1.a. Full Title: A gene-centric association study of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE) Study (for CARe-VTE R01, PI: Weihong Tang)

b. Abbreviated Title (Length 26 characters): CARe IBC SNPs and VTE

2. Writing Group:
   Writing group members: Weihong Tang, Mary Cushman, James Pankow, Saonli Basu, Susan Heckbert, and Aaron Folsom (other coauthors from ARIC and LITE are welcome)

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

First author: Weihong Tang
Address: Division of Epidemiology and Community Health, School of Public Health, University of Minnesota
         1300 South Second Street, Suite 300
         Minneapolis, MN 55454
         Phone: 612-626-9140    Fax: 612-624-0315
         E-mail: tang0097@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: Aaron Folsom
Address:

   Phone:       Fax:
   E-mail:  folso001@umn.edu

3. Timeline: Begin 10/2011

4. Rationale:
I have received an R01 award from NIH, titled “Genetic Epidemiological Study of Venous Thromboembolism and Hemostatic Factors” (R01 HL095603), which aims to utilize the CARe candidate gene resources to understand the genetic determinants of VTE in LITE and coagulation intermediate phenotypes in CARe cohorts including ARIC. Incident VTE data is only available in ARIC among CARe cohorts and therefore does not belong to the CARe (incident VTE data was not submitted to CARe). This MS proposal serves to cover the analysis of VTE proposed in this R01. The ARIC ancillary study ID# for this R01 is 2008.08.

5. Main Hypothesis/Study Questions:

Genetic variants in cardiovascular-related candidate genes are associated with the risk of VTE.

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: cohort—pooled ARIC and CHS samples for VTE (LITE study). Caucasians and African Americans will be analyzed separately. African American data will be used to replicate the signals detected in Caucasians.

Inclusions: all participants with CARe IBC SNP data and approval to use DNA.

SNP data: CARe IBC SNPs in ARIC.

Outcome: validated VTE in LITE.

Covariates: Basic adjustment includes baseline age, sex, and field center. Principal components derived from EIGENSTRAT analysis of GWAS data will be added if VTE is influenced by population stratification. BMI, smoking, and diabetes will be additionally adjusted for in secondary analyses.

Analysis: Analysis will be stratified by race. Examine frequencies of SNPs. Test Hardy-Weinberg equilibrium. Use standard cohort study analysis methods (e.g., Cox models) relating frequencies (dosages) of risk alleles to occurrence of VTE.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ 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_DÑA = “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.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)?

#1535: Genome Wide Association Study (GWAS) for Venous Thromboembolism

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 and 2008.08)

_____ 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.csc.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.

Yes.