Human Genomics

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HMGCR genetic variation and risk of new-onset type 2 diabetes in statin users

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Abstract

Background Statins are widely prescribed lipid-lowering agents, but their use is associated with an increased risk of new-onset type 2 diabetes mellitus (NO-T2DM) ranging from 9% to 13%. While genetic variants in 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR)*, the pharmacological target of statins, and the solute carrier organic anion transporter family, member 1B1 (*SLCO1B1)*, a key hepatic transporter, have been implicated in statin response and toxicity, their role in statin-associated diabetogenesis remains unclear.

Objective To investigate the association of four common *HMGCR* variants (rs17671591, rs12916, rs17238484, and rs2303152) and the *SLCO1B1* (rs4149056) with the risk of NO-T2DM among statin-treated cohort.

Methods In a matched case-control study, 194 adults receiving atorvastatin or rosuvastatin were enrolled. The cases were patients who developed NO-T2DM within four years of initiating statin therapy ($n=97$), while controls remained diabetes-free after four years of use ($n=97$). Participants were matched for age, sex, ethnicity, BMI, and statin intensity. Genotyping was performed using TaqMan assays, and associations were evaluated using genetic models, linkage disequilibrium (LD), and haplotype analyses.

Results The *HMGCR* rs17238484 variant showed a nominal association with NO-T2DM in statin users. Carriers of the T allele (GT + TT) showed a lower risk compared with the GG genotype (OR = 0.56, 95% CI: 0.36–0.99, $P=0.044$); however, this association did not remain significant after correction for multiple testing. Haplotype analysis identified that the T–T–T haplotype of rs17671591–rs17238484–rs12916 was significantly associated with reduced risk of NO-T2DM (OR = 0.12, 95% CI: 0.02–0.58, $P=0.009$). Other *HMGCR* SNPs and *SLCO1B1* rs4149056 showed no significant associations.

Conclusion These findings suggest that *HMGCR* haplotypes may be associated with NO-T2DM risk among statin users, further studies in larger and more diverse populations are needed to validate these results.

Keywords Statins, New onset type 2 diabetes, Pharmacogenetics.

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Background

Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a key enzyme at the early steps of the mevalonate pathway, which is responsible for the biosynthesis of numerous important cellular lipids, including cholesterol, dolichol, isopentenyl tRNA, ubiquinone, and others [1]. Statins are the primary and most effective treatments for hypercholesterolemia by lowering blood low-density lipoprotein cholesterol (LDL-C) levels [2]. Consequently, they have been used to prevent both primary and secondary cardiovascular diseases (CVDs). Generally, statin treatment reduces LDL-C by 30–50% [3]. In addition, the health benefits of statins are thought to extend beyond their cholesterol-lowering properties, contributing to their pleiotropic effects on cardiovascular and cerebrovascular diseases [4].

However, statin use is associated with adverse effects, the most common muscle pain, hepatic transaminase elevations, dizziness, digestive system problems, and the development of new-onset type 2 diabetes mellitus (NO-T2DM) [5–7]. Several studies have reported an increased risk of NO-T2DM following statin initiation [8, 9]. Meta-analyses indicated an excess risk ranging from 9% to 13%, with the highest risk of NO-T2DM seen in patients taking high-intensity statin therapy [10]. Overall, cumulative evidence supports a class effect of statins in increasing the risk of diabetes across multiple statin types [6]. This is further supported by meta-analysis, which demonstrated that ezetimibe a non-statin LDL-C–lowering therapy - does not increase the risk of NO-T2DM, highlighting that the diabetogenic effect is specific to statin [11], Subsequently, in 2012, the U.S. Food and Drug Administration (FDA) updated statin labels to include information regarding the increased incidence of diabetes and potential elevations in blood glucose levels associated with the use of statins.

HMG-CoA reductase is the rate-limiting enzyme in the cholesterol biosynthesis pathway. Its activity is tightly regulated through a negative feedback mechanism mediated by sterols and non-sterol metabolites derived from mevalonate. Statins exert their lipid-lowering effect by competitively inhibiting HMG-CoA reductase, thereby suppressing the synthesis of mevalonate, cholesterol, and downstream metabolites essential for various cellular functions [12].

The *HMGCR* gene, which encodes HMG-CoA reductase, has been identified as a potential genetic risk factor for NO-T2DM [13, 14]. Interestingly, genetically determined higher HMG-CoA reductase activity, inferred from increased genetically proxied *HMGCR* expression, has been associated with a reduced risk of NO-T2DM [13]. To provide a comprehensive overview of the *HMGCR* variants used as proxies for statin effects, Supplementary Table S1 summarizes the four commonly studied SNPs (rs17671591, rs17238484, rs12916, and rs2303152), effect alleles, reported effects on LDL-C, and their use as genetic proxies in previous studies.

Existing evidence linking *HMGCR* inhibition to NO-T2DM falls into two main categories: clinical trials (which estimate the overall risk of statin drug exposure) and Mendelian Randomization (MR) models, which simulate the lifelong effects of reduced *HMGCR* activity via genetic variants. However, neither approach fully addresses the pharmacogenetic question, the clinical trials rarely included *HMGCR* genotyping, and the genetic models were conducted in populations not specifically selected for statin treatment. Consequently, the crucial interaction between *HMGCR* polymorphisms and statin therapy remains poorly understood. It is still unclear whether constitutional *HMGCR* variants independently predispose individuals to NO-T2DM, or whether statin exposure significantly amplifies this genetic susceptibility in those already receiving treatment.

Another important genetic factor influencing statin response is the *SLCO1B1* gene, which encodes the hepatic transporter OATP1B1 responsible for statin uptake into the liver. A common variant, *SLCO1B1* (rs4149056), has been strongly associated with reduced transporter function, leading to increased plasma statin concentrations and a higher risk of statin-induced adverse effects, particularly myopathy [15, 16], Beyond muscle toxicity, *SLCO1B1* polymorphisms may also modulate statin efficacy and metabolic outcomes [17]. However, the association between *SLCO1B*1 variants and NO-T2DM risk remains underexplored, underscoring the need for further investigation into its role in statin-induced diabetogenesis.

