ARIC Manuscript Proposal # 1687

PC Reviewed: 9/14/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
SCN5A Variant S1102Y and Arrhythmic Risk in African-Americans

b. Abbreviated Title (Length 26 characters): SCN5A S1102Y and Arrhythmia

2. Writing Group: Dan E. Arking, Alvaro Alonso, coauthors from other cohorts. Additional ARIC coauthors will be included based on interest and participation.

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:
We expect that it will be only a few weeks after manuscript approval before we have a final manuscript for review.

4. Rationale:
The voltage-gated cardiac sodium channel, responsible for initiating the cardiac action potential, plays an important role in depolarization as well as repolarization (1). Mutations in the alpha subunit gene (SCN5A) of the cardiac sodium channel can result in several hereditary conditions associated with ventricular arrhythmias and sudden death, including Long QT Syndrome (2), Brugada Syndrome (3), and cardiac conduction

disease (4,5). Sodium channels are also the molecular targets for class I antiarrhythmic drugs. Treatment with these drugs to prevent SCD in patients with prior myocardial infarction is associated with a paradoxical increase in the incidence of VF and sudden arrhythmic death (6). In addition to an association with ventricular arrhythmias, recent evidence has implicated variants in SCN5A with atrial arrhythmias, including lone AF (13), and cardiomyopathy and AF (14). Furthermore, common variation in this gene has been associated with modification of ECG parameters, including PR, QRS and QT intervals (7).

A variant of the SCN5A sodium channel gene (S1102Y), present in African-Americans (allele frequency 6.8%) but absent in Caucasians, has been associated with arrhythmias, acquired QT prolongation, and syncope. This variant (also known as S1103Y) has been implicated with sudden infant death syndrome (SIDS) in African-American infants (9). In cell systems, the Y1102 variant accelerates channel activation, increasing the likelihood of abnormal cardiac repolarization and subsequent ventricular arrhythmias (8). In one extended family, the average QT interval for three homozygous wild-type (S1102) subjects was 400ms, for the 9 subjects who carried one copy of the variant allele (S1102Y heterozygotes), the average QT interval was prolonged at 434ms, while for the 11 subjects homozygous for the rare variant (Y1102), the average QT interval was markedly prolonged at 474ms, suggesting a marked electrical predisposition for ventricular arrhythmias from repolarization abnormalities (8). An autopsy study of African-Americans with the Y1102 variant and sudden cardiac death (10) has shown an elevated relative risk of unexplained arrhythmic death of 8.4 (95% CI 2.1 to 28.6, p=0.001). Furthermore, a case-control study of African-American subjects published in the journal *Science*, 57% of 23 cases and 13% of 100 control subjects carried the Y1102 allele, yielding an odds ratio of 8.7 (95% CI 3.2-23.9, p=0.00003) (8). The authors' conclusion, that Y1102 is a common variant in the African-American community, and that this variant may be a useful molecular marker for the prediction of ventricular arrhythmias in the setting of additional acquired risk factors, such as medications or hypokalemia, needs to be confirmed in longitudinal studies.

This proposal will test the association of this variant with cardiovascular outcomes in a population-based cohort (ARIC) followed prospectively. The ARIC African-American cohort is a unique and well-suited population to further explore the hypothesis that this variant is common in the African-American community and is associated with an increased risk of SCD and arrhythmias, including atrial fibrillation and ventricular arrhythmias. We will also examine whether this variant is associated with ECG parameters, such as PR interval, QRS duration, and QT interval, in addition to subclinical markers of ventricular arrhythmias (PVCs).

5. Main Hypothesis/Study Questions:

Our specific aims are:

(1) Y1102 variant will be associated with electrocardiographic characteristics, including measures of cardiac depolarization (PR, QRS durations) and repolarization (QT interval).

(2) Y1102 variant will be associated with cardiac arrhythmias and mortality, including atrial fibrillation, sudden cardiac death, and presence of frequent PVCs and PACs on 2-min ECG rhythm strips (MN codes 8-1-2 and 8-1-1, respectively).

(3) The association of Y1102 with electrocardiographic characteristics and risk of atrial and ventricular arrhythmias will be influenced by medications that modify potassium levels or adrenergic stimulation, such as diuretics and beta-blockers.

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).

Study design. All African-American participants with GWAS data (this SNP is directly genotyped on the Affymetrix 6.0 platform) who have given consent for use of genetic material will be included in the analysis to determine the relative importance of a newly discovered variant in this population.

For the first aim, the outcomes are the ECG phenotypes, including PR, QRS, and QT/QTc intervals. ECG data are available on the full African-American cohort. We will use a GEE methodology to model the mean levels of these intervals to take full advantage of the ECG data available for the study participants from multiple visits. The ECG phenotypes have been previously measured and ascertained. We will use linear regression with an additive as well as dominant model, given the few individuals that will be homozygous for the variant.

For the second aim, we will examine the association of the Y1102 variant with atrial and ventricular arrhythmias, specifically atrial fibrillation and sudden cardiac death in the ARIC cohort. Atrial fibrillation will have been documented either by the presence of atrial fibrillation noted on an ECG during anytime in the study follow-up or as ascertained by subject hospitalization for atrial fibrillation as documented by discharge diagnosis codes. The outcome of SCD has previously been adjudicated by cardiologist record review as part of Reynolds SCD network and defined using the following definition: a sudden pulseless condition presumed due to a ventricular arrhythmia from a primary cardiac etiology in an otherwise stable individual occurring out-of-hospital or in the emergency room.

Moreover, we will determine whether the Y1102 variant is associated with premature ventricular and atrial contractions (PVCs and PACs) on 2-min ECG rhythm strip.

For the third aim, we will test the association of Y1102 with ECG parameters and outcomes of atrial fibrillation and sudden cardiac death and whether these ECG parameters or outcomes will be influenced by current medication use. We will explore modification of genotype-phenotype associations by structural heart disease or by use of medications that affect potassium balance or QT interval, such as diuretics, and adrenergic stimulation, such as beta blockers.

Analytic methods. We will first assess for deviations from Hardy-Weinberg equilibrium to identify potential biases in the distribution. We will then perform descriptive statistics on categorical and continuous baseline measures using the chi-squared and ANOVA tests, respectively. For specific aim one, we will explore the association of intermediate phenotypes, namely ECG parameters with genotype. For these cross-sectional analyses, we will use linear regression. For specific aim two, a cohort study design will be used to assess the association of genotype with the outcome of SCD and atrial fibrillation using the analytic method of Cox proportional hazard regression. Finally, in specific aim three, we will test for interactions with clinical characteristics and current medication use using the likelihood ratio test with Cox proportional hazard regression for the outcome of SCD and atrial fibrillation separately.

As opportunities become available to collaborate with other cohorts that may genotype this variant (CHS has already done this), these analyses may be folded into a larger meta-analysis of the association of S1102Y on EKG and arrhythmic phenotypes as detailed above.

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)?
MS #1396 CHARGE GWAS for atrial fibrillation
MS #1397 CHARGE GWAS for lone atrial fibrillation.

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

___ A. primarily the result of an ancillary study (list number* 2008.09)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.03, 2007.02)

*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.

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