

Uncovering Coenzyme Q10-Related Genetic Determinants of Statin-Associated Muscle Symptoms: Evidence from the UK Biobank and the All of Us Research Program

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Statin-associated muscle symptoms (SAMS) are frequent adverse effects of statin therapy and have been hypothesized to result from impaired coenzyme Q10 (CoQ10) biosynthesis. Although genetic determinants of CoQ10 levels have been reported, genome-wide association studies (GWASs) conducted specifically in statin users are lacking. Moreover, direct CoQ10 measurements are unavailable in large-scale proteomic resources, necessitating suitable proxy biomarkers. COQ7, a key enzyme in the late steps of CoQ10 biosynthesis, was used as a proxy for CoQ10 biosynthetic capacity. We performed a GWAS of COQ7 protein levels in statin-treated participants from the UK Biobank. The lead variant was evaluated for association with SAMS in an independent cohort of statin users from the All of Us, followed by replication in an independent SAMS cohort from the UK Biobank. Gene–statin interaction analyses were conducted to assess statin-specific genetic effects. In addition, polygenic risk score (PRS) analyses were performed using previously reported CoQ10-associated variants from non-statin-specific cohorts. The GWAS identified the lead variant, rs66554427, with the A allele associated with lower COQ7 protein levels ($\beta = -0.13$, $SE = 0.018$, $P = 1.1 \times 10^{-13}$). In the All of Us, the rs66554427 A allele was associated with an increased risk of SAMS ($OR = 1.27$, 95% CI: 1.16–1.39, $P = 5.16 \times 10^{-8}$). These findings were consistently replicated in the UK Biobank SAMS cohort ($OR = 1.23$, 95% CI: 1.06–1.43, $P = 6.89 \times 10^{-3}$). Significant additive and multiplicative interactions between statin and rs66554427 were observed ($P < 0.001$). PRS analyses further demonstrated that genetically predicted lower CoQ10 levels were associated with a higher risk of SAMS. Using COQ7 protein levels as a proxy for CoQ10 biosynthesis, we identified statin-specific genetic susceptibility to SAMS and supported a causal role of impaired CoQ10 biosynthesis in SAMS.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Statin-associated muscle symptoms (SAMS) are a common adverse effect of statin therapy and have been hypothesized to result from impaired coenzyme Q10 (CoQ10) biosynthesis. However, genetic determinants of CoQ10-related pathways have not been systematically evaluated in statin-treated populations.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study investigated whether genetic polymorphisms affecting CoQ10 biosynthesis, proxied by plasma COQ7 protein levels, are associated with statin-associated muscle symptoms (SAMS) and whether these genetic effects are statin-specific.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We identified rs66554427 as a lead genetic variant associated with plasma COQ7 levels among statin users and demonstrated significant gene–statin interactions for muscle symptoms. These findings provide protein-level and genetic evidence linking impaired CoQ10 biosynthesis to SAMS.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our results suggest that CoQ10-related genetic markers may help identify individuals at increased risk of SAMS, supporting the development of genetically informed risk stratification and personalized statin therapy.

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Statins have been used to treat dyslipidemia and prevent cardiovascular disease through competitive inhibition of hydroxymethylglutaryl-CoA (HMG-CoA) reductase.¹ They reduce low-density lipoprotein (LDL) cholesterol, thereby preventing atherosclerosis. For instance, atorvastatin 80 mg, a high-intensity statin, was known to decrease LDL cholesterol by 49.2%.² Baigent *et al.* reported that statin therapy reduced the incidence of major vascular events like myocardial infarction and coronary death per mmol/L LDL reduction.³ Consistent with this evidence, recent clinical guidelines recommend statin therapy for individuals at elevated atherosclerotic cardiovascular disease risk, particularly those with LDL cholesterol levels ≥ 190 mg/dL.⁴

Although statins have been effective for lipid-lowering activity, a substantial proportion of statin users experience adverse events related to myotoxicity in clinical practice.⁵ Statin-associated muscle symptoms (SAMS) are among the best-known adverse events and occur across various phenotypes, ranging from mild myalgia or asymptomatic creatine kinase elevation to severe manifestations such as rhabdomyolysis.⁶ In clinical practice, SAMS frequently lead to dose reduction or discontinuation of statin therapy, which can compromise long-term adherence and attenuate the cardiovascular benefits of statins, particularly in high-risk populations.

Among the proposed mechanisms of SAMS, the hypothesis that statin therapy reduces coenzyme Q10 (CoQ10) levels, thereby increasing oxidative stress and subsequent mitochondrial dysfunction, has gained strength.⁷ CoQ10 and statins share the mevalonate pathway, and inhibition of HMG-CoA reductase by statins may consequently impair CoQ10 biosynthesis. Supporting this hypothesis, CoQ10 treatment normalized oxidative stress levels in rhabdomyosarcoma cells exposed to simvastatin.⁸ Furthermore, systematic reviews demonstrated that individuals receiving CoQ10 supplementation exhibited reduced oxidative stress and inflammatory biomarker levels, while clinical outcomes regarding the alleviation of SAMS remain inconsistent across various studies.^{9–11}

Because the CoQ10 biosynthesis pathway comprises multiple steps, numerous genes are involved.¹² Among these, *COQ2* rs4693075 has been the most frequently investigated, yet the results have remained controversial.^{13–19} To address this limitation, our previous study examined the association between SAMS and CoQ10-related single nucleotide polymorphisms (SNPs), including rs4693075, and identified significant associations.²⁰ Nevertheless, this analysis remained constrained by the absence of protein biomarkers that directly reflect CoQ10 biosynthetic activity.

Therefore, in the present study, we aimed to investigate the association between SAMS and the CoQ10 biosynthesis pathway using protein-level biomarkers. Although CoQ10 protein levels themselves are not measurable in current large-scale proteomic datasets, COQ7—a key enzyme involved in the later steps of CoQ10 biosynthesis—has been quantified at the plasma protein level. Leveraging plasma proteomic data from the UK Biobank, we used plasma COQ7 protein levels as a representative marker of CoQ10 biosynthesis. We conducted a genome-wide association study (GWAS) of COQ7 levels to identify genetic variants exhibiting statin-specific effects. Subsequently, we evaluated a lead SNP for associations with SAMS in an independent cohort of statin users from the All of Us

Research Program and replicated the association in an independent SAMS cohort from the UK Biobank. We further examined whether genetic associations differed according to statin exposure.

MATERIALS AND METHODS

UK Biobank COQ7 cohort

The UK Biobank is a large-scale, population-based, prospective cohort study with biomedical data that recruited nearly 500,000 participants aged 40–69 years in England, Wales, and Scotland between 2006 and 2010.²¹ It includes a range of phenotypes derived from touchscreen questionnaires, in-person interviews, electronic health records, and genomics and proteomics data. Data have been collected through August 16, 2020, in England and Wales and through July 19, 2020, in Scotland. Ethical approval for the resource was granted by the National Research Ethics Committee (16/NW/0274).

For the discovery GWAS, we selected participants of British, Irish, or other White backgrounds receiving statin therapy with available plasma protein measurements. Plasma COQ7 protein levels served as a proxy biomarker for CoQ10 biosynthesis, as direct CoQ10 measurements were unavailable. We excluded participants without genetic sex data, without COQ7 measurements, or with records of CoQ10 supplements to rule out the exogenous effects.

Baseline characteristics included age, sex, comorbidities, and other lipid-lowering drug use. For comorbidities, hypertension, diabetes mellitus, atrial fibrillation, myocardial infarction, ischemic stroke, kidney diseases, and liver diseases were included. For other lipid-lowering drugs, ezetimibe, fibrate, nicotinic acid derivatives, bile acid sequestrants, and pyridoxal were included.

Discovery GWAS of COQ7 levels

Genotyping of approximately 800,000 markers in the UK Biobank was carried out choosing one of two arrays, the UK Biobank Axiom Array or UK BiLEVE Array. Genomic DNA was extracted from whole blood, and quality control was applied at both the variant and sample levels. Variants were excluded if they showed evidence of deviation from Hardy–Weinberg equilibrium ($P < 1.0 \times 10^{-12}$), low call rates ($< 95\%$), or low minor allele frequency (MAF < 0.01). Samples were flagged and excluded based on indicators of poor DNA quality, discordance between reported and genetic sex, or excessive homozygosity. Genotype data were phased using Eagle v2.4 and imputed with Minimac4 v1.0.2, using the Genomics England reference panel. Post-imputation filtering removed variants with MAF < 0.01 . To control for population stratification, principal components derived by the UK Biobank were incorporated into downstream analyses.

The GWAS was conducted using PLINK 2.0.²² Linear regression models were used with an additive genetic effect, adjusting for age, sex, and the first ten principal components. Analyses were restricted to autosomal variants passing standard quality criteria (MAF > 0.01 , Hardy–Weinberg equilibrium $P > 1 \times 10^{-8}$, SNP and sample call rates $\geq 95\%$). Genome-wide statistical significance was defined as $P < 5 \times 10^{-8}$.²³ Effect estimates were reported as regression coefficients (β) with corresponding standard errors (SEs). Independent lead SNP was selected based on the smallest p -values among signals in low linkage disequilibrium ($R^2 < 0.1$). Results were visualized using Manhattan and quantile–quantile (QQ) plots, and regional association plots were generated with LocusZoom.²⁴

All of Us cohort

The All of Us Research Program is a large-scale, longitudinal cohort with biomedical data that enrolled approximately 500,000 participants aged not less than 18 years in the United States of America between 2018 and 2023.²⁵ The program integrates multimodal biomedical data, including participant-reported survey responses, electronic health records (EHRs), and genomic information. Within the EHR data, diagnostic information is harmonized using the Systematized Nomenclature of Medicine

(SNOMED), while medication records are standardized according to the Observational Medical Outcomes Partnership (OMOP) common data model. Informed consent was obtained from all participants either electronically or in-person, and the study protocol was approved by a central Institutional Review Board (IRB) in accordance with NIH human-subjects protections. This study used the Controlled Tier Dataset v8 (C2024Q3R4; February 2025 release), with follow-up available through October 1, 2023.

To maintain consistency with the UK Biobank analysis, we included White participants aged ≥ 40 years receiving statin treatment. We excluded participants without sex data, those diagnosed with muscle disorders (SNOMED Concept Id: 137275) within one year before statin initiation, and those taking CoQ10 supplements. SAMS cases were defined as individuals experiencing muscle symptoms within one year following statin initiation, identified using clinically relevant muscle disorder concepts (Table S2). Controls consisted of participants with at least two documented statin prescriptions who did not develop any muscle disorder during the entire follow-up period. We also collected baseline data on the same demographic and clinical factors as those in the UK Biobank.

Association analysis with SAMS

In the All of Us cohort, genetic data from short-read whole-genome sequencing were used, specifically the Allele Count/Alele Frequency threshold call set including SNPs with allele frequency $> 1\%$ or allele count > 100 in any ancestry subpopulation. The lead SNP identified from the COQ7 GWAS was tested for association with SAMS using additive logistic regression. Model 1 adjusted for age, sex, and ten principal components, while Model 2 additionally included baseline characteristics.