Importantly, data on these pharmacogenetic relationships in Middle Eastern populations are scarce, despite the region's high burden of dyslipidemia, diabetes, and widespread statin use. No previous study has simultaneously examined *HMGCR* and *SLCO1B1* variants within a clinically validated cohort of statin -treated patients who were carefully phenotyped for NO-T2DM.

To address this gap, we investigated the association of four common *HMGCR* variants (rs17671591, rs12916, rs17238484, and rs2303152) and the *SLCO1B1* rs4149056 variant with NO-T2DM in a matched cohort of statin-treated adults. By integrating pharmacodynamic and pharmacokinetic genetic determinants, this study aimed to provide a more complete understanding of the genomic architecture underlying susceptibility to diabetes after statin treatment.

Method and materials

This case-control study included a total of 194 adult participants who had been prescribed either atorvastatin or rosuvastatin. The case group (n = 97) consisted

of patients who developed NO-T2DM within four years of initiating statin therapy. In contrast, the control group (n = 97) comprised individuals who had received statin treatment for at least four years without developing NO-T2DM.The four-year observation window was selected to capture early metabolic changes following statin initiation, as previous longitudinal studies have reported that increased risk of NO-T2DM among statin user becomes detectable within the first few years of treatment [18]. Importantly, the classification of NO-T2DM was based on retrospective assessment of electronic medical records (EMR). Although participants were enrolled and followed prospectively for up to one year as part of the EmHeart study, data on statin initiation and diabetes onset were obtained through longitudinal EMR review.

To minimize potential confounding, cases and controls were matched in a 1:1 ratio using a nearest-neighbor matching approach based on five predefined variables: age, sex, ethnicity, body mass index (BMI), and statin intensity. Age matching was performed within a ± 5-year range, and BMI matching was based on the closest available value. Statin intensity matching ensured that participants receiving rosuvastatin (moderate intensity: 5–10 mg; high intensity: 20–40 mg) or atorvastatin (moderate intensity: 10–20 mg; high intensity: 40–80 mg) were paired with controls receiving comparable treatment regimens.

Because the number of eligible controls within some strata was limited, exact matching across all variables was not always feasible. Therefore, approximate nearest-neighbor matching was applied, selecting the closest available matches within the predefined criteria.

Participants were recruited from two clinical sites in the United Arab Emirates (Al Ain and Abu Dhabi) between October 2021 and October 2023.This study represents a nested case–control analysis within the EmHeart study [19, 20], a multicenter pharmacogenomic study including approximately 900 statin-treated participants in the UAE. Participants underwent pharmacogenomic testing for variants relevant to statin therapy, with results interpreted according to established guidelines.

Exclusion criteria included severe hepatic impairment, a family history of type 2 diabetes (T2DM) to reduce confounding by strong genetic predisposition, active malignancy or ongoing chemotherapy, known hematologic disorders, pregnancy, and prediabetes. Participants were classified as having NO-T2DM if diabetes was diagnosed within four years of starting statin therapy, based on glycated hemoglobin (HbA1c) levels (≥ 6.5%) or the initiation of anti-diabetic medication.

All participants provided written informed consent in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Abu Dhabi Health Research and Technology Ethics Committee (reference number: DOH/CVDC/2020/1187) as part of the EmHeart Study.

Data collection

Data were collected from patients's EMR, including demographic information (age, sex, ethnicity, and BMI), comorbidities, and concomitant medications. Comorbidities were identified based on documented physician diagnoses recorded in the medical records.

To obtain detailed information on statin use, adherence, and the development of NO-T2DM, we conducted a thorough review of each patient's EMR for physician-documented evidence of diabetes following statin therapy, including the timing of diagnosis and laboratory confirmation.

Statin exposure and adherence were determined using prescription records documented in the EMR. Then, participants were contacted directly by phone to confirm statin use, treatment duration, and to further clarify the occurrence and characteristics of diabetes.

Blood sampling and genotyping

Peripheral blood samples (3 mL) were collected from each participant via venipuncture into EDTA-containing vacutainer tubes (BD Inc., UK) and stored at − 20 °C until further analysis. Genomic DNA was extracted from whole blood using either the FlexiGene® DNA Kit or the QIAamp® DNA Kit (Qiagen, Germany), following the manufacturer's instructions. DNA quality and concentration were assessed using a NanoDrop One Spectrophotometer (Thermo Fisher Scientific, USA).

Genotyping of five selected variants was performed, including four *HMGCR* variants (rs17671591, rs12916, rs17238484, and rs2303152) and one *SLCO1B1* variant (rs4149056, 521T > C). TaqMan® SNP Genotyping Assays (assay IDs: C__33431867_10, C__7445046_10, C__33431934_10, C__15971097_10, and C__8898463_10, respectively) were used in combination with the TaqMan SNP Genotyping Master Mix on a QuantStudio 7 Flex Real-Time PCR System (Applied Biosystems, Thermo Fisher Scientific, USA).

Genotyping results were analyzed using TaqMan Genotyper Software version 1.6.0 (Applied Biosystems, Thermo Fisher Scientific). A subset of samples was validated by Sanger sequencing, which demonstrated 100% concordance between genotyping methods. To investigate the non-random association between alleles at different loci, we conducted LD analysis among rs17671591, rs12916, rs17238484, and rs2303152 variants. Haplotype analysis was performed to investigate the combined effect of the *HMGCR* variants (rs17671591, rs12916, rs17238484, and rs2303152) on statin-induced NO-T2DM.

Statistical analysis

Continuous variables (Age, BMI) were reported as mean ± SD and compared using the two-tailed Independent Samples t-test. Categorical variables (Sex, Ethnicity, Statin Intensity) were summarized as counts (n, %) and compared using Fisher's exact test. Statistical significance was set at a two-tailed P-value of <0.05. The common odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated to compare cases and controls, with a two-tailed p-value <0.05 considered statistically significant. Haplotype analysis was conducted using the SNPStats online tool (https://www.snpstats.net/start.htm).

