLCO1B1 gene T521C polymorphism and statin-related myopathy risk, considerable discrepancies among them have made the real relationship vague. Moreover, statin-related myopathy particularly severe myopathy or rhabdomyolysis

has created great health and economic burden because of the widely use of statins in clinical practice, even though the incidence of myopathy is not very high. Thus, whether the genetic test before statin initiation in high risk individuals is cost-effective or not is very important. In order to overcome the limitations of individual studies and estimate the predictive value of genetic testing, we conducted a comprehensive and quantitative analysis to systematically assess the genetic association between T521C polymorphism and the risk of statin-related myopathy.

METHODS

Literature Search

The EndNote software version X7 (Thomson Reuters Corporation, Toronto, Ontario, Canada) was used throughout the searching process. The electronic databases of PubMed, EMBASE, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database, and Wanfang Data were searched till June 17, 2015. The combination of the following keywords was used: (solute carrier organic anion transporter 1B1 or SLCO1B1 or organic anion transporter polypeptide 1B1 or OATP1B1) and (myopathy or myalgia or myositis or rhabdomyolysis or creatine kinase or CK) and (statin or rosuvastatin or fluvastatin or pravastatin or simvastatin or cerivastatin or lovastatin or atorvastatin or pitavastatin). The Medical Subject Heading (MeSH) was also used during search when available. Bibliographies of identified studies were searched to make sure all the potentially relevant studies included. We also contacted with the author by Email for sufficient data. The language was limited to either English or Chinese. No ethical approval and patient consent are required because all analyses were based on previous published studies.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: the case-control design investigated the association between SLCO1B1 gene T521C polymorphism and the risk of statin-related myopathy; the study provided enough information to calculate the gene frequencies in both case and control group; myopathy was defined according to CK elevations or muscle symptoms or both.

Study Selection

Two reviewers (QH and SL) independently screened the titles and abstracts, and then the full texts for eligibility. Discrepancies between the 2 reviewers' selections were resolved by consensus.

Data Extraction and Quality Assessment

The following information was extracted from each study by 2 reviewers (QH and SL) independently: first author, year of publication, country, ethnicity, genotyping method, case definition, control source, age, gender, baseline matching, statin type, sample size (case/control), genotype, and/or allele frequencies in cases and controls. The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of included studies.^{9,10} Any disagreements were resolved through discussion.

Statistical Analysis

The STATA software version 12.0 (STATA Corporation, College Station, TX) was used throughout the analyses.

Between-study heterogeneity was estimated using the chi-squared test and quantified with the I^2 statistic, and $P < 0.10$ was considered the presence of statistical heterogeneity.¹¹ The odds ratios (ORs) with their 95% confidence intervals (CIs) were estimated on the basis of a dominant model (TC + CC vs TT) and an allelic model (C vs T). The pooled ORs were determined by the Z-test and a P value below 0.05 was considered statistically significant. Subgroup analyses by statin type, control source, and age were also conducted to explore the sources of heterogeneity. Sensitivity analysis was carried out to determine the robustness. Begg's test and Egger's test were employed to evaluate the publication bias.¹²

RESULTS

Study Characteristics

A total of 336 articles were originally identified. After excluding 78 duplicate articles, 258 articles were left for abstract screening and full-text assessment. After abstract screening, 13 studies¹³⁻²⁵ were left for full-text assessment. After evaluating the full-text according to inclusion and exclusion criteria, 9 studies¹⁴⁻²² including 1360 cases and 3082 controls were eligible for further meta-analyses (Figure 1). The baseline characteristics of studies included are displayed in Table 1. Genotype and allele frequencies are shown in Table 2. The definitions of statin-related myopathy were based on elevations of serum CK level with or without muscular symptoms except for 1 study.¹⁸ In which patients with self-reported myalgia were classified as cases. Severe statin-related myopathy was defined as $CK > 10 \times$ the upper limit of normal (ULN) or rhabdomyolysis.²⁶ There were 4^{14,15,17,19} studies performing on simvastatin, 4^{15,17,19,22} on atorvastatin, and 4^{14,15,17,20} on severe myopathy. Seven studies^{14-18,20,21} examined Caucasian subjects, whereas 2 studies^{19,22} examined mixed Caucasians. One study²² reported the association of SLCO1B1 genotypes with myalgia and CK elevation separately from the same population group, so we just extracted the data based on CK elevation, because most existing definitions of statin-related myopathy were based on biochemical standards rather than clinical phenotypes.²⁷ Valid genotyping methods were applied throughout all the studies. The distribution of genotypes in the control group deviated from Hardy-Weinberg equilibrium (HWE) in 1 study¹⁵ with a P value 0.04.

