ARIC Manuscript Proposal #2132

PC Reviewed: 5/14/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Genome wide association study of serum magnesium levels in African Americans

b. Abbreviated Title (Length 26 characters):
Genetics of magnesium in AA

2. Writing Group:
Adrienne Tin, Aaron Folsom, Fred Brancati, Chris Friedrich, Josef Coresh, Nisa Maruthur, Eric Boerwinkle, WH Linda Kao, and others

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

First author: Adrienne Tin
Address: 615 N. Wolfe Street, Suite W6012
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD 21205
Phone: 201-281-9577 Fax:
E-mail: atin@jhsph.edu

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).
Name: Linda WH Kao
Address: 615 N. Wolfe Street, Suite W6012
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD 21205
Phone: 410 614-0945 Fax: 410 955 0863
E-mail: wkao@jhsph.edu

3. Timeline:
Start of analysis: April, 2013
Draft of manuscript: August, 2013

4. Rationale:

Magnesium, the second most common intracellular cation, is important in many enzymatic reactions and the regulation of mitochondria function and vascular tone.[1] Low serum magnesium levels have been shown to be associated with cardiovascular diseases[2, 3] and incident hypertension,[4] and diabetes.[5] In addition, population-based studies, including the ARIC study, have shown that African Americans (AA) have lower magnesium levels then European Americans (EA)[4]. African Americans were reported to have lower dietary magnesium intake.[6] However, no studies have examined the influence of genetics on magnesium levels in AA.

A previous genome-wide association study in individuals of European Ancestry identified five significant loci associated with serum magnesium levels with each index single nucleotide polymorphisms (SNPs) explaining 0.1% to 0.57% of the phenotypic variance.[7] However, there has been no genome-wide study of serum magnesium levels in AA. Therefore, we would like to determine whether the loci that are associated with serum magnesium in EA are also associated in AA and whether additional loci exist in this population. Testing for the association of known EA loci in AA may help fine mapping the known loci if these populations share the same causal gene or variants. Identifying common genetic variants associated with serum magnesium levels in African Americans may potentially inform the possible causes of lower magnesium levels in this population and the mechanisms underlying the association of magnesium levels and common diseases.

5. Main Hypothesis/Study Questions:

1. Common genetic variants are associated with serum magnesium levels in AA
2. The associated common variants may partly explain the racial disparity in magnesium levels between AA and EA

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).

Study design

Genetic association study

Inclusion criteria

All individuals in ARIC with self-reported race of white or black and serum magnesium and genome-wide array data.

Exclusion:

1. Individuals with estimate glomerular filtration rate < 30 because research indicated the kidney's ability to maintain magnesium homeostasis through

reabsorption and excretion deteriorates sharply in individuals with advanced chronic kidney disease.[8]

2. Individuals whose genome-wide array data did not pass quality control, which included the identification of related individuals, genetic outliers, sex check, and missing genotype data rate > 5%.

Outcome

Average ofserum magnesium levels at visits 1 and 2 because the average of repeated measures can provide more statistical power than a single measure by reducing measurement errors.[9]

Covariates

Age at visit 1, gender, center

Predictor

Imputed genotype dosage using 1000 genomes reference panels

Statistical analysis

All SNP association analyses will be stratified by self-reported race (EA vs AA)

1. **Test of genetic association**. We will perform linear regression to test for the association between genetic variants and serum magnesium levels assuming an additive genetic model. For the GWAS of serum magnesium levels in AA, the suggestive significant threshold is set at 10^{-6}.[10]
2. **Interrogation of known loci.** For published associated loci in EA, we will interrogate the region within 1Mb of the EA index SNP in the African American data in ARIC. Significant threshold is set at the 0.05 divided by the number of SNPs with variance inflation factor<2 within the 1Mb region or between two closest recombination hot spots, whichever is smaller.
3. **Power for interrogation of known loci**. The percentage of phenotypic variance explained by the published index SNPs in EA ranged from 0.1% to 0.57%.[7] Based on a sample size of 2750 in ARIC AA, at an alpha level of 0.05, we have over 79% power to detect an index SNP that explains at least 0.3% of the phenotypic variance. For region interrogation, assuming having 10 independent SNPs in a region, at an alpha of 0.005, we have 77% power to detect an association that explains 0.5% of the phenotypic variance. SNPs with lower minor allele frequency (MAF) would need larger effect sizes to explain the same amount of phenotypic variance as a SNP with higher minor allele frequency. To explain a phenotypic variance of 0.5%, a SNP with MAF of 45% would have an additive beta of approximately 0.01mmol/L, and a SNP with MAF of 30% would need an additive beta of approximately 0.24mmol/L.

Power at genome-wide level. For genome-wide significance, based on a sample size of 2750 in ARIC AA, we have 64% power to detect a SNP explaining 1% of the phenotypic variance at an alpha level of 10^{-6}.

4. **Associated loci and racial disparity in serum magnesium level**. To examine whether associated variants in EA and AA may partly explain the racial disparity in serum magnesium levels, we will compute a genetic score based on the effect size and imputed dosage of the associated index SNPs in each population and conduct regression analyses combining both EA and AA populations to assess whether including the genetic score as a covariate changes the association between serum magnesium levels and self-reported race controlling for age and gender.
5. **Association of serum magnesium index SNPs in AA with blood pressure and diabetes traits**. To examine whether serum magnesium associated loci in AA may partly explain the association between serum magnesium levels and hypertension and diabetes, we will test for the association of the associated index SNPs and the genetic score with systolic blood pressure and fasting glucose in AA.

Strengths and Limitations

A strength of this study is sufficient sample size for testing the association of known EA loci in the ARIC AA population. The limitations include low statistical power for detecting novel loci with modest effect size in AA and the lack of external AA cohort for replicating potential novel loci in AA.

7.a. Will the data be used for non-CVD analysis in this manuscript?__X 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?__X 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)?
No previous proposal in ARIC focus specifically on predicting ESRD using genetic information.

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

__ 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/

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.

References

1. Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clinical Kidney Journal* 2012; **5:** i3-i14.

2. Ohira T, Peacock JM, Iso H, *et al.* Serum and dietary magnesium and risk of ischemic stroke: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2009; **169:** 1437-1444.

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4. Peacock JM, Folsom AR, Arnett DK, *et al.* Relationship of serum and dietary magnesium to incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 1999; **9:** 159-165.

5. Kao WH, Folsom AR, Nieto FJ, *et al.* Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Arch Intern Med* 1999; **159:** 2151-2159.

6. Ford ES. Race, education, and dietary cations: findings from the Third National Health And Nutrition Examination Survey. *Ethn Dis* 1998; **8:** 10-20.

7. Meyer TE, Verwoert GC, Hwang SJ, *et al.* Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six Loci influencing serum magnesium levels. *PLoS Genet* 2010; **6**.

8. Cunningham J, Rodriguez M, Messa P. Magnesium in chronic kidney disease Stages 3 and 4 and in dialysis patients. *Clinical Kidney Journal* 2012; **5:** i39-i51.

9. Rasmussen-Torvik LJ, Alonso A, Li M*, et al.* Impact of repeated measures and sample selection on genome-wide association studies of fasting glucose. *Genet Epidemiol* 2010; **34:** 665-673.

10. Duggal P, Gillanders EM, Holmes TN*, et al.* Establishing an adjusted p-value threshold to control the family-wide type 1 error in genome wide association studies. *BMC genomics* 2008; **9:** 516.