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Common genetic variation in six lipid- and statin-related genes, statin use and risk of incident nonfatal myocardial infarction and stroke

Lucia A. Hindorff, PhD, MPH, **Rozenn N. Lemaitre, PhD, MPH**, **Nicholas L. Smith, PhD, MS**, **Joshua C. Bis, PhD, MS**, **Kristin D. Marciante, PhD**, **Kenneth M. Rice, PhD**, **Thomas Lumley, PhD**, **Daniel A. Enquobahrie, MD, PhD**, **Guo Li, MS**, **Susan R. Heckbert, MD, PhD**, and **Bruce M. Psaty, MD, PhD.**
From the Cardiovascular Health Research Unit, Department of Medicine (LAH, RNL, NLS, JCB, KDM, KMR, TL, DAE, GL, SRH, BMP), and the Departments of Epidemiology (LAH, NLS, SRH, BMP), Biostatistics (KMR, TL, GL), and Health Services (BMP), University of Washington, Seattle, WA and the Center for Health Studies, Group Health, Seattle, WA (BMP).

Abstract

Objective—Genetic polymorphisms are associated with lipid-lowering response to statins, but generalizeability to disease endpoints is unclear. The association between 82 common single nucleotide polymorphisms (SNPs) in 6 lipid- or statin-related genes (*ABCB1, CETP, HMGCR, LDLR, LIPC, NOS3*) and incident nonfatal myocardial infarction (MI) and ischemic stroke was analyzed according to current statin use and overall in a population-based case-control study (856 MI, 368 stroke, 2686 controls).

Methods—Common SNPs were chosen from resequencing data using pairwise linkage disequilibrium. Gene-level analyses (testing global association within a gene) and SNP-level analyses (comparing the number of observed versus expected associations across all genes) were performed using logistic regression, setting nominal statistical significance at $p<0.05$.

Results—No gene-level interactions with statin use on MI or stroke were identified. Across all genes, 2 SNP-statin interactions on MI were observed (1 *ABCB1*, 1 *LIPC*) and 5 interactions on stroke (1 *CETP*, 4 *LIPC*). The strongest SNP-statin interaction was for synonymous *CETP* SNP rs5883 on stroke ($p = 0.008$). Gene-level associations were present for *LIPC* and MI ($p = 0.026$), but not other genes or outcomes. SNP-level associations included 3 SNPs with MI (1 *LDLR*, 2 *LIPC*) and 2 SNPs with stroke (1 *CETP*, 1 *LDLR*). The number of observed SNP associations was no greater than expected by chance.

Conclusions—Several potential novel associations or interactions of SNPs in *ABCB1*, *CETP*, *LDLR* and *LIPC* with MI and stroke were identified; however, our results should be regarded as hypothesis-generating until corroborated by other studies.

Keywords

Pharmacogenetics; epidemiology; myocardial infarction; stroke; statins; HMG-CoA

Corresponding author: Lucia A. Hindorff, PhD, MPH. National Human Genome Research Institute, National Institutes of Health, 5635 Fishers Lane, Suite 4076, Bethesda, MD, 20892-9305; hindorffl@mail.nih.gov.

Introduction

Though clinical use of statins has consistently reduced risks of coronary heart disease and stroke, the degree of interindividual variability in lipid-lowering response to statins is marked and may differ within subgroups[1–4]. These differences are consistent with the presence of genetic and/or environmental influences on risk. Recent pharmacogenetic studies identified genetic variants in *HMGCR* and *ABCB1* that were associated with degree of cholesterol lowering in response to statins[5,6], and other candidate genes have similarly been proposed[3, 4]. Because primary prevention of cardiovascular disease is a fundamental aim of statin treatment, whether existing pharmacogenetic studies of intermediate endpoints generalize to disease endpoints is of clinical and public health interest. However, data on whether genes related to lipid metabolism modify the association between statin use and clinical coronary or cerebrovascular events are limited.

