ARIC Manuscript Proposal #2422

PC Reviewed: 9/9/14  Status: A  Priority: 2
SC Reviewed: __________  Status: _____  Priority: ____

1.a. Full Title: The epidemiology of retinal eye disease in individuals with sickle cell trait.

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

2. Writing Group:
   Writing group members: Abhijit V. Kshirsagar, Seema Garg, Vimal K. Derebail, Laura Loehr, Nigel Key, Ronald Klein, Barbara Klein, 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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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: Projected timeline 6 months after approval of proposal.

4. Rationale:
Retinal eye disease in patients with sickle cell anemia is well described\(^1\) and results from rheologic impairment.\(^2\) Vascular beds with low flow and high oxygen extraction are more prone to sickling of affected red blood cells. Secondary vascular occlusion results with the peripheral retina and macula appearing to be most susceptible to vascular occlusion.\(^3\)

Retinal eye disease among individuals with sickle cell trait (SCT) has not been well characterized, consisting of case reports and series.\(^4-6\) Indeed, SCT has long been regarded as a benign carrier state with serious health consequences occurring only under conditions of extreme hypoxemia or metabolic stress.\(^7\) Yet, it is known that certain vascular beds are susceptible to disruption in the presence of SCT,\(^8-10\) and evidence of disease associated with SCT in other organ systems is emerging.\(^11-13\) The low partial pressure of oxygen in areas of the retina may trigger sludging of red blood cells containing hemoglobin S and lead to vascular occlusion. Over time, changes to vessel thickness and tortuosity. Additionally, choroidal perfusion may be decreased, potentially contributing to the generation of macular edema.

With the recent genotyping of the hemoglobin S mutation, ARIC now has one of the largest and best characterized cohorts in the United States of individuals with sickle cell trait. We propose to describe the epidemiology of retinal eye disease in these individuals.

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

We hypothesize that African American participants with SCT will have a higher prevalence of retinal abnormalities than African American participants with normal hemoglobin. More specifically, we will quantify the cross-sectional association of SCT with retinal vascular characteristics (narrower central retinal arteriolar equivalent (CRAE), wider central retinal vein equivalent (CRVE) and presence of AV nicking, focal arteriolar narrowing, macular degeneration, and other measures of retinopathy.

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 who have been assessed for the hemoglobin S mutation as part of Ancillary Study 2010.16.

Exclusion criteria: 1) Sickling disorders or other hemoglobinopathies including: homozygosity for hemoglobin S (HbSS), homozygosity for hemoglobin C (HbCC), double heterozygosity (HbSC), 2) Lack of or low quality genotyping data 3) Absence of retinal photography

Outcomes
Retinal variables, in the eye the randomly chosen to be photographed: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysm, soft exudates and hard exudates. Retinal arteriolar narrowing quantified as branch retinal arteriole-to-venular ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent, and macular degeneration (large retinal drusen and other pigmentary abnormalities).

Analysis Plan: Data analysis will be performed by Drs. Derebail and Kshirsagar at the University of North Carolina. 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 variables without normal distribution. Following univariate analyses, we will construct logistic regression models to determine the association of HbAS v. HbAA (normal hemoglobin) and prevalence of retinal abnormalities. Covariates include age, gender, race, history of diabetes, history of hypertension, mean arterial blood pressure, smoking status, total cholesterol, and total triglycerides; those covariables identified in univariate analyses as potential confounders and effect modifiers and will be included in models as indicated.

As a sensitivity analysis, the association of HbAS with retinopathy will be stratified by history of hypertension and a history of diabetes given that both are strong risk factor for retinopathy.

7.a. Will the data be used for non-CVD analysis in this manuscript?  __X__ 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?  __X__ 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.cscce.unc.edu/ARIC/search.php
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 proposals are examining sickle trait and retinopathy.

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/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed.

**References**
