ARIC Manuscript Proposal #1947

PC Reviewed: 5/29/12 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

Population Architecture using Genomics and Epidemiology (PAGE)

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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: ____ Submission Date : _May 2012___ [Approval Date: ___]

Title of Proposed Ms.: Genetic association of Ankle Brachial Index (ABI) and Lower Extremity Peripheral Artery Disease (PAD) in African American, European, and Hispanic individuals using the MetaboChip array: The PAGE Study

I. INVESTIGATOR INFORMATION:

Name of Lead Author: Christina L. Wassel (CALiCo/SOL) | **Junior Investigator? Yes**
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Partner studies in PAGE not collaborating in this ms. proposal:

Study	Contacted? Y/N	Declined? / Other?
MESA	N	
NOMAS	N	
eMERGE network	N	

Names, affiliations, email address of non-PAGE investigators proposed as co-authors: **None at this time, but will likely be added as we contact the studies**

II. SCIENTIFIC RATIONALE (Please be specific and concise) Peripheral artery disease (PAD) is associated with an increased risk for incident cardiovascular disease events and mortality[1, 2]. In the Reduction of Atherothrombosis for Continued Health (REACH) registry, almost two-thirds of the individuals with PAD had concomitant clinically-evident atherosclerotic disease in the cerebrovascular or coronary artery disease (CAD) territories whereas only one-quarter of the individuals with coronary disease had clinically-evident atherosclerotic involvement of other arterial beds[3]. While PAD and CAD share many common risk factors, cigarette smoking and type 2 diabetes are stronger risk factors for PAD than for coronary artery disease[4]. The variable distribution of the burden of atherosclerosis across vascular beds among subjects at risk suggests that other factors exist, including possibly genetic factors, that may contribute to the predilection of atherosclerosis to develop in a given anatomic location. Currently, little is known about the genetic susceptibility to PAD but familial aggregation of PAD and heritability estimates suggest a significant genetic contribution[5-10].

The ankle brachial index (ABI) is an easy and reliable diagnostic test used to detect symptomatic as well as asymptomatic PAD[11]. A genome-wide linkage scan for ABI identified several potential candidate genes under six linkage signals in pathways of inflammation, coagulation, blood pressure regulation, and lipid metabolism[6]. A recent large genome-wide association study (GWAS) meta-analysis of European descent participants found variants in the 9p21 locus significantly associated with ABI[12]. Additionally, a recent large-scale candidate gene analysis found a variant in *TCF7L2* significantly associated with ABI in the discovery phase, but it was not replicated[13]. However, overall there have been few large scale candidate gene studies conducted concentrating on the ABI and PAD phenotypes, and most of which have been limited by small sample size, lack of ethnic diversity, lack of modest number of genes examined, and lack of robust independent replication of initial findings[14]. In particular, very little is known regarding possible genetic variants for ABI and PAD in Hispanics.

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

a. **Study Questions/Hypotheses**.

1. For loci represented in the MetaboChip array, are there *possible* novel associations with ankle brachial index and peripheral artery disease in African American and Hispanic individuals (potential new loci)? Currently very little is known about genetic variants for ABI and/or PAD in Hispanics. We will also examine this association in European Americans so that they can be used as a comparison group.

2. For known loci associated with atherosclerotic, subclinical cardiovascular disease (CVD) and clinical CVD traits and represented in the MetaboChip, are there one of more independent signals in African Americans and/or Hispanics (generalization and fine mapping)? We will

also use European results as necessary here to aid in generalization and fine-mapping efforts.

b. **Study populations, study design for each**

All PAGE study populations with Metabochip data and measured ankle brachial index and/or peripheral artery disease, which includes ARIC, CHS, WHI, HCHS/SOL, and EAGLE.

c. Variant/SNPs (Specify)

We will evaluate all the variants in the MetaboChip that passed quality control (QC) from a range of allele frequencies (0.05% or more allele frequency) for our discovery effort and fine mapping of known loci. QC will be performed at the PAGE CC.

d. **Phenotype(s) (Specify)**

The phenotypes to be used for analyses are:

1. The ABI as a quantitative trait, i.e. the systolic blood pressure in the ankle divided by the systolic blood pressure in the arm. Those with ABI > 1.4 will be removed. This phenotype will be harmonized as closely as possible among all of the studies. The lead author has previously performed ABI harmonization for several of the PAGE studies (as well as possible replication studies) already as part of the Candidate Gene Association Resource (CARe) consortium.

