

ARIC Manuscript Proposal #2003

PC Reviewed: 9/11/12
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Association of *APOLI* variants with microvascular and cardiovascular disease in African Americans

b. Abbreviated Title (Length 26 characters): *APOLI* & microvascular disease

2. Writing Group:

Writing group members: Meredith Foster, Linda Kao, Joe Coresh, Myriam Fornage, Eric Boerwinkle, Aaron Folsom, A Richey Sharrett, Elizabeth Selvin, Thomas Mosley, Ching-Yu Cheng, others welcome.

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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3. Timeline: Data analysis to start immediately. Plan to submit abstract to EPI/NPAM Spring 2013 Scientific Sessions. First draft of manuscript expected in 2013.

4. Rationale:

African Americans carry an increased burden of multiple forms of vascular disease when compared to whites in the United States, including retinopathy, peripheral artery disease, stroke, end-stage renal disease (ESRD), and heart failure.¹⁻⁶ Differences in socioeconomic status, obesity, and environmental factors associated with the high rates of hypertension and diabetes

observed in African Americans likely contribute substantially to the racial disparities in vascular disease, although genetic factors may also play an important role in explaining this excess disease burden and risk observed in African Americans. The association of ESRD with variants in *APOLI* has been the most promising finding in this area.⁷⁻¹¹ Risk variants in *APOLI*, termed G1 and G2,⁷ are associated with 5-29 fold increased odds of ESRD in African Americans, based on case-control studies of non-diabetic ESRD, hypertensive ESRD, focal segmental glomerulosclerosis, and HIV-related nephropathy.^{7,9,10} These variants alter the structure of apolipoprotein L1 (a component of HDL particles that also plays a role in trypanolysis¹²), providing protection against a form of African sleeping sickness;¹² thus through positive selection these risk variants are now common among persons with African ancestry compared to European ancestry (22% and 14% for G1 and G2, respectively, among African Americans in ARIC compared to 0.028-0.057% among adults of European ancestry¹³). In addition to the strong association with ESRD observed in case-control studies,⁷⁻¹¹ we have shown prospectively in ARIC that African Americans carrying 2 *APOLI* risk alleles is associated with an increased risk of incident chronic kidney disease, incident ESRD, progression of CKD to ESRD, and higher odds of microalbuminuria when compared to those carrying 0 or 1 risk allele (Foster *et al*, Manuscript in ARIC Review; MP#1414).

The biological mechanisms underlying the association of *APOLI* risk variants with chronic kidney disease and ESRD in African Americans remains to be determined; however, it has been proposed that the altered version of apolipoprotein L1 may have direct effects on podocyte cell death or may lead to kidney microvascular damage through changes HDL particles or apolipoprotein L1 levels in systemic circulation.¹⁴ Our observed association of *APOLI* risk variants with albuminuria, a potential marker of endothelial dysfunction,¹⁵ suggests that a systemic, circulatory component may be involved. If *APOLI* risk variants do cause damage in the kidney microvasculature via changes in circulating molecules, then damage could also occur in other microvascular beds throughout the body, potentially impacting the risk of microvascular disease, including retinopathy and peripheral artery disease, and future cardiovascular events, such as coronary heart disease, stroke, or heart failure.

Thus, we seek to investigate the association of *APOLI* risk variants with other forms of vascular phenotypes beyond ESRD and chronic kidney disease in African Americans in ARIC. Our findings can provide insight into the local versus systemic role of *APOLI* and help elucidate whether the *APOLI* variants are uniquely associated with kidney disease or potentially contribute to the increased burden of other microvascular or cardiovascular diseases observed in African Americans.

5. Main Hypothesis/Study Questions:

Our primary goal is to evaluate the association of *APOLI* risk variants with prevalent and incident microvascular and cardiovascular disease events in African Americans from the ARIC study.

We hypothesize that *APOLI* risk variants impact kidney function through systemic circulatory mechanisms and are associated with other forms of microvascular and cardiovascular disease and

that the associations are independent of common cardiovascular risk factors and independent of kidney disease.

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).

We propose to evaluate the association of *APOLI* risk variants with microvascular and cardiovascular outcomes in African Americans in ARIC who have consented to having their DNA used for research with surveillance follow-up for incident events through 2009.

Primary exposure: *APOLI* risk variants G1 and G2, based on genotyped SNPs rs73885319, rs60910145, and rs71785313.

Primary outcomes: Prevalent and incident microvascular disease, including peripheral artery disease (based on ABI data collected during Visit 1 and through hospitalization surveillance) and retinopathy and its major components of microaneurysms and hemorrhage, arteriovenous nicking, and generalized and focal arteriolar narrowing (examining associations for retinopathy separately in participants with and without diabetes) identified through retinal photography. Prevalent and incident cardiovascular disease will include events based on surveillance through 2009 (ARIC visit 1 as baseline), including myocardial infarction, fatal coronary heart disease, stroke (definite/probable overall and by subtype), and heart failure.

Data analyses: We plan to evaluate the association of the *APOLI* risk variants with prevalent disease at baseline using logistic regression and incident events using Kaplan-Meier survival curves (unadjusted, stratified by number of *APOLI* risk alleles present) and Cox proportional hazards models. Models will initially be adjusted for age, sex, and study center with further adjustment for population substructure by accounting for global percentage of European ancestry as estimated using ANCESTRYMAP based on approximately 1350 ancestry informative markers.^{16,17} Prior work⁷ and our findings in ARIC (Foster *et al.* Manuscript submitted for ARIC review; MP#1414) suggests that the *APOLI* risk variants are associated with increased CKD and ESRD risk based on a recessive genetic model. However, the underlying genetic model is not known for other outcomes and therefore we will initially model the *APOLI* risk variants using a co-dominant genetic model to determine whether dominant, additive, or recessive genetic models would be appropriate. We plan to additionally adjust for common cardiovascular risk factors, including those related to blood pressure and hypertension (systolic/diastolic blood pressure levels, hypertension, hypertension medication use), diabetes status, lipid measurements, and other behavioral risk factors. Given the association of the *APOLI* risk variants with CKD, ESRD, and albuminuria observed in our study sample, we plan to evaluate potential mediation by these factors.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? Yes No

(This file ICTDER03 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? 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"? 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.csc.unc.edu/ARIC/search.php>
 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)?

ARIC Manuscript Proposal #1414 Association between MYH9 SNPs and chronic kidney disease
ARIC Manuscript Proposal #1685 Association of ApoL1 variants with plasma lipids in African-Americans

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* 2008.06)**
 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.csc.unc.edu/anic/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. Accepted

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.csc.unc.edu/anic/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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