1.a. Full Title: Association of Cell Adhesion Molecule Genetic Variation with Carotid Artery Plaque Characteristics: the ARIC Carotid MRI Study

b. Abbreviated Title (Length 26 characters): CAM Gene Variation and Carotid MRI

2. Writing Group: Kelly Volcik, Christie Ballantyne, Eric Boerwinkle, Ron Hoogeveen, Weihong Tang (others welcome)

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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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: All data (genotype and carotid artery plaque characteristics) are available, so analyses can begin immediately upon approval. For this MS proposal, we will focus on those cell adhesion molecules (ICAM-1, PECAM-1, VCAM-1, SELE, SELP, PSGL-1) that were genotyped as part of the ARIC Carotid MRI study (Illumina candidate gene chip).

4. Rationale: An early phase of atherosclerosis involves the recruitment and transendothelial migration of inflammatory cells, a process predominantly mediated by cellular adhesion molecules (CAMs).1-4 CAMs are expressed on the vascular endothelium and circulating leukocytes in response to inflammatory stimuli.1,5 Selectins (E, L, P) and their ligand (PSGL-1) are involved in the rolling and tethering of leukocytes on the vascular wall. ICAM-1 and VCAM-1 induce the firm adhesion of inflammatory cells to the vascular surface.1 PECAM-1 is involved in the extravasation of cells into the vessel and underlying tissue.1 Several studies support the
role of CAMs in the development of atherosclerosis and plaque instability. Expression of
VCAM-1, ICAM-1 and SELL has been consistently observed in atherosclerotic plaques, but
there are not many studies investigating the relationship of CAM genetic polymorphisms with
atherosclerosis.  Therefore, we propose to investigate the association of CAM genetic
variation (including ICAM-1, PECAM-1, VCAM-1, SELE, SELL, SELP and PSGL-1) with multiple
carotid artery plaque characteristics in the ARIC carotid MRI cohort.

5. Main Hypothesis/Study Questions:

1. CAM gene variation is associated with carotid artery wall thickness measures (total wall
   volume; max wall thickness).
2. CAM gene variation is associated with cap measures (mean min cap thickness; mean
   cap thickness).

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).

   All analyses will be based on methods appropriate for a stratified random sample. In
   particular, all analyses will be weighted by the inverse of the sampling fractions in the eight
   sampling strata (4 field centers X 2 IMT groups). Analyses will be conducted utilizing
   STATA/SE 10 for descriptive statistics, with the STATA SURVEY procedure utilized for linear
   regression. Tests of differences in weighted means or proportions between groups will be from
   weighted linear regression models that account for the sampling. Mr. Kim Lawson, a statistician
   with Eric Boerwinkle’s group who has worked with ARIC datasets extensively over the years, as
   well as performing replication analyses of recent Carotid MRI datasets, will be the primary
   statistician for this proposed work.

   Genotype frequencies will be calculated as weighted frequencies, and the test for Hardy-
   Weinberg equilibrium will use the weighted genotype frequencies to obtain the test statistic.
   Variant alleles will be identified as the low frequency allele in whites, and homozygous wildtype
   (non-variant) genotypes will be designated as the referent group in the statistical analyses. An
   additive genetic model will be utilized in initial analyses. However, when the sample size is low
   in homozygous genotype groups, we will utilize a dominant model that combines homozygous
   and heterozygous variant genotypes.

   The issue of multiple comparisons will undoubtedly arise since we will be investigating a
   large number of SNPs in multiple genes. The false discovery rate and Bonferroni correction are
two methods by which we can adjust for multiple testing. Although tagSNPs were specifically
selected for the Carotid MRI Illumina panel gene chip, we will evaluate LD patterns for each of
the selected genes/SNPs in the interpretation of our results. The number of SNPs that will be
investigated for each gene are as follows: ICAM-1 (13), PECAM-1 (20), VCAM-1 (16), SELE
(19), SELL (21), SELP (41), PSGL-1 (4).

   The usual DNA restriction and missing data exclusion criteria will be used. Races will be
combined for all initial analyses due the potentially small sample size in genotype groups, but
additional analyses may be conducted to evaluate races separately for further interpretation of
potentially interesting results. Analysis variables include but are not limited to CAM genotype
status, wall thickness measures, cap measures, and traditional risk factors such as age, gender, race and smoking.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X_ 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 MS proposal has reviewed the list of existing ARIC Study MS proposals and found no overlap between this proposal and previously approved proposals either published or still in active status.

_ X_ Yes ____ No

10. What are the most related MS proposals in ARIC?

491: (D Ellsworth et al.) E-selectin S128R polymorphism and the occurrence of atherosclerosis and incident CHD

1002: (K Volcik et al.) P-selectin Thr715Pro polymorphism predicts PSEL levels but not risk of incident CHD or ischemic stroke in a cohort of 14595 participants: the ARIC study

1002b: (K Volcik et al.) Specific P-selectin and P-selectin glycoprotein ligand-1 genotypes/haplotypes are associated with risk of incident CHD and ischemic stroke: the ARIC study

1224: (K Volcik et al.) ICAM-1 genetic variation, ICAM-1 levels and risk of incident CHD and ischemic stroke: the ARIC study.

1221: (K Volcik et al.) P-selectin gene variation influences (does not influence) cell surface levels of P-selectin and P-selectin ligand: the ARIC Carotid MRI Study.

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* ___2004.11___)

___ B. primarily based on ARIC data with ancillary data playing a minor role

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 MS proposal will expire.  Agreed

References:


