ARIC Manuscript Proposal #2038

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Population Architecture using Genomics and Epidemiology (PAGE)

PAGE Manuscript Proposal

PAGE Ms. Number: _____ Submission Date : _____ [Approval Date: _____]

Title of Proposed Ms.: Fine mapping of previously identified QRS loci to multi-ethnic populations: The PAGE Study

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II. SCIENTIFIC RATIONALE (Please be specific and concise)

The QRS interval measured on the standard, resting 12-lead electrocardiogram represents the period of ventricular depolarization. A prolonged QRS is observed in the presence of asymmetric conduction delay in the His-Purkinje system or prolonged intramyocardial conduction. Prolongation of the QRS is therefore reflective of infra-AV nodal conduction system disease or ventricular myocardial disease. A prolonged QRS has been independently associated with increased cardiovascular mortality in the general population[1] and in those with existing cardiovascular disease[2, 3]. A prolonged QRS has also been predictive of incident heart failure[4] and atrial fibrillation[5].

Studies of familial aggregation and in twins have estimated that the heritability of QRS duration is approximately 36-43%[6, 7]. A small candidate gene studies identified association between common variation in *SCN5A* and QRS duration in European[8] and African American cohorts[9]. An *SCN10A* locus was first identified on GWAS in an Indian Asian cohort and replicated in a European Cohort[10]. A large-scale genome wide association (GWA) study in an Icelandic cohort reported genome wide associations between QRS duration loci in the *SCN10A*, *CDKN1A*, and *TBX5* genes[11]. A subsequent GWA study in a larger European cohort reported common variants in twenty two loci genome-wide significantly associated with QRS, including the three previously published loci[12].

Thus far, however, there have been no GWA studies of QRS duration performed in African American or Hispanic cohorts and the significance of these loci in these minority populations has not been established. Given the augmented genomic diversity in ancestral populations, there also are opportunities to further narrow and fine-map established QRS loci[13]. We propose to evaluate the 9 loci that have previously been associated with QRS duration in the European cohorts (Table 1) for evidence of generalization and locus refinement in the multi-ethnic PAGE populations genotyped on the Metabochip platform. Similar techniques were used by PAGE investigators to evaluate eleven European QT loci in a combined African American population and resulted in successful narrowing of several loci (Avery et. al., in press *PLoS Genetics,* 2012).

III. OBJECTIVES AND PLAN

a. **Study Questions/Hypotheses**.

First, we will evaluate twenty two QRS loci previously identified in populations of European descent in African American and Latino populations. In addition to testing the previously reported QRS index SNPs at the known loci, we also will search for stronger markers of the index signal in the two populations and investigate evidence for independent, novel SNPs influencing the QRS interval. For loci associated with QRS at our population-specific significance thresholds (defined below), we also will investigate whether patterns of linkage disequilibrium (LD) within the PAGE populations can narrow the regions likely to harbor the biologically relevant variant(s). Finally, we will query bioinformatic databases and perform related *in silico* analyses to propose candidate polymorphisms for follow-up functional evaluation.

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

All PAGE study populations with Metabochip data and measures of QRS.

c. **Variant/SNPs (Specify)**

SNPs fine-mapped on the Metabochip for the 22 previously identified QRS loci (Table 1), restricting to SNPs with population-specific minor allele frequency estimates $\geq$ 0.01.

TABLE 1. Characterization of 22 genomic regions fine-mapped for the QRS interval. The 9 SNPs covered by the metabochip that will be included in this study have been marked in bold.