We hypothesized that the association between genetic variants in known lipid- and statin-related genes and cardiovascular events differs in subgroups defined by statin use. Because several of these genes have been implicated in atherosclerosis or coronary heart disease independently of statin use, an additional aim of this study focused on associations between each gene and MI or stroke in the overall population. Common variants across the following genes were of interest: *ABCB1*, a drug transporter implicated in statin metabolism; *CETP*, *LIPC* and *LDLR*, genes involved in lipid metabolism; *HMGCR*, the target protein of statins; and *NOS3*, a key gene involved in maintaining the endothelium, which in turn mediates several effects of statins. The aims of this study were to determine whether common genetic variants in lipid-or statin-related genes were associated with cardiovascular events, and whether the association between genetic variants and disease differed according to current statin use in a large population-based case-control study of incident nonfatal myocardial infarction (MI) and ischemic stroke.

Methods

Study setting and participants

Participants in this study were part of ongoing case-control studies of myocardial infarction (MI) and stroke at Group Health (GH), a large health care delivery system based in western Washington State. Cases were either men or women with pharmacologically treated hypertension or peri- or postmenopausal women who had an incident nonfatal MI or ischemic stroke during 1995–2002 and were 30 to 79 years old [7, 8]. A common control group of randomly selected members of GH was frequency matched to MI cases on the basis of age (by decade), sex, and treated hypertension status. Participants were free of prior MI or stroke. We excluded patients with fewer than four visits before their index dates to increase the likelihood that information would be available in the medical record on important clinical characteristics. We excluded cases whose MI or stroke was a complication of a procedure or surgery. The GH institutional review board approved the study, and all participants gave written informed consent.

Data collection and definitions

All participants were assigned an index date. For cases, the index date was the date of the MI or stroke; for controls, the index date was a computer-generated random date within the calendar year for which they were selected. Data on characteristics prior to each participant's index date were collected from the GH outpatient record, and a venous blood sample, from which DNA was extracted, was collected in-person. A woman was classified as postmenopausal if her medical record noted a cessation of menses, symptoms of menopause among women who had a hysterectomy, or, in the absence of information on symptoms and

menses, if she was age 55 or older at the index date. Participants with a physician diagnosis of hypertension using antihypertensive medications at the index date were considered treated hypertensives. History of cardiovascular disease (CVD) was defined as a record of angina, stroke, claudication, or vascular procedures, including coronary artery bypass grafting, angioplasty, carotid endarterectomy, or peripheral vascular procedure. Self-described race was classified into three categories: white/Caucasian, black/African-American, or other.

Data on medication use were obtained from the GH computerized pharmacy database, which includes a record of all prescriptions dispensed to GH enrollees since 1977. A participant was classified as a current statin user if enough medication was dispensed at the most recent statin prescription prior to the index date to last until the index date, assuming 80% compliance[9].

SNP selection, genotyping and haplotype inference

Single nucleotide polymorphisms (SNPs) in each gene were identified from resequencing data generated by SeattleSNPs (http://pga.gs.washington.edu/) and PARC (http://droog.gs.washington.edu/parc/; Supplemental Table 1.) We used the LDSelect algorithm to classify common SNPs (minor allele frequency ≥ 5%) into bins such that, within each bin, at least one SNP (the tagSNP) would be in linkage disequilibrium with all other SNPs at a LD threshold of $r^2 = 0.64$[10]. For *HMGCR*, *LDLR* and *NOS3*, SNP selection was optimized for both white and black individuals (http://droog.gs.washington.edu/parc/); for the other genes, selection was optimized for white individuals only. We also included the *HMGCR* 24558 SNP (rs17238540) on the basis of previous work (SNP 29 from Chasman, et al.[5]).

SNPs were genotyped using an Illumina GoldenGate custom panel. Of the 126 SNPs successfully genotyped on 3910 individuals, 742 genotype calls failed across all SNPs and all participants, yielding a call rate of 99.85%. SNPs were excluded if the minor allele frequency was less than 5% in the study sample or if the pairwise r^2 with another genotyped SNP was greater than 0.8. Out of the 82 remaining SNPs, all SNPs except for 7 were in Hardy-Weinberg equilibrium within white controls (Supplemental Table 1). Haplotypes were inferred using PHASE 2.0.

