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Differential Lipid Response to Statins is Associated with Variants in the *BUD13-APOA5* Gene Region

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Abstract

Genetic variants within the *BUD13-APOA5* gene region are known to be associated with high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels. Recent studies suggest that single-nucleotide polymorphisms (SNPs) within this region affect HDL-C response to statin-fibrate combination therapy and low-density lipoprotein cholesterol (LDL-C) response to statin therapy. We hypothesized that SNPs within the *BUD13-APOA5* region are associated with TG, HDL-C, and LDL-C response to statin therapy.

We examined 1520 observations for 1086 patients from the Personalized Medicine Research Project, a large biorepository at the Marshfield Clinic Research Foundation, who had received statin therapy and been previously genotyped for polymorphisms in the 11q23 chromosomal region.

A significant differential response to statin therapy was observed for three SNPs. The minor allele at rs11605293 significantly attenuated TG-lowering response to pravastatin ($P=1.59E-04$) while the minor allele at rs12806755 was associated with a similar response to lovastatin ($P=1.92E-04$). Genotypes at rs947990 significantly attenuated LDL-C reduction to atorvastatin therapy ($P=6.68E-04$) with some patients with the minor allele having LDL-C increase following therapy. No SNPs within the *BUD13-APOA5* region were associated with a significant effect on HDL-C reduction in response to statin therapy.

In conclusion, this study suggests that common SNPs within the *BUD13-APOA5* can affect TG and LDL-C response to statin therapy in a North American population.

Keywords

pharmacogenetics; statin response; genetic association; triglycerides; HDL-C; LDL-C

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Introduction

Statin therapy is the major treatment for low-density lipoprotein cholesterol (LDL-C) reduction, and the only treatment that has been shown to clearly improve cardiovascular outcomes.¹ Statins have additional positive effects on reducing triglycerides (TG), increasing high-density lipoprotein cholesterol (HDL-C), and reducing inflammation. Multiple studies have examined the effect of common single-nucleotide polymorphisms (SNPs) on LDL-C statin response. SNPs within the *APOE* gene have been shown to affect LDL-C response to statins in multiple studies,² while GWAS studies had variable results.³⁻⁵ A number of studies examined genes in the metabolic and absorption pathways of statins,^{6,7} but not the SNPs effect on TG and HDL-C response to statins. The *APOA5* gene has been previously associated with HDL-C and TG levels in multiple studies, and recently rare variants within this gene were associated with early coronary events.⁸ We have previously shown that SNPs in the *BUD13-APOA5* region affect HDL-C response to fibrate-statin combination therapy.^{9,10} A recent study by Hubacek et al¹¹ showed that SNPs within the *APOA5* gene region had an effect on LDL-C response to statins. In this study, we examined the association between common genetic variants in the *APOA5-BUD13* gene region and change in LDL-C, HDL-C, and TG levels in response to statin therapy in the context of a longitudinal population study.

Methods

Ethics Statement

The study was reviewed and approved by Marshfield Clinic Research Foundation's (MCRF) Institutional Review Board. Participants originally provided informed consent to join the Personalized Medicine Research Project biorepository.

Study Population

Subjects were selected from the Personalized Medicine Research Project (PMRP), a central Wisconsin adult population-based, biorepository of stored DNA, plasma, and serum from >20,000 participants with linked electronic medical records extending an average of >30 years. The PMRP is housed at MCRF and has been previously described.^{12,13} This cohort is highly stable and homogeneous, consisting of predominately white Americans of Northwestern European ancestry (>98%; see Supplemental Table 1 for definition of ethno-racial distributions in the study population). PMRP has been successfully used in previous mapping efforts of common diseases.¹⁴⁻¹⁶

The subset of PMRP individuals selected for the study were >50 years-of-age, not previously diagnosed with type 1 diabetes, had received at least one first-time prescription for a statin, fibrate, and/or niacin over the time period between 2003-2012, and had dual observations for pre- and post- prescription lipid levels. The pre-prescription lipid level was required to be within 90 days before the prescription, and the post-prescription lipid test had to be within 365 days after the first-time prescription (Fig. 1). Some patients included may have met this definition for multiple statin exposures during the temporal observational window, albeit with exposure to only one lipid lowering agent at a time. Data from 1086

subjects were included in the study. However, since >77% of observations were attributable to statin exposures, exposures to other agents including fibrates, niacins, or statins in combination with another agent, were excluded from analyses reported in this study.

