ARIC Manuscript Proposal #2746

PC Reviewed: 4/12/16 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Electrocardiographic Intervals and their Interaction with Common Genetic Variants: Impact on the Risk of Incident Atrial Fibrillation.

b. Abbreviated Title (Length 26 characters):

The ECG, Genes, and AF

2. Writing Group:
Writing group members:

Jason D. Roberts, MD MAS (jason.roberts@lhsc.on.ca)
Elsayed Z. Soliman, MD (esoliman@wakehealth.edu)
Alvaro Alonso, MD PhD MPH (Alonso@umn.edu)
Lin Y. Chen, MD MS (chenx484@umn.edu)
Dan Arking, PhD (arking@jhmi.edu); INVITED
Laura Loehr, MD PhD MS (lloehr@email.unc.edu)
Gregory M. Marcus, MD MAS (greg.marcus@ucsf.edu)

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]**

First author: Jason Roberts
Address: B6-129B
339 Windermere Road
London, ON
Canada N6A 5A5

Phone: (519)663-3746 Fax: (519)663-3782
E-mail: jason.roberts@lhsc.on.ca

Senior and Co-corresponding author:

Gregory M. Marcus, MD, MAS
Director of Clinical Research, Division of Cardiology
University of California, San Francisco
505 Parnassus Ave, M-1180B, Box 0124
San Francisco, CA 94143-0124
Phone (415) 476-5706
Fax (415) 353-9190
Email: greg.marcus@ucsf.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Elsayed Z. Soliman, MD
Address: Wake Forest School of Medicine
Medical Center Boulevard
Winston Salem, NC
27157

Phone: 336-716-8632 Fax: 336-716-0834
E-mail: esoliman@wakehealth.edu

3. Timeline: We anticipate that the data analysis and manuscript preparation will be completed within 6 months to1 year following approval of the study.

4. Rationale:

Electrical abnormalities, including atrial depolarization and repolarization, are important in the pathogenesis of atrial fibrillation.[1] Many of the ion channels responsible for atrial electrical activity are also expressed in the ventricle, where they perform analogous functions.[2] As a result, the QRS complex and QT-interval may serve as proxies of atrial electrical activity. Our group previously demonstrated that a prolonged QT-interval is a risk factor for atrial fibrillation.[3] The QT-interval is composed of multiple different components (QRS complex: intrinsicoid deflection and peak of R-wave to J-point; JT-interval: ST-segment, T-wave onset to T-peak, and T-peak to T-end). Although the QT-interval has previously been associated with atrial fibrillation, the precise mechanism accounting for this association is unclear. In this study, we propose to evaluate for associations between the different components of the QT-interval and the risk of incident atrial fibrillation.

Following this initial set of analyses, we will subsequently analyze for effect modification of ECG indices found to be significantly associated with incident atrial fibrillation by carrier status of single nucleotide polymorphisms (SNPs) known to be associated with atrial fibrillation. A total of 14 separate SNPs have been documented to exhibits associations with atrial fibrillation through large scale genome wide association

analyses.[4,5] The mechanisms through which these SNPs predispose to atrial fibrillation remain unclear, however they likely involve multiple heterogeneous biological pathways. Previous work has suggested that certain of these SNPs may interact with rare genetic variants to increase the risk of developing the arrhythmia.[6] In our current study, we wish to determine if carrier status of these SNPs interact with ECG indices to further modify the risk of developing atrial fibrillation.

References

1. Roberts JD, Gollob MH. Impact of genetic discoveries on the classification of lone atrial fibrillation. *J Am Coll Cardiol*. 2010;55:705–712.

2. Roberts JD, Gollob MH. The genetic and clinical features of cardiac channelopathies. *Future Cardiol*. 2010;6:491–506.

3. Mandyam MC, Soliman EZ, Alonso A, Dewland TA, Heckbert SR, Vittinghoff E, Cummings SR, Ellinor PT, Chaitman BR, Stocke K, Applegate WB, Arking DE, Butler J, Loehr LR, Magnani JW, Murphy RA, Satterfield S, Newman AB, Marcus GM. The QT interval and risk of incident atrial fibrillation. *Heart Rhythm Off J Heart Rhythm Soc*. 2013;10:1562–1568.

4. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Müller-Nurasyid M, Krijthe BP, Lubitz SA, Bis JC, Chung MK, Dörr M, Ozaki K, Roberts JD, Smith JG, Pfeufer A, Sinner MF, Lohman K, Ding J, Smith NL, Smith JD, Rienstra M, Rice KM, Van Wagoner DR, Magnani JW, Wakili R, Clauss S, Rotter JI, Steinbeck G, Launer LJ, Davies RW, Borkovich M, Harris TB, Lin H, Völker U, Völzke H, Milan DJ, Hofman A, Boerwinkle E, Chen LY, Soliman EZ, Voight BF, Li G, Chakravarti A, Kubo M, Tedrow UB, Rose LM, Ridker PM, Conen D, Tsunoda T, Furukawa T, Sotoodehnia N, Xu S, Kamatani N, Levy D, Nakamura Y, Parvez B, Mahida S, Furie KL, Rosand J, Muhammad R, Psaty BM, Meitinger T, Perz S, Wichmann H-E, Witteman JCM, Kao WHL, Kathiresan S, Roden DM, Uitterlinden AG, Rivadeneira F, McKnight B, Sjögren M, Newman AB, Liu Y, Gollob MH, Melander O, Tanaka T, Stricker BHC, Felix SB, Alonso A, Darbar D, Barnard J, Chasman DI, Heckbert SR, Benjamin EJ, Gudnason V, Kääb S. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat Genet*. 2012;44:670–675.

