ARIC Manuscript Proposal #3658

PC Reviewed: 7/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Evaluation of Epigenetic Age Acceleration as a Risk Factor for Incident Atrial Fibrillation.

b. Abbreviated Title (Length 26 characters): Epigenetic Age and Atrial Fibrillation

2. Writing Group:

Writing group members: Jason Roberts, Greg Marcus, Eric Vittinghoff, Alvaro Alonso, Jim Pankow, Dan Arking, Myriam Fornage; coauthors from other cohorts in the AFGen consortium

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _JR__

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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).

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3. Timeline: This project will be pursued through involvement of the AFGen consortium. We anticipate the study being completed and submitted for publication within 1 year of its initiation.

4. Rationale:

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is a growing health epidemic associated with increased risks of heart failure, stroke, and death.[1–3] The direct costs

for treating the arrhythmia in the United States alone have been estimated to be $26 billion dollars annually.[4] The clinical and economic burdens of AF are anticipated to grow dramatically in the coming years secondary to its expanding prevalence.[5] The devastating impact of the arrhythmia is further exacerbated by a lack of highly effective treatment strategies, which likely stems from our limited understanding of its underlying pathophysiology.[6]

Advancing age is the most critical risk factor for the development of AF, reflected by its prevalence ranging from less than 0.1% among individuals younger than 55 years of age to upwards of 10% among octogenarians.[7,8] Despite the dramatic impact of age on the risk of AF, the mechanisms responsible for this relationship remain unclear. Utilizing the CHS cohort, we previously conducted a study that revealed no association between leukocyte telomere length and the risk of incident AF.[9]

Robust familial and large-scale population-based epidemiologic studies have firmly established a heritable contribution to the risk of developing of AF.[10,11] Although the importance of genetic factors on AF susceptibility has been clearly established, a majority of AF heritability remains unexplained.[12] DNA methylation is an epigenetic mechanism that is heritable and correlates strongly with aging. Addition of methyl groups, most often at cytosine-guanine dinucleotides, alters DNA conformation and accessibility of promoter sites to transcription factors, leading to changes in gene expression. The pattern of DNA methylation at specific cytosine-guanine dinucleotide sites has been incorporated into algorithms capable of approximating chronological age.[13,14] Notably, in some individuals, epigenetic age exceeds chronological age, a process referred to as epigenetic age acceleration.

A recent methylome-wide association study involving the Framingham Heart Study identified multiple methylation sites that associated with increased risks of prevalent and incident AF.[15] The current study proposal seeks to evaluate for associations between epigenetic age acceleration and the risk of incident AF.

5. Main Hypothesis/Study Questions:

Aim: To determine if epigenetic age acceleration, as determined using the methods of Horvath and Hannum, is associated with an increased risk of developing incident AF.

Hypothesis: Epigenetic age acceleration will be associated with an increased risk of developing incident 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).

We are proposing to perform the specified analysis using cohorts from the CHARGE epigenetics consortium that have ascertained incident AF, including ARIC, Framingham, Rotterdam, and the Women's Health Initiative.

Data to be used in this study includes the following:

- Baseline demographic and medical data: Age, sex, race, body mass index (BMI), prevalent AF status, smoking status, systolic blood pressure, diastolic blood pressure, diabetes, history

of myocardial infarction, history of heart failure, and moderate to severe valvular heart disease.

- Epigenetic Data: Horvath and Hannum estimates of epigenetic age; cell type distributions and technical covariates
- Incident Events: Incident atrial fibrillation

Each cohort will perform survival analyses using multivariate Cox proportional hazards models for both Horvath and Hannum estimates of epigenetic age. The primary predictor in each model will be the epigenetic estimate of age. Chronological age will be included as a covariate and the hazard ratio identified for epigenetic age will correspond to epigenetic age acceleration. Potential confounders, including cell type proportions, sex, race, visit, BMI, hypertension, diabetes, history of myocardial infarction, history of heart failure, and moderate to severe valvular heart disease will be included in the models. Results from each cohort will subsequently be meta-analyzed using a random effects model.

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)?

Nil 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.

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