

ARIC Manuscript Proposal # 1464

PC Reviewed: 01/13/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Genome-wide association study of P-selectin and ICAM in white adults of European descent: CHARGE Consortium

b. Abbreviated Title (Length 26 characters): GWAS of P-selectin and ICAM

2. Writing Group:

Writing group members: Maja Barbalic, Ron C. Hoogeveen, Vijay Nambi, Christie Ballantyne, Eric Boerwinkle, the authors from other CHARGE cohorts will be included

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

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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).

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3. Timeline:

Genotyping is complete. Data analysis will begin immediately.

4. Rationale:

Inflammation, with activation of both the innate immune system and the coagulation/fibrinolysis systems, is observed in cardiovascular diseases and a number of other chronic diseases of aging (1). The important step of the inflammation process is the leukocyte adhesion and subsequent migration into the vascular wall; steps mediated by adhesion molecules such as P-selectin and ICAM (2).

P-selectin is expressed mainly at the surface of platelets and endothelial cells. It plays a crucial role in leucocyte adhesion by supporting leukocyte rolling (2). The intercellular adhesion molecule, ICAM-1, is a member of the immunoglobulin gene superfamily of adhesion molecules. It is expressed on leukocytes, fibroblasts, epithelial cells, and endothelial cells (2).

Both P-selectin and ICAM have high heritability estimates (45-70% former and 34-59% later) (3,4). The genetic analyses of ICAM and P-selectin led to identification of several genes (3,4). We propose a genome wide association analysis in ARIC and the other cohorts in the CHARGE consortium in order to find additional loci associated with levels of those two biomarkers.

5. Main Hypothesis/Study Questions: To investigate the association of genome-wide genetic variation with inter-individual variation in ICAM and P-selectin levels in adults of European ancestry

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).

Additive genetic effects on ICAM and P-selectin levels will be assessed by linear regression using ProbABEL software. All ARIC white participants with biomarker levels (P-selectin or ICAM) measured and genotype data available will be included.

Both P-selectin and ICAM levels were measured for a subset of ARIC (P-selectin on individuals from Table 2 and ICAM on individuals from Table 4). In order to account for the case status that could be related to ICAM/P-selectin levels, we will include the case status as a covariate in the model. The covariates will include sex and age in addition. We will run a weighted analysis based on the inverse of the sampling fractions for the top SNPs from the GWAS results to validate our results from the initial non-weighted analyses. Metaanalysis combining the results from individual CHARGE studies will be performed using inverse variance weighting with a fixed effects model.

Exposure: 2.5 million HapMap genetic variants identified in CEPH trios

Outcome: ICAM, P-selectin

Exclusions: Those without consent for genetic research

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_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? 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"?
 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?
 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>

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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2006.03 (Stampede, genotyping in Caucasians)_____)

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.

References:

1. Tracy RP. Thrombin, inflammation, and cardiovascular disease: an epidemiologic perspective. *Chest*. 2003 Sep;124(3 Suppl):49S-57S.
2. Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2007 Nov;27(11):2292-301.
3. Reiner AP, Carlson CS, Thyagarajan B, Rieder MJ, Polak JF, Siscovick DS, Nickerson DA, Jacobs DR Jr, Gross MD. Soluble P-selectin, SELP polymorphisms, and atherosclerotic risk in European-American and African-American young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Arterioscler Thromb Vasc Biol*. 2008 Aug;28(8):1549-55.
4. Paré G, Chasman DI, Kellogg M, Zee RY, Rifai N, Badola S, Miletich JP, Ridker PM. Novel association of ABO histo-blood group antigen with soluble ICAM-1: results of a genome-wide association study of 6,578 women. *PLoS Genet*. 2008 Jul 4;4(7)