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PHARMACOKINETICS AND DISPOSITION

Correlation between single-nucleotide polymorphisms and statin-induced myopathy: a mixed-effects model meta-analysis

Qian Xiang[1] · Xiao-Dan Zhang[1] · Guang-Yan Mu[1] · Zhe Wang[1] · Zhi-Yan Liu[1] · Qiu-Fen Xie[1] · Kun Hu[1] · Zhuo Zhang[1] · Ling-Yue Ma[1] · Jie Jiang[2] · Yi-Min Cui[1,3]

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Abstract

Purpose A meta-analysis was performed to evaluate the correlation between single-nucleotide polymorphisms (SNPs) and risk of statin-induced myopathy (SIM).

Methods We retrieved the studies published on SIM until April 2019 from the PubMed, Embase, and Cochrane Library databases. We collected data from 32 studies that analyzed 10 SNPs in five genes and included 21,692 individuals and nine statins.

Results The analysis of the heterozygous ($p = 0.017$), homozygous ($p = 0.002$), dominant ($p = 0.005$), and recessive models ($p = 0.009$) of *SLCO1B1* rs4149056 showed that this SNP increases the risk of SIM. Conversely, heterozygous ($p = 0.048$) and dominant models ($p = 0.030$) of *SLCO1B1* rs4363657 demonstrated that this SNP is associated with a reduced risk of SIM. Moreover, an increased risk of SIM was predicted for carriers of the rs4149056 C allele among simvastatin-treated patients, whereas carriers of the *GATM* rs9806699 A allele among rosuvastatin-treated patients had a lower risk of SIM.

Conclusion The meta-analysis revealed that the rs4149056 and rs4363657 SNPs in *SLCO1B1* and the rs9806699 SNP in *GATM* are correlated with the risk of SIM.

Keywords Meta-analysis · Single-nucleotide polymorphism · Mitochondrial myopathy · Hydroxymethylglutaryl-CoA reductase inhibitor

Introduction

Statins act as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby competitively inhibiting the synthesis of endogenous cholesterol. Although modern proprotein convertase subtilisin/kexin type 9 (PCSK9) serine protease inhibitors can also be used to lower serum lipid levels, statins are still widely used in clinical treatment, since they are well-tolerated and improve the condition of patients with cardiovascular disease [1]. However, the prolonged use of statins may result in statin-induced myopathy (SIM), myalgia, and life-threatening rhabdomyolysis. The clinical manifestations of SIM include acute or chronic muscle pain, myasthenia, and elevated levels of creatine kinase (CK) in asymptomatic patients. The potential pathogenic mechanism underlying the emergence of SIM includes cholesterol deficiency, decreased stability and permeability of the myocyte membrane, coenzyme Q10 deficiency leading to dysfunctional mitochondrial respiration and energy generation in myocytes, and decreased synthesis of isozymes resulting in enhanced risk of muscle toxicity [2, 3]. However, the occurrence of SIM varies among individuals depending on drug tolerance, underlying health conditions, and genetic factors. On average, SIM affects 1 in 1000 patients undergoing statin treatment. As a consequence, SIM is the major reason for non-adherence to and/or discontinuation of

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✉ Yi-Min Cui
cui.pharm@pkufh.com

[1] Department of Pharmacy, Peking University First Hospital, Beijing 100034, China

[2] Department of Cardiology, Peking University First Hospital, Beijing 100034, China

[3] Beijing, China

statin treatment, which results in adverse cardiovascular outcomes [4].

The genetic factors associated with SIM have been widely studied. In particular, single-nucleotide polymorphisms (SNPs) in some genes have been reported to affect SIM incidence. For instance, SNP-dependent dysfunction of solute carrier organic anion transporter family member 1B1 (SLCO1B1 or OATP1B1), a major transporter of statins involved in drug detoxification in the liver, is one of the factors influencing the specific efficacy and side effects of statins in different individuals. Additionally, SNPs in genes involved in drug metabolism, such as cytochrome P450 family genes (*CYPs*), *COQ2*, and *ABCB1*, have been reported to be associated with SIM [5]. However, these studies are limited and still inconclusive.

Our previous meta-analysis indicated that the *SLCO1B1* T521C polymorphism is correlated with a markedly higher risk of SIM, especially upon treatment with simvastatin, rosuvastatin, and cerivastatin [6]. Moreover, the results of other meta-analyses were consistent with our findings [7]. However, another meta-analysis revealed that *COQ2* rs4693075 is not correlated with SIM [8]. Similarly, another study reported that there was no significant correlation between the *ABCB1* C3435T polymorphism and SIM, but that SIM risk was increased in patients using statins for longer than 5 months [9]. Most of these meta-analyses focused on one or two SNPs and used a random-effect or fixed-effect model according to the results of a homogeneity test. To overcome such limitations, in this study, we employed a mixed-effects model that could decompose the random error term into the corresponding level of the hierarchical structure. Furthermore, this model allowed to examine factors affecting the heterogeneity among the considered studies. Therefore, to comprehensively analyze current evidence of the correlation between genetic polymorphisms and the risk of developing SIM upon treatment with various statin types, we systematically screened the literature to include all reported genetic polymorphisms related to SIM and different types of statins.

Methods

Data source, search strategy, and study selection

This study was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [10]. Two authors searched the literature through the PubMed, Embase, and Cochrane Library databases for studies published in English from inception to April 2019. The following terms were used in the search strategy: statin, statins, myalgia, myopathy, muscle injury, muscle pain myalgias, rhabdomyolysis, myotoxicity, polymorphism, SNP, genetic, mutation, variation, allelic, allele, and genotype. The details of the search strategy in PubMed are shown in Table S1. The reference lists of the retrieved studies and relevant reviews were also manually searched to obtain potentially new eligible studies.