5. Sinner MF, Tucker NR, Lunetta KL, Ozaki K, Smith JG, Trompet S, Bis JC, Lin H, Chung MK, Nielsen JB, Lubitz SA, Krijthe BP, Magnani JW, Ye J, Gollob MH, Tsunoda T, Müller-Nurasyid M, Lichtner P, Peters A, Dolmatova E, Kubo M, Smith JD, Psaty BM, Smith NL, Jukema JW, Chasman DI, Albert CM, Ebana Y, Furukawa T, Macfarlane PW, Harris TB, Darbar D, Dörr M, Holst AG, Svendsen JH, Hofman A, Uitterlinden AG, Gudnason V, Isobe M, Malik R, Dichgans M, Rosand J, Van Wagoner DR, METASTROKE Consortium, AFGen Consortium, Benjamin EJ, Milan DJ, Melander O, Heckbert SR, Ford I, Liu Y, Barnard J, Olesen MS, Stricker BHC, Tanaka T, Kääb S, Ellinor PT. Integrating genetic, transcriptional, and

functional analyses to identify 5 novel genes for atrial fibrillation. *Circulation*. 2014;130:1225–1235.

6. Ritchie MD, Rowan S, Kucera G, Stubblefield T, Blair M, Carter S, Roden DM, Darbar D. Chromosome 4q25 variants are genetic modifiers of rare ion channel mutations associated with familial atrial fibrillation. *J Am Coll Cardiol*. 2012;60:1173–1181.

5. Main Hypothesis/Study Questions:

1. Electrocardiographic indices (intrinsicoid QRS deflection, R-wave peak to J-point, ST-segment, T-onset to T-peak, and T-peak to T-end) are associated with the risk of incident atrial fibrillation.

2. Common genetic variants associated with atrial fibrillation interact with electrocardiographic indices to modify the risk of incident atrial fibrillation.

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).

We will first evaluate for an association between ECG indices and the risk of incident atrial fibrillation. Subsequent to these analyses, we will examine for interactions between ECG indices that significantly associate with incident atrial fibrillation and 14 known atrial fibrillation associated-SNPs with respect to the risk of incident atrial fibrillation.

ECG indices to be evaluated: 1) intrinsicoid QRS deflection, 2) R-wave peak to J-point, 3) ST-segment, 4) T-onset to T-peak, and 5) T-peak to T-end.

AF-associated SNPs to be evaluated in interaction analyses with ECG indices:

1. rs2200733 (4q25)
2. rs2106261 (16q22)
3. rs666258 (1q21)
4. rs3903239 (1q24)
5. rs3807989 (7q31)
6. rs10821415 (9q22)
7. rs10824026 (10q22)
8. rs1152591 (14q23)
9. rs7164883 (15q24)
10. rs12415501 (NEURL)
11. rs13216675 (GJA1)
12. rs10507248 (TBX5)
13. rs4642101 (CAND2)
14. rs6490029 (CUX2)

Inclusion Criteria: Study Participants enrolled in the ARIC cohort

Exclusion Criteria:

1. Prevalent Atrial Fibrillation
2. Active use of Vaughan-Williams class I or III Anti-Arrhythmic Drugs
3. Ventricular Pacing
4. Ventricular Pre-excitation

Primary outcome of the study: Incident atrial fibrillation

Data Analysis

Time-to-event analyses using Cox proportional hazards models will be employed to evaluate for associations between ECG indices, SNPs, and incident AF. Incident AF will be identified from study visit ECGs, hospital discharge diagnoses, and death certificates as previously described. Multivariable Cox proportional hazards models will be utilized to adjust for potential confounding. Covariates in the models will include baseline age, sex, hypertension, diabetes, body mass index, congestive heart failure and coronary artery disease. The predictor in the initial set of analyses will be the ECG index of interest. Each of the listed ECG indices will be evaluated for association with incident atrial fibrillation in succession. The second set of analyses will evaluate for effect modification of the association between incident atrial fibrillation and the ECG index by SNP carrier status. This component of the analysis will be restricted to individuals of Western European ancestry. SNP-ECG index interaction analyses will be performed using both dominant and additive genetic models. Two-tailed p-values < 0.05 will be considered statistically significant. In the event a SNP-ECG index interaction is found to be statistically significant, replication will be sought using another prospective cohort (potentially Cardiovascular Health Study [CHS] or Multi-Ethnic Study of Atherosclerosis [MESA]).

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 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.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)?

None identified.

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.cscc.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.cscc.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.