ARIC Manuscript Proposal # 1511

PC Reviewed: 5/12/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genomewide association of event-free survival and other longevity-related phenotypes: the CHARGE Consortium

b. Abbreviated Title (Length 26 characters): Genomewide association of longevity phenotypes

2. Writing Group: Ellen Demerath, Nora Franceschini, Aaron Folsom, Eric Boerwinkle, Tom Mosley, other welcome.

The study will include CHARGE collaborators from the Framingham study, Rotterdam study, Cardiovascular health Study and AGES

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

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3. Timeline: Analyses will begin when all genotyping and QC is completed.

4. Rationale:
To conduct a genome-wide association analysis of event-free survival among ARIC participants and a meta-analysis across CHARGE cohorts.

To conduct a genome-wide association analysis of time to death among ARIC participants and a meta-analysis across CHARGE cohorts.

5. Main Hypothesis/Study Questions:
To identify novel genetic loci associated with human longevity and event-free aging among individuals of European ancestry, we propose to perform a genomewide association analyses of morbidity free survival and time to death using the set of genotyped and imputed SNPs in ARIC.

We plan to expand our analyses to African Americans as the genotyping data is available. Use of GWAS data in African-Americans will follow CARE procedures.

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).

Subjects: 4792 ARIC participants 55+ years of age at baseline (2,441 males and 2,351 females) of European ancestry and African descent will be included. Use of GWAS data in African-Americans will follow CARE procedures.

Phenotypes:

1) Event-free survival: Time in years to first event of any of the following: MI, stroke, cancer, heart failure, or death. Hip fracture and dementia are not available. Individuals without events will be censored at the last follow-up.
2) Time to death in years from baseline

Stroke, MI, and CHF were based on hospital surveillance, and then medical record review (MI, CHF through ’05; Stroke through ’04). Cancer was based on cancer registries and additionally hospital surveillance and medical record review (through 2000). Therefore, we will include only events for all conditions through 2000.

Exclusions: age less than 55 at baseline (visit 1), prevalent heart failure, MI, stroke, and cancer will be excluded

Exposure: 2.5 million HapMap genetic variants identified in CEPH trios for whites and 1.0 million genetic variants in African American. We will not pursue imputation in

African descent samples at this point but would consider it if adequate accuracy of imputation using HapMap YRB samples is demonstrated.
Model: Cox proportional hazard models with additive genetic effects. Analyses will be conducted using age, sex and center as covariates. We will perform analysis using all available SNPs that pass QC. We will adjust for population stratification by adding as a covariate principal components significantly associated with the phenotype (at alpha=0.05).
Covariates: Basic model: age at visit 1, sex and center adjusted.
Statistical significance: Bonferroni correction adjustment (1/ number of tests performed) (~10^{-7})
Meta-analyses: We will conduct meta-analysis of p-values reported by the CHARGE longevity working group, using fixed effects and the program METAL.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

We did not identify a genetic or epidemiologic study related to event-free survival and longevity in ARIC

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* 2006.03 (Stampede and Geneva genotype funding in Caucasians) and 2007.02 (CARe, genotyping in African Americans).

___ 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/

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.