Selection of observations

Lipid and drug observations made on each individual were collected for analysis. For subjects prescribed drugs from more than one drug group over time, multiple lipid observations were selected, but only one observation was chosen for each drug group—the observation corresponding to the first time the particular statin drug was prescribed. Lipids investigated were triglyceride concentration (TG), HDL-C, and LDL-C concentrations (Supplemental Table 1). The study investigated lipid response to statins individually in the absence of other statins, niacins, or fenofibrates. Descriptive statistics for the three lipids were calculated for the pre-statin and post-statin laboratory test results (see Supplemental Table 1). We excluded observations if two drug groups were newly prescribed on the same date, since determination of impact on lipid response for each drug individually was preempted. Observations were also excluded if a different new prescription was given between the pre- and post-test, because the new prescription would make it impossible to associate the percentage of lipid change to a specific drug. (See Supplemental Table 2 for the observation selection rules.) An example illustrating the application of these rules is demonstrated in Supplemental Figure 1. Observations were abstracted from Marshfield Clinic electronic medical records collected from November 1, 2003 through October 21, 2012. The selected observations include first-time prescriptions from October 20, 2003 through August 27, 2012.

Data were collected on relevant covariates including body mass index (BMI), smoking status (current, former, never), and type 2 diabetes status. Age was recorded at the time of the first prescription for a particular drug, whereas the other covariates represent the more recent data at the time of data abstraction. A total of 1086 subjects contributed observations (first-time drug prescription, pre- and post-lipid test result), for a total of 1520 observations. More than 77% of the observations were for statins, which is the focus of this investigation. The prevalence of mixed dyslipidemia within drug groups varied. Overall, 25.5% of observations were made on individuals having mixed dyslipidemia, defined as males having TG ≥ 150 mg/dL and HDL < 40 mg/dL when tested at the same time, and females having TG ≥ 150 mg/dL and HDL < 50 mg/dL when tested at the same time.

The number of days for the post-test lipid levels from the first prescription time ranged from 1 to 364 days, with a median of 92.5 days. Median TG, LDL-C, and HDL-C levels at the pre-test were 136, 108, and 46 mg/dL, respectively. In comparison, post-test median values were 128, 96, and 46 mg/dL, respectively (Supplemental Table 1).

Genotyping and SNP selection

All study participants were genotyped on the Illumina 660W QUAD-W high density SNP array. Individuals were randomized to avoid batch effects. Genotyping procedures, quality control, and results were previously described.¹⁴ The SNP array provides good coverage of the common allelic architecture across the genome. Genotype data were linked to electronic

medical record information including laboratory values, prescription medications, and diagnostic codes within the Biomedical Informatics Research Center at MCRF.

Taking a targeted approach, the *BUD13-APOA5* gene region on chr 11q23 was selected for interrogation based on previous lipid level associations and drug response results. The BUD13-APOA5 region in hg19 coordinates spans the following coordinates—Chr11: 116158912-117128271. All 204 SNPs available on the Illumina 660W-QUAD array within this region were evaluated (Supplemental Table 3). Blinded to phenotype data, quality control checks were performed on the genotype data to ensure that (1) only subjects with 90% call rate were used in the analysis, (2) SNPs were filtered to have a minor allele frequency 1%, and (3) a call rate of >95% was required for each SNP. In addition, deviation from Hardy-Weinberg equilibrium was tested using Weir's exact test, showing no evidence of systematic deviation (all $P>0.001$). No samples were excluded on the basis of these quality control measures. One SNP (rs11556024) was excluded for failure to genotype in most samples, leaving 203 SNPs for analysis.

Analyses

Selection of subjects and observations and specific analyses were performed using SAS® software (Version 9.3© 2013 SAS Institute Inc, Cary, NC, USA). Genetic association analyses were performed using the PLINK software package, Version V1.07.¹⁷ Data were analyzed separately by statin type, so that each subject contributed to only one set of observations (first prescription and pre-/post-lipid measurements). Linear regression was performed using PLINK and SAS to test for association between genotypes and percent change in lipid levels following the drug. The permutation routine performed in PLINK permutes the endpoint against each SNP in the absence of covariates. The epithelial membrane protein (EMP) 1 is the nominal, permuted P -value from this routine, and the EMP2 value is the family-wise permuted P -value accounting for all SNPs in the region.

The regression model was adjusted for age, BMI, smoking status, race, gender, type 2 diabetes status, and time on the drug (the number of days between the first prescription date and the post-lipid test date). SNP association results were plotted across the region to generate positional plots for the topmost associated SNPs ($P<0.001$) using SNAP.⁹

The effect and distribution of lipid response were visualized through boxplots generated in SAS relating change in lipid levels to genotypes for the most highly associated SNPs in the region. To assess these association data for multiple independent signals, pairwise linkage disequilibrium (LD) levels among the top SNPs (linear regression $P<0.001$) were characterized through PLINK for this study and compared to LD values within the HapMap CEU population. Both D' and r^2 values were calculated.¹⁸

As the study examined multiple SNPs and three lipids, there was a multiple testing burden that might produce spurious results, using only nominal P -values. Hence, PLINK was used to generate experiment-wise P -values, correcting for multiple testing through 10,000 permutation runs on all data for the top individual SNPs.

