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No evidence of interaction between known lipid-associated genetic variants and smoking in the multi-ethnic PAGE population

Logan Dumitrescu,
Center for Human Genetics Research, Vanderbilt University, 2215 Garland Avenue, 515B Light Hall, Nashville, TN 37232, USA

Cara L. Carty,
Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Nora Franceschini,
Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

Lucia A. Hindorff,
Office of Population Genomics, National Human Genome Research Institute, Bethesda, MD, USA

Shelley A. Cole,
Department of Genetics, Texas Biomedical Research Institute, San Antonio, TX, USA

Petra Bůžková,
Department of Biostatistics, University of Washington, Seattle, WA, USA

Fredrick R. Schumacher,
Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Charles B. Eaton,
Department of Family Medicine, Warren Alpert Medical School Brown University, Providence, RI, USA

Robert J. Goodloe,
Center for Human Genetics Research, Vanderbilt University, 2215 Garland Avenue, 515B Light Hall, Nashville, TN 37232, USA

David J. Duggan,
Translational Genomic Science Institute, Phoenix, AZ, USA

Jeff Haessler,
Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Barbara Cochran,
Baylor College of Medicine, Houston, TX, USA

Brian E. Henderson,
Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

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Correspondence to: Dana C. Crawford, crawford@chgr.mc.vanderbilt.edu.

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Iona Cheng,
Cancer Research Center, University of Hawaii, Honolulu, HI, USA

Karen C. Johnson,
Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Chris S. Carlson,
Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Shelly-Anne Love,
Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

Kristin Brown-Gentry,
Center for Human Genetics Research, Vanderbilt University, 2215 Garland Avenue, 515B Light Hall, Nashville, TN 37232, USA

Alejandro Q. Nato,
Department of Genetics, Rutgers University, Piscataway, NJ, USA

Miguel Quibrera,
Gillings School of Public Health, University of North Carolina, Chapel Hill, NC, USA

Ralph V. Shohet,
John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

José Luis Ambite,
Information Sciences Institute, University of Southern California, Marina del Rey, CA, USA

Lynne R. Wilkens,
Cancer Research Center, University of Hawaii, Honolulu, HI, USA

Loïc Le Marchand,
Cancer Research Center, University of Hawaii, Honolulu, HI, USA

Christopher A. Haiman,
Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Steven Buyske,
Department of Genetics, Rutgers University, Piscataway, NJ, USA

Department of Statistics, Rutgers University, Piscataway, NJ, USA

Charles Kooperberg,
Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Kari E. North,
Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Myriam Fornage, and
Division of Epidemiology, Human Genetics, and Environmental Sciences, School of Public Health, University of Texas Health Sciences Center at Houston, Houston, TX, USA

Institute of Molecular Medicine, University of Texas Health Sciences Center at Houston, Houston, TX, USA

Dana C. Crawford

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Center for Human Genetics Research, Vanderbilt University, 2215 Garland Avenue, 515B Light Hall, Nashville, TN 37232, USA

Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN, USA

Logan Dumitrescu: logan.dumitrescu@chgr.mc.vanderbilt.edu; Dana C. Crawford: crawford@chgr.mc.vanderbilt.edu

Abstract

Genome-wide association studies (GWAS) have identified many variants that influence high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and/or triglycerides. However, environmental modifiers, such as smoking, of these known genotype–phenotype associations are just recently emerging in the literature. We have tested for interactions between smoking and 49 GWAS-identified variants in over 41,000 racially/ethnically diverse samples with lipid levels from the Population Architecture Using Genomics and Epidemiology (PAGE) study. Despite their biological plausibility, we were unable to detect significant SNP × smoking interactions.

Short report

Candidate gene and genome-wide association studies (GWAS) have identified numerous common variants associated with high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). However, examination of possible interactions with environmental factors such as smoking is still lacking (Ordovas et al. 2011). Smoking has been associated with a poor lipid profile, including decreased HDL-C and increased triglycerides (Chelland et al. 2008). Here, we assess the influence of smoking as a modifier of known lipid-related genotype–phenotype associations across four racial/ethnic groups.

Study samples were drawn from the Population Architecture Using Genomics and Epidemiology (PAGE) study, which consists of four population-based studies and numerous racial/ethnic populations, including those examined here: European Americans (n = 24,700), African Americans (n = 9,782), American Indians (n = 3,607), and Mexican Americans/Hispanics (n = 3,357) (Matise et al. 2011). Mean lipid levels by population and self-reported smoking status (dichotomized into current and former/never smokers) for all PAGE participants are listed in Table 1. Study specific demographics are presented in Table S1.

