ARIC Manuscript Proposal #2888

PC Reviewed: 11/08/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Replication study of thrombomodulin genetic variant predictors of venous thromboembolism in African Americans

b. Abbreviated Title (Length 26 characters): *THBD* variants and VTE in blacks

2. Writing Group:
Writing group members: Aaron R. Folsom, Nathan Pankratz, Nicholas S. Roetker, and Weihong Tang

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

First author: **Aaron Folsom**
Address:

Phone: Fax:
E-mail: folso001@umn.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).
Name:
Address:

Phone: Fax:
E-mail:

3. Timeline: 1 month

4. Rationale:
African Americans have a higher risk of venous thromboembolism (VTE) than most other ethnic groups. A recent case-control, genome-wide association study of VTE in African Americans by

Hernandez et al reported that having minor alleles of three intergenic single-nucleotide polymorphisms (SNPs) on chromosome 20 (rs2144940, rs2567617, and rs1998081) were associated with more than a doubling of VTE risk.[1] The study replicated its findings in an independent case-control sample and reported that the risk variants for these SNPs are more frequent in African Americans (>20%) than other ethnic groups (<10%). Expression studies by Hernandez et al. suggested that the SNPs are markers for thrombomodulin (*THBD*), and *THBD* expression was lower among VTE cases than controls.

The doubling of VTE risk would make these *THBD* variants as strongly related to VTE risk as non-O blood type. We seek to replicate the potentially important association of these SNPs with VTE in an independent prospective cohort study of African Americans.

1.Hernandez W, Gamazon ER, Smithberger E, et al. Novel genetic predictors of venous thromboembolism risk in African Americans. *Blood.* 2016;127(15):1923-1929.

5. Main Hypothesis/Study Questions:
Does the association of *THBD* variants with VTE in African Americans replicate?

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).

Design: Prospective

Sample: ARIC African Americans without VTE or anticoagulant use at baseline who have the 3 SNPs and no DNA exlusion

Exposure: rs2144940, rs2567617, and rs1998081 alleles

Outcome: VTE

Main Analysis: Cox proportional hazards model to compute hazards ratios (HRs) per 1 copy increment of the minor allele dosage for each SNP, adjusted for age, sex, center, and first four principal components of ancestry.

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 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)?

None, except our LITE papers.

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* ____2006.16_____)
___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _x__ No.