Studies were included in the meta-analysis if they belonged to one of the following categories: (1) Case-control or cohort studies comparing patients developing SIM and patients exhibiting statin tolerance (no myopathy) after statin treatment; (2) studies assessing the correlation between genetic polymorphisms and risk of SIM; and (3) studies reporting the frequencies of specific alleles or the effect sizes of individual genotypes between SIM cases and controls. The exclusion criteria for the meta-analysis were set as follows: (1) Studies designed as case series; (2) studies not involving SIM; (3) studies using the healthy population as control group; (4) studies not involving SNPs; and (5) studies that did not report allelic frequencies or effect sizes. Additionally, reviews, case reports, and family genetic studies were excluded.

Data extraction and quality assessment

Two authors independently extracted the following data from the studies included in the meta-analysis: first author's name, publication year, study location, study design, sample size and age, purpose of steroid treatment, types of statins employed, and genes of interest. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies [11]. Through the NOS, it is possible to assign a rating to a study according to its scores in the following three categories: selection (four items, four stars), comparability (one item, two stars), and exposure (three items, three stars). The study quality was assessed by two authors, and any disagreement was resolved by another author after perusal of the original article.

Statistical analysis

Deviations of allele frequencies from Hardy-Weinberg equilibrium (HWE) were tested to assess the consistency of allele frequencies between subgroups of the included population [12]. Correlation analysis was performed using five genetic models: allelic (M vs W), dominant (MM + WM vs WW), recessive (MM vs WM + WW), heterozygous (WM vs WW), and homozygous (MM vs WW), where W represents the major (wild-type) allele and M represents the minor (mutant-type) allele [13]. The odds ratio (OR) and its 95% confidence interval (CI) were calculated to estimate pooled effect sizes, while heterogeneity across the included studies was assessed by I^2 statistic. A random-effect model was applied to calculate the pooled effect size when $I^2 \geq 50\%$, otherwise fixed-effect models were used. Subgroup analyses were performed with respect to the country-specific population if data were obtained from more than three studies. In addition, a meta-analysis using a mixed-effects model was conducted to assess the

potential impacts of specific types of statins and SNPs on the risk of developing SIM. Publication biases for the investigated SNPs were assessed using two-tailed Egger's and Begg's tests. A p value of 0.05 was considered a threshold for statistical significance. The STATA software (version 10.0; Stata Corporation College Station, TX, USA) was employed for all statistical analyses in this study.

Results

In total, 1457 studies were identified from the various databases. Among these, 1379 studies were excluded after screening of the title and abstract. The full text of the remaining 78 articles was then examined. During the full-text screening process, the following number of studies were excluded based on the following exclusion criteria: case-control studies not related to SIM (n = 22); studies lacking data on the number of SNP carriers or on effect size in each group (n = 7); studies that used the healthy population as control group (n = 6); reviews (n = 6); case reports (n = 2); conference articles (n = 2); and duplicated research (n = 1). Finally, 32 studies examining a total of 21,692 patients undergoing statin treatment were included in our analysis [14–45] (Table 1, Fig. 1).

The studies included in the meta-analysis were published between 2005 and 2018. Additionally, the test populations in these studies were from Europe and North America. All studies were designed as case-control studies, except for one retrospective study [38]. The average age of the patients was generally between 50 and 70 years. However, three studies did not specify the age of the patients [24–26]. The statins used in these studies were mainly simvastatin, rosuvastatin, pravastatin, atorvastatin, lovastatin, fluvastatin, pitavastatin, and cerivastatin. The NOS scores of the included studies were 7–9 points. Hence, the overall quality of the considered observational studies was ideal for our meta-analysis (Table 1).

In this study, we comprehensively analyzed the following SNPs: rs4149056, rs2306283, and rs4363657 in *SLCO1B1*; rs1045642 and rs2231142 in *ABCB1*; rs4693075 in *COQ2*; rs776746 in *CYP3A5*; and rs9806699, rs1719247, and rs1346268 in *GATM*. Each of these SNPs was examined in more than three studies included in the analysis. The effect of each SNP on SIM in each model is summarized in Table S2. For this analysis, we did not distinguish the effects of statins based on their type.

The analysis of heterozygous (OR: 1.51; 95% CI: 1.08–2.13; p = 0.017), homozygous (OR: 2.65; 95% CI: 1.43–4.92; p = 0.002), dominant (OR: 1.63; 95% CI: 1.16–2.29; p = 0.005), and recessive models (OR: 2.19; 95% CI: 1.33–3.61; p = 0.009) of *SLCO1B1* rs4149056 showed that this SNP is associated with an increased risk of SIM. However, there was no significant correlation between this mutation and risk of SIM in the allelic model (OR: 1.34; 95% CI: 0.98–1.83; p = 0.069). On the contrary, the analysis of heterozygous (OR: 0.87; 95% CI: 0.76–1.00; p = 0.048) and dominant models (OR: 0.87; 95% CI: 0.76–0.99; p = 0.030) of *SLCO1B1* rs4363657 revealed that the presence of the C allele decreases the risk of SIM. There were no other significant correlations between SNPs and the risk of SIM (Table 2). In addition, subgroup analysis of the UK and US populations revealed that heterogeneity was not reduced with respect to the general population. However, we observed a significant correlation between rs4149056 and the risk of SIM in the UK population, whereas no significant correlation was found in the US population. Subgroup analysis was not performed for the other *SLCO1B1* SNPs because of the limited number of studies that reported these SNPs in each country (Table 2).