Statistical methods

Analyses were conducted using Intercooled STATA 8.0. All analyses adjusted for race and the study design variables of index year, age, sex, and hypertension status. Analyses of statin main effects or interactions additionally adjusted for history of CVD, diabetes, and hyperlipidemia, variables that confounded the statin associations with MI and stroke. Odds ratios (OR) and 95% confidence intervals (CI) for the association between each SNP and outcome were calculated using logistic regression, assuming a log-additive model. This model estimates the relative risk of the outcome comparing persons with one additional copy of the minor allele to persons with an additional copy of the major allele. Interactions were assessed by introducing a multiplicative term into multivariate models that included statin and SNP or haplotype main effects, and significance of all interaction terms in the model was assessed using a Wald test statistic.

The approach to evaluating the importance of genetic variation was two-fold. First, a global measure of association was used to evaluate variation within a gene. Second, a comparison of observed versus expected number of SNP associations characterized variation across all genes. For ease of reference, these approaches are described as “gene-level” and “SNP-level,” respectively. For the gene-level analyses, a Wald test of all haplotype terms assessed the global hypothesis that no haplotype had an association with the outcome that was significantly different from one. Haplotype estimates were derived from weighted logistic regression and robust standard errors, where weights correspond to the probability for each possible inferred

haplotype combination estimated by PHASE 2.0. The most common haplotype among controls was arbitrarily selected as the reference. No common haplotypes were observed for the *LIPC* gene and thus the Wald global hypothesis test was not possible. To evaluate significant findings from *LIPC* on a gene-wide context, the smallest observed test statistic among all SNPs was compared to a distribution of test statistics obtained through a parametric bootstrap test (n = 1000 iterations). Here, new datasets were generated via simulation from estimates obtained from models under the null hypothesis (either no main effects or no interactions). The p-values for *LIPC* are interpreted as the probability of the *LIPC* gene having a lowest p-value at least as extreme as the one we observed. In cases where the simulation analysis yielded a p-value < 0.05, we repeated the simulation using 10,000 iterations. The synergy index (SI), the ratio of the OR in current statin users to the OR in non- users, and its 95% confidence interval were used to summarize interactions in selected tables. For the SNP-level analyses, the number of observed significant results was compared to the expected number based on chance alone. For example, at $\alpha = 0.05$, out of 100 SNP associations, 5 would be expected by chance. This SNP-based analysis was repeated separately for each hypothesis (main effects or interactions) and each outcome. The association of genetic variants in CETP with MI and stroke have been reported separately[11]. Power calculations were performed using QUANTO (version 1.2.3).

Results

Characteristics of the case and control participants at index date are shown in Table 1. As expected, MI and stroke cases were more likely than controls to have a higher BMI, SBP, or cholesterol, or to have diabetes or a history of CVD. MI cases were more likely than controls to have hyperlipidemia and to use statins, but this was not true for stroke cases. The prevalence of statin use was 11.6% in MI cases, 7.9% in stroke cases, and 9.8% in controls. Current use of statins was associated with a decreased risk of both MI (OR 0.62, 95% CI 0.41 to 0.94) and stroke (OR 0.54, 95% CI 0.28 to 1.04) after adjustment for age, sex, race, hypertension status, index year, history of cardiovascular disease, diabetes, and hyperlipidemia. Among statin users, the average time between the first statin prescription and the index date was 2.6 years among MI cases, 2.6 years among stroke cases, and 2.8 years among controls. Simvastatin was the most common type of statin prescribed (77% of statin users), followed by lovastatin (11.9%) and pravastatin (7.1%).

The six genes in this study are summarized in Table 2 and individual SNPs are summarized in Supplemental Table 1. A total of 82 common SNPs and 31 common haplotypes were assessed. Results of each gene analysis are presented in detail in Supplemental Tables 2–12. At a gene-wide level, none of the six genes displayed suggestion of an interaction with statin use (Table 2). At the SNP level, approximately five SNP-statin interactions on each outcome were expected by chance. Two SNP-statin interactions on MI and five interactions on stroke were observed (Table 3). These included one SNP in *ABCB1* (with MI), one SNP in *CETP* (with stroke), and five SNPs in *LIPC* (four with MI, one with stroke). The interaction most strongly associated with either outcome was a synonymous SNP in *CETP* (rs5883), which was associated with risk of stroke among statin users (OR 3.06, 95% CI 1.22, 7.70) but not otherwise (OR 1.01, 95% CI 0.70, 1.44; p = 0.008). SNP-outcome associations were significantly greater than one among statin users for five of the seven interactions.

