ARIC Manuscript Proposal # 1426

PC Reviewed: 09/09/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide association study of blood sodium, potassium, and magnesium in whites

b. Abbreviated Title (Length 26 characters): GWAS of blood ions

2. Writing Group:
Writing group members: Tamra Meyer; Anna Kottgen, Josef Coresh; Eric Boerwinkle; other ARIC authors are invited

Other authors from the CHARGE consortium will be included. The plan is to maintain symmetry across cohorts.

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

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3. Timeline:

Genotyping is complete. Data analysis will begin immediately.

4. Rationale:

Homeostasis of ions such as sodium, potassium, and magnesium is important for maintaining health and preventing disease,[1-12] yet the mechanisms of ion homeostasis are not yet clear. Blood sodium, potassium, and magnesium levels are heritable traits.[13, 14] Genome-wide association (GWA) analysis of sodium, potassium, and magnesium levels can provide new information about genetic contributions to homeostasis of these important ions.

A recent GWA study in the BRIGHT study found no significant associations with blood levels of sodium and potassium in hypertensive whites.[15] Since hypertension and related treatments can alter sodium and potassium levels, it is important to explore GWA of these ions in samples from the general population as well as among untreated individuals. GWA analysis of blood magnesium has not yet been reported. We propose a GWA study of blood sodium, potassium, and magnesium levels in whites from ARIC and other cohorts participating in the CHARGE consortium (AGES, CHS, FHS, and RS) to better understand the genetics of ion homeostasis in the general population. For the SNPs that reach genome-wide significance ($5x10^{-7}$) in association with blood ion levels, we propose to examine the association between the SNPs and important health outcomes including hypertension and type 2 diabetes.

5. Main Hypothesis/Study Questions:

Primary Hypothesis: Common SNPs are associated with baseline quantitative measures of blood sodium, potassium and magnesium.

Secondary Hypothesis: SNPs found to be associated with baseline blood sodium, potassium and magnesium will be associated with cardiovascular outcomes including hypertension and type 2 diabetes.

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).

Overview:

The analysis will be conducted by Tamra Meyer and supervised by Eric Boerwinkle. Both parties have signed the data distribution agreement. Both observed genotypes and genotypes imputed to the HapMap (Build35) will be modeled. To ensure quality of genotyping, SNPs will be excluded for missing data >10% and for deviation from Hardy-Weinberg equilibrium ($P<10^{-4}$). Individuals missing >5% of SNP data will also be excluded. Additive genetic effects on sodium, potassium, and magnesium levels will be determined using linear regression in ProbABEL software. The ProbABEL software allows consideration of covariables and probability estimates for imputed SNPs. A *P*-value of $5x10^{-7}$ will be considered statistically significant at the genome-wide level. Since

hypertension treatment can affect blood ion levels, we will confirm findings from the entire ARIC cohort in those without treated hypertension at baseline.

Outcome variables:

Primary Hypothesis: Baseline blood sodium, potassium, and magnesium levels

Secondary Hypothesis: Baseline hypertension and type 2 diabetes

Exposure variables: 2.5 million HapMap SNPs

Exclusions:

All analyses: Race other than white; restrictions on DNA use

Sensitivity analysis: treated hypertension

Covariables: Age, sex, field center

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 ICTDER03 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)?

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* 2007.02; 2006.03)

___ 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. Agree

References

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