Due to the complexity of population characteristics in each included study, we analyzed the impact of different statin types and genetic polymorphisms on the risk of SIM using a mixed-effects model. In this analysis, we mainly included studies examining the effects of simvastatin, rosuvastatin, and atorvastatin. The other types of statins were not included as the respective studies did not separately report the results relative to those statins. The results of the analysis based on statin type are reported in Table 3. Within the simvastatin-treated population, the carriers of the mutation (TC/CC) responsible for the *SLCO1B1* rs4149056 SNP exhibited a greater risk of SIM when compared to the wild-type population (OR: 3.10; 95% CI: 2.11–4.55; p < 0.001). Similar results were obtained when analyses were conducted separately for heterozygote (TC) carriers vs wild-type population (OR: 2.80; 95% CI: 1.81–4.31; p < 0.001) and homozygote (CC) carriers vs wild-type population (OR: 9.27; 95% CI: 4.04–21.22; p < 0.001). Interestingly, the rs4149056 SNP in heterozygote carriers within the rosuvastatin-treated population was associated with a reduced risk of SIM (OR: 0.82; 95% CI: 0.70–0.95; p = 0.012) (Table 3). However, this may be due to the greater heterogeneity and to the smaller number of studies dealing with these factors. In particular, this significant correlation could be biased towards the study conducted by Bai et al. [14], which included a large number of individuals carrying the rs4149056 SNP in the rosuvastatin-treated population. Additionally, *GATM* rs9806699 (mutant A allele) carriers within the rosuvastatin-treated population exhibited a lower risk of SIM when compared to the wild-type population (OR: 0.37; 95% CI: 0.17–0.78; p = 0.009). Similar results were obtained when the analyses were conducted separately for heterozygote carriers vs wild-type population (OR: 0.36; 95% CI: 0.17–0.76; p = 0.007) and homozygote carriers vs wild-type population (OR: 0.36; 95% CI: 0.18–0.72; p = 0.004) (Table 3).

Table 1 Characteristics of the included studies

Author	Year	Country	Study design	Sample sizeTotal (case/control)	Age†	Types of statin	Genes	Definition of SIM	NOS
Xue Bai [14]	2018	China	Case-control	758 (51/707)	Case: 61.40 ± 10.93; Control: 63.19 ± 10.33	Rosu	*ABCG2, ABCB1, SLCO1B1, SLCO1B3, CYP2C9, GATM*	Muscular pain and creatine kinase elevation	9
NS Bakar [15]	2018	UK	Case-control	601 (125/476)	Case: 60.3 (58.1–62.5); Control: 60.9 (59.8–62.1)	Sim; Ator	*GPX1;GPX4;OATP2B1; MCT1; MCT4; ABCC2; ABCG2; SLC16A1*	Intolerable muscle pain or weakness, with or without elevation of creatine kinase, onset within 6 months of starting therapy	7
B Alghalyini [16]	2018	Saudi Arabia	Case-control	50 (22/28)	Case: 51 ± 11.9; Control: 48.7 ± 11.2	Rosu; Sim; Ator	*SLCO1B1*	Muscle symptoms and elevations in serum creatine kinase	7
MK Siddiqui [17]	2018	Scotland	Case-control	661 (229/432)	Case: 60 ± 10; Control: 62 ± 10; Control2:60 ± 10	Sim; Rosu	*LILRB5*	Muscle symptoms from myalgia to autoimmune-mediated necrotizing myositis	6
JE Liu [18]	2017	China	Case-control	403 (148/255)	Case: 60.56 ± 10.81; Control: 63.25 ± 10.27	Rosu; Sim; Ator; Flu; Pra	*CYP3A5; SLCO1B1; ApoE*	Muscle symptoms with muscle pain, soreness, weakness, or twitches with defined anatomical site	9
JA Hubacek [19]	2017	Czech	Case-control	556 (274/282)	Case: 62.9 ± 13.3; Control: 59.9 ± 14.2	Sim; Ator	*COQ2*	Muscle aches/tenderness/weakness occurring within 4 weeks from the therapy initiation and resolving with its interruption, family history of SIM, and creatine kinase elevation	8
ML Ovesjo [20]	2017	Sweden	Case-control	127 (16/111)	Case: 65 (39–86); Control: 65 (32–89)	Rosu; Sim; Ator; Flu; Pra	*VDR*	Obvious muscular symptoms were evaluated to be "probably caused by statin therapy" according to the WHO criteria	8
H Khine [21]	2017	USA	Case-control	278 (97/181)	Case: 57 (50–64); Control: 54 (46–62)	Sim; Rosu; Pra; Ator; Lo; Flu; Pita	*SLCO1B1*	Muscle symptoms such as muscle aches, weakness, cramps, stiffness, "heaviness," flu-like symptoms while taking a statin, severe enough to stop therapy.	8
JA Luzum [22]	2016	USA	Case-control	715 (609/106)	All: 58 ± 11	Ator; Sim; Rosu; Pra; Lo et al.	*GATM*	Participants with muscle aches and pains associated with the initiation of statin therapy that were reversible with cessation of therapy	8
JA Hubacek [23]	2015	Czech	Case-control	993 (286/707)	Case: 63.5 ± 13.2; Control: 60.2 ± 14.1	Sim; Ator	*SLCO1B1*	Muscle tenderness, cramping, and muscle aches to weakness and, the far more serious, rhabdomyolysis	9
Lara M. Mangravite [24]	2013	USA	Case-control	4421 (172/4249)	NA	Sim	*GATM*	Creatine kinase concentrations > 3-fold normal with evidence in the charts of muscle complaints	8
D.F. Carr [25]	2013	UK	Case-control	737 (150/587)	NA	Sim et al.	*SLCO1B1;GATM*	Creatine kinase > 10 × ULN or rhabdomyolysis	7
	2013	USA	Case-control	820 (175/645)	NA		*GATM*	Rhabdomyolysis	7