A total of 49 SNPs (Table S2) previously associated with one or more lipid trait in published (as of 2008) candidate gene and GWA studies were selected and successfully genotyped in PAGE (Dumitrescu et al. 2011). Regression modeling was used to assess the effect of a multiplicative interaction between each variant and smoking status on HDL-C, LDL-C, and ln(TG) levels. Race-specific models were adjusted for age, sex, and marginal effects. Analyses were performed by each PAGE study site and summary statistics were meta-analyzed using METAL (Willer et al. 2010). Given that the lipid traits are correlated and the associations tested are not assumed to be completely independent, significance was defined as $p < 1.0\text{E}{-}03$ to account for the 49 SNPs tested (=0.05/49 SNPs). Effect sizes needed to detect significant interactions with 80 % power were calculated using Quanto (Gauderman and Morrison 2006). Variant main effect sizes used in the power calculation were drawn from a previous single-SNP association analysis for LDL-C (Dumitrescu et al. 2011).

No significant SNP × smoking interactions were detected (Fig. 1). Indeed, only 28 interactions (out of 588 tested) had p values <0.05, consistent with chance alone. The most significant interaction was *TTC39B* rs471364x-smoking (p = 2.55E−03) for HDL-C levels among Mexican Americans/Hispanics. Only one interaction (*CETP* rs1566439 for TG) was nominally associated in more than one population; however, the direction of effect was

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inconsistent (p = 1.35E–02, β = –0.031 in European Americans; p = 6.84E–03, β = 0.106 in Mexican Americans/Hispanics).

Several reasons may underlie the lack of significant interactions. First, not all PAGE study sites collected sufficient data to assess smoking status as recommended by harmonization work groups such as the consensus measures for phenotypes and eXposures [PhenX; (Hamilton et al. 2011)]. Additionally, quantitative measures of smoking exposure such as serum cotinine levels or number of pack-years, were not available for all PAGE study sites. Therefore, our binary categorization of smoking (though a commonly used metric of exposure) may have inhibited our ability to detect existing interactions.

Second, our power to detect to small interaction effects was limited, especially in minority populations and for variants with low minor allele frequencies (examples in Table 2). For example, we had 80 % power to detect a minimum interaction beta of 3.5 in European Americans, 5.0 in African Americans, 7.4 in American Indians, and 9.4 in Mexican Americans/Hispanics for *HMGCR* rs12654264 (allele frequency = 0.55–0.62). However, the effect sizes needed to detect a significant interaction with *PCSK9* rs11591147 (allele frequency = 0.004–0.02) were four to seven times larger than those needed for rs12654264, despite the fact that the main effect of rs11591147 size was very large (β_G = −15.67 to 23.39 mg/dl; Dumitrescu et al. 2011).

Another factor that has implications for power is the range of smoking prevalence, both across (Table 1) and within (Table S1) racial/ethnic groups. All other measures being equal, increased prevalence of the environmental exposure results in increased power to detect a gene–environment interaction. The populations studied here demonstrated a range of smoking exposures, with American Indians (33.7 %) having the largest percentage of current smokers and Mexican Americans/Hispanics having the smallest (16.9 %). As one can see from Table 2, we were powered to detect smaller interaction effect sizes in American Indians compared to Mexican Americans/Hispanics for all four modeled interactions. Therefore, when designing gene–environment interaction studies, even larger sample sizes may be necessary for populations in which the environmental exposure is rare.

Last, the lack of significant interactions may simply be due to the fact that none exists for the variants and populations studied here. However, for some interactions, it is impractical to draw this conclusion given we cannot distinguish between a true negative and a false negative due to lack of statistical power.