Quality Assessment

The NOS was adopted to evaluate the methodological quality of all included studies. All studies showed a relatively high quality with a mean score of 7, ranging from 6 to 9 (Table 1). Four studies^{14-16,20} used matched controls while the other 5 studies^{17-19,21,22} did not provide available data on baseline matching. Three studies^{14,19,20} genotyped participants from previous clinical trials, while 6^{15-18,21,22} recruited patients from the real world. One study²¹ was carried out in patients with type 2 diabetes.

Meta-Analysis

The overall and subgroup analyses are shown in Table 3. A statistically significant association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk was found (TC + CC vs TT: OR = 2.09, 95% CI = 1.27-3.43, $P = 0.003$; C vs T: OR = 2.10, 95% CI = 1.43-3.09, $P < 0.001$), indicating that the allele C carriers may be more intolerant to statins. The association was more obvious when statin-related myopathy was defined as $CK > 10 \times$ ULN or rhabdomyolysis

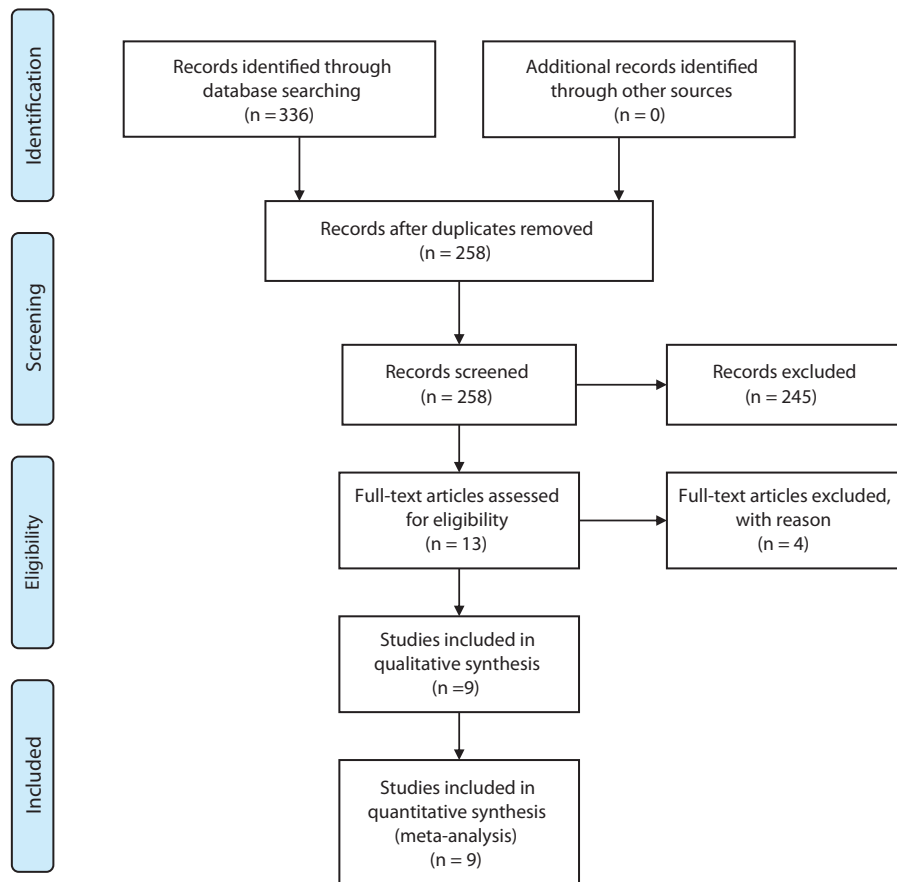


FIGURE 1. Flow diagram for study identification and inclusion.

(TC + CC vs TT: OR = 3.83, 95% CI = 1.41–10.39, $P = 0.008$; C vs T: OR = 2.94, 95% CI = 1.47–5.89, $P = 0.002$). However, the results were inconsistent when stratified by statin type. The association was statistically significant in individuals receiving simvastatin (TC + CC vs TT: OR = 3.09, 95% CI = 1.64–5.85, $P = 0.001$; C vs T: OR = 3.00, 95% CI = 1.38–6.49, $P = 0.005$) (Figures 2 and 3), but not in those receiving atorvastatin (TC + CC vs TT: OR = 1.31, 95% CI = 0.74–2.30, $P = 0.35$; C vs T: OR = 1.33, 95% CI = 0.57–3.12, $P = 0.52$) (Figures 4 and 5).