Table 1 (continued)

Author	Year	Country	Study design	Sample sizeTotal (case/control)	Age†	Types of statin	Genes	Definition of SIM	NOS
James S. Floyd [26]						Lo; Sim; Pra; Ator; Flu; Ceri			
Marco Ferrai [27]	2014	Italy	Case-control	66 (33/33)	Case: 62.1 ± 9.9; Control: 61.2 ± 9.9	Ator; Sim; Rosu	*SLCO1B1;ABCB1;ABCG2*	Statin-induced elevations in serum creatine kinase of > 3 × UNL, irrespective of symptoms	9
JS Danik [28]	2013	Multinational	Case-control	4404 (1282/3122)	All: 66 (60–71)	Rosu	*SLCO1B1*	Myalgia, or the broader categories of muscle weakness, stiffness, or pain	9
D.F. Carr [29]	2013	UK	Case-control	448 (76/372)	Case: 69.9 ± 10.4; Control: 71.2 ± 8.7	Sim; Ator; Ceri; Pra; Rosu; Flu	*SLCO1B1;COQ2*	Muscle symptoms with CPK > 10 × ULN	9
PC Santos [30]	2012	Brazil	Case-control	143 (14/129)	Case: 54.3 ± 13.2; Control: 52.5 ± 14.9	Ator	*SLCO1B1*	Myalgia (atorvastatin-induced muscle pain, irrespective of creatine kinase values, at onset of treatment or in dose uptitration until the first year of follow-up), and creatine kinase elevations of more than 3 times the upper limit of the normal range (irrespective of symptoms)	9
LR Brunham [31]	2011	Netherlands	Case-control	108 (25/83)	Case: 53 ± 13; Control: 57 ± 12	Sim; Ator	*SLCO1B1*	Plasma creatine kinase values greater than ten times the upper limit of normal for the reference laboratory	9
GD Vladutiu [32]	2011	USA/Canada	Case-control	493 (360/133)	Case 1: 59 (28–80); Case 2:62 (45–80); Control: 50 (26–78)	NA	*RYR1*	Onset of incapacitating muscle pain and/or weakness often accompanied by rhabdomyolysis or abnormal elevations of plasma creatine kinase and directly related to the use of statin therapy with no pre-therapy symptoms of muscle disease	8
KD Marciante [33]	2011	USA	Case-control	917 (185/732)	Case: 63.5 ± 10.6; Control 1: 73.6 ± 4.1; Control 2: 64.5 ± 9.4	Cases used Ceri	GWAS	Muscle pain or weakness associated with creatine kinase levels greater than 10 times the upper limit of laboratory normal	8
PJ Isackson [34]	2011	USA/ Canada/ Australia	Case-control	399 (229/170)	Case 1:61 ± 14; Case 2:57 ± 11; Control 1: 57 ± 11; Control 2: 59 ± 12	Ator; Sim; Ceru; Pra; Lo et al.	*EYS*	Symptoms of severe and incapacitating muscle pain and/or weakness with onset following initiation of statin therapy	8
MR Hoenig [35]	2011	Australia	Case-control	117 (10/107)	All: 67 ± 10	Ator	*ABCB1*	Symptoms of muscle pain after statin therapy	7
LA Donnelly [36]	2011	UK	Case-control	2091 (816/1275)	All: 63 ± 10.6	Sim; Ator; Pra; Flu; Ceri; Rosu	*SLCO1B1*	Those exceeding the upper limit of the normal ranges for both alanine	8

Table 1 (continued)

Author	Year	Country	Study design	Sample sizeTotal (case/control)	Age†	Types of statin	Genes	Definition of SIM	NOS
								aminotransferase and creatinine kinase	
L Puccetti [37]	2010	Italy	Case-control	NA (76/NA)	Case: 47.5 ± 5.8; Control: NA	Ator; Rosu	*SLCO1B1;COQ2*	Creatine kinase > 10× the upper limit of normal in those with symptoms and > 3× in those without symptoms	6
R Linde [38]	2010	USA	Retrospective	46 (27/19)	Case: 59.5 ± 10; Control: 59.3 ± 13.8	Sim; Ator; Lo; Pra; Rosu; Flu	*SLCO1B1*	Muscular pain or weakness as reported by the patients, who graded their symptoms as mild, moderate, or severe	8
The SEARCH group [39]	2008	UK	Case-control	175 (85/90)	All: 67 ± 10	Sim	GWAS	Muscle symptoms, with creatine kinase levels that were more than 10 times the upper limit of the normal range	9
P Zuccaro [40]	2007	Italy	Case-control	100 (50/50)	All: 61 ± 9	Sim; Flu	*CYP*	Symptoms of muscle pain as assessed with a standardized medical record review form	9
JS Oh [41]	2007	Canada	Case-control	291 (133/158)	Case: 57.1 ± 12.1; Control: 55.9 ± 11.3	Ator; Rosu et al.	*COQ2*	Symptomatic muscle weakness, tenderness, and/or pain with at least one of (1) medically advised discontinuation of statin medication on at least two occasions; (2) serum CK elevated to > 3-fold of the upper limit of normal while on a statin on at least one occasion; and (3) medically diagnosed rhabdomyolysis	8
TN Frudakis [42]	2007	USA	Case-control	432 (158/274)	Case: 63.6 (NA); Control: 64.4 (NA)	Ator; Sim; Pra; Lo; Ceri	*CYP2D6*	Muscle cramps, muscle weakness, and muscle deterioration/muscle disorder	8
NM Fisher [43]	2007	USA	Case-control	13 (7/6)	All: 57.9 ± 8.25	Ator; Pra	*AMPD1*	Myopathic side effects after statin therapy	8
RA Wilke [44]	2005	USA	Case-control	137 (68/69)	Case: 58.1 ± 11.5; Control: 63.1 ± 11.3	Ator	*CYP3A4;CYP3A5*	Perceived to be muscle pain related to the use of the drug	8
M Fiegenbaum [45]	2005	Brazil	Case-control	116 (17/99)	Case: 59.2 ± 10.7; Control: 63 ± 9.87	Sim	*ABCB1;CYP3A4*	Proximal or diffuse muscle pain, tenderness, or weakness, or both pain and weakness, with normal or slightly increased serum creatine phosphokinase levels	9

