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
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   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:**
- 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 x 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


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:

<table>
<thead>
<tr>
<th>db SNP ID</th>
<th>Chromosome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1333049</td>
<td>9p21</td>
<td>(1) (2)</td>
</tr>
<tr>
<td>rs17672135</td>
<td>1q43</td>
<td>(1)</td>
</tr>
<tr>
<td>rs383830</td>
<td>5q21</td>
<td>(1)</td>
</tr>
<tr>
<td>rs6922269</td>
<td>6q25</td>
<td>(1) (2)</td>
</tr>
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<td>rs8055236</td>
<td>16q23</td>
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</tr>
<tr>
<td>rs7250581</td>
<td>19q12</td>
<td>(1)</td>
</tr>
<tr>
<td>rs688034</td>
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</tr>
<tr>
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</tr>
<tr>
<td>rs17465637</td>
<td>1q14</td>
<td>(2)</td>
</tr>
<tr>
<td>rs501120</td>
<td>10q11</td>
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</tr>
<tr>
<td>rs17228212</td>
<td>15q22</td>
<td>(2)</td>
</tr>
</tbody>
</table>

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  ____ 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?  ____ 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”?  ____ 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 Chakrabarti, McKusick – Nathan Institute of Genetic Medicine, Johns Hopkins University School of Medicine, 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.csc.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.