1.a. Full Title: Sickle cell trait and retinal mirovascular abnormalities

b. Abbreviated Title (Length 26 characters): Sickle trait and retina

2. Writing Group:
   Writing group members: Aaron Folsom, Kristen George, Barbara Klein, Ron Klein, others welcome

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

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3. Timeline: start immediately

4. Rationale:

   Carriers of sickle cell trait have a hemoglobin genotype AS, rather than a normal AA. Sickle cell trait is considered generally benign; however sickle cell trait carriers may experience hypoxia at high altitude and ARIC showed they have an increased risk of pulmonary embolism and chronic kidney disease.

   Although homozygous sickle cell disease is associated with increased retinopathy risk, whether sickle cell trait may affect the retinal vasculature is unknown. ARIC has shown that arteriolar narrowing and venular dilation are associated with inflammation and hypertension. The possible presence of retinal hypoxia may be associated with retinopathy or wider retinal venules.

5. Main Hypothesis/Study Questions:

   Sickle cell trait is associated with wider venular diameter and narrower arteriolar diameter in African Americans in ARIC.
Sickle cell trait is also associated with retinopathy presence and severity.

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).

Hemoglobin S genotype was measured by TaqMan and these provide the basis for defining sickle cell trait (HbAS). Retinal variables were measured in one random eye at Visit 3 at the University of Wisconsin. Visit 3 was chosen to provide the maximum sample size. Although retinal findings are available on some subsets at later visits, they will not be analyzed here.

Design: cross-sectional study

Endpoints: (1) standardized measurements of diameters of retinal venules and arterioles at Visit 3 and (2) presence (y,n) and severity of retinopathy (5 categories: none, minimal nonproliferative, moderate nonproliferative, severe nonproliferative, proliferative).

Exposures: sickle trait

Exclusions: missing retinal data, exclusion from DNA use, missing sickle trait, homozygous for sickle cell disease.

Main covariates (though none are expected to confound): age, principal components of ancestry, sex, BMI, diabetes, eGFR, smoking status, SBP and BP meds, TC and HDL-C.

Analysis: Univariate chi-square and t-tests. Linear regression (diameters) and logistic regression (retinopathy prevalence) in relation to sickle cell trait. We will stratify by diabetes and hypertension status as needed in so far as sample size permits.

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.cscnc.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 (*)

_____ 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.cscnc.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.cscnc.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.