Ator, atorvastatin; *Ceri*, cerivastatin; *Flu*, fluvastatin; *GWAS*, Genome Wide Association Study; *Lo*, lovastatin; *NA*, not available; *NOS*, Newcastle-Ottawa Scale; *Pita*, pitavastatin; *Pra*, pravastatin; *Rosu*, rosuvastatin; *Sim*, simvastatin; *Mean/Median* (Minimum-Maximum); *SIM*, statin-induced myotoxicity

†Mean ± standardization

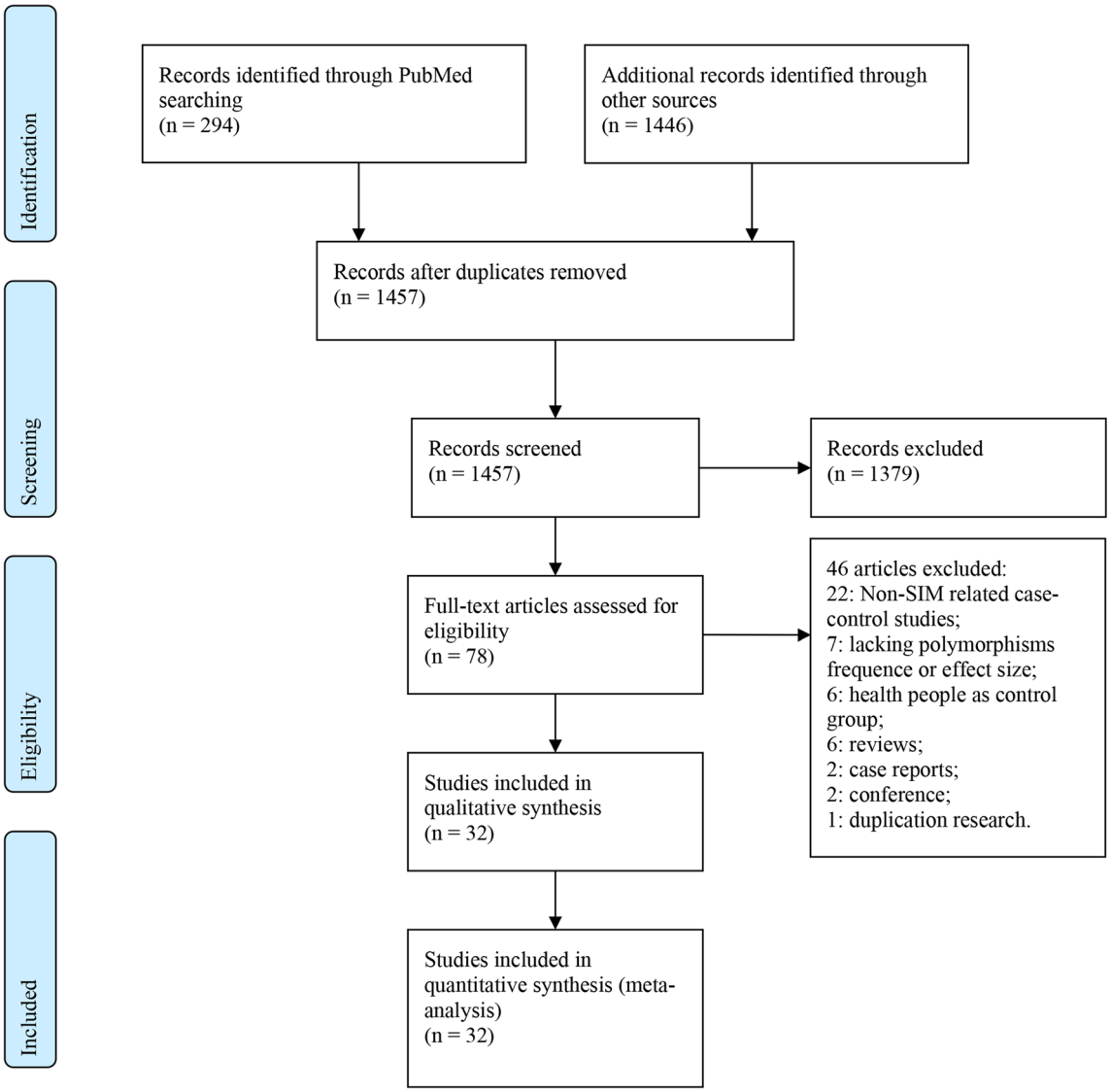

Fig. 1 Details of the processes of literature search and study selection

Discussion

This study analyzed the correlation between genetic polymorphisms and risk of SIM within the statin-treated population using SNPs that had been reported in more than three studies. The analysis included 10 SNPs in five genes. Additionally, we performed a subgroup analysis in different populations and analyzed the impact of different statin types and genetic polymorphisms on the risk of SIM. The summary OR of the heterozygous, homozygous, dominant, and recessive models indicated a positive correlation between the nonsynonymous rs4149056 mutation in *SLCO1B1* and SIM incidence. Conversely, the rs4363657 SNP, which exhibited nearly complete linkage disequilibrium with the rs4149056 SNP [39], was correlated with reduced SIM incidence in the heterozygous and dominant models. On the contrary, the rs1045642 SNP in *ABCB1*; the rs4693075 SNP in *COQ2*; the rs776746 SNP in *CYP3A5*; and the rs9806699, rs1719247, and rs1346268 SNPs in *GATM* were not correlated with the risk of SIM when the effects of all statins were analyzed together. However, when the analysis was stratified based on statin type, we observed that rs4149056 C carriers within the simvastatin-treated population presented an increased risk of SIM when compared to that within the wild-type population. Furthermore, *GATM* rs9806699 A carriers within the rosuvastatin-treated population exhibited a reduced risk of SIM. These findings could provide useful indications for the treatment of individuals carrying certain genetic polymorphisms with specific statins, in order to avoid excessive SIM risk.

The effect of the rs4149056 SNP in *SLCO1B1* on the risk of SIM was consistent with previous meta-analyses [6, 7],

Table 2 Meta-analysis of correlation between single-nucleotide polymorphisms (SNPs) and statin-induced myopathy (SIM)

Gene	Ethnic	SNP/HWE test	Model[#]	Comparisons	No. of studies	Sample size	OR	LCI	UCI	*p* value	I^2	*p* for I^2	Begg	Egger
SLCO1B1	Multinational	rs4149056 (T > C)	Allelic model	C vs T	13	9160	1.34	0.98	1.83	0.069	89.30%	< 0.001	0.583	0.155
			Heterozygous model	TC vs TT	9	8117	1. 51	1.08	2.13	0.017	82.10%	< 0.001	0.371	0.016
		Case: 0.0003	Homozygous model	CC vs TT	9	8117	2.65	1.43	4.92	0.002	69.0%	0.001	0.348	0.121
		Control: 0.1170	Dominant model	TCCC vs TT	12	8663	1.63	1.16	2.29	0.005	85.10%	< 0.001	0.631	0.026
