ARIC Manuscript Proposal # 1535

PC Reviewed: 7/14/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome Wide Association Study (GWAS) for Venous Thromboembolism

b. Abbreviated Title (Length 26 characters): **GWAS for VTE**

2. Writing Group:

Writing group members: This involves a consortium, and here are tentative authors:
ARIC: Aaron Folsom, Weihong Tang, Saonli Basu, Jim Pankow, Eric Boerwinkle
CHS: Mary Cushman, Susan Heckbert
Seattle case-control study: Nick Smith, Bruce Psaty
Rotterdam: Bruno Stricker and others
Mayo (tentative): John Heit

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]**

First author: **Aaron Folsom**
Address: UMN

Phone: 612-626-8962 Fax: 612-624-0315
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: Summer 2009

4. Rationale:

VTE is an important vascular disease and public health problem. It clearly has a genetic component and several uncommon mutations (e.g., Factor V Leiden) have been identified. Some individual studies have identified a few common variants in coagulation genes related to VTE (1,2), but only one small whole GWAS has been done. The GWAS found no new SNP associations with VTE (3).

One of the main aims of the LITE (ARIC/CHS) renewal was to perform a GWAS of VTE. We have put together a consortium from multiple studies to accomplish that aim.

References

1. Bezemer ID, Bare LA, Doggen CJ, Arellano AR, Tong C, Rowland CM, Catanese J, Young BA, Reitsma PH, Devlin JJ, Rosendaal FR. Gene variants associated with deep vein thrombosis. JAMA. 2008 Mar 19;299(11):1306-14.

2. Smith NL, Hindorff LA, Heckbert SR, Lemaitre RN, Marciante KD, Rice K, Lumley T, Bis JC, Wiggins KL, Rosendaal FR, Psaty BM. Association of genetic variations with nonfatal venous thrombosis in postmenopausal women. JAMA. 2007 Feb 7;297(5):489-98.

3. Trégouët DA, Heath S, Saut N, Biron-Andreani C, Schved JF, Pernod G, Galan P, Drouet L, Zelenika D, Juhan-Vague I, Alessi MC, Tiret L, Lathrop M, Emmerich J, Morange PE. Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. Blood. 2009 May 21;113(21):5298-303.

5. Main Hypothesis/Study Questions:

Common variants for VTE in whites will be found.

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).

The ARIC data on VTE will be analyzed in relation to measured and imputed SNP data available on ARIC subjects. Subjects on warfarin at baseline will be excluded. This will be a meta analysis, based on each study's results, following recommended CHARGE analysis methods. Associations for ARIC/CHS will be assessed using proportional hazards regression models. The main model will be minimally adjusted (e.g., by sex and age). VTE risk factors (obesity, factor VIII, diabetes, possibly smoking and alcohol) may be considered in additional models. At this point, interactions have not been discussed but may be an additional focus of the working group.

If any SNPS are associated with VTE, replication will be sought and follow-up studies to identify possible mechanisms.

The following table summarizes the key studies to date:

CHARGE GWAS on Venous Thromboembolism (VTE) in Whites

	Rotterdam	ARIC	CHS	Group Health
Design	Cohort	Cohort	Cohort	Case-Control
Sample	10,994, 55+ y (89% white)	15,792, 45-64 y (73% white)	5,888 65+ y (84% white)	~*600* cases ~*600* controls
Female				100%
Matching	--	--	--	Frequency matched to another case group
Mean age	69 y @ start	54 y @ start 67 y @ VTE	72 y @ start 80 y @ VTE	65 y @ VTE
Follow-up, max	18 y	19 y	13 y	--
VTE Events	247 (219 white)	517 (341 white)	210 (162 white)	~600 (~550 white)
PE	124	181	67	
VT only	123	406	174	
Provoked	NA	321	89	
Unprovoked	NA	196	121	
Genotype *n*				~1200 (~1100 white)
Total	7,869	11,433	3,865 w/o CVD	
Whites	?	?	?	
Platform	Illimina, 530K	Affy6.0, 870K	Illumina, 370K	Illumina 370CNV
Covariates				
BMI	y	y	y	Y
Smoking	y	y	y	Y
Alcohol	y	y	y	Y
fVIII	some	y	y	No
vWF	some	y	some	No
V Leiden	*n*	some	some	Y
prothG20210A	*n*	some	some	y

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)?

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
_x__ A. primarily the result of an ancillary study (list number* __1998.03__)
___ 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/

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.**