2. PAD as a binary trait, including participants with ABI<0.90, hospitalization for PAD (WHI and SOL), or previous leg revascularization. Those with ABI > 1.4 will be removed. If information on intermittent claudication is available in enough studies (as assessed by the Rose claudication questionnaire), and the sample size is sufficient, this may also be either added to the PAD definition as a sensitivity analysis, or examined as separate outcome.

e. **Covariates (Specify)**

Continuous age, sex, study center or region (if needed), and ancestry principal components. We will also adjust for local ancestry estimates if available. Additional levels of adjustment for traditional cardiovascular disease risk factors (i.e. smoking, hypertension, lipids, body mass index, diabetes) may be performed to determine whether any novel loci identified for ABI or PAD are actually working through another closely associated trait or disease (i.e. mediation).

f. **Main statistical analysis methods**

Analyses will be stratified by self-reported race and within each PAGE study. We will use linear regression models for ABI and logistic regression models for the PAD. We will use additive genetic models adjusted for age, sex (except WHI), study center or region (if needed), and ancestry principal components (PCs). PCs will be centrally generated at the PAGE CC to ensure consistency across analyses and manuscripts. Adjustment for local ancestry estimates will take place as needed, and if available in time. The number of PCs adjusted for will be guided via QQ plots, and also strength of the associations of the PCs with the kidney traits of interest. It is difficult to determine beforehand, without the actual data, how many PCs we will need to adjust for, exactly what type of analyses may need to be conducted, and how this may or may not differ among the

ethnic Hispanic groups (i.e. Dominican, Mexican, Cuban). Additional levels of adjustment may be carried out as described above in the "Covariates" section. Those with ABI > 1.4 will be removed from both continuous ABI and binary PAD analyses, as this generally indicates arterial stiffening or medial calcification, and it cannot be effectively determined with ABI only whether these participants have atherosclerosis in the lower extremities. Additionally, WHI will not contribute to ABI analyses, as they do not have ABI but rather PAD determined from hospital records. Because individuals were recruited using a probability sampling in the SOL, all analyses of this study will use weights to account for identification and selection of community areas and random selection of households within those areas[15]. Study-specific association results will be combined across race-specific samples using a fixed effects inverse variance meta-analysis approach implemented in METAL[16] or PLINK[17].

For aim 1. Possible Discovery. We will perform single variant test for all variants with minor allele frequency (MAF) >1% and use Bonferroni correction to declare a significant p-value threshold based on multiple testing. Although we acknowledge that power may be suboptimal in certain groups for this aim (i.e. not all studies have ABI (WHI)), there is still potential to discover new loci in groups such as Hispanics, which are very understudied with regard to genetic variants for ABI and PAD. For example of result reporting see Example Table 1.

For aim 2. Generalization and fine mapping. We will perform comprehensive analyses of all known loci for atherosclerotic, subclinical CVD and clinical CVD traits represented in the MetaboChip. We will use single variant test approach for variants with MAF>1% and adjust for the number of independent tests using a Monte Carlo approach that accounts for linkage disequilibrium (LD) between variants across the tested loci[18]. We will perform conditional analyses using the most significant variant as covariate if there is suggestive evidence for secondary independent signals in these regions. For low frequency variants (0.1%<MAF<5%), we will explore novel methods for collapsing variants across regions including a recent method developed by Lin et al[19], as well as rare variants burden tests of Madsen and Browning[20], Li and Leal[21], Liu and Leal[22], and Pan and Shen[23]. In order to adequately evaluate SNPs within the 0.1-5% MAF range for PAD as a binary trait, we will use the methods of Li et al[24], which are appropriate for analysis of rare variants from GWAS and imputed GWAS data. Briefly, these methods include a weighted haplotype-based test, and an imputation-based test. These methods do not rely on the availability of external sequence data, but it can be incorporated, and also improve the power over traditional rare variant methods that are more appropriate for sequence data. For novel variants identified in known loci, we will further use bioinformatics tools for functional characterization of the variants. For example of result reporting see Example Table 2 and Example Figures.