Results

Population characteristics and statin exposures are summarized in Supplemental Table 1. Among the 1086 subjects included in the study 53% were female, 9% were current smokers, 43% were former smokers, 23% had a diagnosis of type 2 diabetes mellitus, 98.7% were white, 1% Asian, and 0.3% reported their racial/ethnic origin as 'other'. The reported BMI ranged from 13.3 to 76.3 kg/m², averaging 30.4 kg/m². The large majority of BMI measurements were taken within 5 years of the drug/lipid observations. Age at observations ranged from 47 to 96 years, with an average of 70 years.

Baseline analyses were run to test top SNPs for association with baseline levels of any of the lipids, and no association could be demonstrated (Table 1). Sanger Genevar eQTL tool was run on the top SNPs, and none of them exhibited significant association with mRNA expression level in the HapMap CEU cell lines.

Data normalcy was examined in two ways. A permutation test was done to obtain *P*-values in a nonparametric manner (this is done in the absence of adjustments for covariates since PLINK does not support adjustment by covariate). Therefore, an additional adjusted analysis was performed using curves. The % change in the three lipids was plotted to assess 'best fit' to normal distributions. Plots demonstrate that there is no notable departure from a normal distribution (Supplemental Figure 2).

Using linear regression to test the association between percent lipid change with statin prescription and individual SNP genotype, we identified two associations with *P* < 0.001 and experiment-wise significance (Table 2). Results for the positional association were generated for all SNPs evaluated and are displayed in Supplemental Fig. 3a-c. For TG change, rs11605293, intergenic, and approximately 180kb upstream to *BUD13* was associated with attenuated response to TG lowering with pravastatin (*P* = 1.59E-04), and rs12806755, intergenic, and approximately 460kb upstream to *BUD13* was associated with attenuated response to TG lowering to lovastatin (*P* = 1.92E-04). In both cases, triglyceride levels actually increased in correlation with copies of the minor allele. Adjusted by age, BMI, gender, race, smoking, type 2 diabetes, and time on drug, there was actually an increase in TG with the addition of each T allele at rs11605293 with pravastatin treatment (Fig. 2a). Similar effects were observed for rs12806755 on TG levels with lovastatin, where the addition of each C allele significantly increased TG instead of the expected decrease (Fig. 2b). Using the permutation testing on the entire dataset to adjust for multiple testing, rs11605293 and rs12806755 had empirical experiment-wise *P*-values of 0.07 (non-significant) and 0.007, respectively.

Genotypes at rs947990 were correlated with LDL-C response to treatment with atorvastatin (*P* = 6.68E-04). Permutation testing showed a significant experiment-wise *P*-value of 0.028 (Fig. 2c). This SNP is approximately 60kb downstream from *BUD13*. Again, the minor allele (A allele) was coupled with an increase of LDL-C levels, rather than the expected decrease in LDL-C levels (Fig. 2c). Pairwise LD patterns specific to the top SNPs described above are shown in Supplemental Table 4. No significant associations were identified for HDL-C that persisted after permutation testing.

Discussion

In this study we have identified SNPs in the *APOA5-BUD13* region that are associated with lipid response to statins. The region of interest was defined to be the 230kbp from (hg38) Chr11:116,639,775-116,869,775, which covers 100kbp centromeric to the 3' end of BUD13, through the 5' end of APOA4. Within this region, there are 25 SNPs in the National Human Genome Research Institute catalog of published genome-wide association studies. Using SNAP from the Broad Institute,⁹ pairwise LD algorithms were run to investigate the r^2 values between our three reported SNPs (rs11605293, rs12806755, and rs947990) and each of the previously GWAS-associated 25 SNPs in the catalog. Only two pairs of SNPs exhibited r^2 values exceeding 0.20. The top two findings with the highest levels of LD between our SNPs and the previously-reported GWAS-significant SNPs are with rs947990 (Supplemental Table 5). Notably, genome-wide significance was reported by Kim et al. for rs11216126 in a large study of HDL levels in East Asian individuals.¹⁰

We have specifically chosen this chromosomal region because SNPs and rare genetic variants in this region have been previously shown to affect triglycerides and HDL-C response to fibrate and fibrate-statin combination therapy levels.^{11,19,20} The same region was also shown in large genome-wide association studies to be associated with baseline triglyceride and HDL-C levels. One limitation of our study—inherent in the sample set—is that previous use of other drug groups (statins, fibrates, niacin) prior to initiating the drug under investigation was not accounted for in the analyses. However, validation was done to ensure that no simultaneous exposure to multiple treatments was included. Thus, the baseline 'pre' measurement for a subsequent statin prescribed to a subject treated with multiple drugs may reflect the level established by exposure to a different drug. Further, whether a drug group was the first drug tried with that individual or a subsequent drug was not factored into the analysis. That said, we believe the genetic association signals from this study represent interesting findings, deserving of additional interrogation.