Subgroup analyses based on control source showed that the association in clinical practice (TC + CC vs TT: OR = 1.68, 95% CI = 1.06–2.65, $P = 0.03$; C vs T: OR = 1.80, 95% CI = 1.13–2.87, $P = 0.01$) was more robust than that in clinical study (TC + CC vs TT: OR = 3.31, 95% CI = 0.85–12.90, $P = 0.09$; C vs T: OR = 2.56, 95% CI = 1.37–4.77, $P = 0.003$) and the relationship in >60 years old age group (TC + CC vs TT: OR = 2.34, 95% CI = 1.22–1.65, $P < 0.001$; C vs T: OR = 2.07, 95% CI = 1.66–2.57, $P < 0.001$) was stronger compared with that in 50–60 years old age group (TC + CC vs TT: OR = 1.65, 95% CI = 1.13–2.42, $P = 0.009$; C vs T: OR = 1.68, 95% CI = 1.19–2.37, $P = 0.003$) when stratified by age (Table 3).

Publication Bias and Sensitivity Analysis

Publication bias was not detected in Begg’s and Egger’s tests for both contrast models (all $P > 0.05$) (Table 4). The

results remained statistically significant by excluding 1 study at a time based on a sensitivity analysis (see Figures S1 and S2, <http://links.lww.com/MD/A405>, which illustrate the results of sensitivity analyses).

DISCUSSION

In summary, we have demonstrated that SLCO1B1 gene T521C polymorphism is significantly associated with statin-related myopathy, the variant C allele may increase the risk of developing statin-related myopathy (especially severe myopathy). Nonetheless, when stratified by stain type, the association is significant in patients receiving simvastatin but not in patients receiving atorvastatin, which suggests that the association may be a statin type-specific. Subgroup analyses based on control source and age have revealed that the association in clinical practice and older age group was more statistically significant.

The SLCO1B1 gene is localized to an SLCO1 gene cluster in the short arm of chromosome 12 and encodes the OATP1B1 on the basolateral membrane of hepatocytes. The OATP1B1 is an influx transporter responsible for hepatic uptake of statins. The T521C polymorphism, rs4149056, is a relatively common nonsynonymous single-nucleotide polymorphism located in exon 5 of SLCO1B1 gene.^{28,29} The functional T→C transition results in a Val→Ala substitution. The substitute alanine is associated with a decreased transport function and an elevated plasma statin concentration, and consequently produces a stronger susceptibility to myopathy.^{28,30} Compared with the normal

TABLE 1. Baseline Characteristics of Studies Included

Author	Year	Country	Method	Case Definition	Control Source	Age*	Gender†	Baseline Matching	Statins	NOS	HWE
Link	2008	UK	PCR	Incipient: CK > 3 × ULN, 5 × baseline; Definite: Muscle symptoms and CK > 10 × ULN	SEARCH	NA	NA	Sex, age, eGFR, use or nonuse of amiodarone	Simvastatin	9	0.15
Brunham	2012	The Netherlands	Illumina GoldenGate	CK > 10 × ULN	Lipid clinic	53/57	21.7/27.4	Sex, age, statin type and dose	Simvastatin, Atorvastatin	7	0.04
Ferrari	2014	Italy	PCR	CK > 3 × ULN	Lipid clinic	62.1/61.2	60.6/60.6	Sex, age, statin type and dose range	Various	8	0.86
Carr	2013	UK	PCR	CK > 4 × ULN	GPRD	71.2/69.9	36/29	NA	Simvastatin, Atorvastatin	6	0.75
Linde	2010	USA	PCR	Self-reported myalgia	EMR	59.5/59.3	46.2/36.0	NA	Various	6	0.61
Voora	2009	USA‡	NA	CK > 3 × ULN, or drug discontinuation, or myalgia	STRENGTH	58/56	67/50	NA	Simvastatin, Atorvastatin, Pravastatin	7	0.34
Marcante	2011	USA, Canada	PCR, Illumina GoldenGate	Muscle pain or weakness with CK > 10 × ULN	HVH, CHS	63.5/73.6 (CHS), 64.5 (HVH)	61.1/61.0 (CHS), 48.0 (HVH)	Sex, age	Cerivastatin	9	NA§
Donnelly	2011	UK	PCR	CK = 1–3 × ULN with prescription change	Go-DARTS	NA	NA	NA	Various	7	0.08
Santos	2012	Brazil	PCR, HRM	CK ≥ 3 × ULN	Lipid clinic	54.3/52.5	78.6/70.5	NA	Atorvastatin	7	0.89

CHS = cardiovascular health study; CK = creatine kinase; eGFR = estimated glomerular filtration rate; EMR = electronic medical records; Go-DARTS = the Genetics of Diabetes Audit and Research database; GPRD = General Practice Research Datalink; HRM = high-resolution melting; HVH = Heart and Vascular Health study; HWE = P value of Hardy-Weinberg equilibrium; NA = not available; NOS = Newcastle-Ottawa Scale; PCR = polymerase chain reaction; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; STRENGTH = Statin Response Examined by Genetic Haplotype Markers study; ULN = upper limit of normal.

