ARIC Manuscript Proposal # 1434

PC Reviewed: 10/14/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: GWA and candidate gene studies for sudden cardiac death

b. Abbreviated Title (Length 26 characters): SCD GWAS

2. Writing Group: ARIC-SCD working group

ARIC writing group members: Dan Arking, Linda Kao, Wendy Post, Eric Boerwinkle (and/or other Houston personnel), Ron Prineas, Joe Coresh, Peter Spooner, Aravinda Chakravarti. Additional ARIC authors may be invited. Other authors from additional consortium cohorts will be included. The plan is to maintain symmetry across cohorts.

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

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3. Timeline: Fall 2008: genotyping of candidate SNPs will begin in October, and GWAS analysis will begin in mid-October (when the additional GWAS data is released). GWAS analysis should be finished mid-December, and SNP genotyping completed early in 2008.

4. Rationale: Sudden cardiac death (SCD) is a major cause of mortality, with >250,000 cases per year in the US alone. Given that 2/3 of victims have no clinical symptoms that would warrant preventive intervention, the need to identify genetic risk

factors is critical to reducing mortality from SCD. We propose a 2-pronged approach to address this issue: 1) screening candidate genes based on their association with QT interval, and 2) GWAS. The first stems from the established association between extreme values of QT interval and risk for SCD, and in fact, has been successfully used to identify common variants in *NOS1AP* as a risk factor for SCD. The second approach, GWAS, is proposed to capture variants that increase risk for SCD through alternative pathways than those of QT interval. To date, there have been no genome wide association studies (GWAS) of SCD.

5. Main Hypothesis/Study Questions:

Gene variants can be identified that associate with incidence of SCD.

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).

Design: candidate gene and GWAS for SCD using prospective data

Phenotypes: incident SCD. All cases of fatal MI and fatal CHD (both inpatient and out of hospital) have been reviewed to determine if they meet criteria for SCD. Sudden cardiac death is defined as a sudden unexpected death that appears to be related to an arrhythmic etiology. Cases of SCD were identified as definite, or possible, which includes cases complicated by other co-morbidities, such as ESRD, CHF or liver failure. For these cases, the patient must have been clinically stable prior to a sudden cardiac arrest. For all events, the individual must have been seen alive within 24 hours and had symptoms for less than one hour.

Candidate genes/SNPs will be drawn from the combined meta-analysis of the QTGEN (led by Chris Netwon-Cheh) and QTSCD consortiums (which includes ARIC, and is led by Aravinda Chakravarti), which have a combined 30,000 samples with GWAS data available. This analysis will include de novo genotyping using ARIC/CHS samples already in-house.

Given the limited number of SCD cases in ARIC, we plan on incorporating the CHS study in the candidate gene analysis (approved CHS Ancillary Study #169), as CHS has already been integrated on the phenotype level as part of the D.W. Reynolds SCD Collaborative Network.

The GWAS analyses will be combined in a meta-analysis with additional cohorts from CHARGE who have adjudicated SCD events available.

1. Model: Cox proportional hazards

Main analysis will include both whites and blacks (stratified by self-reported race) for the candidate gene studies, and only whites for the GWAS studies (within the CHARGE framework).

Genetic model: additive.

2. Transformation: no transformation, no re-scaling.

3. Covariates: primary analysis-time to event (or last follow-up), age, sex, study site; secondary (for top hits only)-age, sex, study site, QT interval, heart rate, HTN (140/90 mm Hg, or treatment), heart failure, history of MI, BMI, DM

4. Exclusions: self-reported race other than white or black, unconfirmed for SCD

5. Control for multiple comparisons: Bonferroni adjustment based on the number of markers. This will be done separately for the candidate gene and GWAS studies.

6. Imputation
Imputation to Hapmap 2.5 M using MACHv1.0.16.

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? ____ 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
__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)?

MP1152

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 (list number* 2006.03, 2008.09)
___ 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.