ARIC Manuscript Proposal # 1224

PC Reviewed: __2/13_/06   **Status:** _A___   **Priority:** _2__
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: ICAM-1 genetic variation, ICAM-1 levels and risk of incident CHD and ischemic stroke: the ARIC study

   b. Abbreviated Title (Length 26 characters): ICAM-1, CHD, Stroke

2.   Writing Group: Kelly Volcik, Ron Hoogeveen, Christie Ballantyne, Aaron Folsom, Eric Boerwinkle

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

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3.   Timeline: Measurements of plasma ICAM-1 concentrations are available for a stratified random sample of the ARIC cohort (Table 2). Genotyping for two SNPs (rs1799969 [G241R] and rs5498 [K469E]) in the ICAM-1 gene is in progress for the entire ARIC cohort. Genotyping should be complete by April. Statistical analyses will begin in April/May, with a first draft manuscript prepared by August 2007.

4.   Rationale:

The pathogenesis of atherosclerosis is known to contain an important inflammatory component, involving the adhesion of circulating leukocytes, particularly monocytes, to the vascular endothelium at sites of injury.[1] The recruitment, binding and migration of circulating leukocytes to the vascular endothelium is mediated through a diverse family of adhesion molecules, including ICAM-1, which has been shown to be increased in pathological studies of atherosclerosis.[2] Plasma levels of ICAM-1 have been previously shown in ARIC to be increased in incident CHD and CAA cases compared to controls.[3] The odds of CHD and CAA were 5.53 and 2.64, respectively, for those with levels of ICAM-1 in the highest quartile compared with those in the lowest quartile.[3] Genetic variation in the ICAM-1 gene has been shown to be associated with ICAM-1 levels such that the ICAM-1 G241R polymorphism was associated with lower sICAM-1 levels in a healthy French population of 412 children and 363 adults.[4]

Only a handful of studies have explored associations between ICAM-1 genetic variation and cardiovascular disease, and these results have proved contradictory. One study of an Irish population of 1,012 individuals from 386 families with at least one member prematurely affected with CAD showed no association between the ICAM-1 K469E polymorphism and CAD.[5] Another study evaluating the association between the K469E polymorphism and CHD in a German population (349 CHD cases, 213 controls) found the 469E variant allele to be significantly associated with a 2-fold increased risk of CHD.[6] The ICAM-1 469EE genotype was also found to be significantly and independently associated with prevalent ischemic stroke in a case-control study of 237 persons with history of stroke and 223 age- and gender-matched controls.[7] To our knowledge, no study has evaluated the association between these two ICAM-1 polymorphisms and cardiovascular disease in a large prospective cohort such as the ARIC study. Therefore, we propose to evaluate the association between the ICAM-1 K469E and G241R polymorphisms and incident CHD and stroke, as well as the association between these two polymorphisms and ICAM-1 levels, in the ARIC cohort. The two ICAM-1 SNPs will be analyzed separately and as haplotypes.

5. Main Hypothesis/Study Questions:

1. Estimate the frequency distribution of ICAM-1 gene variation in the ARIC cohort. *If allele frequencies are markedly disparate between whites and African Americans, all of the following analyses will be conducted separately by race.*

2. Utilizing Cox regression, evaluate the ability of ICAM-1 gene variation to predict incident CHD. Models will be adjusted for age, gender, race, BMI, HDL and total cholesterol, smoking, diabetes and hypertension status.

3. Utilizing Cox regression, evaluate the ability of ICAM-1 gene variation to predict incident ischemic stroke. Models will be adjusted for age, gender, race, smoking, diabetes and hypertension status.

4. Evaluate whether ICAM-1 gene variation is associated with ICAM-1 levels. These analyses will be evaluated utilizing the SUDAAN software package to adjust for the sampling strategy. Age, gender, race and case status (CHD and stroke) will be included as covariates.

5. Evaluate whether ICAM-1 levels are associated with disease status (CHD and stroke). The analyses will be evaluated utilizing the SUDAAN software package to adjust for the sampling strategy. Age, gender and race will be included as covariates.

6. The survival analyses described above (#s 2 and 3) for incident CHD and stroke will be repeated including ICAM-1 levels as a covariate. The method of Barlow will be used to adjust for the sampling strategy. Covariates will be the same as listed above in #s 2 and 3.

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 two ICAM-1 SNPs (rs1799969 [G241R] and rs5498 [K469E]) are being genotyped on the entire ARIC cohort and will be evaluated for associations with incident CHD and stroke, as well as evaluated for correlations with ICAM-1 plasma levels. ICAM-1 levels are available for only a subset (stratified random sample) of the ARIC cohort. Therefore, analyses involving ICAM-1 levels will be evaluated utilizing the SUDAAN software package / method of Barlow to adjust for the sampling strategy where appropriate. All analyses will be done for each SNP separately and as haplotypes. Haplotypes will be inferred using PHASE version 2.1. Goodness of fit to Hardy-Weinberg expectations will be carried out using a chi-square test.

ARIC's incident CHD and ischemic stroke case status will be the primary dependent variables. The usual DNA restriction, ethnic group and missing data exclusion criteria will be used. Exclusions will include the following: 1) positive or unknown history of prevalent CHD or stroke or history of TIA/stroke, 2) prohibited use of DNA, 3) ethnic background other than white or African

American, as well as African Americans not from Jackson or Forsyth. For incident CHD analyses, we will use the variable IN_03SP. For incident ischemic stroke analyses, we will use the variable IN03ISC. Independent variables include but are not limited to ICAM-1 genotype status and traditional risk factors such as age, gender, smoking, diabetes and hypertension status.

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 ICTDER02 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

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 ICTDER02 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. _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)?
The most closely related MS proposal is #941 (R Hoogeveen, a writing member of the current proposal), which was approved 06/19/03 but withdrawn on 2/4/04. The current proposal will expand on this previously approved and withdrawn proposal.

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

11.b. If yes, is the proposal
     ___   A. primarily the result of an ancillary study (list number* _____)
     ___   B. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

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. *Agreed*

References:
1. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340:115-126.
2. Albelda SM, Smith CW, Ward PA. Adhesion molecules and inflammatory injury. FASEB J 1994;8:504-12.
3. Hwang SJ, Ballantyne CM, Sharrett AR, Smith LC, Davis CE, Gotto AM, Boerwinkle E. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the ARIC study. Circulation 1997;96:4219-4225.
4. Ponthieux A, Lambert D, Herbeth B, Droesch S, Pfister M, Visvikis S. Association between G241R ICAM-1 gene polymorphism and serum ICAM-1 concentration in the Stanislas cohort. Eur J Hum Genet 2003; 11:679-686.
5. McGlinchey PG, Spence MS, Patterson CC, Allen AR, Murphy G, Belton C, McKeown PP. The ICAM-1 gene K469E polymorphism is not associated with ischaemic heart disease: an investigation using family-based tests of association. Eur J Immunogenet 2004;31:201-206.
6. Jiang H, Klein RM, Niederacher D, Du M, Marx R, Horlitz M, Boerrigter G, Lapp H, Scheffold T, Krakau I, Gulker H. C/T polymorphism of the ICAM-1 gene. A risk factor for CHD and MI. Int J Cardiol 2002;84:171-177.
7. Flex A, Gaetani E, Papaleo P, Straface G, Proia A, Pecorini G, Tondi P, Pola P, Pola R. Proinflammatory genetic profiles in subjects with history of ischemic stroke. Stroke 2004;35:2270-2275.