1.a. Full Title: Whole-exome sequencing study of diabetic nephropathy among participants of the Chronic Renal Insufficiency and Atherosclerosis Risk in Communities cohorts

b. Abbreviated Title (Length 26 characters): WES study of DN

2. Writing Group:
   Writing group* members:
   
   Tanika N. Kelly, PhD, MPH
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   *This is an ancillary of both the CRIC and ARIC studies. A CRIC manuscript proposal is being submitted in tandem with this proposal and it is likely that several additional CRIC investigators will be included in the writing group upon review by the CRIC steering committee.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. TK [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:** Discovery stage data analysis should begin within the next few weeks. Within two to 3 months, replication stage analysis will be conducted, at which point we will begin drafting the manuscript. A draft of the manuscript will tentatively be ready be March 1st, 2017.

4. **Rationale:** Diabetic nephropathy (DN) is a major public health challenge due to its high prevalence and associated increases in risks of end-stage-renal disease (ESRD), cardiovascular disease (CVD) and death (1-5). With rapid increases in obesity and T2D prevalence in the US population, it is anticipated that the burden of DN will continue to grow. A strong familial aggregation of DN has been established (6-12), suggesting an important contribution of genetic factors to its development. Although previous genetic studies have identified multiple loci associated with DN, such variants have modest effects and explain only a small portion of the DN risk that has been attributed to genetic factors (13-15). These data support expanded genomic research of DN, including efforts aimed at identifying rare variants which may have large effects and play an important role in susceptibility to DN. Whole-exome sequencing represents a new era of variant discovery (including identification of rare variants) for comprehensive characterization of the genetic architecture of DN.


5. Main Hypothesis/Study Questions: Genes and genetic variants influence susceptibility to diabetic nephropathy.

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).

The proposed whole-exome sequencing study aims to identify novel genes and functional variants associated with diabetic nephropathy among ARIC and CRIC participants who previously underwent whole-exome sequencing and have available phenotype data. We will compare 600 CRIC study cases with diabetic nephropathy to 10,884 ARIC study controls, who are free from diabetic nephropathy. The 600 CRIC DN cases are comprised of 300 African-Americans and 300 whites with a history of T2D, reduced glomerular filtration rate, and elevated 24-hour urinary albumin excretion at the CRIC baseline examination, along with rapid progression of kidney function decline in up to 10-years follow-up. Controls will include 10,884 DN free ARIC study participants (3,126 AA and 7,758 EA) with whole-exome sequencing data (generated by the same sequencing platform, exome-capture, and protocol which was used for sequencing CRIC DN cases). Single variant and aggregate rare variant analysis methods will be used to test the association between genetic variants and DN in African-American and white
participants, separately, and after adjusting for important confounding factors. Replication efforts will leverage publicly available whole-genome, whole-exome, and GWAS data.

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 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)?

No related manuscripts.

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

Yes A. primarily the result of an ancillary study (list number* 2009.12)

___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes X No.