1.a. Full Title: Effects on longitudinal change of FVII activity of genetic variants identified for association with plasma levels of FVII from a large genome-wide association study: The Atherosclerosis Risk in Communities (ARIC) Study.

2. Writing Group:
Writing group members: Phillip Kirsch, Weihong Tang, Pamela Schreiner, Aaron Folsom, others are welcome

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

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3. Timeline:
Starting Analyses: October 25, 2010
First Draft: December 20, 2010
Submission for Publication: February 15, 2011
4. **Rationale:**
The tissue factor pathway of the coagulation cascade is the mechanism by which the body reacts to injury by ultimately forming a clot. This process is initiated when Factor VII (FVII), which circulates in the bloodstream, forms a clot when coming into contact with tissue factor. Tissue factor is released into the bloodstream upon cellular injury where it interacts with FVII. From the union of FVII with tissue factor the clotting cascade is activated leading to the formation of an injury-limiting fibrin clot at the end of the process.

The leading cause of death in both men and women in the United States is cardiovascular disease, accounting for more than one in four deaths. Factoring in the cost of treatment and lost productivity, the 2010 projected cost of heart disease stands at $316.4 billion.

At present it is believed that there is a potential association between elevated FVII levels and increased risk of CHD. In the bloodstream, FVII levels are determined by factors of both genetic and environmental origins. Estimates on the heritability of FVII levels range from 0.52 to 0.63.

The ARIC study showed a 12% decrease in the mean levels of plasma FVII activity over a six-year course of measurement, while net increases (or smaller decreases) were observed in several groups, including younger participants, women, those with BMI increasing 5 kg/m², those who quit smoking, and diabetics.

In a genome-wide association study (GWAS) based on the data from the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) Consortium, which included ARIC, there were 5 independent loci that were significantly associated with FVII activity/antigen, and the top SNPs are: rs1260326 in GCKR, rs1126670 in ADH4, rs11230180 near MS4A6A, rs488703 in F7, and rs867186 in PROCR. It is unknown whether these loci also influence longitudinal changes in FVII activity.

This study will examine the influence of the top loci identified in the CHARGE FVII GWAS on the longitudinal change in FVII activity levels in the ARIC study.

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

We hypothesize that the top loci associated with FVII activity in CHARGE are also associated with longitudinal changes in FVII activity over 6 years 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 design: Longitudinal
Outcome: Changes in FVII activity from baseline (1987-1989) to six years later (1993-1995). FVII activity was measured in the entire cohort during the 1987 through 1989 examination and in a stratified sample in the 1993 through 1995 examination (n=989, 75% whites).

Study sample: Caucasians who had FVII activity measured at both baseline and 6 year examinations (n=741). We limit the analysis to Caucasians because the study population in the CHARGE GWAS for FVII included Caucasians only.

Exposure: The top loci reported in the CHARGE GWAS for FVII: rs1260326, rs1126670, rs11230180, rs488703, and rs867186. These were the top independent SNPs reported in the GWAS.

Exclusions: Participants who were missing for the SNP genotypes or used anti-coagulation therapy at the time of phenotype measurement

Covariates include, but are not limited to, traditional risk factors (baseline and follow-up) including age, sex, field center, BMI, smoking status, triglycerides, and diabetes.

Analysis Plan
Data analysis to be conducted locally at the University of Minnesota using SAS version 9.2.
1) Test of genotypes in Hardy-Weinberg equilibrium will be conducted using a modified chi-square test (SURVEYFREQ) that takes into account of the sample weighting.
2) The primary SNP model will be an additive effect model in which genotypes will be coded as 0, 1, or 2 copies of the at-risk allele, to be consistent with the model used in the CHARGE GWAS. If appropriate, a dominant model will be also tested.
3) Linear regressions will be carried out in SAS using SURVEYREG and the analyses will be weighted by the inverse of the sampling fractions in the sampling strata to test the null hypothesis that the phenotypic levels are not associated with genotypes.
4) The distribution of the outcome variable (changes in FVII activity) will be examined and outliers will be excluded.
5) Basic adjustment will include as covariates age, gender, and field center, to be consistent with the CHARGE GWAS analysis; In a secondary analysis, the analysis will additionally adjust for baseline FVII level and other risk factors that were associated with FVII change (i.e., change in BMI, smoking status, diabetes status, and triglycerides)

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

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)?

    Dr. Folsom is a coauthor on this proposal.

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
   ____   A. primarily the result of an ancillary study (list number* _________)
   __X__   B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.03, 2007.02__
                     __________ __________)

   *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.

References


