1.a. Full Title: Chromosome 9 CHD locus is associated with carotid artery plaque characteristics: The ARIC study.

b. Abbreviated Title (Length 26 characters): Chr 9 and plaque characteristics

2. Writing Group: Eric Boerwinkle (Chair)
   Writing group members (alphabetically for now): Stephen Campbell, Jonathan Cohen, Aaron Folsom and Bruce Wasserman

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

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3. Timeline: The data are available now.
The coordinating center PI has indicated that there is ample available analysis personnel.

4. Rationale:
The ARIC study has recently been involved in the initial discovery of a novel locus on human chromosome 9 harboring sequence variation(s) contributing to risk of CHD in ARIC and multiple other studies. The mechanism by which this sequence variation is translated into differences in CHD risk is totally unknown. Since the initial publication, work by the same collaborative team has taken several directions including fine scale mapping and experimental animal research. Interestingly, this locus does not seem to be
associated with traditional CHD risk factors leading to the hypothesis of a novel pathway leading to atherosclerosis and/or clinical CHD. The purpose of this study is to ask whether previously identified DNA sequence variations in this region (rs10757274 (from original paper) and rs7028570 (from fine mapping efforts)) are associated with differences in carotid artery plaque morphology in the ARIC carMRI study.

5. Main Hypothesis/Study Questions:
   Null hypothesis 1: DNA sequence variations on chromosome 9 (rs10757274 and rs7028570) are not associated with presence of visible plaque.

   Null hypothesis 2: DNA sequence variations on chromosome 9 (rs10757274 and rs7028570) are not associated with lipid core volume.

   Null hypothesis 3: DNA sequence variations on chromosome 9 (rs10757274 and rs7028570) are not associated with fibrous 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).
   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. The other variables will be analyzed as continuous. Based on our previous experience, we have identified the following variables to be of particular interest and to be measured with satisfactory reproducibility.

   Carotid artery wall thickness
     Total wall volume
     Max wall thickness
   Lipid core measures (those with zero coded as missing)
     Total lipid core area
     Mean lipid core area
   Lipid core measures in those with lipid core in two adjacent
     Total lipid core area
     Mean lipid core area
   Cap measures
     Mean min cap thickness in 2 adjacent
     Mean cap thickness in 2 adjacent

   The proposed analysis plan should follow the final analysis plan for MS#1204 (MMPs and plaque characteristics). Tables 1, 2 and 3 from that paper should constitute beginning skeleton tables for this manuscript. 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)? There is no overlap with other manuscript proposals.

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 (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. Agree.