ARIC Manuscript Proposal # 1338

PC Reviewed: 02/12/08	**Status: ___A_**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genetic polymorphisms identified in a European case-control genome-wide association study (GWAS) of coronary heart disease (CHD) and incident CHD in ARIC

b. Abbreviated Title (Length 26 characters): GWAS variants and incident CHD

2. Writing Group:

Writing group members: Jan Bressler
Aaron Folsom
Kelly Volcik
David Couper
Eric Boerwinkle

Other investigators welcome

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]** JB

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3. Timeline: Statistical analyses: February 2008 –June 2008
Manuscript preparation: July 2008 – August 2008
Manuscript revision: September 2008
Manuscript submission: October 2008

4. Rationale:

Recent genetic studies have focused on genome-wide association analysis of the relationships between large numbers of single nucleotide polymorphisms (SNPs) measured simultaneously and risk for common diseases to identify novel genes influencing a given phenotype. The primary advantage of this analysis strategy is that it does not depend on the *a priori* identification of genes required for the candidate gene approach which is constrained by prior knowledge of statistical association, biological function, or membership in defined pathways.

The Wellcome Case Control Consortium (WTCCC) was formed in Great Britain to carry out an experiment in which approximately 2,000 cases for each of seven complex diseases and 3,000 shared controls were genotyped (*1*). Seven SNPs showing either strong ($p < 5 \times 10^{-7}$) or moderate ($p = 10^{-5} – 10^{-7}$) association with CHD were identified in a sample enriched for premature myocardial infarction or coronary revascularization occurring before the sixty-sixth birthday. A second report was subsequently published by the same consortium that presented evidence for replication in the German Myocardial Infarction Family Study for three genetic variants (*2*) The SNPs meeting the criteria for replication included two out of the seven most likely susceptibility loci for CHD from the first report. Four additional loci were then identified when a combined analysis of the data from the original WTCCC study and the German Myocardial Infarction Family Study was undertaken. The aim of this proposal is to determine whether any of the twelve SNPs described by the WTCCC is associated with incident CHD in the large biracial population-based ARIC cohort.

References

1. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447:661-678, 2007
2. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, Konig IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR, Schunkert H: Genomewide association analysis of coronary artery disease. *N Engl J Med* 357:443-453, 2007

5. Main Hypothesis/Study Questions:

1. To estimate the frequency distributions of the alleles and genotypes for the twelve SNPS identified by the WTCCC in the ARIC cohort.

2. To determine if SNPS identified in a case-control genome-wide association study of CHD are associated with incident CHD in the ARIC cohort. Age and gender will be included in all analyses as covariates. Analysis models will also be adjusted for BMI, lipid variables, smoking, diabetes status, and hypertension status.

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).

Caucasian and African-American participants will be evaluated separately for statistical analysis. The usual DNA restriction, ethnic group, and missing data exclusion criteria will be used. An additional exclusion criterion will be the presence of prevalent cardiovascular disease at the initial visit. Cardiovascular risk factors and other covariates will be taken from the baseline examination in this proposed study. These will include but are not limited to self-reported race, sex, age, lipid variables (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), BMI, cigarette smoking, hypertension status, diabetes status, systolic and diastolic blood pressure, and use of medication to control blood pressure and diabetes.

Twelve SNPs in genes or regions associated with CHD by the WTCCC will be genotyped in the entire ARIC cohort and will be used as independent variables in this analysis. The association of genetic variation in each of the SNPs and incident CHD over a 15-year period will be analyzed individually. These analyses will be performed by Jan Bressler under the supervision of Eric Boerwinkle; a signed data distribution agreement has been completed. A table showing a list of these polymorphisms is found below:

db SNP ID	Chromosome	Reference
rs1333049	9p21	(*1*) (*2*)
rs17672135	1q43	(*1*)
rs383830	5q21	(*1*)
rs6922269	6q25	(*1*) (*2*)
rs8055236	16q23	(*1*)
rs7250581	19q12	(*1*)
rs688034	22q12	(*1*)
rs2943634	2q36	(*2*)
rs599839	1p13	(*2*)
rs17465637	1q14	(*2*)
rs501120	10q11	(*2*)
rs17228212	15q22	(*2*)

CHD will be defined as a definite or probable myocardial infarction, a silent myocardial infarction detected by electrocardiographic interval changes consistent with an intercurrent ischemic event, death due to CHD, or a coronary revascularization

procedure. The follow-up data in this study used to determine incident CHD will include events from 1987 through December 31, 2004 (variable IN_04SP).

For statistical analysis, comparison of risk factor levels between individuals with the three possible genotypes for each SNP will be performed using contingency chi-square tests for categorical variables, and t-tests for comparison of group means for continuous variables. Cox proportional hazards modeling will be used to test the hypothesis that the incidence of CHD does not differ between individuals with different genotypes for each of the SNPs conferring risk for CHD identified by the WTCCC. Hazard ratios (HRs) based on the regression coefficients from Cox proportional hazards modeling will be reported. Multiple testing issues will be addressed by evaluating consistency of effect between the two racial/ethnic groups.

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)?

#1152 Genomic predictors of sudden cardiac death (Lead author: Aravinda Chakravarti, McKusick – Nathan Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD)

#1237 Association between genetic variants conferring risk for type 2 diabetes mellitus and incident chronic kidney disease (Lead author: Anna Kottgen, Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, MD)

#1265r Common allele on chromosome 9p21 and risk of heart failure, stroke, and atherosclerosis in the Atherosclerosis in Communities (ARIC) Study

#1273 Genetic risk score for type 2 diabetes (Lead author: Jim Pankow, Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN)

#1274 Genome-wide association analysis identifies region at 20q11.2 with consistent effect on human height (Lead author: Serena Sanna, Department of Biostatistics, University of Michigan, Ann Arbor, MI)

#1280 Interactions between diabetes, diabetes genes, and the androgen receptor gene on risk of prostate cancer (Lead author: Tamra E. Meyer, Human Genetics Center, University of Texas School of Public Health, Houston, TX)

#1307 Gene-by-environment interaction for type 2 diabetes (Lead author: Audrey Chu, Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD)

The manuscript proposals listed above all describe studies in which genetic variants from genome-wide association studies will be investigated using the ARIC cohort. None of these proposals evaluate the association between SNPs and incident CHD.

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/

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**.**