Results

Baseline demographics and clinical characteristics of the participants

Table 1 presents the baseline demographic and clinical characteristics of the study participants. No significant differences were observed between cases and controls in terms of ethnicity, sex distribution, statin treatment intensity (high vs. low), or age. The mean BMI was slightly higher in the case group (30.1 ± 40) compared to the control group (29.3 ± 3.9), although this difference did not reach statistical significance ($p = 0.082$). Baseline HbA1c levels showed a statistically significant difference between cases and controls (5.3 ± 0.3 vs. 5.1 ± 0.4, $p < 0.001$); however, both values remained within the non-diabetic range, indicating no clinically meaningful difference between the groups. The use of concomitant medications, including ACE inhibitors/angiotensin receptor blockers (ACEI/ARBs), antiplatelet agents, diuretics, and ezetimibe, was comparable between cases and controls. In contrast, beta-blocker use was more frequent among cases than controls Similarly, no statistically significant differences were observed between the two groups in the prevalence of cardiovascular disease, stroke, hypertension, or dyslipidemia.

Table 1 Baseline demographics and clinical characteristics of the participants

Characteristics	Case ($N = 97$)	Control ($N = 97$)	P-value
Ethnicity			
Arab	54 (55.7%)	47 (48.5%)	0.56
Others	43 (44.3%)	50 (51.5%)	
Sex			
Male	59 (60.8%)	60 (61.9%)	1
Female	38 (39.2%)	37 (38.1%)	
High-intensity statin/	35 (36.1%)	32 (32.9%)	0.763
Low-intensity statin	62 (63.9%)	65 (67%)	
Age (mean ± SD)	53.6 ± 10.27	51.3 ± 10.8	0.15
BMI (mean ± SD)	30.1 ± 4.0	29.3 ± 3.9	0.082
HbA1c	5.3 ± 0.3	5.1 ± 0.4	< 0.001
Medication			
ACEI/ARBs	61 (62.8%)	61 (62.8%)	1
Antiplatelet drugs	30 (30.9%)	22 (22.6%)	0.26
Diuretics	73 (75.2%)	78 (80.4%)	0.49
Beta blockers	43 (44.3%)	29 (29.89%)	0.053
Ezetimibe	33(34%)	36 (37.1%)	0.76
Comorbidity			
Cardiovascular disease	26 (26.8%)	20 (20.6%)	0.38
Stroke	5 (5%)	5 (5%)	1
Hypertension	89 (91.7%)	80 (82.4%)	0.07
Dyslipidemia	80 (82.4%)	79 (81.4%)	1

ACEI/ARBs: angiotensin converting enzyme inhibitors/angiotensin receptor blockers, BMI: Body Mass Index. Other ethnicity category primarily included participants of South Asian origin (Indian, Pakistani, and Bangladeshi), HbA1c reading before statin initiation

Association of *HMGCR* polymorphisms with NO-T2DM

As shown in Table 2, Genotype and allele frequencies of rs17238484, rs12916, rs17671591, rs2303152, and *SLCO1B1* rs4149056 were compared between cases and controls. For rs17238484, the GG genotype was more frequent among cases (54%) compared to controls (39%). In the unadjusted analysis, carriers of the T allele (GT + TT) showed a significantly lower risk compared with the GG genotype (OR = 0.56, 95% CI: 0.36–0.99, $P = 0.044$), suggesting a potential protective effect. However, this association did not remain statistically significant after correction for multiple testing using the Benjamini–Hochberg method (q = 0.210). The allelic comparison showed a similar protective trend for the T allele (OR = 0.66, 95% CI: 0.43–1.02, $P = 0.060$).

For rs12916, no significant differences were detected in genotype or allele frequencies between cases and controls (dominant model OR = 0.65, 95% CI = 0.34–1.24, $P = 0.095$; $P = 0.19$). Similarly, rs17671591 showed no significant association under any genetic model (dominant OR = 1.30, 95% CI = 0.70–2.30, $P = 0.44$). For rs2303152, genotype and allele distributions did not differ significantly between groups (dominant OR = 0.81, 95% CI = 0.46–1.43, $P = 0.47$).

Regarding *SLCO1B1* rs4149056, the TT genotype was the most frequent in both groups. The variant showed no significant association with the outcome (dominant OR = 0.66, 95% CI = 0.11–4.00, $P = 0.65$; allelic $P = 0.084$).

Linkage disequilibrium analysis

Linkage disequilibrium (LD) analysis was performed among the four SNPs (rs17671591, rs17238484, rs12916, and rs2303152) within the *HMGCR* gene. The pairwise D′ values ranged from 0.49 to 0.91, indicating varying degrees of LD across loci. The strongest LD was observed between rs17671591 and rs17238484 (D′ = 0.91), followed by moderate LD between rs17671591–rs12916 (D′ = 0.71) and rs17238484–rs12916 (D′ = 0.75). Lower LD was observed between rs12916–rs2303152 (D′ = 0.49) and rs17238484–rs2303152 (D′ = 0.51). Figure 1

