ARIC Manuscript Proposal # 1414

PC Reviewed: 08/12/08    Status: A    Priority: 2
SC Reviewed: _________    Status: _____    Priority: ____

1.a. Full Title: Association between MYH9 SNPs and chronic kidney disease

b. Abbreviated Title (Length 26 characters): MYH9 and CKD

2. Writing Group:
   Writing group members: Linda Kao, Rula Parekh, Anna Kottgen, Ching-Yu Cheng, Lori Bash, Joe Coresh, Eric Boerwinkle, Brad Astor (others to be suggested by the publications committee)

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

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3. Timeline: Data analysis to start immediately. First draft on manuscript expected by November 2008.
4. **Rationale:** African Americans suffer disproportionally from progressive chronic kidney disease (CKD) and end stage renal disease (ESRD), even after accounting for differences in socioeconomic factors\(^1\)\(^-\)\(^5\). In 2005, we began a genome-wide mapping by admixture linkage disequilibrium (MALD) study in African Americans with and without ESRD to test the hypothesis that not only can a subset of ESRD susceptibility alleles be identified through the cursory admixture scan across the genome but that such alleles can partially account for the excess risk of ESRD observed in African Americans compared to European Americans. Since the initiation of funding support from the NIDDK, we have completed a MALD analysis and identified common alleles in the gene \textit{MYH9}, which codes the protein nonmuscle myosin heavy chain class II isoform A (NMMHCIIA), to be significantly associated with increased risk of non-diabetic ESRD in the African Americans recruited from the Johns Hopkins MALD component of the Family Investigation of Nephropathy and Diabetes consortium (JH-FIND). Approximately 40\% of African Americans carry the \textit{MYH9} susceptibility allele, which is associated with a two-fold higher risk of non-diabetic ESRD (Kao et al. provisional accepted Nat Gen). Thus, we identified a major locus accounting for a large fraction of the excess risk of ESRD observed in African Americans compared to European Americans. Three SNPs of unknown functional relevance have been demonstrated to tag the causal variant well; therefore, we propose the genotyping of those SNPs in the initial round of analysis. Sequencing effort of \textit{MYH9} is currently ongoing to identify the potential causal variant.

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

The primary goal of this proposal is to continue establishing the impact of \textit{MYH9} on CKD risk, progression to ESRD, and other related phenotypes in the African Americans from the ARIC study.

We hypothesize that \textit{MYH9} susceptibility alleles are associated with

a. **CKD markers:** decreased estimated glomerular filtration rate (eGFR), albuminuria, and elevated cystatin C

We hypothesize that carriers of \textit{MYH9} susceptibility will first manifest with increased albuminuria followed by elevation in serum cystatin C and creatinine levels leading to clinical CKD. Characterization of the subclinical and clinical CKD phenotypic expression across the life course will rapidly shed light on the magnitude and effect of \textit{MYH9} susceptibility on CKD prior to ESRD.

b. **Pleiotropic phenotypes:** blood pressure and hemostatic factors.

Rare Mendelian forms of \textit{MYH9}-associated disorders, primarily in Caucasians and Asian, have been described to include a range of phenotypic expression marked by platelet abnormalities, deafness, and hypertension aside from kidney damage. We will test the hypothesis that common \textit{MYH9} susceptibility allele in African Americans result in similar phenotypic expressions.
c. **Interacting factors:** gender, blood pressure control, diabetes, use of antihypertensive medication, and other environmental/behavioral factors.

*The lack of association between MYH9 and ESRD among diabetic individuals in the JH-FIND study suggests the presence of significant interactions with the highly prevalent MYH9 susceptibility allele. We will test for additional susceptibility interactions in the rich set of data on comorbidities and environmental/behavioral factors collected over follow up in ARIC.*

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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 propose to genotype 3 tagging SNPs in all African Americans who consented to having their DNA used for research. Due to the low prevalence of the tagging SNPs in Caucasian populations, we are not proposing to type the SNPs in this population. However, when/if the causal SNP is identified, we will submit an addendum to also study the SNP in the ARIC whites.

**Primary exposure:** Genotypes of MYH9 SNPs

**Primary outcomes:**

The primary outcome will be a binary outcome of cumulative CKD. Cases are all prevalent CKD cases at baseline (eGFRscr < 60 at visit 1) and all incident CKD. Incident CKD will be defined by either 1) a decrease in eGFR < 60 mL/min/1.73 m2 at the 3- or 9-year follow-up examination or 2) a death or hospitalization with an ICD-9 code indicating CKD during the extended follow-up. Additional analyses also have replaced the eGFR<60 with an increase in SCr of >0.4 mg/dL from baseline to the 3- or 9-year follow-up examination. This amount of change represents twice the normal short term variation in SCr. Controls are all non-cases. This outcome is referred to as “CKD”.

Secondary outcomes will include continuous measures of kidney function including eGFR, serum cystatin-C levels at Visit 4, and urine albumin to creatinine ratio (UACR) at Visit 4.

Secondary outcome: Baseline systolic and diastolic blood pressures were measured following a five minutes rest. Three seated measurements were taken by certified technicians using a random-zero sphygmomanometer. The average of the second and third readings was recorded. Systolic (SBP) and diastolic (DBP) blood pressure will be collapsed into a joint categorical variable (normal: SBP<120 and DBP<80; prehypertension: SBP 120 139 or DBP 80 89; stage 1 hypertension: SBP 140 159 or DBP 90 99; stage 2 hypertension SBP ≥160 or DBP ≥100)\(^6\).
**Data analysis:** Each of the SNPs to be examined will be analyzed individually for association with phenotype of interest while conditioning on individual admixture both globally and locally in regression models. Global population substructure will be estimated with ~1350 ancestry informative markers from Dr. Kao’s admixture mapping ancillary study using ANCESTRYMAP⁷. For qualitative outcomes, e.g. CKD, logistic regression models and the Wald statistic for significance testing will be used. For quantitative traits, e.g. platelet and serum cystatin-C levels and UACR, general linear regression models and the F-statistic for significance test will be used. We will compute the overall test of genotypic association with two degrees of freedom and the statistical contrasts defined by the three genetic models, dominant, additive and recessive models, respectively (each with one degree of freedom), with and without adjustment for covariates. If the test of general association is significant, then three a priori genetic models will be explored and the best genetic model will be selected without further adjustment for multiple comparisons. In addition, an interaction term for gender, hypertension, and diabetes status with genotype will be included and test of significance will be performed.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ 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?  ____ 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?  ____ 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 D̅N̅A = “No use/storage DNA”?  ____ X__ Yes ___ No

8.c. Is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  ____ 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.csecc.unc.edu/ARIC/search.php](http://www.csecc.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)?
None

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* _
2006.16  Longitudinal Study of Predictors and Consequences of Chronic Kidney Disease

_____ 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.

Reference List