Despite the known impact of smoking on lipids and the relevant role of the loci studied here in lipid metabolism, we were unable to identify significant SNP × smoking interactions. We demonstrate that studies of gene–environment interactions require very large sample sizes, greatly impeding the investigation of minority populations and complex environmental exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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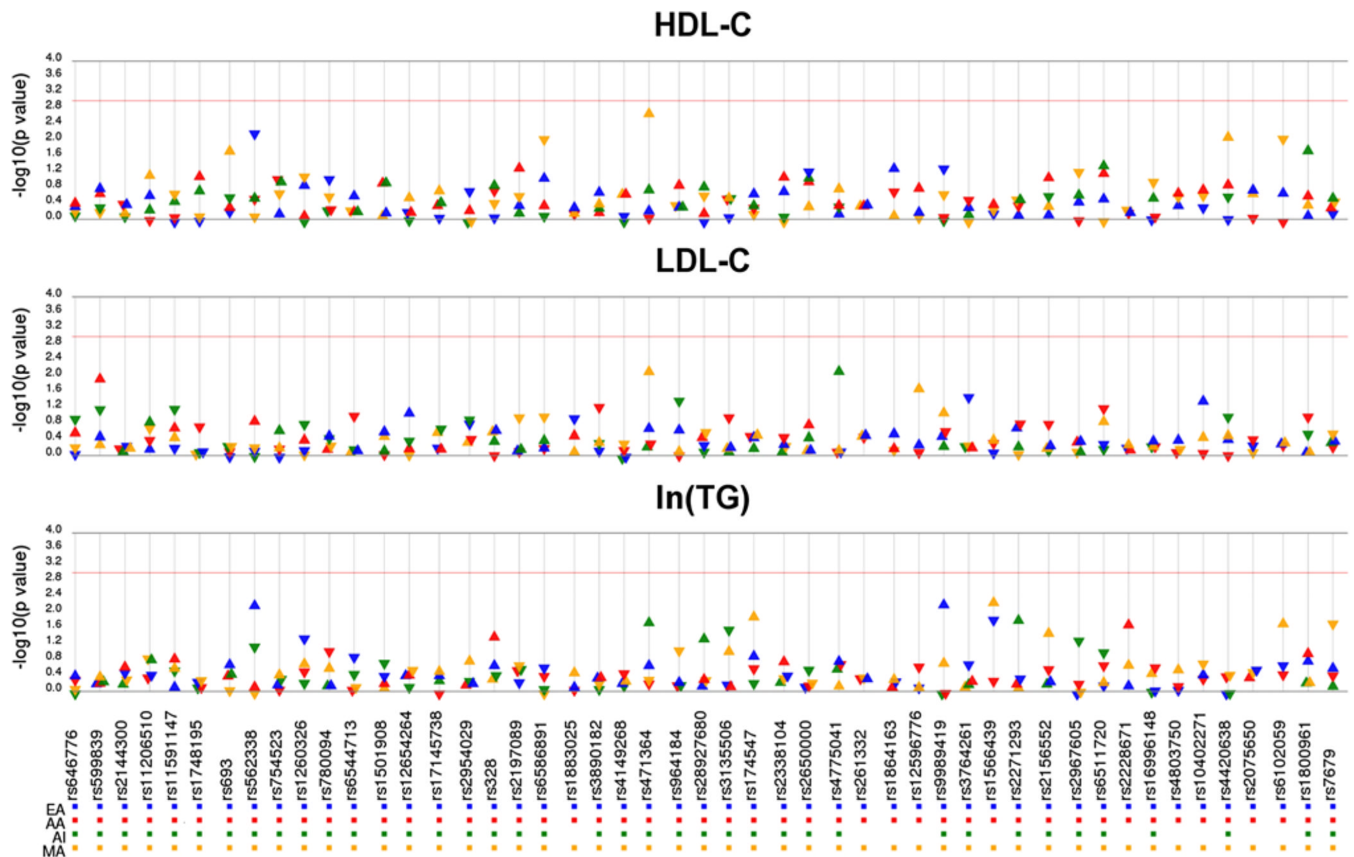

Fig. 1.

SNP × smoking interaction results by lipid trait and population. Each SNP × smoking interaction was tested for an association with the indicated lipid trait after adjustment for age and sex. *p* values ($-\log_{10}$ transformed) of the meta-analysis are plotted along the *y*-axis. SNPs are ordered on the *x*-axis based on chromosomal location. Each *triangle* represents a meta-analysis *p* value for each population. The direction of the *arrows* corresponds to the direction of the beta coefficient. Populations are color-coded as denoted in the legend: European Americans (EA), African Americans (AA), American Indians (AI), and Mexican Americans/Hispanics (MA). The significance threshold (p = 1.0E−03) is indicated by the *red line*

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Table 1

Characteristics of PAGE study participants

Trait	European Americans		African Americans		American Indians		Mexican Americans/Hispanics	
	Former/never smokers	Current smokers	Former/never smokers	Current smokers	Former/never smokers	Current smokers	Former/never smokers	Current smokers
N_{max} (%)	19,975 (80.9)	4,725 (19.1)	7,241 (74.0)	2,541 (26.0)	2,390 (66.3)	1,217 (33.7)	2,788 (83.1)	569 (16.9)
HDL-C (mg/dl)	53.7 ± 15.9	49.3 ± 15.9	56.1 ± 15.7	54.3 ± 17.1	46.6 ± 13.6	45.3 ± 14.3	50.1 ± 13.6	47.9 ± 14.5
LDL-C (mg/dl)	129.9 ± 36.1	133.9 ± 38.6	129.3 ± 39.6	123.4 ± 40.8	115.5 ± 33.6	120.4 ± 34.0	122.3 ± 34.3	123.0 ± 34.5
TG (mg/dl)	137.2 ± 83.2	136.5 ± 80.8	100.3 ± 56.6	104.6 ± 65.0	146.6 ± 100.5	144.6 ± 97.7	160.6 ± 101.1	165.6 ± 112.5

All values reported as mean ± SD unless otherwise indicated

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Table 2

Minimum interaction effect sizes needed to detect representative SNP × smoking interactions

SNP	Allele frequency in EA, AA, AI, MA/H	Minimum β_{GE} needed to detect interaction with smoking			
		European Americans	African Americans	American Indians	Mexican Americans/ Hispanics
rs12654264	0.62, 0.67, 0.62, 0.55	3.5	5.0	7.4	9.4
rs599839	0.77, 0.28, 0.78, 0.79	4.0	5.3	8.4	11.2
rs562338	0.18, 0.60, 0.15, 0.07	4.3	4.8	10.0	18.0
rs11591147	0.02, 0.004, 0.01, 0.01	13.5	35.5	34.2	44.9

Effect sizes (β_{GE}) were estimated for SNP × smoking interactions on LDL-C levels