ARIC Manuscript Proposal #4121

PC Reviewed: 12/13/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Replication of protein and metabolomic correlates of sickle cell trait

b. Abbreviated Title (Length 26 characters): $PM_{2.5}$ proteomics

2. Writing Group:

Writing group members: Morgan Grams, Aditya Surapaneni, Josef Coresh, Bing Yu, Alex Reiner *others welcome*

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

First author: Alex Reiner
Address: University of Washington
Phone: 206-667-2710 Fax:
E-mail: apreiner@uw.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Morgan Grams
Address: 227 East 30th Street, #825
New York, NY 10016
Phone: 646.501.2732 Fax:
E-mail: morgan.grams@nyulangone.edu

3. Timeline: Analysis will begin upon receipt of the data and approval of the manuscript proposal. Manuscript will be written and submitted for ARIC Publications Committee review within one year of manuscript proposal approval.

4. Rationale:

Sickle cell trait, a condition in which the affected individual has one abnormal hemoglobin beta gene allele, has been identified as a risk factor for hematuria, rhabdomyolysis, splenic infarction, papillary necrosis, venous thromboembolism, and more recently, chronic kidney disease. The mechanism by which this occurs is incompletely characterized; however, it is thought to involve low-grade sickling and increased adhesion with inflammatory cells and platelets, resulting in ischemia. Understanding the metabolomic and proteomic correlates of

sickle cell trait may help pinpoint targetable pathways that aid in the prevention of sickle cell trait-related adverse outcomes.

The Women's Health Initiative has evaluated the correlation of sickle cell trait with metabolites and proteins in 1984 participants. Metabolites were profiled at Metabolon. Proteins were profiled by Olink. This proposal is a request for replication in African Americans from ARIC using the Metabolon platform at visit 1 and visit 5, SOMA proteins at visit 2 and visit 5, and Olink proteins at visit 5. The earlier visits will be used in the case of very low sample size at visit 5.

5. Main Hypothesis/Study Questions:

1. Replicate metabolite associations with sickle cell trait observed in the WHI cohort
2. Replicate protein associations with sickle cell trait observed in the WHI cohort

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 & Study Population
We will perform cross-sectional analyses of sickle cell trait and metabolite and protein units. We will include ARIC participants at visits 1, 2, and 5 for whom metabolomic or proteomic profiling was done. We will restrict our analysis to African Americans with genotyping.

Exposure
Sickle cell trait as assessed by a single T allele in the rs334 SNP.

Proteomic measures
Our primary protein outcome will be plasma protein levels using the SomaScan version 4 proteomic platform. 4877 plasma proteins were quantified from plasma from visits 2 and 5. In this assay, modified nuclear aptamer bind specific proteins, and these complexes are quantified in relative fluorescent units (RFU). We will focus on the proteins discovered in WHI: CX3CL1, HAVCR1, TGFBR2, EPHB4, MMP7, IL10RB, FAS, TNFRSF21, IGFBP4, FCER2, CCL2, AGRP, PLAUR, EPHA1, GDF15, COLEC12, TNFRSF1B, FGFR2, FSTL3, ADM, SCARB2, NCR1, STC1, LTBR, CSF1, EPO, EPHA2, TNRSF11A, DSC2.

This amendment adds three additional proteins that were statistically significant in meta-analysis of WHI and Jackson Heart Study: hemoglobin, haptoglobin, and testican-2.

Metabolomic measures
Our primary metabolomic outcomes will be plasma metabolite levels using the Metabolon platform. We will focus on the metabolites discovered in the WHI cohort, which include: N2,N2-dimethylguanosine, orotate, N1-methylinosine, N-acetylserine, erythronate, X-21283, (N(1)+ N(8))-acetylspermidine, gamma-glutamylisoleucine, 7-methylxanthine, cysteine-glutathione disulfide. The less adjusted model has additional metabolites that reached statistical significance.

Additional Covariates

Additional covariates include age, sex, hemoglobin levels (as available), eGFR, as well as African Ancestry.

Statistical Analysis
We will perform multivariable linear regression to estimate the association of each protein or metabolite with the sickle cell trait. Proteins and metabolites will be log2-transformed, as was done in WHI. We will evaluate several models: model 1) age, sex; model 2) age, sex, hemoglobin; model 3) age, sex, eGFR; model 4) age, sex, African ancestry; model 5) age, African ancestry, hemoglobin; model 6) age, African ancestry, eGFR. We will apply a Bonferroni-corrected P value of < 0.05/# of metabolites or proteins tested to indicate statistical significance.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? __x__ Yes ____ No
(The 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 current derived consent file ICTDER05 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/aricproposals/dtSearch.html

____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)?

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.