ARIC Manuscript Proposal #2263

PC Reviewed: 11/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Is sickle cell trait a risk factor for kidney disease?

b. Abbreviated Title (Length 26 characters): sickle cell trait and kidney disease

2. Writing Group:
   Writing group members: Abhijit V. Kshirsagar, Vimal K. Derebail, Nigel Key, Wayne Rosamond, Wendy Kao, Morgan Grams (Others welcome)

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

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3. Timeline: Projected timeline is one year following genotyping of sickle cell trait polymorphism (rs334).

4. Rationale:
Sickle cell trait (SCT) has long been regarded as a benign carrier state. Serious health consequences are thought to be rare, occurring only under conditions of extreme hypoxemia or metabolic stress. However, evidence is growing that heterozygous possession of the hemoglobin S gene may have more associated morbidity than previously appreciated, particularly with respect to kidney disease.

The unique physiology of the kidney may routinely facilitate an adverse interaction between red blood cells containing hemoglobin S and the renal vasculature. Physiological conditions common in the renal medulla\(^1\) are known to induce sickling of these susceptible red blood cells\(^2\), leading to sludging in the small vessels of the kidney and to tissue ischemia\(^3,4\). These changes manifest histologically into the loss and disruption of the vasa recta seen among individuals with homozygous and heterozygous sickle hemoglobinopathies\(^5,6\).

While the clinical consequences of these structural changes (microscopic hematuria, isosthenuria, and papillary necrosis\(^7,8,9\)) have been considered modest among individuals with HbAS, more serious functional consequences may also result. We and others have demonstrated HbAS to be present at a higher than expected frequency among African-American dialysis patients, 11-15% of the population\(^10,11,12\) The prevalence of sickle trait, furthermore, has been shown to be high among African-American populations at risk for kidney disease, ranging from\(^13,14,15\)18 to 33%, well above the published reports of 7-9%. Thus, HbAS may also augment the effect of other risk factors. Lastly, we have also demonstrated that the presence of sickle trait may add to the morbidity of patients who have progressed to ESRD, especially with respect to anemia\(^16\).

We propose to examine the association of SCT with the prevalence and incidence of kidney disease based on estimated glomerular filtration rate and diagnosis codes. SCT trait genotyping has been funded by ancillary study 2010.16, and performed at the central research laboratory. Genotyping has now been completed.

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

Is sickle cell trait associated with kidney disease?

We hypothesize that African American participants with SCT will have a higher prevalence of kidney disease at the baseline visit, and a higher incidence of kidney disease over 25 years of follow up.

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).**
Sickle cell trait will be defined by heterozygosity for hemoglobin S (single nucleotide polymorphism rs334).

Inclusion criteria: All African-American participants with available genetic material
Exclusion criteria: 1) Sickling disorders or other hemoglobinopathies including;
   homozygosity for hemoglobin S (HbSS), homozygosity for hemoglobin C (HbCC),
   double heterozygosity (HbSC), β-thalassemia trait or Sickle-β-thalassemia; 2) Insufficient
   sample of DNA; 3) Glomerular filtration rate < 60 ml/min/1.73 m2 at the baseline visit
   (Visit 1).

Outcomes
Serum creatinine concentration, obtained at ARIC study Visits 1, 2, & 4 will be used to
estimate glomerular filtration rate (GFR) based on the modified MDRD equation:

\[
GFR (\text{mL/min/1.73 m2}) = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})
\]

Calculation of eGFR for the ARIC baseline visit (Visit 1) will require subtraction of
0.24mg/dl from the measured value of creatinine for calibration to the Cleveland Clinic
laboratory.(17)

Albuminuria will be determined as previously reported in the ARIC cohort (18) and
defined as urine albumin-to-creatinine ratio (ACR) ≥ 30 µg/mg from visit 4.

The renal outcomes of this proposed study will be based on previously published
outcomes in the ARIC study: (18,19,20, 21)

1) Prevalence of CKD at any exam visit – defined as eGFR <60ml/min/1.73m2
2) Development of eGFR < 60 ml/min/1.73 m2
3) Development of eGFR < 60 ml/min/1.73 m2 & ≥ 25% decline
4) Development of ESRD, ascertained by linkage of the cohort to the United States
   Renal Data System (USRDS) & hospitalizations.
5) Prevalence of albuminuria at visit 4.

Covariates:
APOL1/MYH9: The association between the MYH9 gene variants and APOL1 gene
variants have been well established to be associated with kidney disease (22, 23) in the
African-American population including in the ARIC cohort (24)

DARC: Expression of the Duffy antigen receptor for chemokines (DARC) has been
previously evaluated in sickle cell disease. Lack of expression of the Duffy antigen on
red blood cells has been associated with a more severe phenotype of sickle cell disease
and associated with proteinuria in sickle cell disease (25). Indicated by the SNP
rs2814778, the polymorphism has already been identified in the ARIC cohort. (26)
Genetic admixture: We will assess the potential contribution of genetic admixture in the African-American population. Using previously established data in ARIC, we will include percentage European ancestry as a continuous variable in our analysis. (27)

Our models will also include age, sex, hypertension, diabetes mellitus, cigarette smoking, BMI, education level, history of cardiovascular disease and cohort-specific field center. Other covariates may be added based on observed differences between the exposure and referent groups.

Analysis Plan: Data analysis will be performed at the University of North Carolina Collaborative Studies Coordinating Center for the ARIC study. We will perform univariate analyses using chi2 tests for categorical variables, and Student’s t-tests for continuous variables with normal distribution or Wilcoxon-rank-sum tests for those variables without a normal distribution. Following univariate analyses, we will construct logistic regression models to determine the association of HbAS and prevalence of CKD and prevalence of albuminuria as defined above. We will construct Cox-proportional hazards models to determine the association of HbAS v. HbAA (normal hemoglobin) and incidence of CKD and ESRD as defined above. As an additional analysis we will explore the use of linear mixed models with random intercepts and slopes to assess the rate of decline of eGFR using data from visits 1, 2 and 4. The beta coefficients for this model will represent the rate of eGFR decline in ml/min/1.73m² per year in sickle cell trait carriers versus non-carriers. Covariates identified in univariate analyses above will be explored as potential confounders and effect modifiers and will be included in models as indicated.

We intend to combine these results with results of similar analyses from other cohort studies including Coronary Artery Risk Development in Young Adults (CARDIA), Multi-Ethnic Study of Atherosclerosis (MESA), Jackson Heart Study (JHS), and Women’s Health Initiative (WHI). Investigators with these cohorts have expressed an interest in pooling our results.

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 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 other study proposal are examining sickle trait and kidney disease.

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* 2010.16)  
____ 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


