ARIC Manuscript Proposal #2530

PC Reviewed: 4/14/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Interaction of potassium measures with potassium channel genetic variants on diabetes risk: The Atherosclerosis Risk in Communities (ARIC) Study and Jackson Heart Study (JHS).

b. Abbreviated Title (Length 26 characters): **K and genetic variants and diabetes risk**

2. Writing Group:

Writing group members:

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Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _RC_ **[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:

Data analysis to begin in Summer 2015.
Preliminary data to be used for abstract submission to ADA in early 1/2016.
Manuscript to be written and submitted for publication by end of 2016.

4. Rationale:

In prior analyses of the ARIC cohort, we have shown low-normal serum potassium (K) to be a risk factor of incident diabetes, independent of traditional risk factors,(1) and to have greater effect on diabetes risk among African-Americans compared to whites.(2, 3) We have confirmed this association in the JHS cohort (unpublished results) However, as with all risk factors, a low-normal serum K was not perfectly predictive of an increased risk of diabetes.

Based on findings from genome-wide association studies, a few genetic variants associated with increased diabetes risk reside on genes encoding K-channels of pancreatic β-cells.(4) These genes include KCNJ11, KCNQ1, and ABCC8.(4, 5) The polymorphisms in KCNJ11, rs5219 and rs5215, are associated with an increased risk of type 2 diabetes in Caucasians and East Asians.(6) And, according to Genecards, rs5219 has also been found to be significant in African cohorts, with an overall allele frequency of 29%. (www.genecards.org) A meta-analyses of GWAS data in African Americans, including data from ARIC, found that 2 mutations within the KCNQ1 gene were significantly associated with increased diabetes risk.(7) While these mutations of K-channels have been studied and associated with functional changes,(5) one could hypothesize that a low serum K could impact the function of these channels, with potentially more impact on a functionally-mutated channel.

A previous study has evaluated the significance of genetic variants on diabetes risk in the entire ARIC cohort; however this study evaluated the impact of only those genetic variants for which data was present in ARIC as well as 2 additional cohorts, including variants of the KCNQ1 gene. (7) The genetic variants that they assessed did not include the more common KCNJ11 polymorphisms.

The potential impact of low-serum K on diabetes risk may be stronger among people with an increased risk of diabetes due to K-channel polymorphisms in the KCNJ11, KCNQ1, and ABCC8 genes. If this is true, then correcting low-serum K through pharmacologic or dietary K supplementation may preferentially help to decrease diabetes risk in people with these genetic variants.

5. Main Hypothesis/Study Questions:

We propose to study the association of the KCNJ11 polymorphisms (rs5219 and rs5215), KCNQ1, and ABCC8 polymorphisms on diabetes risk in the ARIC and JHS cohort. And we propose to test for an interaction between serum K and these genetic variants. By testing for such an interaction, we will determine if, among participants with these genetic variants, a low-normal serum K was a stronger predictor of diabetes risk compared to those participants without these genetic variants.

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).

Exclusions:
Similar exclusions to be used for main analyses of ARIC and JHS cohorts to include: Diabetes prevalent at baseline visit; missing information on diabetes status at follow-up exams; missing information on serum K at baseline; eGFR < 30 mL/min.

Inclusions:
ARIC and JHS participants free of diabetes at baseline and who have agreed to have DNA information used for research purposes.

Outcome:
Incident diabetes at any of the follow-up visits. In ARIC, may also include Self-reported cases/medication use reported during the annual telephone calls after V4.

Variables of interest:
Main exposures:

1. Serum K
2. KCNJ11 polymorphisms: rs5219, rs5215
3. KCNQ1 polymorphisms: rs231356, rs2283228, rs2237892, rs2237895, rs2237897, and rs231362
4. ABCC8: rs757110

Interaction term:
Will evaluate for possible interaction between serum K and these genetic variants

Covariates of interest:
-Age, sex, race, center, BMI, waist circumference, serum creatinine/eGFR, physical activity, parental history of diabetes, presence of hypertension, systolic blood pressure, serum sodium, fasting glucose and insulin levels, income, use of diuretics.

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 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? __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)?

Yang J, Zhao J. Cumulative Effect of Common Genetic Variants Predicts Incident Type 2 Diabetes: A Study of 21,183 Subjects from Three Large Prospective Cohorts. Epidemiology (Sunnyvale). 2011, November 1.

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* Boerwinkle (GxE) Linda Kao, AS #2004.**)**
___ 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/

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.cscc.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.

References:

1. Chatterjee R, Yeh H, Shafi T, Selvin E, Anderson C, Pankow JS, et al. Serum and dietary potassium and risk of incident type 2 diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. Archives of Internal Medicine. 2010;170(19):1745-51.
2. Chatterjee R, Brancati FL, Shafi T, Edelman D, Pankow JS, Mosley TH, et al. Non-Traditional Risk Factors are Important Contributors to the Racial Disparity in Diabetes Risk: The Atherosclerosis Risk in Communities Study. J Gen Intern Med. 2013.
3. Chatterjee R, Yeh HC, Shafi T, Anderson C, Pankow JS, Miller ER, et al. Serum potassium and the racial disparity in diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr. 2011;93(5):1087-91.
4. Brunetti A, Chiefari E, Foti D**.** Recent advances in the molecular genetics of type 2 diabetes mellitus. World J Diabetes. 2014;5(2):128-40.
5. Ashcroft FM, Rorsman P**.** K(ATP) channels and islet hormone secretion: new insights and controversies. Nat Rev Endocrinol. 2013;9(11):660-9.
6. Gong B, Yu J, Li H, Li W, Tong X**.** The effect of KCNJ11 polymorphism on the risk of type 2 diabetes: a global meta-analysis based on 49 case-control studies. DNA Cell Biol. 2012;31(5):801-10.
7. Ng MC, Shriner D, Chen BH, Li J, Chen WM, Guo X, et al. Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes. PLoS Genet. 2014;10(8):e1004517.