Excluding *CETP* (reported elsewhere), four of the five remaining genes (*ABCB1*, *HMGCR*, *LDLR*, and *NOS3*), were not significantly associated with MI or stroke (gene-based global p-values > 0.05; Table 2). *LIPC* was globally associated with MI (global p = 0.026). At the SNP level, five of 82 common SNPs were significantly associated with either MI or stroke (Table 4). These included one SNP in *CETP* (with stroke); two SNPs in *LDLR* (one with MI, one with stroke) and two SNPs in *LIPC* (both with MI). The associations were relatively modest in magnitude, none exceeding a 1.3-fold increase in risk (*LIPC*086229, OR 1.29, 95% CI 1.11 to

1.51). Overall, about 5 SNPs would be expected to show main effects with each outcome, so our results are consistent with chance. Raising the minor allele threshold from a minimum of 5% to 10% excluded 2 SNPs (*CETP*013384 and *LIPC*113696). Of the resulting 80 SNPs, the following associations were observed: 2 SNP-statin interactions on MI (1 *ABCB1*, 1 *LIPC*); 4 SNP-statin interactions on stroke (4 *LIPC*); 3 SNP associations with MI (2 *LIPC*, 1 *LDLR*) and 2 SNP associations with stroke (1 *CETP*, 1 *LDLR*). Four SNPs per analysis would be expected by chance, and the observed results are consistent with this possibility.

Discussion

In this population-based case-control study, common SNPs and haplotypes in six genes related to lipid metabolism were generally not associated with incident nonfatal MI and stroke, nor did these associations differ according to current or past/never use of statin therapy. One exception was for the LIPC gene, where 30 common SNPs across the gene were significantly associated with MI (global p = 0.026). Of these *LIPC* SNPs, the A allele of LIPC086229 (rs11630220) was associated with a 30% increase in the relative risk of MI (OR 1.29, 95% CI 1.11 to 1.51) and the A allele of *LIPC*002426 (rs8192701) was associated with a 20% increase (OR 1.21, 95% CI 1.04 to 1.41). Across all genes, the number of statistically significant SNP results was consistent with the number expected by chance.

Our results expand on previous studies of interactions between statins and genetic polymorphisms on cholesterol-lowering response. Of the six genes examined here, five (*ABCB1*, *CETP*, *LDLR*, *LIPC* and *HMGCR*) were analyzed in recent pharmacogenetic studies[3,5,6,12], and CETP was recently reviewed in the literature[13]. Kajinami, et al. reported that the *ABCB1* 3435C allele (tagged by the *ABCB1*205995 SNP, rs2235048) was associated with smaller reductions in LDL and greater increases in HDL with atorvastatin therapy in females[3]. HDL response to simvastatin was more marked in CETP Taq1B B2 (tagged by *CETP*557, rs17231506) homozygotes but did not differ according to LIPC variant A-250G (tagged by *LIPC*1534, rs1077834)[12]. Chasman, et al. reported that two common and tightly linked SNPs in *HMGCR* (including *HMGCR*11898, rs17238540) were associated with smaller reductions in cholesterol following pravastatin treatment[5]. Finally, a meta-analysis showed an absence of interaction between pravastatin and *CETP* Taq1B genotype [13]. We did not observe interactions with *CETP*000557 (rs17231506; a proxy for Taq1B at r^2 ~0.5) in our data, which suggests that these pharmacogenetic interactions may not extend to cardiovascular and cerebrovascular events, at least not in the context of simvastatin use. We identified different SNPs in *ABCB1*, *CETP LDLR* and *LIPC* that may interact with statins at the level of cardiovascular events. Except for *CETP*013384 (rs5883), a synonymous substitution, these SNPs were located in introns and were not in linkage disequilibrium with coding variants. If these associations are confirmed, additional research would be necessary to clarify the mechanism by which these variants increase MI or stroke risk.

