

ARIC Manuscript Proposal #2506

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Population Architecture using Genomics and Epidemiology (PAGE)

Ver. 06/14/10

PAGE Manuscript Proposal Template

Submit proposals by email to the PAGE Coordinating Center at Purn@biology.rutgers.edu

*All sections must be completed; incomplete applications will be returned.
Do not exceed 3 pages in length (not including references).*

PAGE Ms. Number: 79

Submission Date: _____

[Approval Date: 2/23/15]

Title of Proposed Ms.: The influence of obesity status on known lipid variants: Population Architecture using Genomics and Epidemiology (PAGE) study

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Junior Investigator? **Y**

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Partner studies in PAGE not collaborating in this ms. proposal:

Study	Contacted? Y/N	Declined? / Other?
TaiChi?		

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II. SCIENTIFIC RATIONALE (Please be specific and concise)

Lipid level profiles have long been known to be associated with coronary heart disease and myocardial infarction. The most commonly measured and studied lipid traits include total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). Lipid traits are heritable, with estimates from twin and family studies ranging from 20 to >70%. In the largest genome-wide association study (GWAS) meta-analysis to date, 157 common genetic variants have been identified in ~188,000 participants from European-descent populations [1, 2]. Collectively, these common variants explained ~15% of the total phenotypic variance for these traits [1, 2]. Both high levels of LDL-C and TG are considered risk factors for CHD while HDL-C levels appear to be protective against CVD. Interestingly, recent genomic studies have demonstrated that obesity may modify the impact of a genetic variant on lipid traits [3-5]. A recent study in European descent individuals identified significant interactions between obese/lean status and applied a weighted genetic risk score for each of TG and HDL-C. These interactions were largely driven by variants tagging *APOA5*, *GCKR* and *LPL* for TG, and *CETP*, *GALNT2*, *LIPG* and *PLTP* for HDL-C[6].

To date, the majority of genetic discovery studies for these traits have been performed in populations of European-descent. Smaller GWA studies exist for African American participants, but no studies yet exist for Hispanic populations. In addition to discovery, we and others have begun the process of generalizing known European-identified variants to diverse populations [7] as well as fine-mapping GWAS-identified genomic regions for these traits in African Americans and Asians [8]. In this proposal, we will use information from our sister generalization paper to identify the best associated SNP in each region for each ancestry group. This ancestry specific top SNP will be used to address our first study question, that is, does continuous BMI or obesity status modify the association between known lipid variants and lipid traits in African American, Hispanic, and Asian participants of the PAGE study. Further, we will seek to identify novel variants associated with these same lipid traits by accounting for effect modification by obesity status. The first hypothesis will only evaluate one index

SNP per race/ancestry group and per established locus. In contrast, the second goal will conduct an array wide study of the 200,000 SNPs of the metabochip.

III. OBJECTIVES AND PLAN (Please be specific and concise)

a. Study Questions/Hypotheses.

1. Specific Aim 1: Our primary aim is to determine if there are distinct genetic effects by obesity status in variants known to be associated with lipid traits in African Americans, Hispanics, and Asians.
2. Specific Aim 2: Our secondary aim is to perform a discovery of novel variants associated with these same lipid traits in African Americans, Hispanics, and Asians if we account for SNP by obesity status interaction.

b. Study populations, study design for each

We plan to access data from PAGE studies with lipid traits (HDL-C, LDL-C, and TG), obesity status as measured by BMI >30 or BMI ≤30, and Metabohip data. The anticipated studies include ARIC, CARDIA, CHS, EAGLE (BioVU), MEC, SOL, and WHI. Individuals fasting less than 8hrs prior to blood draw will be excluded.

c. Variant/SNPs (Specify)

Metabohip

d. Phenotype(s) (Specify)

Low-density lipoprotein cholesterol (LDL-C)
High-density lipoprotein cholesterol (HDL-C)
Triglycerides (TG)
Obesity status as measured by BMI

For the proposed analyses, we anticipate the following sample sizes by study site and race/ethnicity based on preliminary inventories for the lipid traits, body weight and medication data:

PAGE Study site	African Americans	Hispanics	Asians
ARIC	2,440	--	--
CARDIA	1,390	--	--
CHS	686	--	--
EAGLE/BioVU	3,858	285	419
MEC**	209	?	576
SOL	--	11,820	--
MSSM	1,612	2,101	--
WHI	10,850	3,700	350
TaiChi (nonPAGE study)	--	--	9,760
MESA (nonPAGE study)	2,524	2,071	709

* This is an estimate of samples with genotype. This will change once phenotype exclusion are made