* Mean age of cases/mean age of controls.

† Percentage of females in cases/% of females in controls.

‡ Mixed ethnicities: Caucasian (mainly), African American, and other.

§ The original study reported the genotype distribution of the control group met HWE.

|| Mixed ethnicities: Caucasian (mainly), Mulatto, and African.

TABLE 2. Genotype and Allele Frequencies of Studies Included

Author	Case/Control	Case					Control						
		TT	TC	CC	T	C	TT	TC	CC	T	C		
Link	All myopathy	85/90	29	35	21	93	77	70	17	3	157	23	
	Definite myopathy	41/90	12	15	14	39	43	70	17	3	157	23	
	Incipient myopathy	44/90	17	20	7	54	34	70	17	3	157	23	
Brunham	All statins	25/83	15	8	2	38	12	57	20	6	134	32	
	Simvastatin	12/39	5	6	1	16	8	27	10	2	64	14	
	Atorvastatin	10/34	7	2	1	16	4	24	7	3	55	13	
Ferrari		33/33	8	13	12	29	37	18	13	2	49	17	
Carr	All Statins	All myopathy	76/372	40	30	6	110	42	260	101	11	621	123
		Severe myopathy	23/372	8	10	5	26	20	260	101	11	621	123
	Simvastatin	All myopathy	59/222	29	25	5	83	35	147	71	4	365	79
		Severe myopathy	18/222	5	9	4	19	17	147	71	4	365	79
	Atorvastatin	All myopathy	11/110	7	4	0	18	4	86	22	2	194	26
		Severe myopathy	3/110	3	0	0	6	0	86	22	2	194	26
Linde		27/19	14	12	1	40	14	15	4	0	34	4	
Voora	All statins	97/351	62	31	4	155	39	263	84	4	610	92	
	Simvastatin	34/158	17	TC + CC: 17				108	TC + CC: 50				
	Atorvastatin	31/146	21	TC + CC: 10				109	TC + CC: 37				
	Pravastatin	31/142	23	TC + CC: 8				106	TC + CC: 36				
Marciante		185/732				281	89				1259	205	
Donnelly		816/1275	565	227	24	1357	275	905	348	22	2158	392	
Santos		16/127	12	TC + CC:4				94	TC + CC: 33				

function of the homozygous wild TT genotype, the heterozygous TC genotype and homozygous mutant CC genotype has an intermediate and a low function, respectively.³¹

Although OATP1B1 is the primary transporter for the uptake of statins, organic anion transporter polypeptide 1B3 (OATP1B3) and organic anion transporter polypeptide 2B1 (OATP2B1) also take part in the process of some specific statins. Our data indicated that T521C polymorphism was mainly associated with simvastatin-related myopathy rather than atorvastatin-

related myopathy. The underlying mechanism may be partly explained by varying degrees of contributions of other organic anion transporter polypeptides (OATPs) to the hepatic uptake that simvastatin is mainly uptaken by OATP1B1, whereas atorvastatin is a substrate of both OATP1B1 and OATP2B1.³² Meanwhile, pharmacokinetic studies have demonstrated that the area under the plasma concentration-time curve of active simvastatin acid and atorvastatin is 221% and 144% greater in 521CC genotype than that in 521TT genotype, respectively.^{33,34}

TABLE 3. Main Results of Meta-analyses based on Dominant and Allelic Models

T521C	N	TC + CC vs TT				C vs T				
		Case/control	OR (95% CI)	P _z	I ² (%)	N	Case/control	OR (95% CI)	P _z	I ² (%)
Total	8	1175/2350	2.09 (1.27–3.43)	0.003	80.9*	8	1344/2955	2.10 (1.43–3.09)	<0.001	85.3*
Severe myopathy	3	89/545	3.83 (1.41–10.39)	0.008	73.9*	4	274/1277	2.94 (1.47–5.89)	0.002	85.1*
Statin type										
Simvastatin	4	190/509	3.09 (1.64–5.85)	0.001	63.2*	3	156/351	3.00 (1.38–6.49)	0.005	78.0*
Atorvastatin	4	68/417	1.31 (0.74–2.30)	0.35	0.0 [†]	2	21/144	1.33 (0.57–3.12)	0.52	0.0 ⁺
Control source										
Clinical study	2	182/441	3.31 (0.85–12.90)	0.09	90.9*	3	367/1173	2.56 (1.37–4.77)	0.003	86.3*
Clinical practice	6	993/1909	1.68 (1.06–2.65)	0.03	61.6*	5	977/1782	1.80 (1.13–2.87)	0.09	75.5*
Age										
50–60 yr old	4	165/580	1.65 (1.13–2.42)	0.009	0.0 [†]	3	149/453	1.68 (1.19–2.37)	0.003	0.0 [†]
>60 yr old	2	109/405	2.34 (1.22–1.65)	<0.001	0.0 [†]	3	294/1137	2.07 (1.66–2.57)	<0.001	24.6 [†]
Not reported	2	901/1365	2.63 (0.44–15.78)	0.29	96.2*	2	901/1365	2.46 (0.50–12.08)	0.27	96.6*

CI = confidence interval; N = number of studies included; OR = odds ratio; P_z = P value for Z test.

* The random-effects model was applied.

[†] The fixed-effects model was applied.

⁺ the fixed-effects model was applied

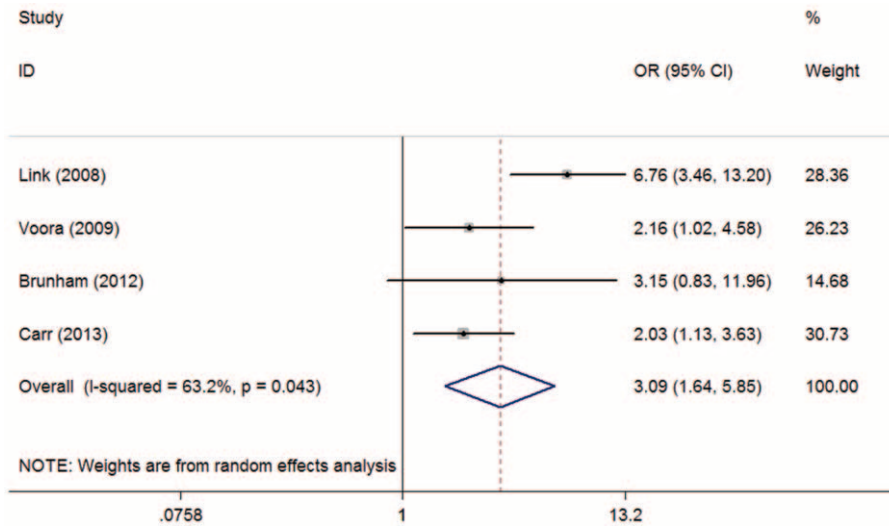


FIGURE 2. Meta-analysis of simvastatin-related myopathy risk and SLCO1B1 gene T521C polymorphism based on dominant model (TC + CC vs TT). CI=confidence interval; OR=odds ratio.

These findings of subgroup analyses based on control source and age can be explained by the following reasons. The incidence of statin-related myopathy in clinical practice is higher than that in clinical studies, because comorbidities and polypharmacy are generally excluded in clinical studies, and moreover, the uncertainty of a precise recording of all adverse events due to the study design in clinical studies may underestimate the association.³⁵ Senior age itself is a risk factor of statin-related myopathy, and it may be explained by some age-dependent physiologies (such as declines in renal and hepatic function) and age-related risk factors for myopathy (such as multisystem diseases and concomitant medications). Thus, we should be more cautious when prescribing statins to the elder patients in clinical practice.⁴

Our findings are consistent with the previous results reported by Carr et al.¹⁷ Moreover, our study is the first one that systematically assessed the association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk in detail based on

a large sample size and different gene contrast models both in the whole population and various subgroups. Other strengths of this study include the relatively high quality of included studies evaluated by the NOS and the robust results verified by the sensitivity analyses. More importantly, the results of our study may serve as evidence for guiding the preemptive SLCO1B1 testing by identifying individuals with high risk of simvastatin-related myopathy and thereby optimizing the statin therapy to avoid drug-related myopathy and promote a stronger adherence. Recently, the Clinical Pharmacogenomics Implementation Consortium Guideline recommended a lower dose of simvastatin or an alternative statin as well as the potential utility of routine CK surveillance for patients with a reduced-function C allele.³¹ Apart from the statin-related myopathy, the T521C polymorphism was also reported to be potentially associated with the cholesterol-lowering effect.^{14,21} Thus, a preemptive genetic test may not only minimize the risk but also maximize the efficacy of statin therapy and therefore get a better risk–benefit ratio.