Previous studies have shown associations between individual SNPs in *CETP*, *NOS3* and cardiovascular endpoints[13,14]. Boekholdt, et al. reported that the B2B2 genotype of the *CETP* Taq1B polymorphism was associated with decreased risk of CAD. We did not genotype this SNP directly, but a SNP in modest LD with Taq1B (*CETP*000557, rs17231506; $r^2 = 0.5$ in PARC European-descent population) was not associated with either MI or stroke in this study[11]. Casas, et al. performed a meta-analysis of the *NOS3* Glu298Asp variant (NOS3007164, rs1799983), which was associated with a slightly increased risk of coronary artery disease (OR 1.17, 95% CI 1.07 to 1.28). This SNP was not associated with MI or stroke in our case-control studies (MI OR 1.01, 95% CI 0.90 to 1.14; stroke OR 0.97, 95% CI 0.82 to 1.15), though the confidence intervals overlap substantially. Conflicting results regarding the C-514T promoter polymorphism in the *LIPC* gene in relation to risk of cardiovascular disease have been reported[15]. We genotyped a SNP in complete LD with this SNP[16],

*LIPC*001534 (rs1077834), which was not associated with either MI or stroke (OR 0.94, 95% CI 0.82 to 1.07).

The strengths of this study include both SNP and haplotype approaches. SNP analyses may help identify causal variants, but haplotype approaches are also relevant in the context of multiple functional SNPs or ungenotyped causal variants arising on a single ancestral haplotype[17]. Thorough resequencing data on common gene-wide variants and objective determination of current statin use are additional strengths. We evaluated statistically significant associations from both SNP- and gene-based approaches, and results were similar with either approach. Several limitations deserve mention. At the current sample size, power was good (at least 80%) to detect a 2.5-fold difference between statin subgroups in the OR of MI associated with a SNP or haplotype (assuming a minimum minor allele frequency of 10%); for stroke this detectable interaction was approximately 3.5-fold. However, power to evaluate interactions with less common SNPs or haplotypes was limited by small numbers of statin users among case groups, and some interactions that were identified were based on very small numbers. Many SNPs were assessed, highlighting the possibility of false positive results. Our approach was to first assess the global association of each gene with outcomes, focusing on SNPs only when the global test was significant. Both this approach and the comparison of observed to expected significant results yielded similar results. Also, the high use of simvastatin reflects prescribing preferences at GH and limited our ability to assess the effects of other statins. Finally, participants in our case-control studies survived their events and associations with case-fatality or survival might have been missed.

Our data suggest that SNPs in several lipid or statin metabolism genes were not associated with incident MI or stroke, and these results did not differ according to current use of statins. In light of the study limitations, the association between SNPs in *LIPC* and MI are preliminary and require further corroboration. These results do not rule out a role of these genes in differentiating cholesterol-lowering or other intermediate responses. Other genes or gene variants related to lipid or statin metabolism that we did not directly study may also be related. Compelling findings from additional observational studies or ideally, clinical trials of genetic variants with clinical endpoints, would be needed to justify the integration of pharmacogenetics into statin treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of MI and stroke cases and controls.

Category	MI N = 856	Stroke N = 368	Control N = 2686
Male sex*	42.6	31	41.9
White	91.1	91	91.2
Age – years*	65.8	68.5	65.3
Body Mass Index - kg/m2	30.1	30	29.5
Visits in prior year – mean	6.7	7	5.7
Treated hypertension*	71.7	71.7	73.5
Diabetes	24.2	24.5	11.4
History of CVD	23.1	13.9	10.8
Hyperlipidemia	16.6	12.2	12.8
Last systolic BP before index – mm Hg	142.2	146.2	138.2
Last diastolic BP before index – mm Hg	80.5	81.6	80.5
Cholesterol - mg/dl	231.3	229.3	220.5
Statin use	11.6	7.9	9.8

*Matching factor.

Values are percentages unless otherwise noted.

Table 2

Summary of statin- and lipid-related genes.