Previously identified locus	Index SNP(s)	Genetic region	BP Position	Base pair range (Build 37)	N SNPs fine-mapped [a,b]
SCN10A/SCN5A	**rs6801957 rs9851724 rs10865879 rs11710077 rs11708996 rs2051211**	**3p22.2**	**ch3:38767315 ch3:38719935 ch3:38577362 ch3:38657899 ch3:38633923 ch3:38559749**	**38515022, 38843963**	**977**
CDKN1A	rs9470361	6p21.31	ch6:36623379	NA	NA
PLN	**rs11153730**	**6q22.31**	**ch6:118667522**	**118428596, 119092253**	**1568**
NFIA	rs9436640	1p31.3	ch1:61873677	NA	NA
HAND1	rs13165478	5q33.2	ch5:153869040	NA	NA
TBX20	rs1362212	7p14.3	ch7:35305306	NA	NA
SIPA1L1	rs11848785	14q24.2	ch14:72057355	NA	NA
TBX5	rs883079	12q24.21	ch12:114793240	NA	NA
TBX3	**rs10850409**	**12q24.21**	**ch12:115381740**	**115334077, 115443997**	**429**
VTI1A	rs7342028	10q25.2	ch10:114479262	NA	NA
SETBP1	rs991014	18q12.3	ch18:42439886	NA	NA
HEATR5B	rs17020136	2p22.2	ch2:37248015	NA	NA
TKT	rs4687718	3p21.1	ch3:53282303	NA	NA
CRIM1	rs7562790	2p22.2	ch2:36673555	NA	NA
C1orf185	rs17391905	1p32.3	ch1:51546140	NA	NA
PRKCA	**rs9912468**	**17q24.2**	**ch17:64318357**	**64195854, 64343764**	**478**
IGFBP3	rs7784776	7p13	ch7:46620145	NA	NA
CASQ2	rs4074536	1p13.1	ch1:116310967	NA	NA
KLF12	rs1886512	13q22.1	ch13:74520186	NA	NA
LRIG1	rs2242285	3p14.1	ch3:66431602	NA	NA
DKK1	rs1733724	10q21.1	ch10:54223977	NA	NA
GOSR2	rs17608766	17q21.32	ch17:45013271	NA	NA

[a]Restricted to SNPs with minor allele frequency > 0.01. [b]We expect numbers to differ slightly by race/ethnicity.

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

QRS is the only phenotype examined in this proposal. For CALiCo studies and the WHI Clinical Trials, certified technicians digitally recorded resting, supine (or semi-recumbent), standard 12-lead ECGs for each participant using Marquette MAC PC, MAC6 or MAC1200 machines (GE Healthcare, Milwaukee, WI, USA). These studies used comparable procedures for preparing participants, placing electrodes, recording, transmitting, processing, and controlling the quality of the ECGs. QRS was measured electronically using either the Marquette 12SL algorithm or the MC MEANS algorithm.

For BioVU data, the population is defined as patients with DNA and without evidence of cardiac disease within 1 month of a "normal" ECG (as defined in Supplemental Table 1) and who did not have abnormal potassium, calcium, or magnesium laboratory values at the time of the ECG. Previous reports of atrioventricular conduction in n=2,334 BioVU samples suggests that electrocardiographic data from electronic medical records can replicate GWA study signals previously reported in population-based cohorts with standardized measurement protocols [14]. Sensitivity analyses will be performed with BioVU data to assure that the methods of ascertaining QRS measurements are comparable by assessing that SNP-QRS association effect sizes are homogenous across study groups prior to combining the data.

Patients with QRS >120ms will be excluded from the analysis as these electrocardiograms often represent bundle branch blocks, paced rhythms, pre-excitation and other clinically and genetically distinct phenotypes. This exclusion is consistent with the QRS phenotype defined in the previously published QRS GWA meta-analysis.

e. **Covariates (Specify)**

To maintain consistency with previous GWA study efforts we will consider age, sex, height, body mass index, study center and principal components measuring global ancestry. Unlike the case with the QT interval, the QRS interval does not vary significantly with heart rate and will therefore not be included as a covariate. In addition, prior meta-analyses of QRS interval have not used heart rate as a covariate[12] and we will attempt to maintain similar covariates for consistency.

f. **Main statistical analysis methods**

Race/ethnic- and study-specific linear regression models will be used to test the association between the QRS interval and approximately 9 SNPs from 22 regions fine-mapped for the QRS interval under an additive genetic model and including age, sex, height, body mass index, study center, and principal components as covariates. The selection of these covariates is consistent with previously published QRS interval GWA analyses which did not include heart rate as a covariate. Weights accounting for the complex sampling design in SOL will be accommodated in all models examining SOL data. Race- and study-specific association results will be combined across cohorts using an inverse variance meta-analysis approach as implemented in METAL [15].