To examine whether the association between the lead SNP and SAMS differed by statin type, we categorized statins dispensed in the All of Us cohort according to their lipophilicity. Rosuvastatin and pravastatin were classified as hydrophilic statins, and all other statins (atorvastatin, simvastatin, fluvastatin, lovastatin, pitavastatin, cerivastatin) were classified as lipophilic statins. The association between the lead SNP and SAMS was evaluated separately within each lipophilicity group using logistic regression adjusted for age, sex, and the first ten principal components.

Replication analysis with SAMS

To replicate the COQ7–SAMS association in an independent UK Biobank cohort, we additionally constructed a SAMS cohort within the UK Biobank using participants who were not included in the COQ7 protein GWAS (referred to as the UK Biobank SAMS cohort). Statin users from the UK Biobank who were not part of the GWAS discovery sample were included, and SAMS cases were identified using Read v2, Read v3, ICD-9, or ICD-10 code for muscle disorder diagnosis within 365 days following the first statin prescription (Table S2). Controls were statin users with no muscle disorder diagnoses throughout the entire follow-up period. Other inclusion and exclusion criteria were applied consistently with those used in the All of Us cohort. The lead SNP was tested for association with SAMS using the same logistic regression framework as in the All of Us cohort.

Sensitivity analyses

We conducted sensitivity analyses to evaluate the robustness of the association between the lead SNP and SAMS. These analyses involved modifications to both the exclusion criteria and the definition of the outcome window. A stricter exclusion strategy was applied in which participants with any muscle disorder diagnosis prior to statin initiation were removed, regardless of timing of the diagnosis. In addition, the definition of SAMS was varied by applying alternative risk windows following statin initiation. Outcomes occurring within 90 days and 180 days were examined alongside the main analysis window of 365 days. To further evaluate the effect of the lead SNP on phenotypic severity, we conducted additional sensitivity analyses using creatine kinase (CK)-based

definitions of SAMS in the All of Us cohort.²⁶ Participants with missing CK measurements, values in uninterpretable units, negative CK values, or extreme outliers ($> 100 \times$ upper limit of normal [ULN]) were excluded from this analysis. Controls were defined as participants with CK levels below $4 \times$ ULN. Two thresholds were applied to define cases: CK $> 4 \times$ ULN and CK $> 10 \times$ ULN. The association between the lead SNP and each CK-defined SAMS phenotype was evaluated using the logistic regression analysis.

Gene–statin interaction analysis

To examine whether the association between the lead SNP and SAMS varied according to statin exposure, we performed gene–statin interaction analyses in the All of Us cohort. In addition to the statin-user cohort described above, a comparison cohort of statin non-users was assembled, consisting of White participants aged 40 years or older with no recorded prescriptions for statins or CoQ10 supplements.

Within the statin non-user cohort, individuals without any diagnosis of muscle disorders or related descendant concepts were classified as controls, whereas those with muscle disorder diagnoses were classified as cases. Interaction effects were evaluated on both the additive and multiplicative scales. Additive interaction was quantified using the relative excess risk due to interaction (RERI) and the attributable proportion (AP), while multiplicative interaction was assessed using regression models including a gene–statin interaction term.

Gene–*SLCO1B1* interaction analysis

To assess the potential synergistic effect of the lead SNP with the *SLCO1B1* rs4149056 (c.521 T>C)—the most established pharmacogenomic predictor of SAMS²⁷—we performed three complementary analyses in the All of Us cohort. First, we evaluated the independent association of *SLCO1B1* rs4149056 with SAMS risk using logistic regression adjusted for age, sex, and the first ten principal components. Second, to determine whether the effect of the lead SNP was independent of *SLCO1B1* genotype status, we performed stratified analyses based on a dominant genetic model of rs4149056. Third, we formally tested the interaction between the lead SNP and *SLCO1B1* rs4149056 on both the multiplicative and additive scales using the same approach described above.

Mendelian randomization analysis

Since COQ7 levels served as a proxy for CoQ10, a two-sample Mendelian randomization (MR) analysis was performed to assess the causal relationship between COQ7 and CoQ10 levels using the Wald ratio method. We selected the identified lead SNP as an instrumental variable and used the GWAS results for COQ7 levels in the UK Biobank as the exposure. For the outcome, we obtained data from Degenhardt *et al.*'s GWAS study on CoQ10 levels.²⁸

Functional annotation and mapping

To investigate the potential functional effects of the lead SNP, we performed functional mapping using the Open Targets Platform.²⁹ We utilized fine-mapping data, including 95% credible sets, and prioritized expression quantitative trait loci (eQTL) and splicing quantitative trait loci (sQTL) data to evaluate the association between the lead SNP and gene expression across various tissues, with a primary focus on skeletal muscle.