We are currently working on possible replication groups for this study, including the Multi-Ethnic Study of Atherosclerosis (MESA) for African American and Hispanic individuals, possibly the Northern Manhattan Study (NOMAS) for Hispanics, as well as the eMERGE network, and will be contacting these studies in the near future.

g. **Ancestry information used? No __ Yes__X_ How is it used in the analyses?**

We will use estimates of global ancestry (principal components) to adjust for population stratification. Because global ancestry may not fully account for population stratification in African Americans and Hispanics, we will also adjust for local ancestry, as available.

h. **Anticipated date of draft manuscript to P&P:** __6-8 months after the data are available_**. Analyses should be done in 1-2 months and remaining time is for replication of main findings in collaborating studies and for manuscript writing.**

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 _X_ 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:

[X] EAGLE; **[X]** CALiCO; **[ ]** MEC; **[X]** WHI; **[ ]** CC; **[ ]** Other:_____
If CALiCo, specify **[X]** ARIC; **[ ]** CARDIA; **[X]** CHS; **[ ]** SHS-Fam; **[ ]** SHS-Cohort; **[X]** SOL

Table of ABI/PAD availability in PAGE

	ABI	PAD
ARIC	Yes	Yes
CHS	Yes	Yes
CARDIA	No	No
SHS	No metabochip data	No metabochip data
EAGLE	Yes	Yes
MEC	No	No
WHI	No	Yes
SOL	Yes	Yes

NOTE: As indicated above, our MAIN definition of PAD will be ABI<0.90, hospitalization for PAD (WHI and SOL), or previous leg revascularization. We will perform sensitivity analysis to determine whether we obtain similar results when using hospital records, i.e. excluding WHI.

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

V. REFERENCES

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Appendix. Example of PAGE Metabochip fine-mapping figures and tables using European and African American data (for SOL P&P)*

