ARIC Manuscript Proposal # 1426A
Note: This is an addendum to the approved ARIC MP #1426

PC Reviewed: 11/9/10  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Interaction Between Genetic Risk Variants for Hypomagnesemia And Intake of Diuretics

b. Abbreviated Title (Length 26 characters): Mg SNPs and Diuretics

2. Writing Group:
   Writing group members: Claudia Hundertmark; Anna Kottgen, Linda Kao, Eric Boerwinkle; other ARIC authors are invited.
   I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _CH__ [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:**

We have previously conducted a genome-wide association study (GWAS) of serum magnesium levels in the CHARGE Consortium (ARIC MP #1426).\(^1\) In this study, we have identified and replicated 6 genomic loci containing alleles associated with serum magnesium levels. The odds ratio of hypomagnesemia, using the clinical definition of serum magnesium levels $<0.7$ mmol/l, for these genomic loci ranges from 1.11 to 1.27 per copy of the magnesium-lowering allele. The most common cause for hypomagnesemia is the intake of loop diuretics such as furosemide and thiazides.\(^2\)

A common criticism of SNPs identified in GWAS is that they are not clinically relevant. They may, however, interact with causes of common clinical conditions and thus be important in this context. We therefore propose to study whether risk alleles associated with lower serum magnesium levels interact with the intake of diuretics, the most common cause of clinical hypomagnesemia.

Further, it is of interest to characterize risk factors for hypomagnesemia as well as the combination of different risk factors since previous epidemiological studies have found hypomagnesemia to be associated with an increased incidence of diabetes mellitus, metabolic syndrome, mortality rate from CAD and all causes.\(^3\)

5. **Main Hypothesis/Study Questions:**

**Primary Hypothesis:** Risk alleles for hypomagnesemia will have a more profound effect on serum magnesium levels when individuals are currently taking loop diuretics and thiazides.

**Secondary Hypothesis:**
- Reimputation of previously identified genomic risk regions will help in fine-mapping the association signals.
- A genetic risk score composed of magnesium lowering alleles at the 6 identified risk regions will show a stronger interaction with the intake of loop diuretics and/or thiazides than the individual SNPs alone.
- not all of the SNPs will show this interaction, consistent with the expression pattern of the encoded proteins, for example in the kidney.

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 study question will be examined as a cross-sectional analysis of the data at ARIC visit 1, when serum magnesium levels were measured. Individuals will be excluded if they were of non-European ancestry, did not consent to genetic research, were not recommended for the analysis of SNP data (eg, likely sample mixup, one member of each first-degree relative pair), or had missing measurements for serum magnesium of important covariates, listed below.
Data analysis will be conducted using R and ProbABEL software for statistical analyses and IMPUTE2 for genotype imputation. An additive genetic model will be used to model the SNP effects on magnesium levels. Statistical significance for interaction will be set at an alpha of 0.05 for each genomic region, as a pre-specified hypothesis exists for each of these regions. Analyses will be conducted separately among loop diuretic users/non-users and thiazide users/non-users, as well as for individuals taking either one or both.

**Outcome variables:**

Primary Hypothesis: Baseline blood magnesium levels, clinically defined hypomagnesemia (serum magnesium <0.7 mmol/l)

**Exposure variables:** 1) The previously identified SNP with the lowest p-value in each of the six genomic regions, 1) potentially the SNP with the lowest p-value after re-imputation of the genomic regions to the 1000 Genomes data if different from 1). Stratification will be conducted based on the intake of loop diuretics (defined as msrmtc1-msrmtc17=372000) and thiazides (msrmtc1-msrmtc17=376000).

**Exclusions:**

All analyses: Race other than white; restrictions on DNA use
Sensitivity analysis: Sensitivity analyses will be conducting indexing serum magnesium levels to serum albumin levels to account for the protein-bound fraction of magnesium.

**Covariables:** Age, sex, field center, BMI, fasting glucose, fasting insulin, hypertension, eGFR, alcohol intake, serum albumin, estimated amount of dietary magnesium intake, magnesium supplement use (msrmtc1-msrmtc17=794000 or 794099)

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
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?  

   ___  Yes     _______ No

11.b. If yes, is the proposal

   ___  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