**An additional 100 Native Hawaiians are also available.

e. Covariates (Specify)

Lipid lowering medication use
Age
Sex
Body mass index
Global and local ancestry (estimated from principal components)

f. Main statistical analysis methods

For all analyses, we expect access to individual-level data. Baseline or median (EAGLE/BioVU only) HDL-C, LDL-C, and TG will each be evaluated as a continuous dependent variables. TG will likely be natural log transformed prior to analysis. We will run models stratified by obesity status (BMI>30 and BMI≤30) and adjusted for age and sex and also incorporating a continuous BMI by SNP interaction in the full model. . For most tests of association involving common genetic variation (>1% minor allele frequency), standard linear regression adjusted for various covariates will be used. Single SNP tests of association will be performed assuming an additive genetic model.

We will adjust levels of significance to account for multiple testing. For Aim 1, the number of statistical tests performed will be limited to the 58 gene regions fine-mapped on the MetaboChip. For Aim 2, the number of statistical tests will be based on the entire MetaboChip dataset (~200,000 variants), making the Bonferroni conservative significance threshold ($<2.5 \times 10^{-7}$) approximate genome-wide significance.

All analyses will also be stratified using a combination of self-reported race/ethnicity and genetic ancestry estimated from AIMs available on the MetaboChip as estimated by the PAGE Coordinating Center. For models that include SQL data, all analyses will be weighted given that participants were recruited using a probability sampling.

We will combine results by ethnic group using METAL, and across all 3 ancestral groups in a trans-ethnic meta-analysis using Metasoft [9] or MANTRA [10] to allow for both fixed and random effects optimized to detect associations under heterogeneity.

g. Ancestry information used? No ☐ Yes ☒ How is it used in the analyses?

Global genetic ancestry estimates will be used for stratification and adjustment in analyses. In some cases, we may also estimate and adjust for local genetic ancestry.

h. Anticipated date of draft manuscript to P&P: April 2015

i. What manuscript proposals listed on www.pagestudy.org/index.php/manuscripts/ are most related to the work proposed here? Approved PAGE ms. numbers: _____

— If any: Have the lead authors of these proposals been contacted for comments and/or collaboration? Yes ☐ No ☐

IV. SOURCE OF DATA TO BE USED (Provide rationale for any data whose relevance to this manuscript is not obvious): **Check all that apply:**

Aggregate/summary data to be generated by investigators of the study(ies) mentioned:

☒ EAGLE; ☒ CALiCO; ☒ MEC; ☒ WHI; ☐ CC; ☐ Other: _____
If CALiCo, specify ☒ ARIC; ☒ CARDIA; ☒ CHS; ☐ SHS-Fam; ☐ SHS-Cohort; ☒ SOL

I, MG, affirm that this proposal has been reviewed and approved by all listed investigators.

V. REFERENCES

1. Teslovich, T.M., et al., *Biological, clinical and population relevance of 95 loci for blood lipids*. Nature, 2010. **466**(7307): p. 707-13.
2. Willer, C.J., et al., *Discovery and refinement of loci associated with lipid levels*. Nat Genet, 2013. **45**(11): p. 1274-83.
3. Franssen, R., et al., *Obesity and dyslipidemia*. Med Clin North Am, 2011. **95**(5): p. 893-902.
4. Howard, B.V., G. Ruotolo, and D.C. Robbins, *Obesity and dyslipidemia*. Endocrinol Metab Clin North Am, 2003. **32**(4): p. 855-67.
5. Klop, B., J.W. Elte, and M.C. Cabezas, *Dyslipidemia in obesity: mechanisms and potential targets*. Nutrients, 2013. **5**(4): p. 1218-40.
6. Cole, C.B., et al., *Adiposity Significantly Modifies Genetic Risk for Dyslipidemia*. J Lipid Res, 2014.
7. Dumitrescu, L., et al., *Genetic determinants of lipid traits in diverse populations from the population architecture using genomics and epidemiology (PAGE) study*. PLoS Genet, 2011. **7**(6): p. e1002138.
8. Wu, Y., et al., *Trans-ethnic fine-mapping of lipid loci identifies population-specific signals and allelic heterogeneity that increases the trait variance explained*. PLoS Genet, 2013. **9**(3): p. e1003379.
9. Han, B. and E. Eskin, *Random-effects model aimed at discovering associations in meta-analysis of genome-wide association studies*. Am J Hum Genet, 2011. **88**(5): p. 586-98.
10. Morris, A.P., Zeggini, E. *An evaluation of statistical approaches to rare variant analysis in genetic association studies*. Genet. Epidemiol., 2010. **34**, 188-193.