ARIC Manuscript Proposal # 3167

PC Reviewed: 5/8/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Associations between de-orphaning human organic anion transporter, SLC22A24, and human steroid metabolites

b. Abbreviated Title (Length 26 characters): SLC22A24 and steroid

2. Writing Group:

Writing group members:
Sook Wah Yee, Adrian Stecula, Huan-Chieh Chien, Ling Zou, Elena Feofanova, Bing Yu, Eric Boerwinkle, Kathy Giacomini

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

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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).
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3. Timeline: 2 months

4. Rationale: Genomewide association studies (GWAS) revealed associations of steroid metabolites levels with genetic variants in *SLC22A24* (Solute Carrier family 22 member 24) in populations of European ancestry. In particular, steroids (e.g. progesterone) and glucuronide conjugates of steroids (e.g. androsterone glucuronide, etiocholanolone glucuronide, pregnanediol glucuronide) are among the metabolites that are significantly associated with SNPs in *SLC22A24* ($p<5x10^{-8}$) (PMID: 26014426, 29362361, 28263315). The human *SLC22A24* has been designated an "orphan" transporter. In this study, we demonstrate, for the first time, that human *SLC22A24* transports sulfate and glucuronide conjugates of steroids as well as bile acids. In addition, we show that a common polymorphism of *SLC22A24*, i.e. a non-sense variant (Tyr501STOP, rs11231341) has no transport activity in an *in vitro* cell-based transporter study. **The goal of this proposal is to replicate the previous GWAS findings for the associations of *SLC22A24*, in particular rs11231341, with the steroid metabolites in ARIC European populations and African American populations.**

5. Main Hypothesis/Study Questions:
We hypothesize that the reduce function *SLC22A24* will reduce the levels of the steroids, bile acids and the conjugates of steroid metabolites in both European and African Americans in ARIC 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:
This study is a cross-sectional study design using information from both European and African Americans in the ARIC study visit 1.

Exclusion criteria:
The individuals will be excluded from this study, whose metabolites data and exome sequencing information are missing, as well as other covariates.

Variables:
Outcome variables: androsterone glucuronide, etiocholanolone glucuronide and pregnanediol-3-glucuronide
Covariates: Age, sex and principal components.
Genetic variation: functional variants in *SLC22A24*, specifically rs11231341.

Statistical analysis: single SNP analysis using linear regression with an additive model.

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)?

MS#2792 Yu et al. "Whole Genome Sequence and Metabolomics for Gene Discovery in the Atherosclerosis Risk in Communities (ARIC) Study"

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* _2008.16 and 2014.20_____)

___ 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.