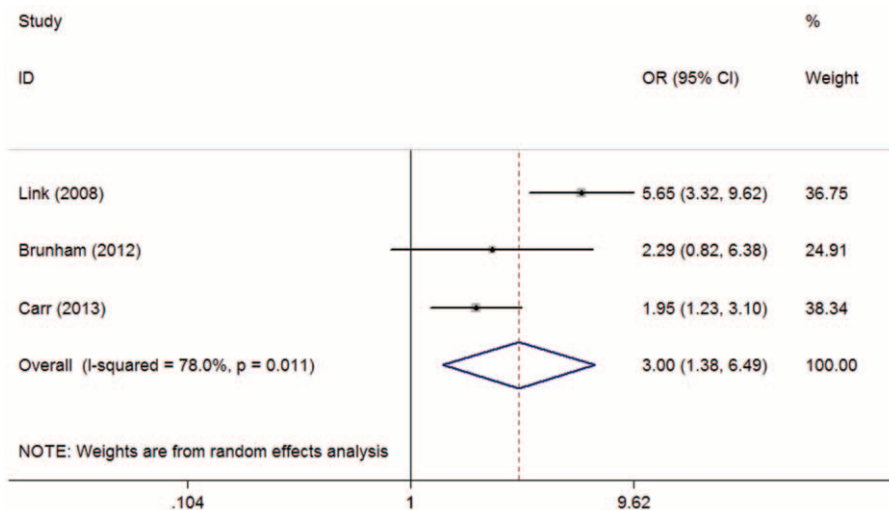


FIGURE 3. Meta-analysis of simvastatin-related myopathy risk and SLCO1B1 gene T521C polymorphism based on allelic model (C vs T). CI=confidence interval; OR=odds ratio.

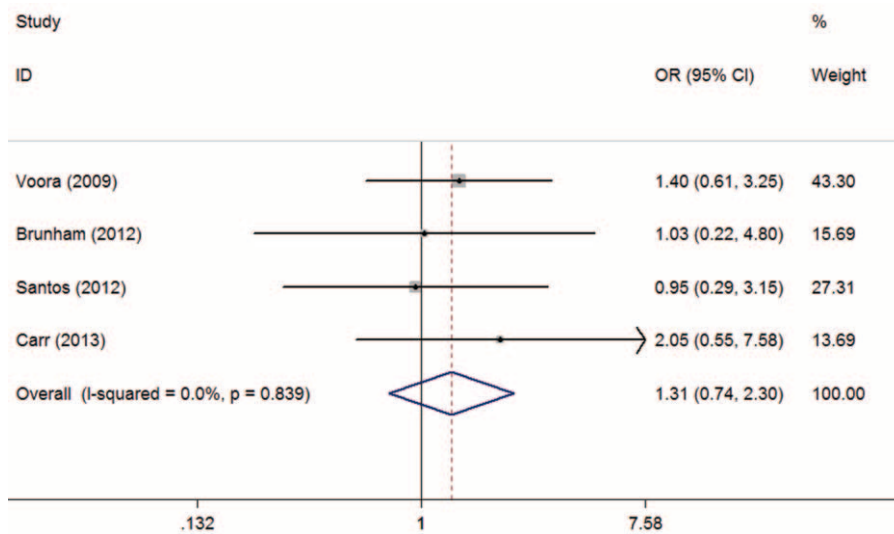


FIGURE 4. Meta-analysis of atorvastatin-related myopathy risk and SLCO1B1 gene T521C polymorphism based on dominant model (TC + CC vs TT). CI = confidence interval; OR = odds ratio.

Evidence of publication bias was not detected in both the dominant and allelic models in Begg’s and Egger’s tests. However, in some ways, the publication bias was unavoidable because of the limited databases searched and only English and Chinese publications included.

There are also several limitations. Firstly, the definitions of statin-related myopathy are various which may be a source of heterogeneity in our study. However, there has been little consensus on the definition of statin-related myopathy since the concept was put forward,^{4,27,36} which has made it difficult to estimate the data based on different definitions. Secondly, subgroup analyses based on statin doses and other statin types were unavailable due to insufficient data. Recently, Hubacek et al found there was no association between SLCO1B1 gene rs4363657 (T89595C) polymorphism and the risk of myalgia/myopathy in Czech patients treated with low statin doses (simvastatin or atorvastatin, 10 or 20 mg per day).²³ Therefore, our results should be interpreted with caution, especially high

dosage is a proved risk factor of statin-related myopathy.^{4,5} Further research is required to confirm the dose-dependent and type-specific risk of statin-related myopathy associated with different candidate SLCO1B1 genes, including rs4149056 (T521C), rs2306283 (A388G),^{21,22,24,37} rs4363657 (T89595C),^{14,23} and rs11045818 (G411A),³⁷ which potentially influence the pharmacokinetics of some specific statins. Thirdly, the baseline characteristics between cases and controls were not well-matched in all the included studies. Now that the development of statin-related myopathy is multifactorial, the potential confounding factors may influence the reliability of our results. More research is necessary to further elucidate on how other genes and nongenetic factors are involved in the pathogenesis of statin-related myopathy. Finally, the ethnicity of our study was mainly focused on the Caucasian, so we may not generalize the results to other ethnicities because the variant C allele frequency differs markedly between populations.^{24,25,38} A study on different ethnicities in Brazil revealed that the