We appreciate that the above analytic strategy, while consistent with previous efforts in populations of European and African descent, may be inadequate for populations of Hispanic/Latino ancestry. We will therefore work closely with other Metabochip working groups and the Coordinating Center to ensure that our analytic approach is appropriate for populations of Hispanic/Latino ancestry.

Examples of figures and tables that will be constructed are presented below in the appendix.

Multiple testing thresholds

For each QRS locus, it is expected that SNPs associated with QRS in African Americans and Latinos will be correlated with the index SNP reported in Europeans. Therefore, we will first identify and test SNPs that are correlated ($r^2 > 0.20$) with the index signals in Europeans using LD statistics estimated in the Malmö Diet and Cancer Study. For loci with numerous reported index SNPs, we will consider SNPs with $r^2 < 0.20$ as representing independent signals. In order to determine the appropriate multiple testing threshold for declaration of whether the independent signals are significantly associated with QRS in PAGE populations, i.e. generalizability, we will then estimate the number of tag SNPs for each race/ethnic group needed to capture all common alleles ($r^2 > 0.80$, MAF > 0.05) using LD patterns specific to that race/ethnicity. As an example, the multiple testing threshold for declaring generalization that was used in a prior QT locus fine-mapping effort was $\alpha_a = 0.05/415$, 415=the total number of tags identified using African American LD patterns.

For all remaining SNPs that are not correlated with the index signal in Europeans, i.e. population-specific SNPs influencing QRS, we will use an efficient Monte Carlo approach calculated by race/ethnic group that accounts for LD between SNPs at the previously identified QRS loci [16]. Conditional analyses are then performed to determine the number of independent signals the significant population-specific SNPs represent. Specifically, analyses will be repeated for each locus including the SNP with the smallest *P* – value as a covariate. This approach will be performed adjusting for successively less significant SNPs until no SNPs with *P* –values lower than the Monte Carlo-defined alpha level are identified.

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

Global ancestry, as measured by principal components (PCs), is included as a covariate in the analysis.

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. The number of PCs adjusted for will be guided via QQ plots and strength of the associations of the PCs with QRS.

h. **Anticipated date of draft manuscript to P&P:** _6 months after the data are available_

i. **What manuscript proposals listed on** *www.pagestudy.org/index.php/manuscripts/* **are most related to the work proposed here? Approved PAGE ms. numbers:** _Metabo007 (QT, pilot data, in press), MS 39 (QRS *SCN5A* fine-mapping, proposed manuscript only uses pilot data), Metabo 44 (QT, all metabochip data), Metabo PR (Seyerle, deferred by P&P). Members of all writing groups with potentially related proposals are included in the current effort.

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

I, _(MVP)_, affirm that this proposal has been reviewed and approved by all listed investigators.

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Supplemental Table 1. BioVU criteria for "normal" ECGs.

Criteria	Source/Method
"Normal" ECG must be:	
• QRSd between 65-120ms	ECG calculations
• ECG designed as "NORMAL"	ECG classification
• Heart Rate between 50-100 bpm	ECG calculations
• ECG Impression must not contain evidence of heart disease concepts[1]	Natural Language Processing (NLP) on ECG impression. Will exclude all but negated terms (e.g., exclude those with possible, probable, or asserted bundle branch blocks). Should also exclude normalization negations like "LBBB no longer present."
• ECGs was not recorded during presence of sodium channel blocking drugs[2]	Taken from last clinic note or problem list before the ECG, can be simplified to "anytime before" the ECG
• ECGs recorded during these lab abnormalities are ignored	EMR Lab values: - K > 6, K < 3.5 - Ca < 8 or Ca > 11 - Mg < 1.7

Notes contain no evidence of heart disease concepts before ECG time or within one month following	• NLP for notes, Problem Lists at or near ECG time, ignoring Family Medical History and Allergy sections (using section tagger)
	• ICD9 and CPT codes at or near ECG time describing heart disease
	• Labs:
	  ○ Positive cardiac enzymes (CPK-MB > 8, Troponin > 0.05)
	  ○ BNP > 100

Must have at least a problem list and/or note containing non-empty (can say "none") medication list and past medical history before or immediately after the time of the ECG.	Note section tagging to detect non-empty past medical history and medication sections.

