ARIC Manuscript Proposal # 1204

PC Reviewed: _12/_19/06	**Status: __D_**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: MMP gene variation influences fibrous cap thickness: The Atherosclerosis Risk in Communities (ARIC) study.

b. Abbreviated Title (Length 26 characters): MMP gene variation influences fibrous cap thickness

2. Writing Group:
Writing group members: Boerwinkle, Volcik, Folsom, Chambless, Heiss, Wagenknecht, Mosley, Coresh, Wasserman, Ni, plus others.

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

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Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author): Same

3. Timeline: Preliminary analyses can begin immediately.
Final analyses will need to await data collection.

4. Rationale:

Matrix metaloproteases are a family of enzymes involved in cleavage and degradation of fibrillar collagen. There is known DNA sequence variation in MMP 1, 2, 3, 7, 9 and 12 that have been previously associated with a variety of CVD-related phenotypes (Yi (2006) Cardiovasc Res 15: 636.). One mechanism by which MMP gene variation may influence CVD risk is via the proteins influence on fibrous cap thickness (Newby (2005) Physiol Rev 85: 1).

One of the primary outcome variables of the carotid MRI protocol is fibrous cap thickness. This study will examine the role of DNA sequence variation in the MMP genes in influencing fibrous cap thickness in those participants in the carotid MRI study having identified plaque. Although the exact variable reflecting cap thickness has not been identified, two variables MEAN_MIN_CAP_THICKNESS and Min_Cap_Thickness will be initially considered for this analysis.

5. Main Hypothesis/Study Questions:

Null hypothesis 1: DNA sequence variation in the MMP genes is not associated with presence of visible plaque.

Null hypothesis 2: DNA sequence variation in the MMP genes is not associated with presence of plaque with a lipid core.

Null hypothesis 3: DNA sequence variation in the MMP genes is not associated with fibrous cap thickness. (continuous variable analyses)

Null hypothesis 4: DNA sequence variation in the MMP genes is not associated with presence of thin walled plaques. (categorical variable analyses)

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).

Routine descriptive statistics will be used for the genotype and allele counts. Presence of visible plaque and presence of a lipid core in those plaques will be considered as categorical (i.e. 0, 1) variables. For the main study hypothesis, the primary dependent variable is fibrous cap thickness. Although the exact variable reflecting cap thickness has not been identified, two variables MEAN_MIN_CAP_THICKNESS and Min_Cap_Thickness will be initially considered for this analysis. Consistent with the May 2006 coordinating center report, the definition of plaque will use a cut point of 6.1. Fibrous cap will be analyzed both as a continuous variable and as a thick/thin categorical variable. Again, consistent with the May 2006 coordinating center report, 0.16 will be used as the cut-point for thick/thin. Race, sex and age will be used as covariates. Because of the recruitment strategy, which incorporated information on carotid artery wall thickness, weighted analyses will be used for the proposed genotype-phenotype analyses.

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
(This file ICTDER02 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 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. 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* _2004.11_)

___ B. primiarly 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.