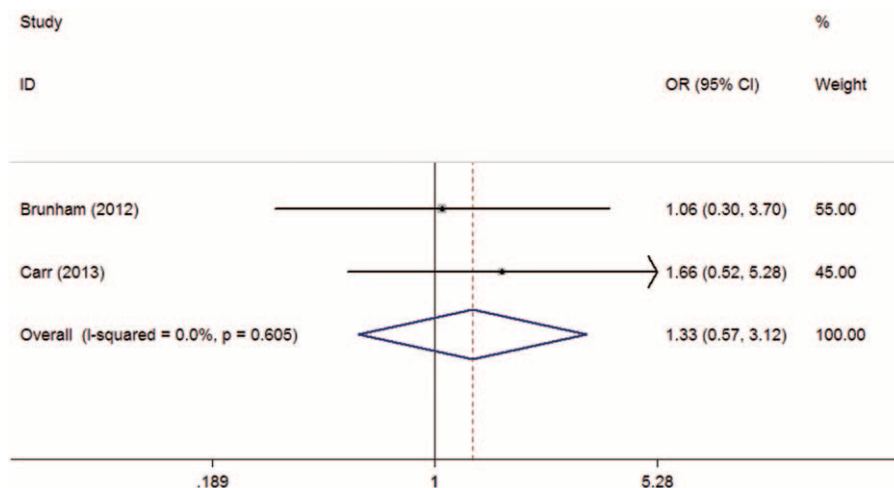


FIGURE 5. Meta-analysis of atorvastatin-related myopathy risk and SLCO1B1 gene T521C polymorphism based on allelic model (C vs T). CI = confidence interval; OR = odds ratio.

TABLE 4. Results of Publication Bias From Begg's and Egger's Tests

Contrast Model	Begg's Test		Egger's Test	
	z	P Value	t	P Value
TC + CC vs TT	0.37	0.71	2.14	0.08
C vs T	0.12	0.90	2.42	0.05

frequencies of the 521C allele were highest in Amerindians (28.3%) and lowest in African descent subjects (5.7%) compared with Mulatto (14.9%) and Caucasian descent (14.8%).³⁹

In conclusion, we found a significant association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk, especially in patients taking simvastatin. The variant C allele may be a strong risk factor of simvastatin-related myopathy. In clinical practice, a genetic testing might help to personalize the prescription of statins and avoid drug-related myopathy. However, genetic contribution and cost-effective analysis based on specific population should be further evaluated before further recommendation.

