ARIC Manuscript Proposal #2251

PC Reviewed: 11/12/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genetic basis of the black-white difference in sRAGE levels: Results from the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

sRAGE genetics

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _NMM_ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

August 2013 - October 2013: Analyses
November-December 2013: Draft abstract for ADA meeting and manuscript
January 2013: Submit abstract for ADA meeting
January 2013-June2013: Revise manuscript and submit for ARIC review

4. Rationale:

The soluble receptor for advanced glycation end-products (sRAGE) has emerged as a marker of cardiovascular disease (1-5) and all-cause mortality (4-7). Interactions between RAGE and its ligands activate signaling pathways resulting in cellular dysfunction (8). sRAGE is a circulating, soluble form of RAGE which prevents binding of RAGE ligands to cellular RAGE thereby serving as a decoy for ligands and preventing these RAGE-ligand interactions (9).

In prospective studies, blood levels of sRAGE have been associated with important clinical outcomes across studies heterogeneous in design and study population, although the direction of associations has varied. Some studies have demonstrated an association between higher sRAGE levels and incident cardiovascular disease (1; 5), cardiovascular mortality (2), and all-cause mortality (2; 5), but others have reported a significant inverse association between sRAGE and cardiovascular disease (4), progression of carotid atherosclerosis by intima media thickness (3), and all-cause mortality (4; 7).

A striking finding from studies of sRAGE in humans is the substantial differences in levels across racial and ethnic groups. In multi-ethnic studies, , non-Hispanic blacks (Dallas Heart Study and Atherosclerosis Risk in Communities Study (4; 10) and Hispanics (Northern Manhattan Study) (11) had statistically significantly lower sRAGE levels (range 229 to 366 pg/ml) than whites, which persisted even after adjustment for multiple potential confounding variables (4; 11). Given the lack of other obvious factors to explain the racial/ethnic difference in circulating sRAGE levels, it is possible that genetic variation may contribute to this difference.

The *AGER* gene encodes RAGE, and the T allele of the promoter SNP, rs114177847, was associated with lower sRAGE levels compared to the C allele in a Dutch population (12). *AGER* variants have not been studied in other racial and ethnic populations and, along with other genetic variation, may contribute to the racial differences seen in prior studies (4; 10; 11). Furthermore, evaluation of the association of genetic determinants of sRAGE with clinical outcomes could clarify mixed findings from prior studies.

5. Main Hypothesis/Study Questions:

The objectives of this study are

1. To evaluate the genetic determinants of sRAGE through 1) genome-wide association studies in whites and blacks separately; 2) evaluation of the association between previously-identified *AGER* SNPs and sRAGE levels

2. To evaluate the association between genetic determinants of sRAGE and outcomes including coronary heart disease, congestive heart failure, diabetes, chronic kidney disease, and mortality

3. To evaluate genetic determinants of the black-white difference in sRAGE through study of local ancestry in blacks.

We hypothesize that we will confirm the prior association between genetic variation in the *AGER* gene and sRAGE levels and that we will identify genetic loci that could explain at least part of the black-white difference in sRAGE levels.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design: Genome wide association study of sRAGE and analysis of local ancestry for sRAGE

Inclusion: Participants with data on sRAGE from visit 1 or visit 2 without prevalent diabetes at visit 2

Exclusions: Participants missing data on visit 2 variables (genotyping and self reported race (Objectives 1-3) and those without sRAGE measured at visit 1 or 2 (Objectives 1 and 3).

Outcomes:

Plasma sRAGE (visit 1 and 2); plasma sRAGE at visit 1 will be calibrated to visit 2 using age as a covariate

Clinical outcomes: Incident coronary heart disease, congestive heart failure, diabetes, chronic kidney disease, and mortality as previously defined in ARIC (through latest available follow up data). Note, for this analysis, we will not restrict to the cohort with sRAGE levels and will include all participants with data on genotyping and clinical outcomes (See exclusions above).

Covariates: age, sex, center, BMI, physical activity, smoking alcohol, hypertension, CHD, eGFR, fasting glucose, fasting LDL, fasting HDL, fasting triglycerides (visit 2); education, income, employment (visit 1)

Data analysis:

GWAS: We will perform linear regression to test for the association between genetic variants and ln plasma sRAGE levels stratified by black and white race, assuming an additive genetic model with a threshold of significance of 5×10^{-8}. We will follow standard ARIC quality control procedures for GWAS and adjust for principal components of ancestry. Sample size: whites: N=2329; blacks: N=589.

Interrogation of known loci: We will evaluate the association between *AGER* SNPs and ln sRAGE levels in the proposed study using linear regression and assuming an additive model.

Local ancestry (in blacks only): Local ancestry (0, 1, or 2 copies of African ancestral alleles) will be estimated using LAMP-LD (13). We will use linear regression evaluate the association between local ancestry and ln sRAGE levels.

Association with clinical outcomes: We will use Cox PH modeling to estimate the effect of SNPs associated with sRAGE levels on clinical outcomes (incident coronary heart disease (whites: n=8562, blacks: n=2754), congestive heart failure (whites: n=8466, blacks: n=2606), diabetes (whites: n=8130, blacks: n=2293), chronic kidney disease (whites: n=8380, blacks: n=2476), and mortality (whites: n=9017, blacks: n=2871)). We will adjust for selected covariates noted above to account for confounding. We will exclude participants with prevalent disease at visit 2.

Limitations: The main limitation of this analysis is limited sample size for analyses of sRAGE. However, a prior GWAS of sRAGE has not been conducted, and the effect size of the black-white difference in sRAGE levels previously-demonstrated in ARIC is quite large.

7.a. Will the data be used for non-CVD analysis in this manuscript? __ Yes __X_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?
_x__ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?
_x__ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
_x__ Yes ____ No

9. **The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

   __x___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

1. sRAGE, progression of subclinical cardiac damage, and risk of heart failure (Mariana Lazo-Elizondo)

2. Soluble RAGE and risk of kidney disease outcomes: the Atherosclerosis Risk in Communities (ARIC) Study (Casey Rebholz)

3. Determinants of sRAGE and its association with cardiovascular disease, diabetes and mortality in a community-based population (MS1890, Elizabeth Selvin)

4. The association of lifestyle factors with circulating levels of the soluble receptor for advanced glycation end products (sRAGE) (MS1905, Julie Bower)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _x__ Yes ____ No

11.b. If yes, is the proposal

_x__ A. primarily the result of an ancillary study (list number* 2006.16)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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