Table 2 Association of *HMGCR* SNPs with NO-T2DM

SNP	Genotype	Case (*N*, %)	Control (*N*, %)	OR (95%CI)	*P*-value	q-value (FDR)
rs17238484	GG	53 (54.6%)	39 (40.2%)			
	GT	37 (38.1%)	48 (49.5%)			
	TT	7 (7.2%)	10 (10.3%)			
	TT vs. GG + GT	7/90	10/87	0.68 (0.25–1.86)	0.44	0.507
	GT + TT vs. GG	44/53	58/39	0.56 (0.36–0.987)	0.044*	0.210
	G allele	143 (73.7%)	126 (64.9%)	1.5 (0.98–2.3)	0.06	0.210
	T allele	51 (26.3%)	68 (35.1%)	0.66 (0.43–1.02)	0.06	
rs12916	CC	22 (22.7%)	29 (29.9%)			
	CT	47 (48.5%)	47 (48.5%)			
	TT	28 (28.9%)	21 (21.6%)			
	CC vs. CT + TT	21/76	29/68	0.65 (0.34–1.24)	0.19	0.317
	TT vs. CT + CC	28/69	22/75	1.38 (0.72–2.6)	0.32	0.436
	C allele	90 (46.4%)	104 (53.6%)	0.75 (0.5–1.1)	0.15	0.281
	T allele	104 (53.6%)	90 (46.4%)	1.34 (0.89–1.9)	0.15	
rs17671591	CC	33 (34.0%)	28 (28.9%)			
	CT	48 (49.5%)	48 (49.5%)			
	TT	16 (16.5%)	21 (21.6%)			
	CC vs. CT + TT	33/64	28/69	1.3 (0.7–2.3)	0.44	0.507
	TT vs. CT + CC	16/81	21/76	0.71 (0.35–1.5)	0.36	0.450
	C allele	114 (58.8%)	104 (53.6%)	1.2 (0.82–1.8)	0.30	0.436
	T allele	80 (41.2%)	90 (46.4%)	0.81 (0.54–1.2)	0.30	
rs2303152	GG	51 (52.6%)	56 (57.7%)			
	GA	39 (40.2%)	35 (36.1%)			
	AA	7 (7.2%)	6 (6.2%)			
	GG vs. GA + AA	51/46	56/41	0.81 (0.46–1.43)	0.47	0.503
	AA vs. GA + GG	7/90	6/91	1.18 (0.38–3.7)	0.77	0.770
	G allele	141 (72.7%)	147 (75.8%)	0.81 (0.51–1.28)	0.38	0.450
	A allele	53 (27.3%)	45 (23.2%)	1.22 (0.77–1.9)	0.38	
SLCO1B1*5 rs4149056	CC	2 (2.1%)	3 (3.1%)			
	CT	13 (13.4%)	22 (22.7%)			
	TT	82 (84.5%)	72 (74.2%)			
	CC vs. CT + TT	2/95	3/94	0.66 (0.11-4)	0.65	0.696
	TT vs. CC + CT	82/15	72/25	1.89 (0.93–3.8)	0.078	0.234
	C allele	17 (8.8%)	28 (14.4%)	0.57 (0.30–1.08)	0.084	0.234
	T allele	177 (91.2%)	166 (85.6%)	1.75 (0.9–3.3)	0.084	

q-value: Adjusted p-value using the Benjamini-Hochberg False Discovery Rate (FDR) procedure to account for multiple testing across 15 genetic models

illustrates the results of this analysis. These results suggest that rs17671591, rs17238484, and rs12916 are moderately to strongly correlated and may form a single haplotype block, while rs2303152 shows weaker linkage with the other variants.

Haplotype association with NO-T2DM

Haplotype analysis of rs17671591, rs17238484, and rs12916 identified five common haplotypes. The most frequent haplotype (C–G–T, 43.0%) was used as the reference. Among the remaining haplotypes, T–T–C (24.1%), T–G–C (12.9%), and C–G–C (11.7%) showed non-significant trends toward reduced risk of NO-T2DM (OR range: 0.58–0.75; all $P > 0.05$). The T–T–T haplotype (5.1%) was significantly associated with a lower risk of NO-T2DM (OR = 0.12, 95% CI: 0.02–0.55; $P = 0.0075$), and this association remained consistent after adjustment for ethnicity (adjusted OR = 0.12, 95% CI: 0.03–0.58; $P = 0.009$). Rare haplotypes with frequencies < 2% were grouped and not analyzed individually due to unstable estimates. Overall, the T–T–T haplotype showed a protective association with NO-T2DM, whereas other common haplotypes were not significantly associated. Haplotype frequencies, odds ratios, and statistical significance are presented in Table 3.

The most frequent haplotype (C–G–T) was used as the reference category. Odds ratios (ORs) were estimated using crude models and models adjusted for ethnicity. Frequencies are reported for the combined study population. Rare haplotypes with frequencies < 2% were grouped and analyzed collectively.

