ARIC Manuscript Proposal # 1879

PC Reviewed: 12/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Interactions of 9p21 with standard risk factors in relation to CHD incidence

b. Abbreviated Title (Length 26 characters): 9p21 interactions & CHD

2. Writing Group:

Writing group members: A Folsom, V Nambi, J Pankow, W Tang, K Farbakhsh, K Yamagishi, E Boerwinkle

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

First author: Aaron Folsom
Address:

Phone: Fax:
E-mail:

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).
Name:
Address:

Phone: Fax:
E-mail:

3. Timeline: paper in 6 months

4. Rationale:

Since first reported by ARIC investigators and colleagues, research has documented consistent associations of common genetic variants on 9p21 with risk of coronary heart disease and some other atherosclerotic diseases, including arterial aneurysms, in genetic epi studies. Mechanisms for 9p21 associations with arterial disease are unclear, but do not seem to involve classical risk factors (1).

ARIC has not explored whether the main 9p21 SNP, rs10757274, is associated similarly with CHD in various strata of other risk factors. In other words, it is unknown whether other major risk factors interact with 9p21. Some potential interactions with 9p21 SNPs have been reported for age (2), fruits and vegetables (3), poor glycemic control (4), and abdominal obesity (5), alcohol, smoking and hypertension (6), but some have reported no interactions with traditional risk factors (7).

5. Main Hypothesis/Study Questions:

9p21 interacts with other risk factors in relation to incident CHD in whites

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).

Inclusion: White only.

Independent variable: 9p21 rs10757274 SNP

Dependent variable: CHD incidence including silent MI and procedures

Main interacting variables: sex, current smoking, diabetes, hypertension, hypercholesterolemia, obesity, carotid IMT. We also might consider using strata of predicted 10y risk. As a secondary analysis, we also will look at interactions with some of the newer biomarkers measured at some post-baseline visits: CRP, LpPLA2, BNP, Troponin and HbA1C.

Genetic model: additive

Analysis: We will first show the frequency of demographic and risk factors by 9p21 allele categories. Based on prior information, we expect no association between 9p21 and risk factor levels.

We will then stratify by dichotomized risk factors and compute age adjusted incidence rates of CHD for the strata. Kaplan Meyer cumulative incidence plots may also be done.

Next, using a Cox model we will examine the main associations of 9p21 and risk factors with CHD incidence. The interaction hypothesis will then be tested by adding to the model all multiplicative 2-way interactions of each risk factor with 9p21 SNPs. A global

test of any interaction will be explored, as well as individual interactions if any are suggested by the global test or stratified analyses. (The writing group will discuss further whether to test additive interactions, but our plan for now is not to.)

Power was evaluated using Quanto (http://hydra.usc.edu/gxe/). Calculations were performed for rs10757274, an index SNP in 9p21 region reported to be associated with multiple CVD phenotypes in populations of European ancestry. For incident CHD, samples sizes (1300 cases, 9000 non-cases) and genetic effect size (RR=1.18 per risk allele) in whites were estimated from published ARIC data (McPherson R et al., Science 2007; 316: 1488-91). Power to detect multiplicative GxE interaction was estimated assuming an additive genetic model and generic environmental risk factor with population prevalence of 50% and effect size of RR=2.00. Given these model parameters, there is at least 80% power to detect an interaction relative risk (RRge) of 1.28 or higher. An interaction of this magnitude is equivalent to relative risks associated with the environmental factor of 2.59, 2.00, and 1.54 in individuals who are homozygous for the risk allele, heterozygous, and homozygous for the non-risk allele, respectively.

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 ICTDER03 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? __x__ Yes ____ No
(This file ICTDER03 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 ICTDER03 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)?
1265: Common Allele on Chromosome 9p21 and Risk of Heart Failure, Stroke, and

Atherosclerosis in The Atherosclerosis Risk in Communities (ARIC) Study

1425: The clinical utility of carotid intimal medial thickness (CIMT) and a single nucleotide polymorphism on chromosome 9p21 in reclassifying risk for incident CHD and stroke in the ARIC study

1466: Association of biochemical and cellular markers with a single SNP in the 9p21 chromosomal region

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. 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

References

(1) Cunnington MS, Keavney B. Curr Atheroscler Rep. DOI 10.1007/s11883-011-0178-z

(2) Dutta A, Henley W, Lang IA, Murray A, Guralnik J, Wallace RB, Melzer D. The coronary artery disease-associated 9p21 variant and later life 20-year survival to cohort extinction. Circ Cardiovasc Genet. 2011 Oct 1;4(5):542-8. Epub 2011 Aug 18. PubMed PMID: 21852414.

(3) Do R, Xie C, Zhang X, M√§nnist√∂ S, Harald K, Islam S, Bailey SD, Rangarajan S, McQueen MJ, Diaz R, Lisheng L, Wang X, Silander K, Peltonen L, Yusuf S, Salomaa V, Engert JC, Anand SS; on behalf of the INTERHEART investigators. The Effect of Chromosome 9p21 Variants on Cardiovascular Disease May Be Modified by Dietary Intake: Evidence from a Case/Control and a Prospective Study. PLoS Med. 2011

Oct;9(10):e1001106. Epub 2011 Oct 11. PubMed PMID: 22022235; PubMed Central PMCID: PMC3191151.

(4) Doria A, Wojcik J, Xu R, Gervino EV, Hauser TH, Johnstone MT, Nolan D, Hu FB, Warram JH. Interaction between poor glycemic control and 9p21 locus on risk of coronary artery disease in type 2 diabetes. JAMA. 2008 Nov 26;300(20):2389-97. PubMed PMID: 19033589; PubMed Central PMCID: PMC2762126.

(5) Ye S, Willeit J, Kronenberg F, Xu Q, Kiechl S. Association of genetic variation on chromosome 9p21 with susceptibility and progression of atherosclerosis: a population-based, prospective study. J Am Coll Cardiol. 2008 Jul 29;52(5):378-84. PubMed PMID: 18652946.

(6) Hu WL, Li SJ, Liu DT, Wang Y, Niu SQ, Yang XC, Zhang Q, Yu SZ, Jin L, Wang XF. Genetic variants on chromosome 9p21 and ischemic stroke in Chinese. Brain Res Bull. 2009 Aug 14;79(6):431-5. Epub 2009 Apr 14. PubMed PMID: 19559344.

(7) Coronary Artery Disease Consortium, Samani NJ, Deloukas P, Erdmann J, Hengstenberg C, Kuulasmaa K, McGinnis R, Schunkert H, Soranzo N, Thompson J, Tiret L, Ziegler A. Large scale association analysis of novel genetic loci for coronary artery disease. Arterioscler Thromb Vasc Biol. 2009 May;29(5):774-80. Epub 2009 Jan 22. PubMed PMID: 19164808.