ARIC Manuscript Proposal # 1853

PC Reviewed: 10/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Genome-Wide Association Study of Heart Failure-related Human Metabolite Profiles among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): GWAS of human metabolites

2. Writing Group:
Writing group members:

Bing Yu, Yan Zheng, Danny Alexander, Teri A. Manolio, Alvaro Alonso, Jennifer A. Nettleton, Eric Boerwinkle

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

Bing Yu, M.D., M.S.
Division of Epidemiology, Human Genetics & Environmental Sciences
University of Texas Health Science Center
1200 Herman Pressler, suite E-435
Houston, TX 77030
Phone: (713) 500-9892
E-mail: Bing.Yu@uth.tmc.edu

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).

Eric Boerwinkle, Ph.D., Professor & Director
Division of Epidemiology, Human Genetics & Environmental Sciences
University of Texas Health Science Center
1200 Herman Pressler, suite E-447
Houston, TX 77030
Phone: (713) 500-9816 Fax: 713-500-0900
Email: Eric.Boerwinkle@uth.tmc.edu

3. Timeline:

Analysis is to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the manuscript will be prepared within nine months from approval of the analysis.

4. Rationale:

The pathogenesis of cardiovascular disease (CVD) includes genetic and environmental factors, however understanding the role of genetic variants and their interactions with environmental factors (GXE) is the key to disease prediction, diagnosis, treatment and prevention. Human metabolites are a direct reflection of GXE, and therefore, can be expected to offer more details on the etiology of CVD[1]. Several genome-wide association studies (GWAS) have been done in Europeans to reveal associations between genetic variants and metabolites, but none of them examines the associations among genetic variants, metabolites and incident heart failure (HF) [2-4]. Here, we plan to explore the etiology of incident HF by performing GWAS on incident HF- related metabolites and quantifying the association between genome-wide significant SNPs and incident HF. (Note: Metabolites associated with incident HF will be identified in another ARIC manuscript proposal, MS#1847 Zheng Y, et al..)

5. Main Hypothesis/Study Questions:

1. Genetic loci associated with HF-related metabolite levels can be identified by performing GWAS in 1379 African Americans with metabolomic and genetic data.
2. As an extension of Aim 1, SNPs that are associated with HF-related metabolites may also be associated with incident HF in all African-American ARIC participants with genetic data (n = 2630).

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).

1. The present study is a GWAS with African-Americans participants in ARIC.
2. Subjects from visit 1 with metabolites measured will be analyzed. Subjects who did not agree to use their DNA information will be excluded.
3. Additive genetic model with linear regression will be performed for GWAS approaches:
i. Outcome – HF-related metabolite levels (ARIC MS#1847)
ii. Covariates – age, gender and principal components to control for average genome-wide admixture.
4. Genome-wide significant SNPs associated with HF-related metabolite levels will be tested for association with incident HF in all African-American ARIC participants using time-to-event and survival analysis (> 80% power would be reached to detect moderate-strong associations).

7. a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes _X_ 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? _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**

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group? _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

Yes. There is no overlap between this proposal and current proposals/published manuscripts. This proposal builds off of the metabolomic HF proposal submitted by Zheng and Nettleton (MS #1847) both of whom are authors here.

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)?

Nettleton J, Follis J L, Alonso A, et al. "Metabolomic predictors of incident heart failure: a case-control study nested within the Atherosclerosis Risk in Communities (ARIC) Study". Poster section presented at American Heart Association(AHA) Epidemiology Council meeting in Atlanta, GA; March 2011.

MS#1847 Zheng Y, et al. Role of the Human Metabolome in Incident Heart Failure Etiology among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study (under review)

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

11.b. If yes, is the proposal

___ **A. primarily the result of an ancillary study (list number*** 2008.16 **)**

___ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*** 2008.16 "Metabolomics & Heart Failure: A Novel Approach to Biomarker Discovery"**)**

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. 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.

Yes, the lead author is aware that manuscript preparation is expected to be completed in 1-3 years, and if this expectation is not met, the manuscript proposal will expire.

Reference

1. Lusis AJ. A thematic review series: systems biology approaches to metabolic and cardiovascular disorders. *J Lipid Res*. 2006; 47(9):1887-90.
2. Gieger C, Geistlinger L, Altmaier E et al. Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. *PLoS Genet*. 2008; 4(11):e1000282.
3. Illig T, Gieger C, Zhai G et al. A genome-wide perspective of genetic variation in human metabolism. *Nat Genet*. 2010; 42(2):137-41.
4. Suhre K, Shin SY, Petersen AK et al. Human metabolic individuality in biomedical and pharmaceutical research. *Nature.* 2011; 477(7362):54-60.