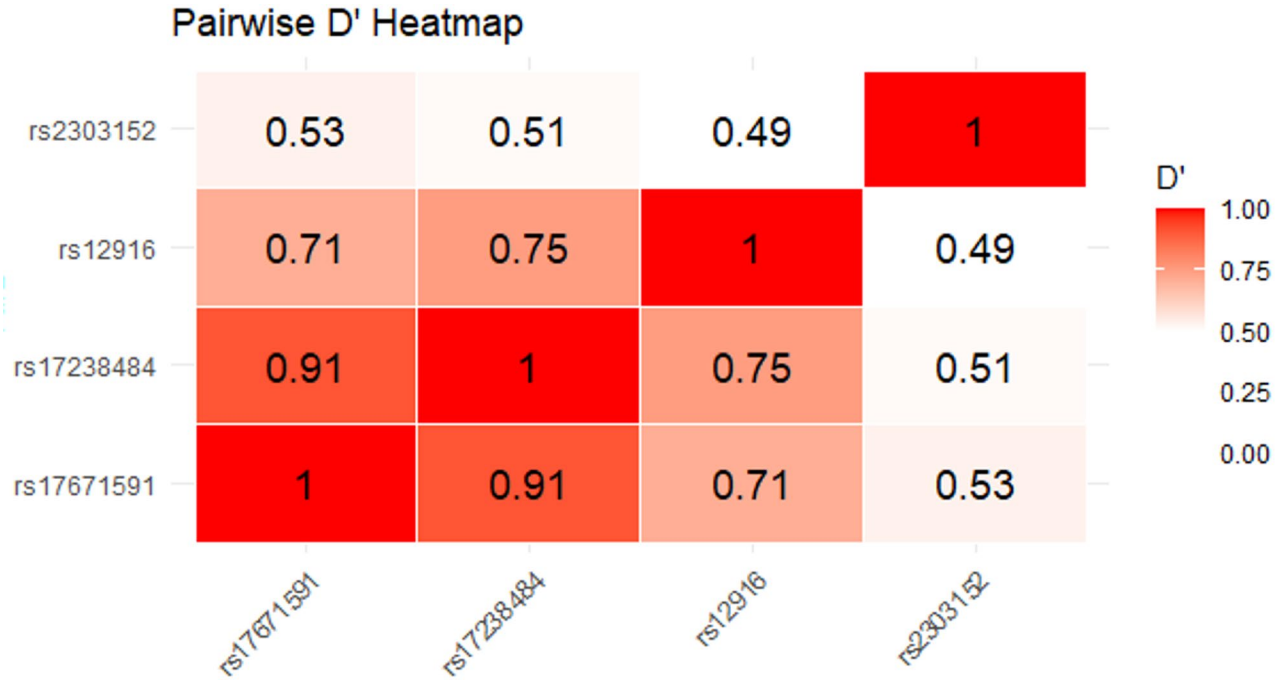

Fig. 1 Linkage disequilibrium (LD) of the four SNPs (rs17671591, rs17238484, rs12916, and rs2303152) within the *HMGCR* gene

Table 3 Haplotype analysis of rs17671591, rs17238484, and rs12916

	rs17671591	rs17238484	rs12916	Freq	OR (95% CI)	*P*-value	OR (95% CI) Adjusted	*P*-value Adjusted
Haplotype 1	C	G	T	0.4302	1.00	–	–	–
Haplotype 2	T	T	C	0.2407	0.72 (0.43–1.21)	0.21	0.72 (0.43–1.22)	0.22
Haplotype 3	T	G	C	0.129	0.75 (0.37–1.51)	0.43	0.76 (0.38–1.54)	0.45
Haplotype 4	C	G	C	0.1168	0.58 (0.31–1.10)	0.096	0.58 (0.31–1.10)	0.099
Haplotype 5	T	T	T	0.0512	0.12 (0.02–0.55)	0.0075	0.12 (0.03–0.58)	0.009
Combined rare haplotypes < 2%	All other haplotypes			0.018	–	–	–	–

Conditional logistic regression

Conditional logistic regression analysis accounting for the matched case–control design demonstrated a significant association between the *HMGCR* T allele and a reduced risk of NO-T2DM. Individuals carrying at least one T allele (GT + TT) had significantly lower odds of developing diabetes compared with GG homozygotes (OR 0.39, 95% CI 0.18–0.87, $p = 0.021$). Body mass index, included as a continuous variable, was not significantly associated with diabetes risk (OR per unit increase 1.03, 95% CI 0.95–1.12, $p = 0.423$). High statin dose also showed no significant association (OR 1.17, 95% CI 0.48–2.85, $p = 0.724$). Clinical covariates, including history of cardiovascular disease (OR 1.97, 95% CI 0.74–5.19, $p = 0.172$), ACEI/ARB use (OR 1.65, 95% CI 0.82–3.33, $p = 0.161$), and beta-blocker use (OR 2.01, 95% CI 0.86–4.67, $p = 0.106$), showed trends toward increased risk, although none reached statistical significance as shown in Fig. 2.

Discussion

This study provides novel pharmacogenetic evidence from a Middle Eastern population suggesting that genetic variation within *HMGCR* may influence susceptibility to NO-T2DM in statin users. Haplotype analysis identified a significant protective effect for the T–T–T combination across rs17671591, rs17238484, and rs12916. By focusing exclusively on statin-treated individuals and using a matched case–control design, our findings extend prior Mendelian randomization and clinical trial data by indicating that constitutional *HMGCR* variation may influence diabetes risk in the context of pharmacologic *HMGCR* inhibition.

Type 2 diabetes (T2DM) is a complex metabolic disorder that results from the interaction between genetic susceptibility and metabolic as well as environmental factors [21]. Although the association between dyslipidemia and atherosclerotic cardiovascular disease is well established, the relationship between lipid profiles and T2DM remains incompletely understood. Previous studies have

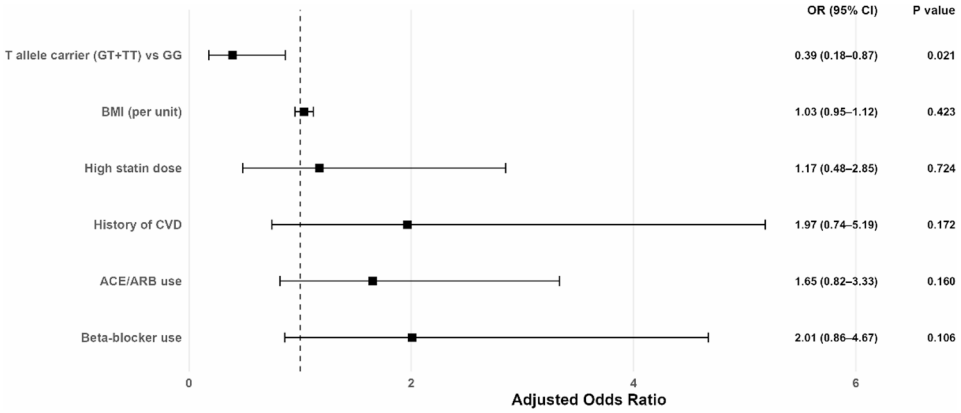

Fig. 2 Forest plot shows adjusted odds ratios (ORs) and 95% confidence intervals (CIs) from conditional logistic regression. The model included the *HMGCR* T allele (rs17238484), BMI (body mass index), statin intensity, history of cardiovascular disease, ACEI/ARB use, and beta-blocker use. Squares represent ORs, horizontal lines indicate 95% CIs, and the dashed line denotes OR = 1. P values are shown for each variable

reported inconsistent findings: some have demonstrated positive associations between elevated LDL-C. and triglyceride (TG) levels with an increased risk of T2DM [22], whereas others have shown the opposite [23]. Notably, low circulating LDL-C concentrations have been linked to a higher prevalence [24] and incidence [25] of T2DM.

