

ARIC Manuscript Proposal #2389

PC Reviewed: 7/8/14
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: GWAS and Grip Strength

b. Abbreviated Title (Length 26 characters): GWAS and Grip Strength

2. Writing Group:

Writing group members: Dan Arking, others welcome investigators from other CHARGE cohorts

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

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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:

Analysis and manuscript to be completed over the next 3 months.

4. Rationale:

One of the most important processes underlying development of frailty and disability with aging is a decline in mass and strength of skeletal muscle that leads to decrements in functional abilities and alterations in metabolic profiles of older adults. Heritability

studies have demonstrated that maximum isometric grip strength is moderately heritable in older adults, with estimates of heritability ranging from 0.22 to 0.65 [1-4]. This study is designed to characterize genetic loci that may contribute to variation in muscle strength in mid- to late-life individuals. Identification of gene variants that modulate muscle strength as one ages can be of use in ultimate prevention and treatment strategies of disability and frailty.

5. Main Hypothesis/Study Questions:

Variability in muscle strength seen among older adults may due to genetic variation in their inherited DNA sequence and resultant variation in protein expression and/or function. We hypothesize that a genome-wide scan results meta-analyzed across several large-scale cohorts will characterize novel genetic loci associated with maximal grip strength.

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).

Caucasian participants from ARIC with visit 5 grip strength measures will be used in this analysis. The primary outcome in this study will be maximal grip strength over all trials taken from either hand. Covariates of interest for these analyses include age, sex, height, weight, and clinic site.

This analysis is cross-sectional, using maximal grip strength measurement at visit 5 as the primary outcome. Both genotyped and imputed genome-wide scan data from Caucasian ARIC participants will be employed as exposures of interest. The association between genetic variants and grip strength will be tested using multiple linear regression. All models will be adjusted for age, sex, height, weight, study site and principal components (to correct for population stratification).

Genetic exposures will be tested via an additive genetic model. Results generated separately in ARIC and the other 14 participating cohorts (CHS, FHS, AGES, InCHIANTI, HABC, HRS, SOFT, MrOS, LBC1921, LBC1936, Rush Aging and Memory Study, TASCOG, Twins UK and SHIP) will be meta-analyzed using a fixed effects model of beta estimates and standard errors from each cohort. A threshold of $p < 5 \times 10^{-8}$ will be used to determine genome-wide statistical significance.

7.a. Will the data be used for non-CVD analysis in this manuscript? **Yes**
 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?

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"?

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.cscce.unc.edu/ARIC/search.php>

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.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes 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.cscce.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.cscce.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.

1. Frederiksen, H., D. Gaist, H.C. Petersen, et al., *Hand grip strength: a phenotype suitable for identifying genetic variants affecting mid- and late-life physical functioning*. Genet Epidemiol, 2002. **23**(2): p. 110-22.

2. Reed, T., R.R. Fabsitz, J.V. Selby, and D. Carmelli, *Genetic influences and grip strength norms in the NHLBI twin study males aged 59-69*. Ann Hum Biol, 1991. **18**(5): p. 425-32.
3. Tiainen, K., S. Sipilä, M. Alen, et al., *Heritability of maximal isometric muscle strength in older female twins*. J Appl Physiol, 2004. **96**(1): p. 173-80.
4. Carmelli, D. and T. Reed, *Stability and change in genetic and environmental influences on hand-grip strength in older male twins*. J Appl Physiol, 2000. **89**(5): p. 1879-83.