		Total: 0.0005	Recessive model	CC vs TTTC	9	8117	2.19	1.33	3.61	0.009	54.30%	0.025	0.602	0.209
	UK	rs4149056 (T > C)	Allelic model	C vs T	4	3315	1.99	1.11	3.57	0.022	91.70%	< 0.001	0.089	0.099
			Heterozygous model	TC vs TT	4	3315	1.93	1.08	3.45	0.026	86.70%	< 0.001	0.308	0.023
		Case: 0.1112	Homozygous model	CC vs TT	4	3315	3.03	1.04	8.87	0.043	76%	0.006	0.734	0.611
		Control: 0.5635	Dominant model	TCCC vs TT	4	3315	2.15	1.12	4.13	0.022	90.40%	< 0.001	0.089	0.053
		Total: 0.4561	Recessive model	CC vs TTTC	4	3315	2.41	1.01	5.76	0.047	64.60%	0.037	1	0.752
	USA	rs4149056 (T > C)	Allelic model	C vs T	3	1241	0.84	0.40	1.74	0.628	76.10%	0.015	0.296	0.161
	Multinational	rs2306283 (A > G)	Allelic model	G vs A	7	3613	1.04	0.81	1.34	0.747	56.30%	0.043	1	0.667
			Heterozygous model	AG vs AA	4	3312	0.93	0.77	1.11	0.412	44.70%	0.143	0.308	0.143
		Case: 0.0021	Homozygous model	GG vs AA	4	3312	0.79	0.61	1.02	0.073	0%	0.662	1	.0.57
		Control: < 0.001	Dominant model	AGGG vs AA	5	3455	0.88	0.75	1.05	0.153	26.50%	0.245	0.027	0.138
		Total: < 0.001	Recessive model	GG vs AAAG	4	3312	1.05	0.65	1.72	0.833	77.30%	0.012	1	.0.573
	Multinational	rs4363657 (T > C)	Allelic model	C vs T	4	5337	1.35	0.79	2.33	0.276	93.50%	< 0.001	0.089	0.290
			Heterozygous model	TC vs TT	3	5162	0.87	0.76	1.00	0.048	19.80%	0.287	1	0.291
		Case: 0.441	Homozygous model	CC vs TT	3	5162	0.83	0.59	1.15	0.256	3.50%	0.355	1	0.469
		Control: < 0.001	Dominant model	TCCC vs TT	3	5162	0.87	0.76	0.99	0.03	0%	0.592	1	0.241
		Total: < 0.001	Recessive model	CC vs TTTC	3	5162	0.83	0.61	1.15	0.265	25.60%	0.261	0.296	0.242
ABCB1	Multinational	rs1045642 (C > T)	Allelic model	T vs C	4	1050	1.24	0.60	2.56	0.557	75.70%	0.006	1	0.889
			Heterozygous model	CT vs CC	4	1050	0.97	0.59	1.61	0.917	0%	0.406	0.734	0.552
		Case: 0.338	Homozygous model	TT vs CC	4	1050	1.63	0.40	6.62	0.493	64.60%	0.037	0.734	0.798
		Control: 0.594	Dominant model	CTTT vs CC	4	1050	1.10	0.69	1.76	0.677	43.60%	0.150	0.734	0.596
		Total: 0.3467	Recessive model	TT vs CCCT	4	1050	1.76	0.62	4.99	0.291	61.20%	0.052	0.734	0.535
		rs2231142 (C > A)	Allelic model	A vs C	3	1421	0.83	0.61	1.13	0.228	48.70%	0.143	0.296	0.091
			Heterozygous model	CA vs CC	3	1421	0.88	0.46	1.69	0.709	59.60%	0.084	1	0.25
		Case: 0.3928	Homozygous model	AA vs CC	3	1421	0.74	0.30	1.79	0.500	0%	0.633	1	.
		Control:0.0744	Dominant model	CAAA vs CC	3	1421	0.89	0.48	1.65	0.703	59.50%	0.085	1	0.242
		Total:0.029	Recessive model	AA vs CCCA	3	1421	0.87	0.36	2.08	0.754	0%	0.748	1	.
COQ2	Multinational	rs4693075 (G > A/C/T)	Allelic model	M vs G	4	1895	1.01	0.87	1.17	0.94	26.10%	0.255	1	0.928
			Heterozygous model	GM vs GG	4	1895	0.94	0.72	1.21	0.608	44.60%	0.144	1	0.248
		Case: 0.0503	Homozygous model	MM vs GG	4	1895	0.98	0.72	1.34	0.911	51.90%	0.101	0.734	0.59
		Control: 0.0214	Dominant model	GMMM vs GG	4	1895	0.97	0.76	1.23	0.778	51.80%	0.101	1	0.312

