ARIC Manuscript Proposal #4026

PC Reviewed: 4/12/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Replication Analyses of Genetic Associations with Neurocognitive Traits identified in the HCHS/SOL Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members: ARIC: Jan Bressler, Eric Boerwinkle, Tom Mosley
SOL: Tamar Sofer, Wassim Tarraf, Hector Gonzalez

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MF___ **[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).

Name: **Tom Mosley, PhD**
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E-mail:

3. Timeline: Summer 2022

4. Rationale: In genome-wide association analyses in the HCHS-SOL study, we have identified several variants associated with MCI and neurocognitive traits and we would like to attempt replication in ARIC, which has a similar cognitive battery. In many cases, we have

identified the likely continental ancestry of origin of the associated allele through estimating ancestry-specific allele frequency in HCHS-SOL.

For example, in association analyses of MCI in HCHS-SOL, we identified interactions for five African enriched variants with APOE-ε4, and two African enriched variants with APOE-ε2. We would like to attempt replication of the interaction effects of APOE alleles with African-enriched variants in ARIC African Americans.

In association analyses of 5 cognitive traits in HCHS-SOL, we identified 10 loci. Using fine-mapping techniques and estimating continental ancestry-specific allele frequencies, we have identified several SNPs in these loci that are enriched on African or European backgrounds. We would like to attempt to replicate these associations in ARIC.

5. Main Hypothesis/Study Questions:

Our hypothesis is that neurocognitive traits-associated variants that are enriched on a specific continental ancestry background will show evidence of replication in the respective ancestry group in ARIC.

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).

Phenotype definition: Our primary outcomes are MCI and neurocognitive function at V5.

Genotype data: We will use TOPmed imputed genotype data and APOE genotype.

Models: Logistic and linear models adjusted for age, sex, education, PCs, and study site.

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" ? ____ 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

   _____ Yes ____X___ 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)?
None.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ 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.