ARIC Manuscript Proposal # 1396B

PC Reviewed: 06/02_/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Novel Susceptibility Regions for Atrial Fibrillation on Chromosome 4q25**

b. Abbreviated Title (Length 26 characters): Chromosome 4q25 and AF

2. Writing Group: Dan Arking, Alvaro Alonso, Eric Boerwinkle
Writing group members:

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

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3. Timeline:
Analysis will be conducted immediately after approval and meta-analyzed with existing results. A manuscript will be then submitted for approval

4. Rationale:

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and is associated with substantial morbidity[1] and societal healthcare costs.[2,3] While many risk factors for AF have been identified, the identification of a common heritable component underlying AF [4,5] points to a role for genetic variation in its pathogenesis.

A recent genome-wide association study conducted in Iceland and replicated in three additional cohorts of European descent and one of Han Chinese descent identified two single nucleotide polymorphisms (SNPs) on chromosome 4q25 associated with AF and atrial flutter.[6] The SNP most significantly associated with AF was rs2200733.[6] These findings were replicated in a subsequent study of 3,508 subjects with AF and 12,173 controls from four additional cohorts of European ancestry.[7] A meta-analysis of the results from both studies revealed an odds ratio (OR) of 1.9 for the rs2200733 risk allele (95% CI 1.60-2.26, P=3.3x10^{-13}).[7]

Although no known gene is present in the genomic region containing these variants, several potential candidate genes are located in close proximity. Among these is *PITX2,* a paired-like homeodomain transcription factor which plays an important role in cardiac development by directing asymmetric morphogenesis of the heart.[8] Knockout of *PITX2* in a mouse model suppresses a default pathway for sinoatrial node formation in the left atrium,[9,10] and blocks the development of myocardial sleeves surrounding the pulmonary veins.[11] These myocardial sleeves have been implicated in AF following observations that pulmonary venous ectopic foci trigger AF in most patients.[12] Whereas *PITX2* is an intriguing candidate, there are no data to support a direct causal relation between this locus on chromosome 4q25 and *PITX2*. Nonetheless, recent evidence demonstrates that phenotypes are often regulated by non-coding regulatory elements, which may act by altering gene expression.[13,14]

In this proposal, we aim to replicate new independent variants at the 4q25 identified in two different populations: the Massachusetts General Hospital AF registry and the German Competence Network for Atrial Fibrillation.

5. Main Hypothesis/Study Questions:

In addition to the previously described region, we will identify potential novel regions on chromosome 4q25 associated with AF.

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

We will determine the independent association of genetic variants in three SNPs with the incidence of AF in white participants in ARIC. Individuals without ECG at baseline or prevalent AF will be excluded from analysis.

AF ascertainment

Cases of AF through the end of 2005 have been identified in the follow-up from three sources: ECGs done at follow-up visits, hospital discharge codes (ICD 9 427.31 or 427.32) and death certificates (Alonso et al, *Am Heart J* 2009, in press)

Statistical analysis

We will run the following analyses:

1. Separate Cox proportional hazards models for rs2200733, rs17570669, and rs3853445 alone, and then again adjusted for rs2200733 genotype for the latter two. All SNPs will be modeled with additive genetic effects and we adjusted for age, sex, and hypertension.

2. An analysis allowing for unique effects of each combination of genotypes at 3 of the SNPs (rs2200733 / rs17570669 / rs3853445), relative to the most common genotype combination (similar to fig 3 in our paper).

3. Because the case samples in the discovery cohort (MGH) and the first replication cohort (AFNET) were generally young, we will run the analysis ending follow-up at age 65.

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

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)?

#1396 CHARGE GWAS for atrial fibrillation

#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

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

_X_ 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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