ARIC Manuscript Proposal #2396

PC Reviewed: 7/8/14  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: SNP score for Venous Thromboembolism

b. Abbreviated Title (Length 26 characters): VTE SNP Score

2. Writing Group:
   Writing group members:  Aaron Folsom, Weihong Tang, Lu-Chen Weng, Nick Roetker, Mary Cushman, Saonli Basu, James Pankow

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

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3. Timeline: hope to finish by late summer 2014

4. Rationale:

   Venous thromboembolism (VTE=deep vein thrombosis (DVT) and pulmonary embolism (PE)) has a moderately strong genetic component, as evidenced by family, candidate gene, and GWAS studies. Recently, de Haan et al. showed that a genetic risk score based on 31 SNPs was strongly predictive of VTE in a large Dutch case-control study (1). A reduced score based on 5 top SNPs (in F5 (Leiden), F2, F11 FGG, ABO) was nearly as predictive (AUC=0.77) as the 31 SNP score. Adding non-genetic variables improved the AUC to 0.82 in this white sample.

   We will try to replicate this in ARIC whites, and explore the association for African Americans. The score is unlikely to predict as well in African Americans due to low frequency of some alleles.
We will first focus on the 5 SNP score, but if all 31 SNPs can be assembled, we may examine the predictivity if the 31 SNP score as well. We will also consider adding any additional SNPs found related to VTE in ARIC, e.g., sickle trait in African Americans.

5. **Main Hypothesis/Study Questions:**

   1. Does a published 5 SNP risk score predict VTE well in ARIC whites? African Americans?
   2. (possibly) Does the 31 SNP risk score predict better 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).**

Study group: ARIC participants without a baseline history of VTE

Events: incident VTEs after baseline

SNP score: SNP information is from the contract genotyping, IBC chip or exome chip. Each SNP is weighted by the average published OR for its relation with VTE, as described by de Haan (1). We will have to account for missing one or more SNPs, probably by imputation.

Nongenetic factors to consider: age, race, sex, center, BMI, HRT in women, diabetes, eGFR.

Main analysis: Cox model, stratified by race, with exposure being the SNP score and time to VTE as the outcome. We will calculate AUC using Chambless’ macro. Other than race, VTE risk factors should not confound but we will see to what degree the nongenetic factors add to the AUC beyond the genetic score. Principal components based on GWAS data will be included as covariates to control for the influence of population admixture in African Americans.

As secondary analyses, if Ns are sufficient, we will examine provoked vs unprovoked VTE and PE vs DVT. We also likely will share this score with ARIC ms 2071, which is examining life-time risk of VTE.

**References**


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.csc.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)?

   The closest is the ARIC GWAS for VTE, and those lead authors are included.

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/