ARIC Manuscript Proposal # 1399

PC Reviewed: 08/12/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between a LPA gene variant and CHD according to aspirin use in the Atherosclerosis Risk in Communities Study.

1.b. Abbreviated Title (Length 25 characters): *LPA* SNP and aspirin use

2. Writing Group: Dov Shiffman, Daniel Chasman, Christie Ballantyne, Vijay Nambi, Aaron Folsom, James Devlin, Eric Boerwinkle

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

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3. Timeline: All analyses will be carried out at the University of Texas Health Science Center at Houston under the supervision of Dr. Eric Boerwinkle. This SNP was genotyped in ancillary study 2004.11; analyses and manuscript preparation is projected to take place over the next 6 months.

4. Rationale: Carriers of the minor allele of the rs3798220 SNP in the LPA gene [encoding apo(a), the apolipoprotien on Lp(a)] were shown to have increased risk for CHD in three case-control studies (Luke et al.) and in the Cardiovascular Health Study (Shiffman et al). Among whites in ARIC, this SNP was not associated with risk of CHD (HR= 1.01, P=0.98; Morrison et al.). This SNP was also investigated in the Women's Health Study (WHS), a randomized trial of low-dose aspirin. In WHS, carriers of the minor allele of this SNP had increased risk of CHD compared with noncarriers in the placebo group, but not in the aspirin group (Chasman et al. submitted for publication). Since apo(a) is homologous to plasminogen, it has been suggested that Lp(a) could be a modifier of thrombosis. The rs3798220 SNP encodes an isoleucine to methionine substitution in the protease-like domain of LPA. Thus, the carriers of the minor (methionine) allele of LPA could have a more pro-thrombotic Lpa(a), which would be consistent with a differential effect aspirin treatment on carriers of the minor allele of the LPA SNP compared with noncarriers. Alternatively, since aspirin has been reported to lower Lp(a) levels (Akaike et al., Kagawa et al.), it could be that LPA variant may be particularly susceptible to Lp(a) reduction by aspirin. Therefore, in ARIC we would like to investigate the association between this SNP and CHD according to aspirin use, specifically to ask if among non-users of aspirin this SNP is associated with CHD, and if this risk is different than that observed among users of aspirin.

5. Main Hypothesis/Study Questions:

Main hypothesis: Among non-users of aspirin, carriers of rs3798220 have increased risk of incident CHD.

Study questions:

Main question: Among non-users of aspirin, do carriers of the minor allele of rs3798220 have increased risk of incident CHD.

Exploratory analyses:

1. Among users of aspirin, do carriers of the minor allele of rs3798220 have increased risk of incident CHD.
2. Is there a significant interaction between aspirin use and rs3798220 for the CHD outcome.

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).

Study design: Prospective follow-up of all ARIC participants meeting the inclusion criteria from visit 4 through December 31, 2005. The rs3798220 SNP was genotyped as part of a collaboration between scientists at Celera and Dr. Boerwinkle as described in ARIC Ancillary Study 2004.11.

Inclusions/exclusions: In ARIC exclusions prior to analysis involve the removal of individuals who at baseline and up to visit 4 had a positive or unknown history of stroke or stroke symptoms, positive history or missing data for CHD, Blacks not from Jackson, MS or Forsyth County, NC, race other than Black or White, and individuals with restricted DNA use. 11,604 participants remain after these exclusions.

Outcome: The primary outcome measure will be time from visit 4 to the first occurrence of a component of the CHD endpoint.

Other variables of interest: Aspirin use will be determined from answers to item 29 in visit 4 " Are you now taking aspirin or aspirin containing medication on a regular basis". Aspirin nonusers are those that answered "no". Aspirin users are those that answered

"yes" and reported taking the medication 7 days a week. Traditional risk factors used to adjust estimates of genetic risk include the following baseline information: systolic and diastolic blood pressure, hypertension medication use, total cholesterol, HDL-cholesterol, LDL-cholesterol, diabetes status, smoking status, gender and family history (age of mother's MI, age of father's MI). We will also use the Annual Follow-Up question regarding regular use of aspirin to investigate the extent to which those that were identified as nonusers of aspirin at visit 4 remained nonusers during follow-up, and the extent to which users of aspirin remained users, and to perform a time-dependent aspirin analysis.

Data analysis

Survival analyses: Analysis will be carried out in white and African American population separately. Event-free participants will be followed starting at visit 4 until the earliest of December 31, 2004, the date of last contact, or death. Incidence rates of CHD will be calculated using person-time methods. Kaplan-Meier estimates of event free survival will be computed, and log-rank tests will be used to compare survival curves among the genotypes.

The primary analysis in this investigation will be time from visit 4 to the first occurrence of a component of the CHD endpoint, separately for visit 4 users of aspirin and visit 4 nonusers of aspirin. Carriers of the minor allele of rs3798220 will be tested for association with incident CHD in Cox proportional hazard analyses separately for each race. In each race, the test will be performed in users and nonusers of aspirin separately. Interaction between rs3798220 and aspirin use status will be evaluated by including in interaction term in the Cox model. Subsequent multivariate models will include basic variables (age, sex), traditional risk factors at baseline (systolic and diastolic blood pressure, hypertension medication use, total cholesterol, HDL-cholesterol, LDL-cholesterol, diabetes status, smoking status, gender and family history). We will also investigate the effect of regular use of aspirin on risk of incident CHD starting at visit 4 among carriers and noncarriers of the minor allele of rs3798220 by including regular

aspirin use as a time-dependent variable in a Cox proportional hazard analysis and use this aspirin variable to test the interaction.

Power: We would have 80% power to detect the association of rs3798220 with risk of incident CHD among non users of aspirin, if we assuming a hazard ratio of 1.8 or greater, that 70% of ARIC participants are non-users, and that 70% of the incident CHD events occur after visit 4. There is less than 80% power to detect the effect described in the exploratory 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)?

MS 1095: Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) Study using a genetic risk score
MP 1142: Genetic risk of Coronary Heart Disease in the Atherosclerosis Risk in Communities (ARIC) study: Application of a Genetic Risk Score

Both of these manuscripts are part of this same ancillary study. Therefore, the investigators can assure lack of overlap or duplication.

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 (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.

References

1. Luke MM, Kane JP, Liu DM, et al. A polymorphism in the protease-like domain of apolipoprotein(a) is associated with severe coronary artery disease. Arterioscler Thromb Vasc Biol. 2007;27:2030-6.
2. Morrison AC, Bare LA, Chambless LE, et al. Prediction of coronary heart disease risk using a genetic risk score: the Atherosclerosis Risk in Communities Study. Am J Epidemiol. 2007;166:28-35.
3. Shiffman D, O'Meara ES, Bare LA, et al. Association of Gene Variants with Incident Myocardial Infarction in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. 2008;28:173-9.
4. Akaike M, Azuma H, Kagawa A, et al. Effect of aspirin treatment on serum concentrations of lipoprotein(a) in patients with atherosclerotic diseases. Clin Chem. 2002;48:1454-9.
5. Kagawa A, Azuma H, Akaike M, et al. Aspirin reduces apolipoprotein(a) (apo(a)) production in human hepatocytes by suppression of apo(a) gene transcription. J Biol Chem. 1999;274:34111-34115.