Polygenic risk score (PRS) analysis

Because GWAS data on circulating CoQ10 levels in statin users were not available, we adopted an alternative strategy leveraging existing GWAS datasets that identified genetic determinants of CoQ10 levels independent of statin exposure. Although these analyses were not conducted specifically in statin-treated populations, they provided a valuable

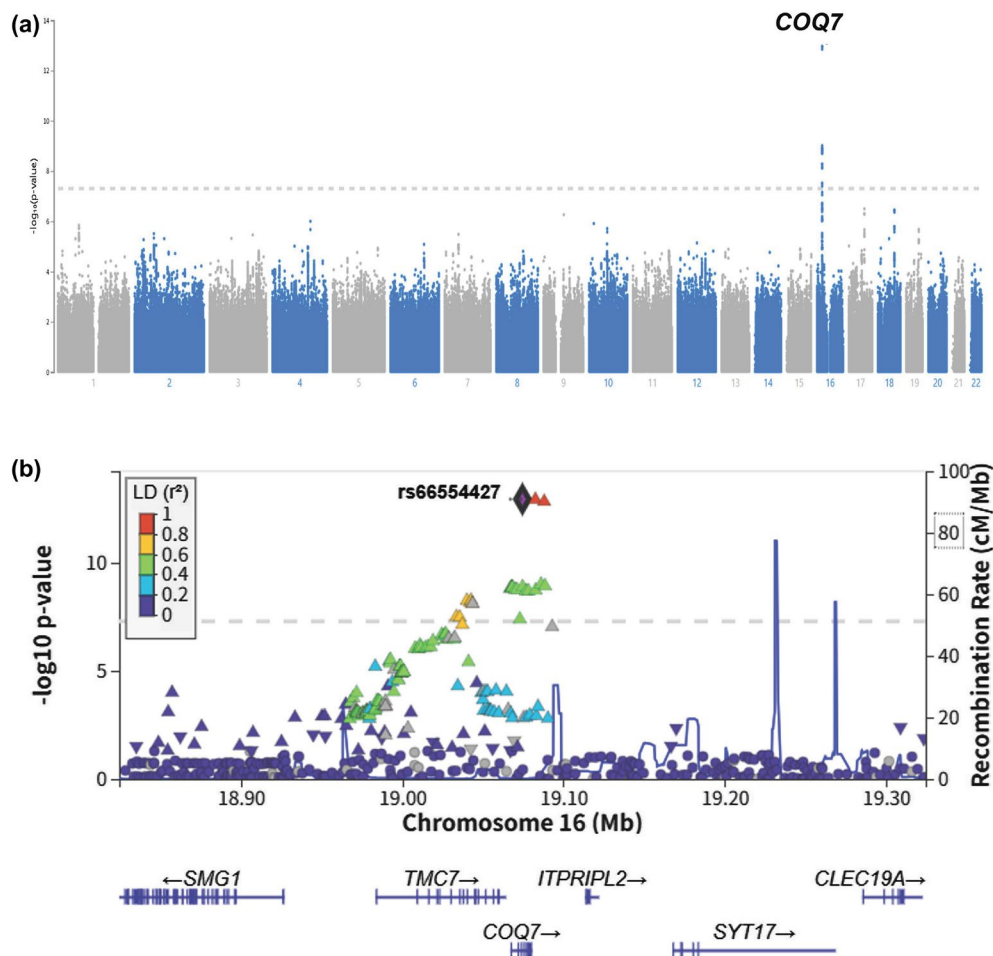


Figure 1 Genome-wide association analysis of COQ7 protein levels in the UK Biobank COQ7 cohort. (a) Manhattan plot showing genome-wide association results. The dashed line indicates genome-wide significance ($P=5 \times 10^{-8}$). (b) Regional association plot for the chromosome 16 locus. SNPs are colored by linkage disequilibrium (r^2) with the lead variant rs66554427.

opportunity to examine whether genetically determined variation in CoQ10 levels is associated with SAMS.

Accordingly, we performed PRS analyses using lead SNPs associated with circulating CoQ10 levels at a significance threshold of $P < 1 \times 10^{-5}$ from GWAS data by Degenhardt *et al.*, derived from the PoPGen and FoCus cohorts.²⁸ We calculated PRS for each individual by summing the number of effect alleles weighted by the corresponding effect sizes. Participants were ranked by PRS and categorized into three groups: lowest quintile (Q1), the middle quintiles (Q2–Q4), and the highest quintile (Q5). Differences in SAMS risk across PRS groups were evaluated using logistic regression, adjusting for age, sex, and the first ten principal components, with Q5 as the reference group. P for trend was calculated using PRS groups as an ordinal variable (Q1, Q2–Q4, Q5) or PRS as a continuous variable.

Statistical analyses

Group differences in categorical variables were evaluated using the chi-squared test or Fisher's exact test, while continuous variables were compared using independent-samples t -tests. Continuous variables are presented as mean values with corresponding standard deviations. Statistical significance was defined using a two-sided p -value threshold of 0.05. Post hoc power analyses were conducted using the genpwr package in R. All analyses were carried out using R (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

GWAS of COQ7 levels in the UK Biobank COQ7 cohort

A total of 7,048 statin-treated participants from the UK Biobank were included in the GWAS of COQ7 levels (Figure S2). A Manhattan plot and regional association plot are shown in Figure 1, highlighting a prominent association signal on chromosome 16. The lead SNP, rs66554427 (c.367 + 498A>C), emerged as the most significant variant within the *COQ7* gene. The A allele of *COQ7* rs66554427 was associated with lower COQ7 levels ($\beta = -0.13$; SE = 0.018; $P = 1.1 \times 10^{-13}$). The QQ plot demonstrated minimal genomic inflation ($\lambda = 1.012$) (Figure S2). Detailed baseline characteristics are shown in Table S3.

Association of rs66554427 with SAMS

To evaluate the clinical relevance of this lead SNP, we examined the association between rs66554427 and SAMS in the All of Us cohort. A total of 1,390 SAMS cases and 37,052 controls were included in the analysis (Figure S3). Atorvastatin was the most prescribed statin (48.4%), followed by simvastatin (25.8%) (Table S4). The rs66554427 A allele was significantly associated with an increased risk of SAMS in both models, corresponding to a 26% higher risk

Table 1 Association between COQ7 variant rs66554427 and SAMS risk in the All of Us and UK Biobank SAMS cohorts

Genotype	SAMS	Control	Total	Model 1		Model 2	
				OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
All of Us cohort				1.26 (1.16–1.37)	9.23×10 ^{−8}	1.27 (1.16–1.39)	5.16×10 ^{−8}
rs66554427 CC	95 (6.8)	3896 (10.5)	3991 (10.4)				
rs66554427 AC	576 (41.4)	15,969 (43.1)	16,545 (43.0)				
rs66554427 AA	719 (51.7)	17,187 (46.4)	17,906 (46.6)				
UK Biobank SAMS cohort ^a				1.22 (1.05–1.42)	9.01×10 ^{−3}	1.23 (1.06–1.43)	6.89×10 ^{−3}
rs66554427 CC	40 (9.6)	9640 (10.8)	9680 (10.8)				
rs66554427 AC	158 (37.8)	39,179 (43.8)	39,337 (43.8)				
rs66554427 AA	220 (52.6)	40,550 (45.4)	40,770 (45.4)				

Note: Model 1 was adjusted for age, sex, and the first 10 principal components, while Model 2 additionally included baseline characteristics. OR and 95% CI were calculated using logistic regression with an additive genetic model, with the A allele as the effect allele. Abbreviations: CI, confidence interval; COQ7, coenzyme Q7; OR, odds ratio; SAMS, statin-associated muscle symptoms. ^aParticipants were drawn from the UK Biobank excluding those included in the COQ7 protein genome-wide association study.

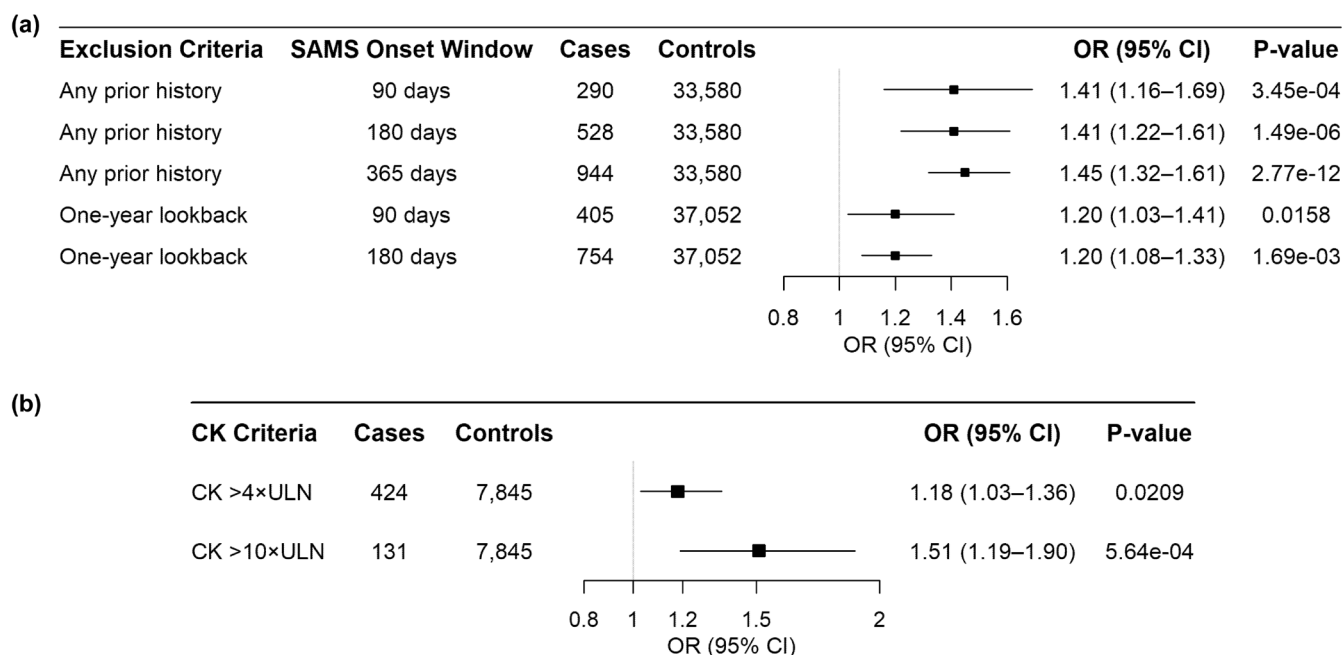


Figure 2 Sensitivity analyses for the association between the COQ7 rs66554427 and SAMS risk in the All of Us cohort. (a) Association across alternative exclusion criteria and outcome definition windows. (b) Association using creatine kinase (CK)-based SAMS definitions (CK >4×ULN and CK >10×ULN). Logistic regression with an additive model was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs), adjusted for age, sex, and 10 principal components, with A as the effect allele.

per allele in Model 1 (Odds ratio [OR] = 1.26; 95% confidence interval [CI]: 1.16–1.37; $P = 9.23 \times 10^{-8}$) and a 27% higher risk per allele in Model 2 (OR = 1.27; 95% CI: 1.16–1.39; $P = 5.16 \times 10^{-8}$) (Table 1). The incidence rates of SAMs among patients with the CC, AC, and AA genotypes were 2.4, 3.5, and 4.0%, respectively.

To evaluate the potential confounding role of statin type, we examined the distribution of prescribed statins across SAMS cases and controls. While lipophilic statins were more frequently used in both groups, the proportion of hydrophilic statin users was significantly higher in the SAMS group compared with the control group (22.8% vs. 17.8%). Hydrophilic statin use was associated with significantly higher risk of SAMS

compared with lipophilic statin use (OR = 1.30; 95% CI: 1.14–1.48; $P = 6.93 \times 10^{-5}$). Furthermore, the association between rs66554427 and SAMS risk remained significant in both lipophilic and hydrophilic statin users (Table S5).

Replication analyses of rs66554427–SAMS association

We further validated the association using the independent UK Biobank SAMS cohort (418 SAMS cases; 89,369 controls) (Figure S4). Baseline characteristics of this replication cohort are presented in Table S6. The rs66554427 A allele was significantly associated with an increased risk of SAMS in Model 1 (OR = 1.22; 95% CI: 1.05–1.42; $P = 9.01 \times 10^{-3}$) and Model 2 (OR = 1.23;

Table 2 Interaction analyses of *COQ7* rs66554427 with statin use and *SLCO1B1* rs4149056 on SAMS risk in the All of Us

	Statin use * rs66554427 ^a	P
Multiplicative scale	1.23 (1.12–1.35)	<0.001
RERI	0.15 (0.09–0.21)	<0.001
AP	0.18 (0.10–0.27)	<0.001
	<i>SLCO1B1</i> rs4149056 * rs66554427 ^b	P
Multiplicative scale	1.33 (1.13–1.56)	<0.001
RERI	0.26 (0.16–0.36)	<0.001
AP	0.22 (0.11–0.34)	<0.001

Abbreviations: AP, attributable proportion; RERI, relative excess risk due to interaction; SAMS, statin-associated muscle symptoms. ^aAnalyses were performed in both statin users and non-users. ^bAnalyses were performed in statin users only.

95% CI: 1.06–1.43; $P = 6.89 \times 10^{-3}$) (Table 1). These findings are directionally consistent with and of similar magnitude to those observed in the All of Us cohort.

Sensitivity analyses

We conducted sensitivity analyses using alternative exclusion criteria and outcome definition windows to test the stability of the observed association (Figure 2a). The rs66554427 A allele consistently demonstrated an elevated risk of SAMS across all sensitivity analyses. When participants with any prior muscle-related conditions were excluded, carriers of the A allele showed a significantly higher risk of SAMS across the 90-day, 180-day, and 365-day onset windows, with ORs ranging from 1.41 to 1.45 ($P < 0.001$). Similar associations were observed when a one-year lookback period was applied, with the A allele remaining associated with increased SAMS risk in both the 90-day and 180-day onset windows (OR = 1.20 for both 90-day and 180-day windows; $P < 0.05$).

We further evaluated the association between *COQ7* rs66554427 and CK-defined SAMS (Figure 2b). A total of 8269 participants were eligible for this analysis, of whom 131 (1.6%) were classified as severe SAMS cases (CK $> 10 \times$ ULN). Carriers of the rs66554427 A allele showed a substantially higher risk of severe SAMS (OR = 1.50; 95% CI: 1.19–1.90; $P = 5.64 \times 10^{-4}$).

Statin–genotype interaction effects of rs66554427

We identified significant multiplicative and additive interactions between statin use and the rs66554427 A allele (Table 2). For the multiplicative interaction, a positive interaction was observed (multiplicative scale = 1.23; 95% CI: 1.12–1.35; $P < 0.001$), with a combined effect exceeding the product of their individual effects. On the additive scale, a significant interaction was detected, with a relative excess risk due to interaction (RERI) of 0.15 (95% CI: 0.09–0.21; $P < 0.001$), with an estimated 18% of muscle symptoms among statin users carrying the rs66554427 A allele attributable to the interaction (95% CI: 0.10–0.27; $P < 0.001$).

SLCO1B1–genotype interaction effects of rs66554427

We examined whether the effect of *COQ7* rs66554427 on SAMS risk was independent of and potentially synergistic with *SLCO1B1* rs4149056 genotype in the All of Us cohort. The *SLCO1B1* rs4149056 C allele was significantly associated with SAMS risk (OR = 1.19; 95% CI: 1.08–1.31; $P = 6.09 \times 10^{-4}$) (Table S7). Stratified analysis revealed that the association between *COQ7* rs66554427 and SAMS remained significant in both the *SLCO1B1* rs4149056 TT group (OR = 1.17; 95% CI: 1.06–1.30; $P = 2.37 \times 10^{-3}$) and the CT/CC group (OR = 1.46; 95% CI: 1.25–1.70; $P = 1.60 \times 10^{-6}$) (Table S8).

We next evaluated their interaction on both multiplicative and additive scales. On the multiplicative scale, the interaction term was statistically significant (OR = 1.33; 95% CI: 1.13–1.56; $P < 0.001$). On the additive scale, a significant positive interaction was detected, with a RERI of 0.26 (95% CI: 0.16–0.36; $P < 0.001$) and an attributable proportion (AP) of 0.22 (95% CI: 0.11–0.34; $P < 0.001$), indicating that approximately 22% of the SAMS risk in individuals carrying both risk alleles was attributable to their synergistic effect (Table 2).

MR analysis of *COQ7* and CoQ10 levels

We conducted the MR analysis using *COQ7* rs66554427 as a single instrumental variable. Genetically predicted *COQ7* levels were positively associated with CoQ10 levels ($\beta = 0.12$; SE = 0.06; $P = 0.035$).

Functional mapping of rs66554427

Functional annotation via Open Targets Platform revealed that a 95% credible set including rs66554427 is a significant eQTL and sQTL for the *COQ7* gene. Notably, this association was most pronounced in skeletal muscle tissue, where the variant within the credible set was significantly associated with *COQ7* expression ($P = 2.73 \times 10^{-19}$) and alternative splicing ($P = 1.13 \times 10^{-8}$).

Associations of CoQ10-related genetic polymorphisms and PRS with SAMS

To further evaluate whether genetic determinants of CoQ10 levels were associated with SAMS beyond *COQ7* levels, we selected a total of 25 SNPs from the previous GWAS study of CoQ10 levels ($P < 1 \times 10^{-5}$), and rs9952641 and rs933585 were genome-wide significant among them ($P < 5 \times 10^{-8}$). We evaluated the relationship between SAMS and each of the 24 SNPs because one SNP, rs184812087, was not genotyped (Table S9). Of the two genome-wide significant SNPs, the most strongly significant SNP, rs9952641, was associated with a higher risk of SAMS per G allele (OR: 1.30; 95% CI: 1.13–1.50; $P < 0.001$).

Furthermore, we constructed the PRS using 24 SNPs associated with CoQ10 levels (Figure 3). Participants in the lowest PRS quintile (Q1) had a 32% higher risk of SAMS compared to those in the highest quintile (OR: 1.32; 95% CI: 1.11–1.57), while the middle quintiles (Q2–Q4) showed a 22% increased risk (OR: 1.22, 95% CI: 1.05–1.41). This inverse relationship between genetically predicted CoQ10 levels and SAMS risk was statistically significant, with p for trend of 0.001 (ordinal) and 5.17×10^{-5} (continuous).

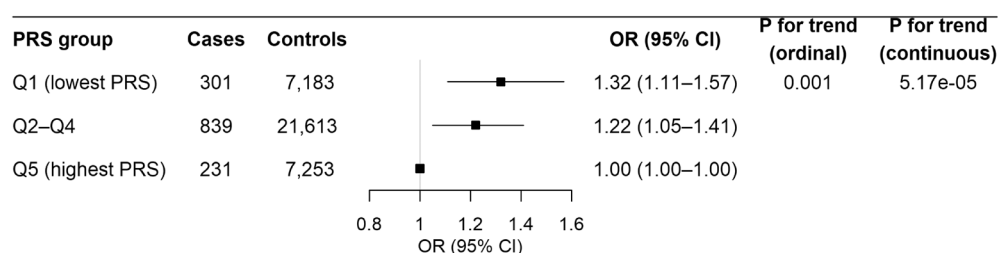


Figure 3 Association between COQ10-level polygenic risk score (PRS) and SAMS. Participants were grouped by PRS: Q1 (lowest quintile), Q2–Q4 (middle quintiles), and Q5 (highest quintile, reference). Logistic regression was adjusted for age, sex, and 10 principal components. P-values for trend were calculated using PRS groups as an ordinal variable (Q1, Q2–Q4, Q5) or PRS as a continuous variable.

DISCUSSION

This study provides genetic and proteomic evidence linking the CoQ10 biosynthesis pathway to SAMS using COQ7 protein levels as a proxy biomarker. We identified rs66554427 as the lead SNP related to COQ7 protein levels in statin users from the UK Biobank. This SNP was associated with a higher SAMS risk per A allele in the independent cohort of statin users from the All of Us and UK Biobank, and these findings were consistent across sensitivity analyses. Notably, we observed significant additive and multiplicative interactions between statin use and rs66554427, indicating a statin-specific genetic effect on muscle symptoms.

COQ7 is a critical enzyme in the CoQ10 biosynthetic pathway, catalyzing one of the final and indispensable steps required for the production of CoQ10^{30,31}. Because this step lies near the end of the pathway, COQ7 activity effectively constrains the cellular capacity to synthesize CoQ10. Experimental studies have reported that COQ7 protein expression was responsive to cellular stress, and its upregulation subsequently enhanced CoQ10 production.^{32,33} Also, our MR analysis demonstrated a positive association between genetically predicted COQ7 levels and CoQ10 levels. Accordingly, COQ7 protein levels may serve as a functional indicator for CoQ10 biosynthetic capacity within cells.

Impairment of COQ7 function disrupts CoQ10 biosynthesis, leading to mitochondrial dysfunction, with prominent effects in energy-demanding tissues such as skeletal muscle.³⁴ In human studies, genetic deficiency of COQ7 results in reduced CoQ10 biosynthesis.^{35–37} Freyer *et al.* reported that a patient with a pathogenic mutation in COQ7 has experienced muscle-related manifestations, including hypotonia and reduced muscle mass, due to primary CoQ10 deficiency.³⁵ These findings support a link between COQ7 dysfunction, impaired CoQ10 biosynthesis, and muscle pathology. Our findings were further strengthened by functional mapping, which shows that the credible set containing rs66554427 is a highly significant eQTL and sQTL in skeletal muscle, providing a robust biological basis for its association with SAMS. However, recent evidence also suggested that COQ7 dysfunction may lead to neurogenic alterations, such as muscle weakness and atrophy.³⁴ This highlights the need for a broader perspective on the neuromuscular mechanisms underlying these associations in future studies. As SAMS have been widely hypothesized to arise from impaired CoQ10 biosynthesis,³⁸ evidence linking COQ7 dysfunction to muscle pathology provides a biological rationale for COQ7 as a contributor to SAMS susceptibility.^{34–37} Consistent with this interpretation, our interaction analyses further support

a statin-specific genetic effect of COQ7 rs66554427. On the additive scale, the joint effect of statin exposure and the rs66554427 A allele exceeded the sum of their individual effects, providing a biological context for how genetic variation in COQ7 may modify statin-related muscle risk. A significant multiplicative interaction was also observed, further reinforcing the effect modification by statin use.

Expanding beyond the statin-specific effect of COQ7 rs66554427, our study revealed a significant synergistic interaction between rs66554427 and SLC01B1 rs4149056. While SLC01B1 rs4149056 is a well-established pharmacokinetic determinant that increases systemic statin exposure,^{39,40} COQ7 rs66554427 appears to operate through a pharmacodynamic mechanism by impairing CoQ10 biosynthesis in muscle cells. Notably, the effect of COQ7 rs66554427 on SAMS risk (OR = 1.26) was comparable in magnitude to that of SLC01B1 rs4149056 (OR = 1.19) in our cohort. Furthermore, with an AP of 22.4%, these findings underscore the importance of considering both pharmacokinetic and pharmacodynamic genetic factors in SAMS risk stratification.

The clinical significance of COQ7 rs66554427 was further underscored by a clear severity-dependent gradient in our results. Specifically, we observed an amplified effect of COQ7 rs66554427 on severe SAMS (OR = 1.50 for CK > 10 × ULN) compared with the broader phenotype, and a moderate effect at CK > 4 × ULN (OR = 1.18), suggesting a severity-dependent relationship between COQ7 rs66554427 and myotoxicity severity. This trend suggested that COQ7 variation is intrinsically linked to the biological processes driving objective muscle damage. Consequently, COQ7 rs66554427 serves as a clinically actionable variant particularly relevant for identifying patients at high risk of severe myotoxicity. In addition, we extended our analyses to evaluate whether SNPs previously reported to be associated with CoQ10 levels were also related to SAMS.²⁸ Because those SNPs were identified in participants regardless of statin use, we validated them in the All of Us cohort, which consisted solely of statin users. This analysis showed that rs99526414, the strongest genetic variant related to CoQ10 levels, was also associated with SAMS risk. When combined into a PRS, CoQ10-associated variants showed a clearer association with SAMS risk, with higher risk observed among individuals genetically predisposed to lower CoQ10 levels.

Although we identified the relationship between SAMS and CoQ10-related genetic polymorphisms, there were some limitations. First, as this study was retrospective, future prospective studies are needed to validate these findings. Second, CoQ10 levels

were not directly measured in the UK Biobank, so we relied on COQ7 protein levels as a proxy. Although COQ7 expression is a critical determinant of CoQ10 biosynthesis, it is important to acknowledge that the expression of other genes also modulates CoQ10 production independent of COQ7 expression. Given the multifactorial nature of SAMS, our findings should be interpreted carefully, as rs66554427 likely represents one of several SNPs contributing to the overall SAMS risk. Third, our MR analysis relied on a single instrumental variable, and the use of plasma COQ7 and CoQ10 levels may not fully reflect intramyocellular status where SAMS pathology is localized. Nevertheless, the instrumental variant showed a strong genome-wide association with COQ7 levels and was located within the COQ7 gene, supporting the biological relevance of the MR framework.⁴¹ Fourth, the analyses were restricted to White individuals due to the limited sample sizes of other ethnic groups. Therefore, the generalizability of these findings to other ethnic populations remains uncertain. Additionally, the analysis of statin lipophilicity as a potential effect modifier was exploratory, and residual confounding by statin type, dose, and duration cannot be fully excluded. Lastly, rs66554427 was associated with decreased COQ7 expression levels, but its impact on molecular structure remains unclear. Therefore, further investigations on protein structures are needed to demonstrate the exact mechanism.

Despite these limitations, this is the first study to integrate both genomic and proteomic data to investigate the association between SAMS and CoQ10-related genetic polymorphisms. This study has several notable strengths. First, we conducted the GWAS of COQ7 protein levels in statin-treated participants from the UK Biobank and subsequently validated the lead SNP in an independent cohort of statin users from the All of Us Research Program, with further replication in an independent UK Biobank SAMS cohort, strengthening the evidence linking COQ7-related genetic variation to SAMS. Second, the observed associations remained consistent across multiple sensitivity analyses, supporting the stability of the results. Third, interaction analyses demonstrated statin-specific genetic effects. Because drug–gene interactions are central to understanding interindividual variability in drug response, elucidating the interaction between statins and COQ7 genetic polymorphism may help explain differential susceptibility to SAMS. Furthermore, the newly identified synergistic interaction between COQ7 rs66554427 and SLC01B1 rs4149056 underscored the complementarity of pharmacokinetic and pharmacodynamic pharmacogenomic predictors for SAMS. Finally, by incorporating previously reported CoQ10-related SNPs and constructing a PRS, we examined the contribution of CoQ10 biosynthesis to SAMS from multiple genetic perspectives. Together, these results offered genetic insights that could help guide future approaches to individualized statin therapy and risk assessment for SAMS.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology and Therapeutics* website (www.cpt-journal.com).

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AUTHOR CONTRIBUTIONS

D.H.L., Y.-A.P., Y.S., J.-M.H., K.H.C., M.G.K., and H.S.G. wrote the manuscript; D.H.L., Y.-A.P., Y.S., and H.S.G. designed the research; D.H.L., Y.-A.P., Y.S., and H.S.G. performed the research; D.H.L., Y.-A.P., and Y.S. analyzed the data.

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CONFLICTS OF INTEREST

The authors declared no competing interests for this work.

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