ARIC Manuscript Proposal #2836

PC Reviewed: 09/13/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Differential Transcriptome Profiling of Chronic Kidney Disease and Hypertension in Older African Americans**

b. Abbreviated Title (Length 26 characters): **Transcriptome, CKD, HTN**

2. Writing Group:
Adrienne Tin, Priyanka Nandakumar, Aravinda Chakravarti, Josef Coresh, Eric Boerwinkle, Megan Grove (others welcome).

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _PN_AT__ **[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:
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 2014.37 (Differential Transcriptome Profiling Of African Americans With Uncontrolled

Hypertension And Chronic Kidney Disease (CKD) versus Controlled Hypertension and without CKD), therefore we will be brief in our rationale and analysis plan.

Hypertension-attributed chronic kidney disease (CKD) is highly resistant to treatment in African Americans.(1, 2) and contributes to racial disparity in hypertension-attributed end-stage renal disease (ESRD). In older adults (aged 70-74), African Americans have 4-fold higher risk of developing hypertension-attributed ESRD than European Americans, and incidence of hypertension-attributed ESRD increases with age.(2) A hypothesized mechanism that links hypertension and progressive CKD is innate immune response and inflammation.(3) Inflammation biomarkers have been associated with kidney function decline and incident hypertension.(4, 5) Gene expression in peripheral blood can provide a view of the innate immune activation profile. Thus, we propose a pilot study of transcriptome profiling in African Americans with treated high blood pressure and CKD as cases and controlled blood pressure and no CKD as controls.

5. Main Hypothesis/Study Questions:

The expression levels of some genes will be significantly associated with case status

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: Matched case-control study

Case-control selection criteria:

The cases and controls will be selected from African-Americans without diabetes and defined by hypertension with treatment and CKD status at visit 5. Hypertension under treatment is defined as on hypertension medication and with systolic blood pressure (SBP) at least 145 mm Hg. CKD is defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2. The cases will be selected from those with both hypertension under treatment and CKD as defined above. The controls will be selected from those with blood pressure controlled by hypertensive medications (SBP <135 mm Hg and diastolic blood pressure < 90 mm Hg) and with eGFR between 75 and 120 mL/min/1.73m2 and urine albumin-to-creatinine ratio < 30mg/g. The cases and controls will be matched by age, gender, body mass index, hypertension medication, APOL1 high risk genotype, and center. The cases will be selected from the extreme of the distribution of the phenotypes (highest SBP and lowest eGFR) to maximize the differences between cases and controls.

Predictor: case status

Data analysis:

1) mRNA and miRNA sequencing were performed by the Baylor College of Medicine Human Genome Sequencing Center. Approximately 30 million paired

end reads of 100 bp were produced for mRNA per sample, and 8 million single end reads were produced for miRNA.

2) For mRNA, the reads are aligned to reference genome using STAR(6) and quantified with featureCounts (7); for miRNA, reads will be aligned and quantified with the miRDeep2 software package (8).
3) All differential gene expression analyses will be performed using DESeq2.(9)
4) Gene coexpression network analysis will be conducted using the Weight Gene Coexpression Network Analysis (WGCNA) package.(10)

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)?

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: 2014.37__)

__ **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.

References

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