MR studies have offered valuable insights into lipid–glucose interactions, showing that genetically proxied inhibition of *HMGCR* - the molecular target of statins - confers an approximate 9% increase in the risk of NO-T2DM per 10 mg/dL LDL-C reduction [10]. This genetic evidence mirrors findings from clinical trials comparing high- and low-intensity statin therapy [6]. Mechanistically, statin-induced LDL receptor (LDLR) upregulation lowers LDL-C but may also contribute to impaired β-cell function and insulin resistance [23, 26]. Disruption of the mevalonate pathway, reduced isoprenoid synthesis, and impaired prenylation may further disrupt insulin granule exocytosis and transcriptional networks essential for β-cell mass maintenance [27]. However, these pathways likely interact in a multifactorial manner, and further work is needed to fully elucidate how *HMGCR* inhibition leads to NO-T2DM.

Broader MR analyses reinforce this pattern across other LDLR-mediated LDL-lowering mechanisms. Genetic variants that reduce LDL-C through *HMGCR* inhibition (statins), or PCSK9 inhibition are all associated with modest but significant increases in the risk of NO-T2DM [28]. Swerdlow et al. [29] demonstrated that *HMGCR* variants rs17238484 and rs12916 are linked to higher BMI, elevated glucose levels, and increased diabetes risk. In our study, rs17238484 T allele showed a nominal association with a reduced risk of NO-T2DM in statin users; however, this did not remain statistically significant after correction for multiple testing. The lack of a significant association for rs12916 in our cohort may be attributable to limited statistical power. Additional evidence from a large meta-analysis of 50,775 T2DM cases and 270,269 controls further supports a diabetogenic signal across LDL-lowering pathways, showing that variants in *NPC1L1*, *HMGCR*, and *PCSK9* all contribute to increasing NO-T2DM risk, with the strongest effects observed for *NPC1L1* [30]. Importantly, Ference et al. [31] demonstrated that *PCSK9* and *HMGCR* provide comparable cardiovascular benefit per unit reduction in LDL-C, accompanied by similar but modest increases in diabetes risk, particularly among individuals with impaired fasting glucose.

Notably, Haplotype analysis revealed that the T–T–T combination across rs17671591, rs17238484, and rs12916 conferred a protective effect against NO-T2DM, supporting the role of combined HMGCR variation in modulating enzyme activity. However, due to its low frequency, this finding should be interpreted cautiously, with replication in larger cohorts is needed. In conditional logistic regression analysis, the HMGCR rs17238484 T allele was associated with a reduced risk of NO-T2DM among statin users, independent of BMI, statin intensity, cardiovascular comorbidities, and concomitant use of ACEI/ARBs or beta-blockers. The absence of independent associations for these established metabolic risk factors likely reflects reduced group variability introduced by matching, rather than a true lack of biological effect. Collectively, these findings suggest that *HMGCR* variation, particularly at the haplotype level, may act as a pharmacogenetic modifier of diabetes risk during statin therapy.

The Solute Carrier Organic Anion Transporter Family 1B1 (*SLCO1B1*) gene, particularly the rs4149056 variant, influences statin pharmacokinetics by regulating hepatic statin uptake, the primary site of action. The T allele is associated with normal transporter function, whereas the C allele reduces transporter activity, leading to higher circulating statin concentrations and an increased risk of

statin-induced myopathy [32, 33] .In the present study, rs4149056 showed no significant association with NO-T2DM, consistent with the findings from the METSIM cohort, where the C-allele was not linked to NO-T2DM or altered glucose metabolism [12]. The absence of an association between *SLCO1B1* rs4149056 and NO-T2DM may suggest that statin-induced diabetogenesis is more closely related to pharmacodynamic target inhibition than to systemic statin exposure. While SLCO1B1 variation clearly influences myopathy risk through altered statin pharmacokinetics, our data suggests that increased circulating statin levels alone may be insufficient to drive diabetes risk.

The combined analysis of *HMGCR* and *SLCO1B1* variants highlights the importance of a holistic approach in pharmacogenetics. While *HMGCR* variants, reflecting the pharmacodynamic target of statins, may influence susceptibility to NO-T2DM through target inhibition, *SLCO1B1* variants primarily affect statin disposition and the risk of muscle-related adverse effects, with reduced C allele function increasing susceptibility to myopathy. Examining these genes together extends pharmacogenetic insights beyond single-gene associations, providing a more comprehensive understanding of statin response: *SLCO1B1* influences the amount of statin reaching the liver, whereas *HMGCR* governs the downstream pharmacodynamic effects. For optimal personalized therapy, both pharmacokinetic (transport) and pharmacodynamic (target) factors should be considered to maximize LDL-C reduction while minimizing patient-specific risks of diabetes and myopathy.

Although statin therapy has been associated with an increased risk of NO-T2DM, this elevated diabetes risk does not outweigh the substantial cardiovascular benefits of statin use, as the overall reduction in cardiovascular risk remains significant [34]. Maintaining long-term LDL-C levels at or below 100 mg/dL has been shown to reduce the incidence of major cardiovascular events by approximately 40% [35].

A major strength of this study is the rigorous clinical phenotyping and careful matching of cases and controls for key metabolic and demographic factors, which reduces confounding and strengthens the internal validity of the findings. This work also represents the first targeted evaluation of *HMGCR* pharmacogenetic markers in a Middle Eastern population, a region with a high prevalence of dyslipidemia and diabetes, thereby contributing valuable data to an underrepresented group in pharmacogenomic research.