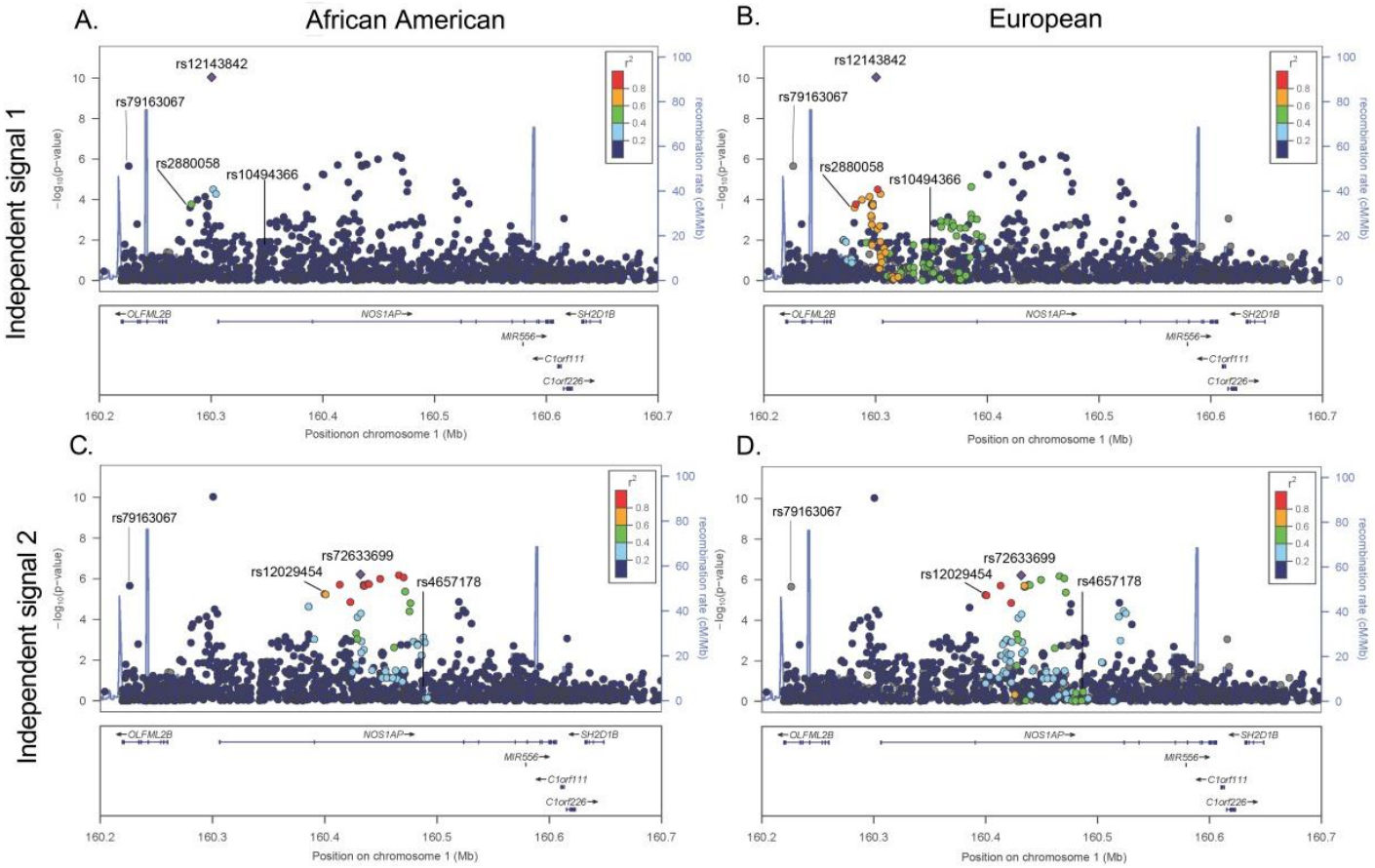

FIGURE 1.–Log *P* plot for common SNPs at the gene independent signal 1 and 2 loci. *P*-values are estimated in African Americans are plotted using linkage disequilibrium estimates from African Americans (panels A and C) and Europeans (panels B and D). SNPs are represented by *circles*, lines indicate index SNPS previously identified in GWA studies of European and Indian Asian populations, and the *large blue diamond* is the best marker in African Americans. Circle color represents correlation with the best marker in African Americans: *blue* indicates weak correlation and *red* indicates strong correlation. Recombination rate is plotted in the background and annotated genes are shown at the bottom of the plot. ***Similar figures will be generated for each ethnic group included in the proposal**

Example of TABLE 1. Novel associations with ABI and PAD in SOL participants.*

SNP	Locus	Chr	Position (Build 36)	Coded/other allele	Coded allele frequency	Beta (se) or OR (se)	*P*-value
			Ankle Brachial Index				
rsxxx							
			Peripheral Artery Disease				

(we will considered showing this results by country of origin)

***Similar results tables will be generated for each ethnic group included in the proposal**

Example of TABLE 2. Associations with common variants at known subclinical CVD loci with ABI and PAD in SOL participants.*

		Index SNPs from GWA studies						Best marker in SOL Hispanics[a]					r^2 with index SNP	
				CAF		*P*-		Position						
Locus	**Position**	**Index SNP**	**Alleles**	**EU[b]**	**Hisp[c]**	**value (AF)**	**Marker**	**(build 36)**	**Alleles**	**CAF**	***P*-value**	**EU[b]**	**Hisp[c]**
						Ankle Brachial Index							
1p23													
2q4													
5p21													
						Peripheral Artery Disease							

***Similar results tables will be generated for each ethnic group included in the proposal**

Example of Descriptive TABLE. Demographic characteristics of SOL and WHI Hispanic participants *

Characteristic	SOL	WHI PAGE	
		Wave 1	Wave 2
N			
Age, years, mean (SD)			
Sex, female, N (%)			
QT duration, ms, mean (SD)			
Heart rate, bpm, mean (SD)			

WHI, Women's Health Initiative; Study of Latinos.

***Similar results tables will be generated for each ethnic group included in the proposal**