1.a. Full Title: EPHX2 Polymorphisms, MRI Abnormalities, and Cognitive Decline in African-Americans

b. Abbreviated Title (Length 26 characters): EPHX2 Gene and MRI

2. Writing Group: Myriam Fornage, Eric Boerwinkle, Dean Shibata, Cliff Jack, Laura Coker, Diane Catellier, Dave Knopman, Tom Mosley

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

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3. Timeline: Analyses completed 12/05; Draft ready 2/06

4. Rationale:
Understanding the relationships between genetic variation and susceptibility to subclinical and clinical cerebrovascular disease (CVD) is fundamental to developing new approaches to detection, treatment, and prevention of brain injury and its associated cognitive sequelae. Soluble epoxide hydrolase catalyses the degradation of epoxyeicosatrienoic acids (EETs), which have potent vasodilator and other properties related to vascular function (1-3). We have recently reported that polymorphisms of the Soluble Epoxide Hydrolase (EPHX2) gene were significantly associated with incident ischemic stroke in African-Americans in the ARIC cohort (4). The proposed manuscript
seeks to investigate whether these same polymorphisms are also associated with subclinical CVD identified on MRI and decline in cognitive function.

5. Main Hypothesis/Study Questions:
   Null Hypothesis 1: Polymorphisms of the EPHX2 are not associated with indices of subclinical CVD, including infarct-like lesions, white matter hyperintensities, and ventricular or sulcal size, after controlling for other risk factors.

   Null Hypothesis 2: Polymorphisms of the EPHX2 are not associated with change in cognitive function after controlling for other risk factors.

6. Data (variables, time window, source, inclusions/exclusions):
   EPHX2 polymorphisms have been typed in African-Americans in the ARIC cohort and will be the focus of this analysis. For Hypothesis 1, the dependent variables of interest are infarct-like lesions (> 3mm, present/absent), white matter hyperintensities (≥ grade 3, present/absent), ventricular size (≥ grade 4, present/absent), and sulcal size (≥ grade 3, present/absent). General linear models will be used to test the association of each EPHX2 SNP with each MRI trait. Statistical significance will be evaluated by permutation tests to account for multiple testing. A score test method will be used to investigate the association of common haplotypes of the gene with traits. Models will adjust for established risk factors, including age, gender, education, alcohol use, hypertension, smoking, and diabetes. For Hypothesis 2, the primary dependent variable will be change in cognitive function from V2 to V4 for the 3 cognitive variables: delayed word recall, information processing speed (digit symbol substitution), and word fluency. Models will adjust for established risk factors as well as medications with CNS effects.

Exclusions/Inclusions:
   1 = Center not J or F
   2 = Race not Black

Visit 1 variables:
   History of stroke/TIA (hom10d tiab01), occupational status at baseline (hom55 hom57), education level (elevel01, elevel02), gender (gender),

Visit 2 variables:
   Age, (v2age22), fasting blood sugar (glusiu21), history of diabetes (diabts22), smoking status (cursmk21, forsmk21, evrsmk21, cigt21), hypertension status incl. antihypertensive meds (hypert25), IMT (mnb45_1s), BMI (bmi21), drinking status and alcohol intake (drnkr21 ethanl24), lipid variables (total chol, HDL, LDL, triglycerides), blood pressure (sbpb21 sbpb22)

   Medications with CNS effects

   Cognitive function: (cnfa01, cnfa02, cnfa04)

Visit 4 variables:
Cognitive function (cnfc1, cnfc2, cnfc4)

**Incident event datasets (variables):**
incident stroke: istrby02 (keep=id ed02dp in02dp)

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 ICTDER02 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 ICTDER02 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

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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](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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes ___ X__ No

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/](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:


