Supplemental Data

Table S1, related to Table 1. Characteristics of propensity-matched cases and controls

Characteristic	All (n = 715)	Matched controls (n = 94; 13%)	Matched SIM cases (n = 94; 13%)	[a]p-value	Unmatched (n = 527; 74%)
Male gender	374 (52%)	42 (46%)	48 (51%)	0.460	284 (54%)
Age (years)	58 (11)	60 (15)	57 (15)	0.332	58 (15)
[b]Atorvastatin dose equivalents (mg)	20 (10)	10 (10)	10 (10)	0.778	20 (30)
Atorvastatin	392 (55%)	64 (68%)	65 (69%)	1.000	263 (50%)
Simvastatin	143 (20%)	11 (12%)	11 (12%)		121 (23%)
Rosuvastatin	83 (12%)	5 (5%)	5 (5%)		73 (14%)
Pravastatin	52 (7%)	7 (7%)	7 (7%)		38 (7%)
Lovastatin	30 (4%)	5 (5%)	4 (4%)		21 (4%)
Other statin	15 (2%)	2 (2%)	2 (2%)		11 (2%)
Coronary artery disease	137 (19%)	8 (9%)	11 (12%)	0.468	118 (22%)
Myocardial infarction	97 (14%)	9 (10%)	13 (14%)	0.364	76 (14%)
Diabetes	109 (15%)	12 (13%)	16 (17%)	0.413	81 (15%)
Hypertension	338 (47%)	29 (31%)	29 (31%)	1.000	279 (53%)
Smoker	245 (34%)	18 (19%)	20 (21%)	0.716	206 (39%)
Family history of heart disease	345 (48%)	22 (23%)	22 (23%)	1.000	301 (57%)
Family history of muscle disease	42 (6%)	3 (3%)	5 (5%)	0.721	34 (6%)
Metabolic muscle disease	19 (3%)	0 (0%)	2 (2%)	0.497	17 (3%)
Inflammatory muscle disease	55 (8%)	1 (1%)	1 (1%)	1.000	53 (10%)
Hypothyroidism	91 (13%)	7 (7%)	4 (4%)	0.351	80 (15%)
Heavy alcohol consumption	17 (2%)	0 (0%)	3 (3%)	0.246	14 (3%)
Obesity	122 (17%)	5 (5%)	9 (10%)	0.267	108 (20%)
Liver disease	17 (2%)	0 (0%)	4 (4%)	0.121	13 (2%)
Kidney disease	14 (2%)	1 (1%)	1 (1%)	1.000	12 (2%)
[c]Participants taking ≥ 1 co-medication(s) that could independently cause myopathy	34 (5%)	1 (1%)	1 (1%)	1.000	32 (6%)
[c]Participants taking ≥ 1 co-medication(s) that could treat SIM	260 (36%)	16 (17%)	15 (16%)	0.844	229 (43%)

[c]Participants taking ≥ 1 co-medication(s) that could increase statin exposure	77 (11%)	10 (11%)	10 (11%)	1.000	57 (11%)
[c]Participants taking ≥ 1 co-medication(s) that could decrease statin exposure	7 (1%)	2 (2%)	0 (0%)	0.497	5 (1%)

[a]Continuous variables are presented as median (interquartile range) and compared with the Kruskal-Wallis test. Categorical variables are presented as counts (%) and compared with the chi-square or Fisher's exact test where necessary. P-values are for the comparison of matched controls vs matched SIM cases.

[b]Atorvastatin dose equivalents were calculated as follows: fluvastatin dose/8, lovastatin dose/4, pravastatin dose/4, rosuvastatin dose*4, and simvastatin dose/2 (Stone et al., 2014). Dose equivalents were missing for cerivastatin (n = 6) and pitavastatin (n = 1).

[c]Categories of potentially confounding co-medications are defined in the Supplemental Experimental Procedures.

GATM = gene encoding glycine amidinotransferase; SIM = statin-induced myopathy

Table S2, related to Figure 1. Summary of studies of *GATM* variants and statin-induced myopathy

Reference	SNP	n cases	n controls	MAF cases	MAF controls	Odds ratio (95% CI)	p-value
[a]Mangravite et al (2013) Marshfield	rs9806699	72	220	0.21	0.30	0.61 (0.39-0.95)	0.03
	rs1719247	72	220	0.19	0.29	0.59 (0.36-0.93)	0.02
	rs1346268	72	220	0.21	0.29	0.66 (0.41-1.02)	0.06
[a]Mangravite et al (2013) SEARCH	rs1719247	100	4,021	0.17	0.25	0.61 (0.42-0.88)	0.01
	rs1346268	100	4,029	0.18	0.26	0.62 (0.43-0.90)	0.01
Carr et al (2014)	rs9806699	150	587	0.28	0.30	0.94 (n/a)	0.68
[a]Floyd et al (2014)	rs9806699	76	643	0.24	0.28	0.84 (0.52-1.36)	0.49
	rs1719247	76	643	0.24	0.25	1.00 (0.64-1.57)	0.99
	rs1346268	76	643	0.24	0.27	0.88 (0.52-1.36)	0.57
[b]Luzum et al (2015)	rs9806699	306	80	0.25	0.28	0.90 (0.60-1.34)	0.60

CI = confidence interval; *GATM* = gene encoding glycine amidinotransferase; MAF = minor allele frequency; SEARCH = Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SNP = single nucleotide polymorphism

[a]Excluding fibrate users

[b]Excluding patients taking any potentially interacting co-medications, as defined in the Supplemental Experimental Procedures

Supplemental Experimental Procedures

Data collection and classification, related to Experimental Procedures: Participants

The following data was collected from the participants via a standardized questionnaire: demographics, type of statin, statin dose, the presence or absence of 12 specific conditions/events in their past medical history (coronary artery disease, myocardial infarction, diabetes, hypertension, smoking, metabolic muscle disease, inflammatory muscle disease, hypothyroidism, heavy alcohol consumption, obesity, liver disease, and kidney disease), family history of heart or muscle disease, and co-medications. Co-medications were categorized into four groups: 1) co-medications that can independently cause myopathy (*e.g.*, systemic corticosteroids and hydroxy/chloroquine); 2) co-medications that can treat SIM (*e.g.*, analgesics, skeletal muscle relaxants, and coenzyme Q10); 3) co-medications that can increase statin exposure (*e.g.* cytochrome P450 [CYP] 3A4 inhibitors in the participants treated with a CYP3A4-metabolized statin); and 4) co-medications that can decrease statin exposure (*e.g.* CYP3A4 inducers in the participants treated with a CYP3A4-metabolized statin).