ARIC Manuscript Proposal #2238

PC Reviewed: 10/8/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: A GWA study meta-analysis for coagulation Factor XI

b. Abbreviated Title (Length 26 characters): FXI GWAs meta-analysis

2. Writing Group:
   Writing group members: Maria Sabater Lleal, Anders Hamsten
   Other co-authors: Mary Cushman, Aaron Folsom, Weihong Tang, Saonli Basu, David Tregouet, Pierre Morange, Jose Manuel Soria, Angel Martinez, Juan Carlos Souto, Angela Silveira, Bengt Sennblad

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: Maria Sabater Lleal
   Address: Group of Cardiovascular Genetics and Genomics
            Atherosclerosis Research Unit
            Department of Medicine, Solna
            CMM Karolinska Institutet/Karolinska University Hospital
            S-171 76 Stockholm
   Phone: +46 851770305  Fax: +468311298
   E-mail: maria.sabater.lleal@ki.se

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: Aaron Folsom
   Address: Division of Epidemiology and Community Health
            University of Minnesota
   Phone: 612-626-8862  Fax: 612-624-0315
   E-mail: folso001@umn.edu

3. Timeline: We plan to ask all cohorts to finalize their individual analyses by the end of the year so we can start meta-analysis early next year.

4. Rationale: Elevated plasma levels of coagulation factor XI (FXI) are implicated in the pathogenesis of venous thromboembolism (VTE) and ischemic stroke.
We recently conducted an unbiased genome-wide association study (GWAS) of the plasma coagulation Factor XI (FXI) concentration in 339 Spanish individuals from GAIT1 project, with replication in a subset of PROCARDIS controls, and found two genome-wide significant loci (KNG1, and F11) (1).

5. **Main Hypothesis/Study Questions**: We hypothesize that increasing sample-size will allow identification of new loci that are important for XI regulation and that could be determinant risk factors for venous and arterial thrombosis. Thus, our aim is to establish a collaboration to perform a meta-analysis of GWAs of plasma FXI concentration.

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**: We would like to use ARIC data (2,3) and LITE (from ARIC and CHS) data (4) on FXI as cohorts participating in the FXI collaborative GWAs meta-analysis.

**Phenotype**: Coagulation FXI (all measurement assays are acceptable). A sub-analysis can be done later to address possible differences between antigen and activity methods. We will examine histograms for the distribution of both FXI and natural log-transformed FXI in each study population. According to our previous results, we expect that lnFXI will fit the normal distribution better. Exclusions: When activity methods are used, use of anticoagulants should be excluded. Units should be given in U/ml.

ARIC has FXI data from a nested case cohort study of CVD (2, 3) and from LITE (4). The first involved 412 random subjects and an equal number of stroke/CHD cases. The second involved 273 VTE cases and 660 non-cases. The lab methods were different for the two studies and this will be assessed as above. This analysis will use all subjects, as case status is unlikely to modify associations of SNPs with FXI levels.

**Main Analysis**: Linear regression analysis according to an additive model of inheritance between 1000 Genome-imputed SNPs and lnFXI levels will be required from all participants, with adjustments for age, sex, and accounting for population stratification (add also case/control status and other cohort-specific covariates when necessary). The 1000 Genomes imputation will follow the guidelines developed for the GIANT consortium.

The ARIC analysis will take place at the University of Minnesota.

Meta-analysis of individual GWAs will be conducted at Karolinska Institutet using an inverse-variance weighted fixed-effects method as implemented in METAL (http://www.sph.umich.edu/csg/abecasis/Metal/index.html). A genomic control coefficient will be computed for each discovery cohort and will be used to correct for cryptic relatedness. The prespecified threshold of genome-wide significance will be set at the conventional level of $P = 5.0 \times 10^{-8}$. 
Further analyses:
- Conditional analyses on the main associated SNPs from the main analysis.
- Association of genome-wide significant SNPs with expression levels of nearby genes.
- Association of genome-wide significant SNPs with related phenotypes (FXII and aPTT) for cohorts that have these phenotypes available.
- Computation of genetic risk scores.

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.cscce.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)?

References above, which are ARIC ms proposals 1294, 777, and 1199, respectively.

Also relevant was: 1383 (CHARGE GWAS for hemostatic factors), although FXI was not 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.cscce.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.cscce.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.