Table 2 (continued)

Gene	Ethnic	SNP/HWE test	Model[#]	Comparisons	No. of studies	Sample size	OR	LCI	UCI	*p* value	I^2	*p* for I^2	Begg	Egger
		Total: 0.0013	Recessive model	MM vs GGGM	4	1895	1.05	0.83	1.32	0.697	0%	0.632	0.734	0.601
CYP3A5	Multinational	rs776746 (A > G)	Allelic model	G vs A	4	713	1.12	0.84	1.50	0.423	0%	0.443	0.734	0.827
			Heterozygous model	AG vs AA	4	713	2.13	0.91	5.01	0.082	.	.	.	.
		Case: 0.8383	Homozygous model	GG vs AA	4	713	1.88	0.81	4.36	0.141	.	.	.	.
		Control: 0.0402	Dominant model	AGGG vs AA	4	713	1.99	0.88	4.51	0.101	.	.	.	.
		Total: 0.1233	Recessive model	GG vs AAAG	4	713	1.03	0.73	1.46	0.855	2.40%	0.381	0.734	0.625
GATM	Multinational	rs9806699(G > A)	Allelic model	A vs G	6	3919	0.88	0.73	1.07	0.21	50.60%	0.072	0.707	0.097
			Heterozygous model	GA vs GG	3	2070	0.80	0.41	1.56	0.513	79.90%	0.007	1	0.111
		Case: 0.6151	Homozygous model	AA vs GG	3	2070	0.72	0.30	1.71	0.453	75.0%	0.018	1	0.957
		Control: < 0.001	Dominant model	GAAA vs GG	3	2070	0.78	0.39	1.56	0.477	83.90%	0.002	1	0.127
		Total: < 0.001	Recessive model	AA vs GGGA	3	2070	0.88	0.60	1.29	0.515	0%	0.597	1	0.48
	Multinational	rs1719247(C > T)	Allelic model	T vs C	3	5241	0.80	0.45	1.43	0.451	85%	0.001	1	0.475
	Multinational	rs1346268(T > C)	Allelic model	C vs T	3	5241	0.81	0.50	1.30	0.386	78.60%	0.009	1	0.486

HWE, Hardy-Weinberg equilibrium; *LCI*, lower confidence intervals; *OR*, odds ratio; *SIM*, statin-induced myopathy; *SNP*, single-nucleotide polymorphism; *UCI*, upper confidence intervals

†Characters in the table indicate that the *p* value is less than 0.05.

#Allelic (M vs W), dominant (MM + WM vs WW), recessive (MM vs WM + WW), heterozygous (WM vs WW), and homozygous (MM vs WW) models, in which W represents the major wild-type allele, and M represents the minor mutant-type allele

Table 3 Analysis of statin types and gene polymorphisms on risk of statin-induced myopathy (SIM) by multilevel mixed-effects logistic regression model

Genes	SNPs	Statin type	Model[#]	Comparisons	No. of studies	Sample size	OR	LCI	UCI	*p* value
SLCO1B1	rs4149056	Atorvastatin	Recessive model	TCCC vs TT	4	545	1.22	0.76	1.96	0.413
			Heterozygous model	TC vs TT	4	545	1.63	0.57	4.67	0.361
			Homozygous model	CC vs TT	4	545	1.21	0.12	11.90	0.873
		Simvastatin	Recessive model	TCCC vs TT†	4	573	3.10	2.11	4.55	< 0.001
			Heterozygous model	TC vs TT	4	573	2.80	1.81	4.31	< 0.001
			Homozygous model	CC vs TT	4	573	9.27	4.04	21.22	< 0.001
		Rosuvastatin	Recessive model	TCCC vs TT	3	4394	0.89	0.77	1.03	0.126
			Heterozygous model	TC vs TT	3	4394	0.82	0.70	0.95	0.012
			Homozygous model	CC vs TT	3	4394	1.33	0.90	1.97	0.153
SLCO1B1	rs2306283	Atorvastatin	Recessive model	AGGG vs AA	2	380	0.77	0.38	1.57	0.477
			Heterozygous model	AG vs AA	2	380	0.62	0.23	1.65	0.338
			Homozygous model	GG vs AA	2	380	1.17	0.46	2.95	0.741
		Rosuvastatin	Recessive model	AGGG vs AA	2	842	0.93	0.32	2.72	0.895
			Heterozygous model	AG vs AA	2	842	0.79	0.25	2.42	0.674
			Homozygous model	GG vs AA	2	842	1.02	0.34	3.03	0.969
CYP3A5	rs776746	Atorvastatin	Heterozygous model	AG vs AA	3	416	3.12	0.84	11.60	0.089
			Homozygous model	GG vs AA	3	416	3.42	0.95	12.41	0.061
		Simvastatin	Heterozygous model	AG vs AA	3	221	1.62	0.30	8.77	0.573
			Homozygous model	GG vs AA	3	221	1.95	0.37	10.17	0.427
CYP2D6	rs3892097	Simvastatin	Recessive model	any*4 vs *1*1	2	192	1.51	0.84	2.73	0.168
GATM	rs9806699	Rosuvastatin	Heterozygous model	GA vs GG	2	839	0.37	0.17	0.78	0.009
			Homozygous model	AA vs GG	2	839	0.36	0.17	0.76	0.007
			Recessive model	GAAA vs GG	2	839	0.36	0.18	0.72	0.004

