1.a. Full Title: Atrial Natriuretic Peptide Gene and Ischemic Cerebrovascular disease

b. Abbreviated Title (Length 26 characters): Atrial Natriuretic Peptide Gene and Ischemic Cerebrovascular disease

2. Writing Group (list individual with lead responsibility first):

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   Writing group members: Josef Coresh, Eric Boerwinkle, Tom Mosley, others welcome.

3. Timeline: 8/03-10/03

4. Rationale:
   Studies involving twins, siblings, or families support the involvement of genetic factors in stroke. (1-3) Given complex entities of the multifactorial disease, the spontaneously hypertensive stroke-prone rat (SHRSP), an inbred animal model resembling human cerebrovascular disease, has provide insights into underlying the genetic etiology of common stroke. Genome wide scans in the rat have mapped one of stroke-susceptibility genes to a locus colocalized with the gene encoding atrial natriuretic factors (NPPA). (4;5) Also, the effect of this locus on responses to cerebral ischemic insult fitted best into a co-dominant model, and was blood pressure independent. (5)

   Atrial natriuretic peptide (ANP) has been identified as a key hormone for the control of extracellular fluid volume and electrolyte homeostatis in the periphery as well as in the brain. (7) Although none of the polymorphisms in the NPPA gene has appeared to significantly affect plasma ANP levels, a missense mutation (G664A) in its exon 1, responsible for a valine-to-methionine substitution in the proANP peptide, was associated with a two fold increased incidence of stroke (subtype unspecified) in a case-control analysis nested in the Physician’s Health Study. (8) However, this finding was not replicated in two case-control studies. (9;10) Further, two small case control studies, one in Japanese and the other one in Africans, observed the 664 A allele at a lower frequency in the hypertensive group. (10;11)

   We propose a case-cohort and a case-control study to further investigate the association of the G664A polymorphism with clinical stroke and subclinical strokes, respectively. The NPPA gene was proposed as part of Table 3 genetic studies.
5. **Main Hypothesis/Study Questions:**

   A. To test the hypothesis that G664A polymorphism increases the risk of clinical ischemic stroke.
   B. To test the hypothesis that G664A polymorphism increases the risk of subclinical ischemic stroke.
   C. To test the hypothesis that G664A polymorphism decreases the risk of hypertension.

6. **Data (variables, time window, source, inclusions/exclusions):**

   The proposed study will include two case-cohort study groups. One comprises 231 incident ischemic strokes occurring by 31 Dec., 1996 and a subset of 989 participants who were randomly sampled with stratification by age, gender, and thin wall and non-thin wall, with exclusion criteria: (1) neither whites nor African Americans, (2) prior CHD, TIA, or stroke. The other one includes 237 prevalent MRI cerebral infarct cases and a stratified random sample (visit 1, age, gender) of 267 participants who had an MRI at visit 3, who are whites or African Americans, and who were classifiable with respect to having had an infarction (3mm) by MRI (preexisting TIA/CVD at baseline were not excluded).

   Exposure variables: G664A polymorphisms in the *NPPA* gene (available only for the two case cohort groups mentioned above, not for CHD cases).

   Outcomes:
   1. Incident ischemic stroke, defined as definite or probable ischemic stroke
   2. Prevalent MRI cerebral infarct case: infarcts at least 3 mm.
   3. Hypertension status, systolic and diastolic blood pressure at visit 1-4.

   Covariates: age, race gender, smoking, alcohol consumption, baseline body-mass-index, plasma lipid level, blood pressure, and hypertension medication.

   Analysis:
   1. Overall and race-specific effects will be examined.
   2. The incident stroke cases and the prevalent MRI cases (only available for two filed centers) will be treated separately.
   3. Genotypes will be assumed to act co-dominantly.
   4. Survival analysis using a weighted proportional hazards regression (Barlow Macro) for aims A.
   5. Multi-variate logistic regression for aim B.
   6. For aim C, the subgroup analyses will be conducted in the subcohort and in the case group separately. To test the genetic effect on baseline blood pressures, multi-variate linear regression will be used. A random effect model will be used for the repeated blood pressure measurements through visit 4.

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

8.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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

___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)? Dr. Eric Boerwinkle

11. 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.

Reference List