REFERENCES

- Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' Guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract.* 2012;18:1–78.
- Guyton JR. Benefit versus risk in statin treatment. *Am J Cardiol.* 2006;97:S95–S97.
- Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Ann Intern Med.* 2009;150:858–868.
- Sewright KA, Clarkson PM, Thompson PD. Statin myopathy: incidence, risk factors, and pathophysiology. *Curr Atheroscler Rep.* 2007;9:389–396.
- Chatzizisis YS, Koskinas KC, Misirli G, et al. Risk factors and drug interactions predisposing to statin-induced myopathy. *Drug Saf.* 2010;33:171–187.
- Needham M, Mastaglia F. Statin myotoxicity: a review of genetic susceptibility factors. *Neuromuscul Disord.* 2014;24:4–15.
- Mastaglia FL. Iatrogenic myopathies. *Curr Opin Neurol.* 2010;23:45–49.
- Ghatak A, Faheem O, Thompson PD. The genetics of statin-induced myopathy. *Atherosclerosis.* 2010;210:337–343.
- Wells GA, Shea B, O'connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *XXX.* 2000 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed June 1, 2011.
- Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25:603–605.
- Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21:1539–1558.
- Hayashino Y, Noguchi Y, Fukui T. Systematic evaluation and comparison of statistical tests for publication bias. *J Epidemiol.* 2005;235–243.
- Puccetti L, Ciani F, Auteri A. Genetic involvement in statins induced myopathy. Preliminary data from an observational case–control study. *Atherosclerosis.* 2010;211:28–29.
- Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy—a genomewide study. *N Engl J Med.* 2008;359:789–799.
- Brunham L, Lansberg P, Zhang L, et al. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. *Pharmacogenomics J.* 2011;12:233–237.
- Ferrari M, Guasti L, Maresca A, et al. Association between statin-induced creatine kinase elevation and genetic polymorphisms in SLCO1B1, ABCB1 and ABCG2. *Eur J Clin Pharmacol.* 2014;70:539–547.
- Carr DF, O'Meara H, Jorgensen AL, et al. SLCO1B1 genetic variant associated with statin-induced myopathy: a proof-of-concept study using the clinical practice research datalink. *Clin Pharmacol Ther.* 2013;94:695–701.
- Linde R, Peng L, Desai M, et al. The role of vitamin D and SLCO1B1*5 gene polymorphism in statin-associated myalgias. *Dermatoendocrinology.* 2010;2:77–84.
- Voorra D, Shah SH, Spasojevic I, et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. *J Am Coll Cardiol.* 2009;54:1609–1616.
- Marcianti KD, Durda JP, Heckbert SR, et al. Cerivastatin, genetic variants, and the risk of rhabdomyolysis. *Pharmacogenet Genomics.* 2011;21:280–288.
- Donnelly L, Doney A, Tavendale R, et al. Common nonsynonymous substitutions in SLCO1B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. *Clin Pharmacol Ther.* 2011;89:210–216.
- Santos PCJL, Gagliardi ACM, Miname MH, et al. SLCO1B1 haplotypes are not associated with atorvastatin-induced myalgia in Brazilian patients with familial hypercholesterolemia. *Eur J Clin Pharmacol.* 2012;68:273–279.
- Hubacek JA, Dlouha D, Adamkova V, et al. SLCO1B1 polymorphism is not associated with risk of statin-induced myalgia/myopathy in a Czech population. *Med Sci Monit.* 2015;21:1454–1459.
- Melo MS, Balanco L, Branco CC, et al. Genetic variation in key genes associated with statin therapy in the Azores Islands (Portugal) healthy population. *Ann Hum Biol.* 2015;42:283–289.
- Mahadevan L, Yesudas A, Sajesh PK, et al. Prevalence of genetic variants associated with cardiovascular disease risk and drug response in the Southern Indian population of Kerala. *Indian J Hum Genet.* 2014;20:175–184.
- Pasternak RC, Smith SC, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol.* 2002;40:567–572.
- Keen HI, Krishnarajah J, Bates TR, et al. Statin myopathy: the fly in the ointment for the prevention of cardiovascular disease in the 21st century? *Expert Opin Drug Saf.* 2014;13:1227–1239.
- Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev.* 2011;63:157–181.
- Iwai M, Suzuki H, Ieiri I, et al. Functional analysis of single nucleotide polymorphisms of hepatic organic anion transporter OATP1B1 (OATP-C). *Pharmacogenet Genomics.* 2004;14:749–757.
- Wilke R, Ramsey L, Johnson S, et al. The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. *Clin Pharmacol Ther.* 2012;92:112–117.
- Ramsey LB, Johnson SG, Caudle KE, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. *Clin Pharmacol Ther.* 2014;96:423–428.
- Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol.* 2009;158:693–705.

33. Pasanen M, Fredrikson H, Neuvonen P, et al. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. *Clin Pharmacol Ther*. 2007;82:726–733.
34. Pasanen MK, Neuvonen M, Neuvonen PJ, et al. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. *Pharmacogenet Genomics*. 2006;16:873–879.
35. Norata GD, Tibolla G, Catapano AL. Statins and skeletal muscles toxicity: from clinical trials to everyday practice. *Pharmacol Res*. 2014;88:107–113.
36. McKenney JM, Davidson MH, Jacobson TA, et al. Final conclusions and recommendations of the national lipid association statin safety assessment task force. *Am J Cardiol*. 2006;97:S89–S94.
37. Giannakopoulou E, Ragia G, Kolovou V, et al. No impact of SLCO1B1 521T>C, 388A>G and 411G>A polymorphisms on response to statin therapy in the Greek population. *Mol Biol Rep*. 2014;41:4631–4638.
38. Pasanen MK, Neuvonen PJ, Niemi M. Global analysis of genetic variation in SLCO1B1. *Pharmacogenomics J*. 2008;9:19–33.
39. Santos PC, Soares RA, Nascimento RM, et al. SLCO1B1 rs4149056 polymorphism associated with statin-induced myopathy is differently distributed according to ethnicity in the Brazilian general population: Amerindians as a high risk ethnic group. *BMC Med Genet*. 2011;12:136.