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]**

F**irst author**: **Abhijit V. Kshirsagar**
Address: UNC Kidney Center
CB #7175
Chapel Hill, NC 27599-7155

Phone: (919) 919-966-2561 Fax: (919) 966-4251
E-mail: abhijit_kshirsagar@med.unc.edu

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).
Name: **Wayne Rosamond**
Address: 137 E. Franklin St., CB 8050 STE 306
Chapel Hill, NC 27514-4145

Phone: 919-962-3232 Fax: 919-966-9800
E-mail: wayne_rosamond@unc.edu

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:60, 61
GFR (mL/min/1.73 m2) = 186 x (Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 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 de 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/1.73m^2 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 __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 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

1. Brezis M, Rosen S. Hypoxia of the renal medulla--its implications for disease. N Engl J Med 1995; **332:** 647-655.

2. Noguchi CT, Torchia DA, Schechter AN. Polymerization of hemoglobin in sickle trait erythrocytes and lysates. J Biol Chem 1981; **256:** 4168-4171.

3. Barabino GA, Wise RJ, Woodbury VA, et al. Inhibition of sickle erythrocyte adhesion to immobilized thrombospondin by von Willebrand factor under dynamic flow conditions. Blood 1997; **89:** 2560-2567.

4. Hebbel RP. Perspectives series: cell adhesion in vascular biology. Adhesive interactions of sickle erythrocytes with endothelium. J Clin Invest 1997; **99:** 2561-2564.

5. Statius van Eps LW, Earley, L.E. The kidney in sickle cell disease. In: Early LE G, CW (ed). Strauss and Welt's Diseases of the Kidney, 3rd edn, vol. 2. Little, Brown, and Co.: Boston, MA, 1979, pp 1229-1240.

6. Statius van Eps LW, Pinedo-Veels C, de Vries GH, et al. Nature of concentrating defect in sickle-cell nephropathy. Microradioangiographic studies. Lancet 1970; **1:** 450-452.

7. Chapman AZ, Reeder PS, Friedman IA, Baker LA. Gross hematuria in sickle cell trait and sickle cell hemoglobin-C disease. Am J Med 1955; **19:** 773-782.

8. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. Am J Med 2009; **122:** 507-512.

9. Sears DA. The morbidity of sickle cell trait: a review of the literature. Am J Med 1978; **64:**1021-1036.

10. Yium J, Gabow P, Johnson A, Kimberling W, Martinez-Maldonado M. Autosomal dominant polycystic kidney disease in blacks: clinical course and effects of sickle-cell hemoglobin. J Am Soc Nephrol 1994; **4:** 1670-1674.

11. Derebail VK, Nachman PH, Key NS, Ansede H, Falk RJ, Kshirsagar AV. High prevalence of sickle cell trait in African Americans with ESRD. J Am Soc Nephrol 2010; **21:** 413-417.

11. Derebail VK, Lacson E, Kshirsagar AV, et al. Sickle trait and ESA dosing in African American hemodialysis patients. In Press, J Am Soc Nephrol 2013.

13. Oli JM, Watkins PJ, Wild B, Adegoke OJ. Albuminuria in Afro-Caribbeans with type

Formatted: Spanish (United States)

Formatted: Spanish (United States)

2 diabetes mellitus: is the sickle trait a risk factor? Diab Med 2004; **21:** 483-486
14. Ajayi AA, Kolawole BA. Sickle cell trait and gender influence type 2 diabetic complications in African patients. Eur J Int Med 2004; **15:** 312-315.
15. Bleyer AJ, Reddy SV, Sujata L, et al. Sickle cell trait and development of microvascular complications in diabetes mellitus. Clin J Am Soc Nephrol, 2010; **5:** 1015-1020.
16. Derebail VK, Nachman PH, Key NS, et al. Variant hemoglobin phenotypes may account for differential erythropoiesis-stimulating agent dosing in African-American hemodialysis patients. Kidney Int 2011; **80:** 992-999.
17. Astor BC, Arnett DK, Brown A, et al. Association of kidney function and hemoglobin with left ventricular morphology among African Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am J Kidney Dis 2004; **43:** 836-845.
18. Hsu CC, Brancati FL, Astor BC, Kao WH, Steffes MW, Folsom AR, Coresh J. Blood pressure, atherosclerosis, and albuminuria in 10,113 participants in the atherosclerosis risk in communities study. J Hypertens. 2009 Feb;27(2):397-409.
19. Bash LD, Astor BC, Coresh J. Risk of incident ESRD: a comprehensive look at cardiovascular risk factors and 17 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis 2010; **55:** 31-41.
20. Bash LD, Coresh J, Kottgen A, et al. Defining incident chronic kidney disease in the research setting: The ARIC Study. Am J Epidemiol 2009; **170:** 414-424.
21. Matsushita K, Selvin E, Bash LD, et al. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis 2010; **55:** 648-659.
22. Kopp, J. B., Smith, M. W., Nelson, G. W., Johnson, R. C., Freedman, B. I., Bowden, D. W., et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nature Genetics 2008; 40(10), 1175–1184.
23. Kao, W. H. L., Klag, M. J., Meoni, L. A., Reich, D., Berthier-Schaad, Y., Li, M., et al. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. Nature Genetics 2008; 40(10), 1185–1192.

Formatted: Spanish (United States)

24. O'Seaghdha, C. M., Parekh, R. S., Hwang, S.-J., Li, M., Köttgen, A., Coresh, J., et al. The MYH9/APOL1 region and chronic kidney disease in European-Americans. Human Molecular Genetics 2011; 20(12), 2450–2456.
25. Afenyi-Annan A, Kail M, Combs MR, Orringer EP, Ashley-Koch A, Telen MJ. Lack of Duffy antigen expression is associated with organ damage in patients with sickle cell disease. Transfusion. 2008 May;48(5):917-24.
26. Reich D, Nalls MA, Kao WH, Akylbekova EL, Tandon A, et al. Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. PLoS Genet 2009; 5: doi:0.1371/journal.pgen.1000360
27. Cheng, C.-Y., Reich, D., Coresh, J., Boerwinkle, E., Patterson, N., Li, M., et al. (2010). Admixture mapping of obesity-related traits in African Americans: the Atherosclerosis Risk in Communities (ARIC) Study. Obesity 2010; 18(3), 563–572.