All statins have a small degree of triglyceride reduction effect including pravastatin and lovastatin.²¹ By lowering cholesterol availability in the cell, there are less apolipoprotein particles produced in the liver and available for chylomicrons and very low-density lipoprotein production. The result of this is lower measurable plasma TG levels. In our study, the rs11605293 attenuated TG reduction in response to pravastatin, and in many individuals TG levels actually increased in correlation with copies of the minor allele. A similar pattern was observed for rs12806755 and lovastatin. Of note, these SNPs had no effect on LDL-C reduction. A possible mechanism by which this region affects TG reduction by statins could be related to a regulatory effect these SNPs may have on *APOA5* expression, as these SNPs are clearly upstream of this gene. However, SNPs outside of the *APOA5* region and promoters such as *ZNF259* have been shown in prior studies to affect the response to statin-fibrate therapy.^{11,19,20} It is possible that these SNPs affect *APOA5* response to statins and, thus, the availability of TGs to be incorporated into lipoproteins such as low-density lipoprotein, very low-density lipoprotein, and chylomicrons.

Common SNPs within the *APOA5* promoter were previously shown to affect LDL-C lowering in individuals receiving statin therapy.¹¹ In our study, the rs947990 minor allele

was associated with lack of response, or a paradoxical response, with LDL-C increase to statins in some individuals who carry the minor allele. It is not clear how this SNP affects LDL-C response to statins, but this again can be related to an indirect regulatory effect on *APOA5*, as has been suggested previously by Hubacek et al.¹¹

In summary we have shown that common genetic variations within the *BUD13-APOA5* gene region can affect TG and LDL-C levels in response to statins. Further studies are needed to confirm the importance of this region to lipid response to statins.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Lipid	n=2488		
	No. with at least one Pre Level in time frame	No. with at least one Post Level in time frame	No. with a paired set of levels in time frame
HDL	1325	2245	1212
LDL	1275	2223	1149
TG	1317	2240	1195

Figure 1. Selection of Subjects

Figure 2. (A) % Change in TG by rs11605293 Genotype for Pravastatin Treatment. (B) % Change in TG by rs12806755 Genotype for Lovastatin Treatment. (C) % Change in LDL by rs947990 Genotype for Atorvastatin Treatment. (adjusted for age, BMI, gender, race, smoking, diabetes2, and time on drug.)

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TABLE 1

SNPS Tested for Association with Baseline Levels of Lipids

	TG pre	TG post	LDL pre	LDL post	HDL pre	HDL post
mean	169.2681	152.8675	113.5754	100.4513	47.42479	47.75692
SD*	119.6753	111.2141	39.37626	34.71163	14.27476	13.88466

TABLE 2

Linear Regression Results for Significant Results

The three SNPs that exhibit experiment-wise statistical significance are reported. The allele listed corresponds to the frequencies and effect sizes. Effect sizes are the beta coefficients from the linear regression. Asymptotic results are presented for both unadjusted and adjusted regression models. The covariates used in the adjustment are: age, BMI, gender, race, smoking, type 2 diabetes, and the time on the drug. To validate the use of limiting distributions for the asymptotic results, a permutation test was also performed using 10,000 iterations. The nominal permuted *P*-value is listed under EMP1, while the experiment-wise permuted *P*-value is listed under EMP2.

Chr. 11q SNPs	Gene	Drug	Lipid	Allele	Minor allele		No. chr. obs.	Unadjusted		Unadjusted 10,000 permutations		Adjusted	
					HapMap CEU freq.	Freq for lipid/drug		Effect Size (beta for % change in mg/dL)	P-value	EMP1	EMP2		Effect Size (beta for % change in mg/dL)
rs11605293	BUD13	Pravastatin	TG	T	0.094	0.095	232	0.3659	0.000136	0.0012	0.0699	0.3827	0.000159
rs12806755	RPL15P15 / BUD13	Lovastatin	TG	C	0.049	0.091	230	0.3059	3.9E-05	0.0003	0.00699	0.2905	0.000192
rs947990	BUD13	Atorvastatin	LDL	A	0.093	0.138	698	0.1445	0.000151	0.0001	0.0277	0.1286	0.000668

SNP, single-nucleotide polymorphism; BMI, body mass index; EMP1, nominal permuted *P*-value ; EMP2, experiment-wise permuted *P*-value; TG, triglyceride; LDL, low-density lipoprotein