ARIC Manuscript Proposal #2759

PC Reviewed: 6/7/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Characterizing the Risk of Chronic Kidney Disease Associated with GSTM1 Copy Number Variation (CNV)**

b. Abbreviated Title (Length 26 characters): **GSTM1 and CKD**

2. Writing Group:
Adrienne Tin, Morgan Grams, Robert B. Scharpf, Michelle Estrella, Josef Coresh, Dan Arking, Megan Grove, Eric Boerwinkle, and others welcome

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

First author: **Adrienne Tin, PhD**
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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, MD, PhD**
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3. Timeline:
Data analysis will start immediately. A manuscript is expected to be prepared within 6 months.

4. Rationale:
This manuscript proposal follows the approved ancillary study proposal 2015.27., therefore we will be brief in our rationale and analysis plan.

Glutathione S- transferase mu 1 (*GSTM1*) catalyzes the conjugation of glutathione with a range of electrophiles. Having 0 copies of (*GSTM1*) has been associated with two-fold higher risk for CKD progression in African Americans with CKD attributed to hypertension.[1] Further, the risk of CKD progression associated with 0 copies of *GSTM1* versus 2 copies of *GSTM1* was reported to be higher in those with 2 copies of the *APOL1* renal risk allele than in those with 0 or 1 copy of the *APOL1* risk allele.[2] Taking advantage of the rich phenotype and genetic data in the ARIC study, we will investigate the association of *GSTM1* copy number with CKD and ESRD. *GSTM1* copy number will be determined using exome sequencing reads.

5. Main Hypothesis/Study Questions:

Having 0 copy of *GSTM1* will be associated with higher risk for kidney function decline compared with those with 1 or 2 copies.

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: prospective cohort study

Inclusion criteria: Participants with exome sequencing data in Freeze 5 and with data in incident kidney outcome, and values in covariates.

Outcomes:

1) incident CKD defined as a composite outcome of eGFR decline to below 60 mL/min/1.73m^2 with at least a 25% drop, CKD related hospitalization, or end-stage renal disease.[3]
2) ESRD

Predictor: *GSTM1* copy numbers estimated using exome sequencing reads

Other variable of interest at visit 1: age, gender, race, diabetes, hypertension, eGFRcr, BMI

Data analysis:

For the determination of *GSTM1* copy numbers, we will process the exome sequencing reads of chromosome 1 where *GSTM1* is located. We will first apply quality control to remove exons with low coverage and mappability and at the extreme of GC content using the CODEX package.[4] Then the coverage at each exon will be normalized using the median coverage of chromosome 1. The number of copies of *GSTM1* will be determined by detecting break points in the distribution of the normalized coverage.

The association between *GSTM1* copy number and kidney outcome will be analyzed in European and African Americans separately to avoid confounding by population. The association will be evaluated using Cox regression controlling for age, sex, baseline eGFR and known risk factors of CKD or ESRD. We will also perform stratified analysis by *APOL1* risk status, hypertension, and diabetes.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ 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)?

#1949 Validation of inter-visit kidney events
#1929 Genome-wide DNA methylation profiling in peripheral blood: quality control and association with demographic characteristics

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: 2015.27)

__ 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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