LCI, lower confidence intervals; *OR*, odds ratio; *SNP*, single-nucleotide polymorphism; *UCI*, upper confidence intervals

†Characters in the table indicate that the *p* value is less than 0.05

#Allelic (W vs M), dominant (WW + WM vs MM), recessive (WW vs WM + MM), heterozygous (WM vs MM), and homozygous (WW vs MM) models, in which W represents the major wild-type allele, and M represents the minor mutant-type allele

although this was not confirmed by the allelic model. This could depend on the fact that, compared with the other models, our allelic model included three more studies from Saudi Arabia, the USA, and Italy [16, 33, 37]. However, these three studies did not report the frequencies of each genotype and hence were not considered in the other models. Moreover, subgroup analysis revealed no significant correlation between rs4149056 and SIM risk in the US population, which was included in our allelic model and in the study reported by Marciante et al. [33]. This study also included a large sample size (n = 917) in which the experimental group was treated with cerivastatin, whereas the control group was treated with lovastatin, simvastatin, atorvastatin, and pravastatin. Additionally, less than 1% of patients received cerivastatin. Therefore, the non-significant correlation that we observed may be due to the small number of studies included in the analysis and to the unbalanced experimental setup of the study conducted by Marciante et al. [33]. Moreover, the effect of the *SLCO1B1* rs4149056 SNP on the risk of SIM varied according to the statin type. This phenomenon could be due to SNP-dependent altered transport activity of the organic anionic transporter SLCO1B1, possibly mediating the absorption of statins in hepatocytes [39, 46, 47].

Interestingly, the *GATM* rs9806699 A carriers within the rosuvastatin-treated population protected against the risk of SIM. This may be due to the involvement of the *GATM* gene in the energy metabolism of skeletal muscles [48]. Indeed, the A allele of *GATM* has been correlated with lower expression of *GATM*, which is responsible for creatine synthesis and thus provides a major energy source in skeletal muscles [24]. Therefore, the *GATM* A allele could induce attenuation of cellular metabolism and, consequently, diminish the energy-storing capacity of myocytes [24]. However, the cases in which *GATM* rs9806699 A carrier patients were treated with other types of statins were not addressed in this meta-analysis, since data were obtained from less than three studies.

In summary, our meta-analysis revealed that the 10 SNPs in five genes and nine statin types are correlated with the risk

of SIM. However, subgroup analysis based on the country-specific population was conducted only for the rs4149056 SNP of *SLCO1B1*. On the contrary, stratified analyses based on the statin type were performed only for the rs4149056 and rs2306283 SNPs of *SLCO1B1*, the rs776746 SNP of *CYP3A5*, the rs3892097 SNP of *CYP2D6*, and the rs9806699 SNP of *GATM*, since a smaller number of studies investigated the remaining SNPs and those results needed further verification.

This meta-analysis is characterized by several strengths: (1) This meta-analysis provides comprehensive analysis of SNPs reported in more than three studies associated with the risk of SIM; (2) the results of a mixed-effects model were calculated to avoid random error; and (3) the analysis was based on a large sample size, and therefore, the results of this meta-analysis are more robust than those of each individual study. However, there are also several limitations in this meta-analysis. Indeed, this analysis was conducted at the study level, but not at the individual level, and did not include non-English literature, possibly resulting in data insufficiency. Furthermore, a mixed-effects model was used in this study, and hence, the effects of country location, patient's clinical status, drug dose, and follow-up time on the outcome of statin treatment are still unclear. Moreover, since the analyses of this study were conducted on SNPs reported in more than three studies related to SIM, some key SNPs may have been overlooked if they had not been studied extensively. In addition, stratified analysis was conducted based on the country-specific population since most studies did not report the specific ethnic background of the patients. Finally, the results of stratified analyses were not conclusive because of the small number of included studies relative to numerous subgroups. Therefore, our study was mainly limited by the number of studies available at the time of analysis.

In conclusion, the rs4149056 SNP of the *SLCO1B1* gene is correlated with an increased risk of SIM. On the contrary, the heterozygous and dominant models of *SLCO1B1* rs4363657 showed that this SNP may protect against the risk of SIM. Additionally, the correlation of *SLCO1B1* rs4149056 and *GATM* rs9806699 with the risk of SIM may depend on the use of simvastatin and rosuvastatin, respectively. A large-scale study should be conducted in the future to verify these findings and evaluate whether these correlations are influenced by the genetic or physiological characteristics of the patient.

Authors' contributions QX and XDZ wrote the manuscript; QX and YMC designed the research; QFX, KH, ZZ, LM, and JJ performed the research; GYM, ZW, and ZYL analyzed the data; ZYL and XDZ contributed new reagents/analytical tools.

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Data Availability The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Code availability Not applicable

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