[1] Heart disease includes: any presence of coronary disease concepts; any type of heart failure; any type of valvular disease; any type of cardiomyopathy; ventricular hypertrophy; any type of arrhythmia; any type of cardiac conduction problem; heart transplant.[2]Flecainide, propafenone, mexiletine, lidocaine, quinidine, procainamide, disopyramide, amiodarone, imipramine, amitryptiline (>25mg total daily dose), lithium, encainide, moricizine, quinine, desipramine, propoxyphene, tocainide

PAGE Metabochip fine-mapping example figures and tables. The below figures and tables were excerpted from a PAGE fine-mapping study of QT interval loci that was conducted in African American populations. Although tables and figures are presented for African American populations, similar tables and figures will be prepared for each race/ethnic group under investigation.

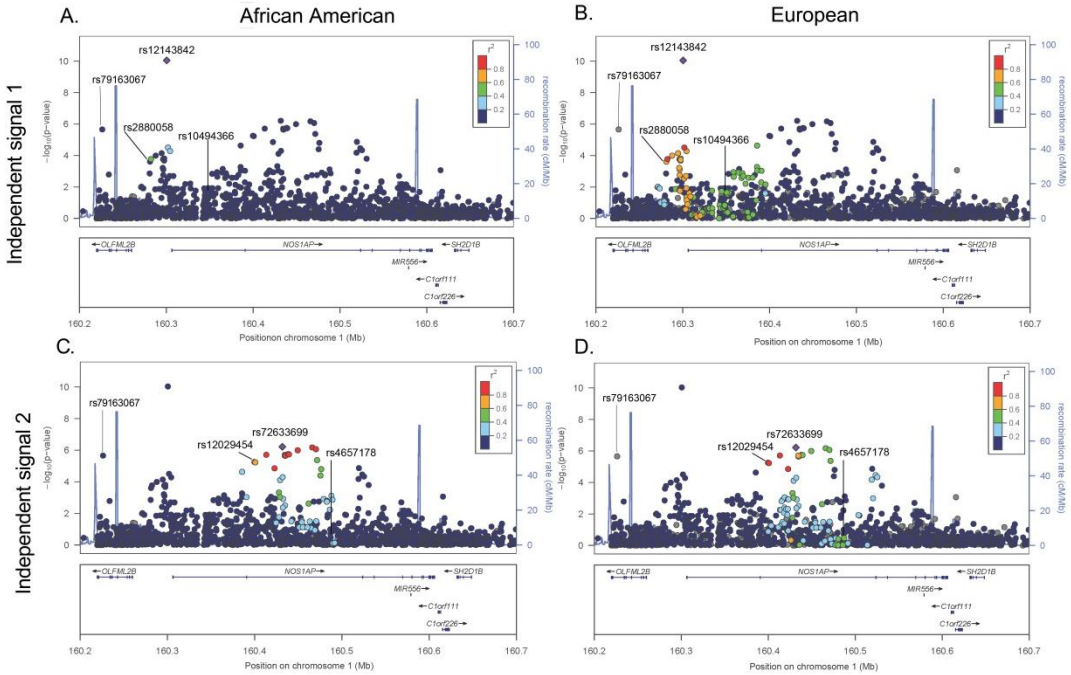

FIGURE 1.–Log *P* plot for common SNPs at the *NOS1AP* independent signal 1 and 2 loci. *P*-values are estimated in African Americans are plotted using linkage disequilibrium estimates from African Americans (panels A and C) and Europeans (panels B and D). SNPs are represented by *circles*, lines indicate 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.

