ARIC Manuscript Proposal #1843

PC Reviewed: 9/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Effects of Rare and Common Blood Pressure Gene Variants on Essential Hypertension: Results from the FBPP, CLUE and ARIC Studies

b. Abbreviated Title (Length 26 characters): EH RS&G

2. Writing Group:

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

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3. Timeline:

September 2011

4. Rationale:

Previous clinical studies have revealed 15 genes that are involved in the Mendelian forms of hypo-/hypertensive syndromes (Geller DS, Seminars in Nephrology, 2010). Our study was designed to determine the contribution of 10 of such genes and angiotensinogen to essential hypertension (EH) and blood pressure (BP) regulation in general populations.

5. Main Hypothesis/Study Questions:
While it is known that each of the 10 genes and angiotensinogen are involved in rare forms of familial hypertension, their effects have been studied in few studies in general population. The goal of this proposal is to study the variant spectrum in these genes in general populations and identify their level of involvement in essential hypertension (EH).

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).
We selected 560 unrelated individuals at the extremes of SBP residuals distribution within each of the 4 gender-by-race strata from GenNet, a network in the Family Blood Pressure Program (FBPP). Equal numbers of subjects were 70 for each of the 4 groups: European American (EA) men and women and African American (AA) men and women. Within each of the 4 gender-by-race strata, BP residuals were obtained after correcting for age, age^2 and BMI. For each individual, we resequenced the 11 genes (*AGT*, *CYP11B1*, *CYP17A1*, *HSD11B2*, *NR3C1*, *NR3C2*, *SCNN1A*, *SCNN1B*, *SCNN1G*, *WNK1*, *WNK4*) for all exons, 50bp exon boundaries and conserved non-coding regions using Sanger dideoxy sequencing technology. We propose to impute polymorphic variants from our study (MAF$\geq$1%) and the 1000 Genomes Project (TGP) variants in the 9,747 EA and 3,207 AA unrelated ARIC participants with GWAS data to study the effects of these variants in SBP, DBP, PP, MAP and hypertension. Imputation will be performed using BEAGLE for the entire gene region $\pm$ 10kb boundaries. We will first impute our polymorphic variants to the panels of Europeans and EAs (EUR) and Africans and AAs (AFR) panels of TGP. Then we will impute ARIC freeze 3 GWAS genotypes on the combined panel of variants from our resequenced project and the TGP. Variants with imputation score (r^2) <0.3 will be removed before association analysis. We will use the 4 BP measurements as quantitative traits and will analyze by regression after coding for an additive model. We will use false discovery rate (FDR) = 0.05 as the threshold for statistical significance in each of the 11 gene regions. The results will help us understand the role of resequencing Mendelian genes in hypertension in general large population.

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)? ARIC 1408

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* 2009.12 and 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.