ARIC Publication

TO: Nell Malone, ARIC Publication Committee

COPY: Julia Higashio

FROM: Gerardo Heiss, for the PAGE Publication Committee

DATE: August 3, 2010

RE: PAGE Manuscript Proposal Including ARIC Data

As you know, CALiCo is an ancillary study of ARIC and a member study of *Population Architecture using Genomics and Epidemiology* (PAGE). Manuscripts originating in PAGE are processed according to the publication policy shared with you in August, 2009. Manuscript proposals approved by the PAGE Publication Committee (PAGE P&P) are submitted for consideration by the publication committees of the parent studies included in the proposed manuscript, for information or coordination with study-specific publication activities, as applicable. If the ARIC publication committee wishes to supplement the authors listed in the enclosed you are welcome to do that. A reminder of the main features of PAGE is listed at the bottom.

Attached is PAGE manuscript proposals number 032 approved by the PAGE P&P, submitted for your information. It is important to note that individual-level data analyses for these manuscripts are conducted by the investigator(s) of each participating study in PAGE, leading to study-specific summary data that are aggregated across collaborating studies at one of the study sites (the PAGE coordinating Center or a designated analysis group). At this time the PAGE P&P reviewed (and has approved) the enclosed manuscript proposals on scientific merit, potential overlap, and adherence to the PAGE P&P publication policy.

At this time we submit the enclosed manuscript proposal(s) for your consideration. Additional PAGE manuscript proposals will follow in the near future. As manuscripts are drafted a copy will be sent for your information, once approved by the PAGE P&P.

I will be glad to address any questions and look forward to your comments. Please address correspondence to me, at gerardo_heiss@unc.edu

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Synopsis. PAGE is a NHGRI-funded consortium that consists of WHI, EAGLE, MEC, and CALiCo. The latter is a consortium of ARIC, CHS, CARDIA, SHS, and SOL. Each study has a PI in PAGE or CALiCo respectively, as shown below. The NHGRI scientific officer is Lucia Hindorff.

EAGLE	MEC	WHI	CALiCo-ARIC	CALiCo-CARDIA	CALiCo-CHS	CALiCo-SHS	CALiCo-SOL
Dana Crawford	Loic LeMarchand	Ulrike Peters	Gerardo Heiss	Sharina Person	Nancy Jenny	Shelley Cole	Gerardo Heiss

The aim of PAGE is to genotype a small number (100s) of SNPs from well replicated variants on large numbers of individuals in the diverse populations represented in its source studies. Instead of gene discovery, the objective of PAGE is to estimate the population impact of mature genetic variants in diverse contexts. There is no overlap or similarity between PAGE and CHARGe, CARe, SHARe, GENEVA, among other GWAs-focused consortia.

ARIC Manuscript Proposal # 1682

PC Reviewed: 8/10/10 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

Population Architecture using Genomics and Epidemiology (PAGE)

Ver. 10/09/09

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: __032____ Submission Date : __6/2/2010____[Approval Date: _____]

Title of Proposed Ms.: Genetic determinants of age at menarche and natural menopause in diverse populations from the Population Architecture using Genomics and Epidemiology (PAGE) Study (tentative)

I. INVESTIGATOR INFORMATION:

Name of Lead Author:
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Junior Investigator?
Yes

Name of Corresponding Author (**if different**):

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Comment [l1]: Representatives from Cardia and CHS are currently being identified.

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

Study	Contacted? Y/N	Declined? / Other?

Names, affiliations, email address of non-PAGE investigators proposed as co-authors:

II. SCIENTIFIC RATIONALE (Please be specific and concise)

Age at menarche has been associated with reproductive cancers, decreased fertility, and many of the components underlying metabolic syndrome, including impaired glucose tolerance, diabetes, and obesity[1]. Timing of natural menopause is associated with cardiovascular disease[2], as well as reproductive cancers and osteoporosis[1]. To date, genome-wide association studies for traits associated with reproductive lifespan have been studied nearly exclusively in Caucasian populations[3-9], despite the fact that age of menarche[10, 11] and menopause[12] vary by ethnicity. More work is needed to understand the genetic variation underlying reproductive lifespan in diverse populations and how environmental factors may interact with genetic variants to alter these traits.

III. OBJECTIVES AND PLAN (Please be specific and concise)
a. **Study Questions/Hypotheses**. Specifically, we will:

1) characterize the association of genetic variants previously associated with age at menarche and menopause by GWAS in the diverse samples represented in PAGE
2) examine environmental modifiers of the SNP associations with age at menarche, including year of birth
3) examine environmental modifiers of the SNP associations with age at natural menopause, including smoking, parity, and use of oral contraceptives

b. **Study populations, study design for each**
The proposed analyses will include all populations participating in the Population Architecture using Genomics and Epidemiology (PAGE) Study.

Table 1. Reproductive Variables Available by Study Site

Asked questions related to:	menarche	menopause	specify natural/surgical
EAGLE	**Yes**	**Yes**	**Yes**
MEC	**Yes**	**Yes**	**Yes**
WHI	**Yes**	**Yes**	**Yes**
ARIC	**Yes**	**Yes**	**Yes**
CARDIA	**Yes**	**Yes**	**Yes**
CHS	No	**Yes**	**Yes**
SHS	No	**Yes**	**Yes**

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

Table 2. Year 2 and Metabochip Reproductive SNPs by Study Site

		Y2 Genotyping				
SNP	**Phenotype**	**Calico**	**EAGLE**	**MEC**	**WHI**	**Reported Gene(s)**
rs314280	menarche	Y2 list	Y2 list	Y2 list	Y2 list	LIN28B
rs314277	menarche	Y2 list	Y2 list	Y2 list	Y2 list	LIN28B
rs7861820	menarche	Y2 list	Y2 list	Y2 list	Y2 list	Intergenic
rs2090409	menarche	metabochip	No	metabochip	metabochip	Intergenic
rs7759938	menarche	metabochip	No	metabochip	metabochip	LIN28B
rs365132	menopause	Y2 list	Y2 list	Y2 list	Y2 list	UIMC1
rs2153157	menopause	Y2 list	Y2 list	Y2 list	Y2 list	SYCP2L
rs7333181	menopause	Y2 list	Y2 list	Y2 list	Y2 list	Intergenic
rs1172822	menopause	Y2 list	Y2 list	Y2 list	Y2 list	BRSK1
rs16991615	menopause	Y2 list	Y2 list	Y2 list	Y2 list	MCM8
rs236114	menopause	metabochip	No	metabochip	metabochip	MCM8
rs4843747	menopause	metabochip	No	metabochip	metabochip	BANP
rs494620	menopause	metabochip	No	metabochip	metabochip	SLC44A4
rs10496265	menopause	metabochip	No	metabochip	metabochip	Intergenic
rs10496262	menopause	metabochip	No	metabochip	metabochip	Intergenic

The metabochip SNPs will be analyzed in the metabochip proposal (submitted separately as the large metabochip project proposal by Kari North). However, they are included here for completeness.

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

Age at menarche:

- EAGLE: age when menstrual cycles started
- MEC: How old were you when you had your first menstrual period? (1=<11 / 2=11-12 / 3=13-14 / 4=15-16 / 5=17 or older)
- WHI: How old were you when you had your first menstrual period (menses)? [9 or less / 10 / 11 / 12 / 13 / 14 / 15 / 16 / 17 or older]
- ARIC: Approximately how old were you when your menstrual periods started?

Age at natural menopause:

- EAGLE: How old when had last period - years? Have you had a hysterectomy? oophorectomy?
- MEC: Have your menstrual periods stopped permanently?(No / Yes)
    - If yes, how old were you when this happened? (1=<40 / 2=40-44 / 3=45-49 / 4=50-54 / 5=55 or older)
    - If yes, for what reason did your menstrual periods stop? (1=Natural menopause / 2=Surgery / 3=Radiation / 4=Medication / 5=Don't Know)--not yet data cleaned
- WHI: How old were you when you last had regular menstrual bleeding (a period)? (Your best guess.) (If you are still having regular bleeding or periods, enter your current age.)
- ARIC: At approximately what age did menapause begin?
    - Was your menopause natural or the result of surgery or radiation? (natural/surgery/radiation/unknown)
- CARDIA: Have you undergone menopause? Have you gone through menopause or the change of life? How old were you when this occurred?
    - How did your periods stop?
- CHS: Age of menopause
- SHS: How old were you when they (your menstrual cycles) stopped completely?
    - Was your menopause natural or surgical? (1=natural, 2=surgical)

The menarche/menopause working group will work to harmonize these variables across study sites.

Table 3. Questions to Determine Natural vs. Surgical/Radiation Menopause by Study Site

Asked ? related to:	hysterectomy	oophorectomy	radiation/chemo	current HRT use	onset following discontinuation birth control pill
EAGLE	Yes	Yes	only NHANES III	Yes	derivable
MEC	Yes	Yes	not yet data cleaned	Yes	?
WHI	Yes	Yes	No	Yes	No-- possibly could be calculated?
ARIC	Yes	Yes	Yes	Yes	?
CARDIA	Yes	Yes	?	Yes	?
CHS	Yes	Yes	No	Yes	?
SHS	Yes	Yes	No	Yes	?

e. **Covariates (Specify)**

Age at menarche: year of birth, center (as appropriate)
Age at natural menopause: year of birth, center, smoking, parity, oral contraceptive use, and hormone replacement therapy

f. **Main statistical analysis methods**

We plan to use linear regression to test for association between the genetic variants and AAM and AANM stratified by race-ethnicity. We will consider transformation of AAM and AANM, if the data are not normally distributed. We will report significance, effect sizes, and confidence intervals

for all associations. We will most likely assume an additive genetic model, but we will consider other models based on the original GWAS or candidate gene publications. All analyses will be performed unweighted and weighted and adjusted for covariates, where appropriate. We will adjust all tests of association, including traditional tests of interaction, for multiple testing. We will work with the Statistical Analysis Committee to determine the best method for correction for these complex data. We will perform a meta-analysis across the study sites using a fixed effects model. Summary estimates and 95% confidence intervals will be generated by the method of DerSimonian and Laird[13].

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

In the initial analysis, we will stratify by race. As data become available, we will incorporate information from AIMs (WHI, EAGLE) or principal components (ARIC, CARDIA, MEC).

h. **Anticipated date of draft manuscript to P&P: ____Fall/Winter 2010_____**

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

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

V. REFERENCES

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