1.a. **Full Title:** “Genetic Investigation into the Paradoxical Differential Risk of Atrial Fibrillation Among Blacks and Whites”

b. **Abbreviated Title (Length 26 characters):** “Genetics and Race in Atrial Fibrillation”

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

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3. Timeline: This ancillary study involving the ARIC cohort is now completed and the manuscript is ready for submission for publication.

4. Rationale: Despite a lower prevalence of risk factors, Whites have an increased risk of developing atrial fibrillation relative to Blacks. This paradoxical racial risk difference for atrial fibrillation may have an underlying genetic etiology, a concept supported by previous work from our group using ARIC data which suggested that increasing percent European ancestry was associated with an increased risk of the arrhythmia.

5. Main Hypothesis/Study Questions: We determined whether 9 single nucleotide polymorphisms (SNPs) known to be associated with AF account for this paradoxical differential racial risk and also used an admixture mapping approach to search genome wide for loci that may account for this phenomenon.

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: Three separate cohorts were utilized for the study, including ARIC, CHS, and Health ABC. A genome wide admixture mapping study was performed utilizing GWAS data from these cohorts. We also performed a mediation analysis using the percent treatment effect to evaluate for SNPs that may account for the differential racial risk of atrial fibrillation among Whites and Blacks.

Inclusion Criteria: 1. White or Black Race  
2. Had undergone genotyping

Exclusion Criteria: 1. Prevalent atrial fibrillation

Outcome: Incident atrial fibrillation
Summary of Data Analysis:

Time-to-event analyses using Cox proportional hazards models were employed to evaluate for an association between each of the 9 SNPs and incident AF. Covariates included in these models were baseline age, gender, body mass index, hypertension, diabetes, heart failure and coronary artery disease. Associations between polygenic risk scores and incident AF were determined using logistic regression models and the aforementioned covariates. The percent treatment effect (PTE) method was utilized to determine if SNP carrier status mediated the association between race and AF through time-to-event analyses using adjusted Cox proportional hazards models and the previously specified covariates. The impact of each SNP was examined in isolation, while a model containing all SNPs also examined their cumulative effect. Confidence intervals were obtained using bootstrap resampling with 1,000 repetitions.

Cox proportional hazards models were also employed to evaluate for an association between locus-specific African ancestry and incident AF in the admixture mapping component of the study. Locus specific ancestry was coded as a continuous variable between 0 and 2 where 0 was equivalent to having 0% probability of any African chromosomes and 2 is equivalent to 100% probability of having 2 African chromosomes at a locus. In order to adjust for potential confounding, covariates added to these models included baseline age, gender, body mass index, hypertension, diabetes, left ventricular hypertrophy, prevalent heart failure, history of myocardial infarction, study site, and % genome-wide African ancestry for each individual (% European ancestry is accounted for by the % African ancestry in the model since the two are, by definition of the model, forced to add up to 100%).

We found that the rs10824026 SNP, located 5 kilobases upstream of SYNPO2L, mediates a modest fraction of the increased risk of AF among Whites relative to Blacks. No additional genetic variants accounting for the differential racial risk of AF were identified with genome wide admixture mapping.

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 ___X__ No

(This file ICTDER 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.cscu.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)?

No relevant closely related manuscripts.

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.cscu.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscu.unc.edu/aric/index.php, under Publications, Policies & Forms, http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.