

ARIC Manuscript Proposal # 1142r

PC Reviewed: 06/18/06 Status: A Priority: 2
SC Reviewed: 05/25/06 Status: CA Priority:

1.a. Full Title: Genetic risk of Coronary Heart Disease in the Atherosclerosis Risk in Communities (ARIC) study: Application of a Genetic Risk Score

b. Abbreviated Title (Length 26 characters): Genetic Risk for CHD

2. Writing Group:

Writing group members: Lance A. Bare, Alanna C. Morrison, Charlie Rowland, Dov Shiffman, Olga Iakoubova, May Luke, James S. Pankow, John Kane, Mary Malloy, Steve Ellis, Bradford Young, Eric Boerwinkle, & James J. Devlin

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

First author: Lance A. Bare

Address: Celera Diagnostics, 1401 Harbor Bay Parkway, Alameda, CA 94502

Phone: 510-749-6226 Fax: 510-749-6200

E-mail: lance.bare@celeradiagnostics.com

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

Corresponding/senior author: Eric Boerwinkle

Address: Human Genetics Center, University of Texas at Houston Health Science Center. 1200 Herman Pressler; Ste 453E, Houston, TX 77030

Phone: 713-500-9816 Fax: 713 500-0900

E-mail: eric.boerwinkle@uth.tmc.edu

3. Timeline:

The analyses will be completed by June 1 and the manuscript will be completed by August 1 2006.

4. Rationale:

Although genetic variants contribute to differential risk of CHD, the algorithms currently used to predict risk of CHD do not consider individual genetic variants since, in common complex disease like CHD, the contribution from any single gene variant to the disease is small. Morrison *et al.* (MP#1095) have demonstrated the concept of aggregating the risk associated with a number of genetic variants into a composite genetic risk score (GRS). With the concept of a genetic risk score firmly established, our next task is to identify the panel of SNPs that could be used to calculate a GRS that will have clinical utility. Three parameters are of special interest: which SNPs to include, what cut point should be used to identify the high GRS group, and how

likely is it that GRS results in ARIC will generalize to other cohorts.

5. Main Hypothesis/Study Questions:

Main hypothesis:

Our hypothesis is that, if we require that each SNP selected for inclusion in the GRS panel have the same risk allele associated with CHD in three studies of White individuals (including ARIC), the high GRS group of ARIC participants will have a significantly higher risk of CHD than the rest of the ARIC participants.

Study Questions:

1. If the White ARIC population is dichotomized based on GRS, is the high GRS group at significantly higher risk of CHD as evaluated by a Cox proportional hazards model for incident CHD that includes traditional CHD risk factors (age, systolic blood pressure, use of hypertension medication, family history, LDL-C, HDL-C, diabetes status, smoking status, and sex)?
2. Given a GRS based on a panel of SNPs selected in three studies of White individuals, if the Black ARIC population is dichotomized based on a GRS, is the high GRS group at significantly higher risk of CHD as evaluated by a Cox proportional hazards model for CHD that includes traditional CHD risk factors? This question will allow us to investigate the feasibility of creating a GRS in one population and applying it to a second population. Alternatively, we may find out that each population may need its own tailored GRS.
3. Given that risk of incident CHD in White ARIC participants was one of the studies used to select SNPs for the GRS panel, to what extent is the risk estimate for the high GRS group in ARIC reduced when subjected to internal validation by bootstrapping or cross validation?
4. To allow comparison of a high GRS with traditional risk factors, ARIC participants will be dichotomously coded for each traditional risk factor (i.e., high or not-high risk). Adjusted hazard ratios for the high-risk group of each risk factor will then be estimated using a Cox model that contains all the dichotomous risk factors as covariables.

6. Data (variables, time window, source, inclusions/exclusions):

Incident CHD cases up to 2001 (i.e. 13-year follow-up) will be identified from the inc_by01 dataset. 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). Genetic variation contributing to the genetic risk score includes SNPs previously genotyped in the entire ARIC cohort as well as SNPs determined by Celera Diagnostics to play a role in cardiovascular risk, also genotyped in the entire ARIC cohort as a part of Ancillary Study 2004.11.

Exclusions prior to analysis involve the removal of individuals with a positive or unknown history of stroke or stroke symptoms, positive history or missing data for prevalent CHD at baseline, Blacks not from Jackson, MS or Forsyth County, NC, race other than Black or White, and individuals with restricted DNA use.

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.csc.unc.edu/ARIC/search.php>

Yes No

The corresponding author, Dr. Eric Boerwinkle has reviewed this.

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)?

The closest manuscript proposal, Manuscript # 1095, has the same corresponding author. Manuscript # 1095 demonstrated the concept of aggregating genetic risk into a genetic risk score (GRS). The current manuscript proposal (#1142) applies the GRS concept by using more stringent criteria for selecting the panel of SNPs used to calculate the GRS: thus, fewer, more highly replicated SNPs will be selected. Another difference is that rather than investigating the significance of the GRS as an ordinal variable, the ARIC population will be dichotomized based on GRS so that it can be determined if the high GRS group is at significantly elevated risk of CHD compared to the rest of the ARIC population. The current proposal will also compare the CHD risk predicted by the GRS to the risk predicted by traditional risk factors as well as investigating potential over fitting of the GRS results to the ARIC data set by internal validation.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any

ancillary study data? Yes No

11. b. If yes, is the proposal

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.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.

We agree.