ARIC Manuscript Proposal # 1606

PC Reviewed: 2/9/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between MYH9 SNPs and chronic kidney disease in individuals of European ancestry in ARIC and Framingham Heart Study

b. Abbreviated Title (Length 26 characters): **MYH9 and CKD in ARIC and FHS**

2. Writing Group:

Writing group members: Conall O'Seadhgha, Rulan Parekh, Caroline Fox, Man Li, Anna Kottgen, Joe Coresh, Linda Kao (others to be added from both studies)

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]**

F**irst author**: Conall O'Seadhgha (Clinical Research Fellow, the Framingham Heart Study National Heart, Lung, and Blood Institute Department of Nephrology)

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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 start immediately. First draft on manuscript expected by March 2010.

4. Rationale: We previously identified MYH9 to be a susceptibility gene for end stage renal disease (ESRD) in African Americans (1). *MYH9* encodes the protein nonmuscle myosin heavy chain class II isoform A (NMMHCIIA), and a common SNP (rs4821480 or rs4821481) was found 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). While this SNP has a minor allele frequency of 40% in African Americans, the corresponding frequency in the HapMap Caucasian samples (CEUI) is only about 2%. It is unknown whether this SNP, or another SNP in this gene, is associated with kidney disease in individuals of European ancestry. Therefore, we propose to integrate the entire region of MYH9 on the Affy GWAS chip and determine whether SNPs in MYH9 are associated with chronic kidney disease in European Americans. Due to the low frequency of the main SNP of interest in this population, we propose a meta-analysis of the results from ARIC and Framingham Heart Study.

5. Main Hypothesis/Study Questions:

The primary goal of this proposal is to examine whether SNPs in MYH9, specifically rs4821480, are associated with CKD in individuals of European ancestry.

We hypothesize that *MYH9* susceptibility alleles are associated with prevalent CKD and lower eGFR at ARIC visit 1. In addition, we hypothesize that the association will be stronger among non-diabetic individuals compared to diabetic individuals.

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 use all the genotype data within the MYH9 region from the Affy GWAS chip. Only individuals who had "cleaned" genotype data from the GWAS will be included. Due to the low prevalence of the main associated SNP in Caucasian populations, we are proposing to combine our results with those from the Framingham Heart Study.

Primary exposure: Genotypes of MYH9 SNPs from GWAS data

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. Controls are all non-cases. This

outcome is referred to as "CKD". Secondary outcomes will include continuous measure of eGFR.

Data analysis: Analysis will be similar to our plan in CKD-GWAS work. Each of the SNPs to be examined will be analyzed individually for association with phenotype of interest while adjusting for age, sex, center, and any of the 10 principal components that are associated with the outcome. For CKD, logistic regression models and the Wald statistic for significance testing will be used. For eGFR, 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 recessive genetic model, which was the one that appeared to be most appropriate in the African Americans from the FIND study. In addition, all analyses will be stratified by diabetes and hypertension status, and an interaction term for diabetes and hypertension will be included and test of significance will be performed. Significance of rs4821480 will be declared with an alpha of 0.05 as that was the original SNP identified in the African Americans. For the rest of the SNPs in MYH9, we will use a Bonferroni-corrected alpha of 0.05/number of SNPs examined.

Each study (ARIC and FHS) will perform their own data analysis. Mandy Li from Johns Hopkins will perform the meta-analysis. The ARIC data will not be distributed to investigators outside of the ARIC study.

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

8.c. If yes, 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.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)?

None

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes ___x_ 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. Kao WHL, Klag MJ, Meoni LA, Reich D, Berthier-Schaad Y, Li M, Coresh J, Patterson N, Tandon A, Powe NR, Fink NE, Sadler JH, Weir MR, Abboud HE, Adler SG, Divers J, Iyengar SK, Freedman BI, Kimmel PL, Knowler WC, Kohn OF, Kramp K, Leehey DJ, Nicholas SB, Pahl MV, Schelling JR, Sedor JR, Thornley-Brown D, Winkler CA, Smith MW, Parekh RS; on behalf of the Family Investigation of Nephropathy and Diabetes (FIND) Research Group. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. Nat Genet. 2008 Oct;40(10):1185-92. Epub 2008 Sep 14.