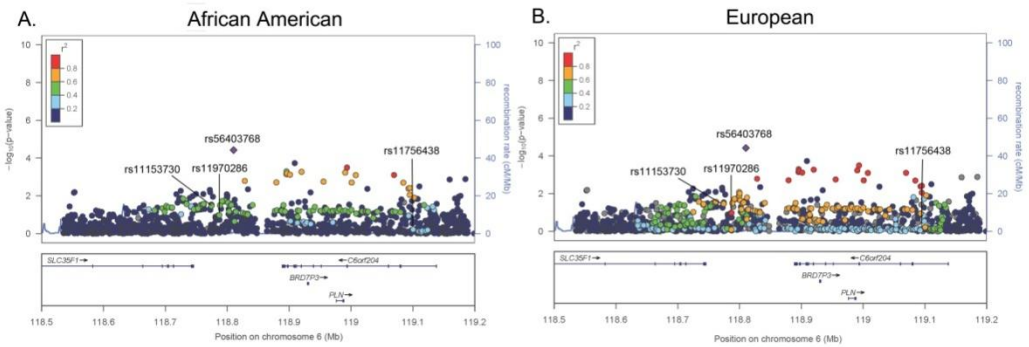

FIGURE 2.–Log *P* plot for common SNPs at the *PLN* independent signal 1 locus. *P*-values are estimated in African Americans are plotted using linkage disequilibrium estimates from African Americans (panel A) and Europeans (panel B). SNPs are represented by *circles*, lines indicate index SNPS previously 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.

TABLE 1. Associations with common variants at known QRS loci in n=8,644 African American participants.

	Index SNPs from GWA studies in European and Indian Asian populations							Best marker in African Americans[a]					r^2 with index SNP	
					CAF									
Locus	Position	Ind. signal	Index SNP	Alleles	EU[b]	AF[c]	*P*-value (AF)	Marker	BP (build 36)	Alleles	CAF	*P*-value	EU[b]	AF[c]

[a]Restricted to SNPs with minor allele frequency > 0.01.[b]Calculated in the Malmö Diet and Cancer Study or 1,000 Genomes CEU data when Malmö data unavailable. [c]Calculated in the Atherosclerosis Risk in Communities Study. [d]SNP not present on Metabochip, SNP proxy substituted. [e]SNP not present on Metabochip, but in very high LD with rs2968863 (r^2> 0.95). [f]SNP failed quality control and no proxy was available. AF, African American. BP, base pair. CAF, coded allele frequency. Est, estimate. European. GWA, genome wide association. Ind, independent. NA, not available. SE, standard error. SNP, single nucleotide polymorphism.

TABLE 2. Novel and independent SNPs associated with QRS at two previously identified QRS loci in n=8,644 African American participants.

African American index SNP[a]	Locus	Chr	Position (Build 36)	Alleles[b]	Coded allele Frequency		*P*-value
					African Americans[c]	Europeans[d]	

[a]Restricted to SNPs with minor allele frequency > 0.01 that passed quality control and defined as locus-specific SNP with the lowest *P*-value.[b]Coded allele listed first. [c]Calculated in the Atherosclerosis Risk in Communities Study. [d]Calculated in the Malmö Diet and Cancer Study.[e]Adjusted for rs12061601. Est, estimate. KB, kilobase. SE, standard error. SNP, single nucleotide polymorphism.

TABLE 3. Comparison of linkage disequilibrium patterns between populations of African and European descent for nine previously identified QRS loci significantly associated with QRS in n=8,644 African American participants from four studies.

		African Americans		Europeans		Region size difference (kb)[d]
Locus	Ind. signal	N. SNPs in LD with best marker[a,b]	Region size (kb)	N. SNPs in LD with index SNPs[a,c]	Region size (kb)	

[a] $r^2 \geq 0.50$. [b] Calculatedusing African American LD patterns. [c] Calculated using European LD patterns. [d] Calculated as (African American region size – European region size (kb)). LD, linkage disequilibrium.

SUPPLEMENTAL TABLE 1. Demographic characteristics of n=8,644 African American participants from four studies.

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

ARIC, Atherosclerosis Risk in Communities Study. Bpm, beats per minute; Ms, milliseconds; PAGE, Population Architecture using Genomics and Epidemiology. SHARe, SNP Health Association Resource. WHI, Women's Health Initiative.

TABLE S2. Associations with common variants at nine previously reported QRS loci that did not generalize to n=8,644 African American participants.

Index SNPs from Published GWA studies in European populations								African Americans			
Locus	**Position**	**Ind. signal**	**Index SNP**	**Alleles**	**CAF**	**Est.**	**SE**	**CAF[a]**	**Est.**	**SE**	***P*-value**

[a]Calculated in the Atherosclerosis Risk in Communities Study. [b]SNP not present on Metabochip, but in very high LD with rs2968863 (r^2 > 0.95). CAF, coded allele frequency. Est, estimate. Ind, independent. NA, not available. SE, standard error. SNP, single nucleotide polymorphism.