ARIC Manuscript Proposal # 1383

PC Reviewed: 06/10/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: CHARGE GWAS for hemostatic factors

b. Abbreviated Title (Length 26 characters): Hemostasis GWAS

2. Writing Group: CHARGE hemostatic factor working group

Writing group members: Authors to be determined. For ARIC it will include those taking part, including possibly Aaron Folsom, Weihong Tang, Saonli Basu, Jim Pankow, David Couper, Eric Boerwinkle, Jing-Fei Dong.

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]**

F**irst author**: TBN. Probably will be several papers with first authors from other cohorts.

Address:

Phone: Fax:
E-mail:

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
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3. Timeline: summer 2008

4. Rationale: CHARGE (ARIC, CHS, Rotterdam, Framingham, and selected other cohorts) is doing a meta analysis of GWAS findings related to hemostatic factors. The group is chaired by Jacqueline Witteman from Rotterdam. Two initial papers are

planned: 1) fibrinogen and 2) factors VII, VIII and von Willebrand. Other papers might be written. ARIC will have authors named—probably 6 per paper.

5. Main Hypothesis/Study Questions:

Gene variants can be identified for hemostatic factors.

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: meta analysis of GWAS studies

Participating groups:

Framingham Study
Rotterdam Study
ARIC
CHS (2400)
MONICA/KORA
British birth cohort

Priority phenotypes: Fibrinogen, VWF, factor VII, factor VIII

Paper proposals/priorities:

1. Fibrinogen
2. VWF, Factor VIII, Factor VII

1. Model: Linear regression for cross-sectional analysis

Based on one measurement per cohort
Genetic model: additive

2. Transform: no transform, no scaling.

3. Covariates:

1. Age and sex adjusted (+ cohort/center where appropriate)

2. Multivariate adjusted: Age (continuous), smoker (current, former, never), BMI (continuous), diabetes (y,n), CVD (y,n), TG (continuous), HDL-C (continuous), total cholesterol, alcohol (continuous, with 0 for nondrinker), SBP, htnrx, HRT.

3. Subgroups / Interactions: Age specific (< 55 and > 55), Sex specific, BMI (< 25 and > 25 kg/m2), Smoking. Secondary analysis, using top SNPs?

4. Exclusions: use of anti-coagulation therapy

5. Control for multiple comparisons: Bonferroni adjustment

6. Imputation
Imputation to Hapmap 2.1 M

7. Meta-analysis:
Meta-analysis based on 2.1 M observed and imputed SNPs

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

___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

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)* _____Boerwinkle's GWAS_____ _____ _____)

*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.