Gene (HUGO)	Gene name	Accession number[1]	Percent sequenced[2]	N, common SNPs[3]	N, common haplotypes[3]	Interaction p-value		Main effects p-value	
						MI	Stroke	MI	Stroke
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	AY910577	43	13	8	0.19	0.85	0.13	0.29
CETP	Cholesteryl ester transfer protein	AY422211	97	12	5	0.09	0.75	0.08[4]	0.62[4]
HMGCR	3-hydroxy-3- methylglutaryl- Coenzyme A reductase	AY321356	99	5	5	0.94	0.46	0.96	0.60
NOS3	Nitric oxide synthase3 (endothelial cell)	AF519768	93	11	8	0.46	0.60	0.99	0.88
LDLR	Low density lipoprotein receptor	AY324609	87	11	5	0.38	0.30	0.85	0.44
LIPC	Lipase, hepatic	N/A	N/A	30	0	0.24	0.23	0.026	0.89
Total		---	---	82	31	---	---	---	---

[1] Accession numbers are those referenced in Entrez Gene.

[2] Refers to percent of mRNA transcript sequenced.

[3] Common = frequency ≥ 5% in any case or control group.

[4] From Enquobahrie, et al., 2007.

Table 3

Significant SNP interactions for either MI or stroke

SNP	Outcome	Statin use	n, cases, 0/1/2 copies	n, controls, 0/1/2 copies	OR (95% CI)
*ABCB1*194581	MI	0	560 / 180 / 17	1843 / 531 / 48	1.12 (0.95 to 1.32)
		1	81 / 17 / 1	189 / 69 / 5	0.60 (0.35 to 1.03)
*CETP*013384	Stroke	0	303 / 35 / 1	2169 / 246 / 7	1.01 (0.70 to 1.44)
		1	23 / 5 / 1	239 / 24 / 0	3.06 (1.22 to 7.70)
*LIPC*002426	Stroke	0	254 / 79 / 5	1798 / 580 / 44	0.98 (0.77 to 1.25)
		1	16 / 12 / 1	199 / 59 / 5	2.29 (1.15 to 4.54)
*LIPC*008944	Stroke	0	253 / 79 / 5	1794 / 569 / 44	1.00 (0.78 to 1.28)
		1	16 / 11 / 1	200 / 58 / 4	2.28 (1.12 to 4.66)
*LIPC*045809	Stroke	0	86 / 165 / 88	638 / 1190 / 593	1.04 (0.89 to 1.22)
		1	12 / 13 / 4	53 / 146 / 64	0.50 (0.27 to 0.91)
*LIPC*086134	Stroke	0	253 / 78 / 8	1800 / 579 / 44	1.00 (0.79 to 1.27)
		1	18 / 10 / 1	209 / 51 / 3	2.73 (1.31 to 5.69)
*LIPC*111995	MI	0	523 / 203 / 31	1576 / 721 / 126	0.85 (0.73 to 0.99)
		1	54 / 40 / 5	181 / 68 / 14	1.47 (1.00 to 2.15)

Statistical significance was declared at a nominal $p < 0.05$.

Odds ratios (OR) are given for each additional copy of the minor allele relative to an additional copy of the major allele and are adjusted for race, index year, age, sex, hypertension status, history of CVD, diabetes, and hyperlipidemia.

Table 4

Significant SNP main effects for either MI or stroke

SNP	Outcome	n, cases, 0/1/2 copies	n, controls, 0/1/2 copies	OR (95% CI)
*CETP*008764	Stroke	---	---	1.25 (1.04 to 1.50)[1]
*LDLR*031163	Stroke	108 / 177 / 83	856 / 1351 / 478	1.20 (1.02 to 1.41)
*LDLR*044243	MI	458 / 333 / 64	1508 / 1029 / 149	1.14 (1.01 to 1.30)
*LIPC*002426	MI	606 / 220 / 28	1997 / 639 / 49	1.21 (1.04 to 1.41)
*LIPC*086229	MI	631 / 197 / 27	2104 / 539 / 43	1.29 (1.11 to 1.51)

[1] From Enquobahrie, et al., 2007

Odds ratios (OR) are given for each additional copy of the minor allele relative to an additional copy of the major allele and are adjusted for race, index year, age, sex, and hypertension status.