However, several limitations should be acknowledged. The modest sample size limits statistical power, particularly for low-frequency variants such as *SLCO1B1* rs4149056, and may have prevented the detection of more subtle genetic effects. The study cohort was restricted mainly to atorvastatin and rosuvastatin users, which may limit the generalizability of the results to other statins with different pharmacokinetic profiles. Additionally, the observational design precludes causal inference, and further functional studies are needed to clarify the biological mechanisms linking *HMGCR* variation to NO-T2DM in statin user.

From a clinical perspective, these findings suggest that *HMGCR* genotyping may have potential utility in future risk stratification for statin-associated NO-T2DM. Although routine clinical implementation remains premature, identifying individuals with genetically increased susceptibility may inform more individualized lipid-lowering approaches, particularly in populations at higher baseline risk of diabetes. However, further studies with larger and more diverse populations are needed to validate these findings.

Conclusion

This study suggests that *HMGCR* genetic variation is associated with susceptibility to NO-T2DM in statin users, with the T–T–T haplotype showing a protective effect. The rs17238484 T allele showed a nominal association with reduced risk, although this did not remain significant after correction for multiple testing. In contrast, *SLCO1B1* rs4149056 was not associated with NO-T2DM, supporting a greater role for pharmacodynamic than pharmacokinetic mechanisms. Further studies with larger and more diverse populations are needed to validate these findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40246-026-00962-7.

Supplementary Material 1.

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Non.

Author contributions
Areej S. Albawa'neh: Conceptualization, Data curation, Formal analysis, Visualization, Investigation, Methodology & Writing the original draft. Mais N. Alqasrawi: Data curation, Investigation, Methodology. Zeina N. Al-Mahayri: Conceptualization, Validation, & Writing– review and editing. Nour al dain Marzouka: Validation, Methodology & Writing– review and editing. Lilas Dabaghie: Data curation. Dana Hamza: Investigation. Lubna Q. Khasawneh: Data curation. Virendra Misra: Investigation & Writing– review and editing, Husam Ouda: Investigation& Writing– review and editing. Bassam R. Ali: Conceptualization, Funding acquisition, Writing– review and editing, Data Curation, supervision, validation &Project administration. All co-authors contributed to the final manuscript and approved it.

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Data availability
The data from the current study (EMHEART) are not publicly available due to regulations of the local ethical committee but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with the Declaration of Helsinki and was approved by the Abu Dhabi Health Research and Technology Ethical Committee (Institutional Review Board - IRB) (Ref. DOH/CVDC/2020/1187). All participants provided written informed consent before enrolment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Friesen JA, Rodwell VW. The 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductases. Genome Biol. 2004. https://doi.org/10.1186/gb-2004-5-11-248.
2. Grundy SM, Feingold KR. Guidelines for the Management of High Blood Cholesterol. Endotext. 2000.
3. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753). https://doi.org/10.1016/S0140-6736(10)61350-5.
4. Morofuji Y, Nakagawa S, Ujifuku K, Fujimoto T, Otsuka K, Niwa M, et al. Beyond Lipid-Lowering: Effects of Statins on Cardiovascular and Cerebrovascular Diseases and Cancer. Pharmaceuticals. 2022. https://doi.org/10.3390/ph15020151.
5. Ruscica M, Ferri N, Banach M, Sirtori CR, Corsini A. Side effects of statins: from pathophysiology and epidemiology to diagnostic and therapeutic implications. Cardiovasc Res. 2022;118(17). https://doi.org/10.1093/cvr/cvac020.
6. Reith C, Preiss D, Blackwell L, Emberson J, Spata E, Davies K, et al. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis. Lancet Diabetes Endocrinol. 2024;12(5):306–19. https://doi.org/10.1016/S2213-8587. (24)00040-8 PubMed PMID: 38554713.
7. Alqasrawi MN, Al-Mahayri ZN, AlBawa'neh AS, Khasawneh LQ, Dabaghie L, Altoum SM, et al. Pharmacogenomic insights into atorvastatin and rosuvastatin adverse effects: a prospective observational study in the UAE's multiethnic population. Hum Genomics. 2025;19(1). https://doi.org/10.1186/s40246-025-00753-6. PubMed PMID: 40281622.
8. Betteridge DJ, Carmena R. The diabetogenic action of statins-mechanisms and clinical implications. Nat Reviews Endocrinol. 2016. https://doi.org/10.1038/nrendo.2015.194.
9. Agarwala A, Kulkarni S, Maddox T. The Association of Statin Therapy with Incident Diabetes: Evidence, Mechanisms, and Recommendations. Curr Cardiol Rep. 2018. https://doi.org/10.1007/s11886-018-0995-6.
10. Sattar N. Statins and diabetes: What are the connections? Best Practice and Research: Clinical Endocrinology and Metabolism. Bailliere Tindall Ltd; 2023. https://doi.org/10.1016/j.beem.2023.101749. PubMed PMID: 36858834.
11. Albawa'neh AS, Alqasrawi MN, Al-Mahayri ZN, Albawaana A, Ahmed G, Al-Rifai RH, et al. Ezetimibe and the risk of new-onset type 2 diabetes: a systematic review and meta-analysis. Ann Med. 2025;57(1):2594355. https://doi.org/10.1080/07853890.2025.2594355. PubMed PMID: 41320800.
12. Laakso M, Fernandes Silva L. Statins and risk of type 2 diabetes: mechanism and clinical implications. Front Endocrinol. 2023. https://doi.org/10.3389/fendo.2023.1239335.
13. Zhang YY, Chen BX, Wan Q. Association of lipid-lowering drugs with the risk of type 2 diabetes and its complications: a mendelian randomized study. Diabetol Metabolic Syndrome. 2024;16(1). https://doi.org/10.1186/s13098-024-01477-8.
14. Sarsenbayeva A, Jui BN, Fanni G, Barbosa P, Ahmed F, Kristófi R, et al. Impaired hmg-coa reductase activity caused by genetic variants or statin exposure: Impact on human adipose tissue, β-cells and metabolome. Metabolites. 2021;11(9). https://doi.org/10.3390/metabo11090574.
15. Kitzmiller JP, Mikulik EB, Dauki AM, Murkherjee C, Luzum JA. Pharmacogenomics of statins: Understanding susceptibility to adverse effects. Pharmacogenomics Personalized Med. 2016. https://doi.org/10.2147/PGPM.S86013.
16. Ramsey LB, Johnson SG, Caudle KE, Haidar CE, Voora D, Wilke RA, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1 and Simvastatin-Induced Myopathy: 2014 Update. Clin Pharmacol Ther. 2014. https://doi.org/10.1038/clpt.2014.125.
17. Saber-Ayad M, Manzoor S, El-Serafi A, Mahmoud I, Abusnana S, Sulaiman N. Statin-induced myopathy SLCO1B1 521T > C is associated with prediabetes, high body mass index and normal lipid profile in Emirati population. Diabetes Res Clin Pract. 2018;139. https://doi.org/10.1016/j.diabres.2018.03.014.
18. Kim TJ, Lee JS, Yoon JS, Oh MS, Kim JW, Park SH, et al. The Impact of Statin Treatment Duration on the Risk of New-Onset Diabetes Mellitus and Recurrent Vascular Events in Ischemic Stroke Patients: A Linked Data Analysis. Cerebrovasc Dis. 2025;54(2). https://doi.org/10.1159/000538485.
19. Alqasrawi MN, Al-Mahayri ZN, Khasawneh LQ, AlBawa'neh AS, Dabaghie L, Altoum SM, et al. A multi-centre observational cohort study on pharmacogenomic predictors of rosuvastatin discontinuation in a multiethnic population. Front Pharmacol. 2025;16. https://doi.org/10.3389/fphar.2025.1656520.
20. Al-Mahayri ZN, Khasawneh LQ, Alqasrawi MN, Altoum SM, Jamil G, Badawi S, et al. Pharmacogenomics implementation in cardiovascular disease in a highly diverse population: initial findings and lessons learned from a pilot study in United Arab Emirates. Hum Genomics. 2022;16(1). https://doi.org/10.1186/s40246-022-00417-9.
21. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21176275.
22. Huang J, Lin H, Wang S, Li M, Wang T, Zhao Z, et al. Association between serum LDL-C concentrations and risk of diabetes: A prospective cohort study. J Diabetes. 2023;15(10). https://doi.org/10.1111/1753-0407.13440.
23. Klimentidis YC, Arora A, Newell M, Zhou J, Ordovas JM, Renquist BJ, et al. Phenotypic and genetic characterization of lower LDL cholesterol and increased type 2 diabetes risk in the UK biobank. Diabetes. 2020;69(10):2194–205. https://doi.org/10.2337/db19-1134. PubMed PMID: 32493714.
24. Feng QP, Wei WQ, Chung CP, Levinson RT, Sundermann AC, Mosley JD, et al. Relationship between very low low-density lipoprotein cholesterol concentrations not due to statin therapy and risk of type 2 diabetes: A US-based cross-sectional observational study using electronic health records. PLoS Med. 2018;15(8). https://doi.org/10.1371/journal.pmed.1002642.
25. Andersson C, Lyass A, Larson MG, Robins SJ, Vasan RS. Low-density-lipoprotein cholesterol concentrations and risk of incident diabetes: epidemiological and genetic insights from the Framingham Heart Study. Diabetologia. 2015;58(12). https://doi.org/10.1007/s00125-015-3762-x.
26. Xiao X, Luo Y, Peng D. Updated Understanding of the Crosstalk Between Glucose/Insulin and Cholesterol Metabolism. Front Cardiovasc Med Front Media S A. 2022. https://doi.org/10.3389/fcvm.2022.879355.
27. Gendaszewska-Darmach E, Garstka MA, Błażewska KM. Targeting Small GTPases and Their Prenylation in Diabetes Mellitus. J Med Chem. 2021. https://doi.org/10.1021/acs.jmedchem.1c00410.
28. Filippatos TD, Panagiotopoulou T, Tzavella E, Elisaf MS. Hypolipidemic Drugs and Diabetes Mellitus—Mechanisms and Data From Genetic Trials. Journal of Cardiovascular Pharmacology and Therapeutics. SAGE Publications Ltd; 2018. pp. 187–91. doi:10.1177/1074248418757011 PubMed PMID: 29409336.
29. Swerdlow DI, Preiss D, Swerdlow D. Genetic insights into statin-associated diabetes risk. Report.
30. Lotta LA, Sharp SJ, Burgess S, Perry JRB, Stewart ID, Willems SM, et al. Association between low-density lipoprotein cholesterol-lowering genetic variants and risk of type 2 diabetes: A meta-analysis. JAMA - J Am Med Association. 2016;316(13):1383–91. https://doi.org/10.1001/jama.2016.14568. PubMed PMID: 27701660.
31. Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, et al. Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes. N Engl J Med. 2016;375(22):2144–53. https://doi.org/10.1056/nejmoa1604304. PubMed PMID: 27959767.
32. SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study. N Engl J Med. 2008;359(8). https://doi.org/10.1056/nejmoa0801936.
33. Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. Clin Pharmacol Ther. 2022;111(5):1007–21. https://doi.org/10.1002/cpt.2557. PubMed PMID: 35152405.

34. Lembo M, Trimarco V, Izzo R, Pacella D, Jankauskas SS, Gallo P, et al. Statin-induced risk of diabetes does not reduce cardiovascular benefits in primary prevention: a 6-year propensity-score matched study in a large population. Cardiovasc Diabetol. 2025;24(1). https://doi.org/10.1186/s12933-025-02798-2. PubMed PMID: 40450251.
35. Trimarco V, Izzo R, Gallo P, Manzi MV, Forzano I, Pacella D, et al. Long-Lasting Control of LDL Cholesterol Induces a 40% Reduction in the Incidence of Cardiovascular Events: New Insights from a 7-Year Study. J Pharmacol Exp Ther. 2024;388(3). https://doi.org/10.1124/jpet.123.001878.

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