ARIC Manuscript Proposal #728

1.a. Full Title: Thrombomodulin Amino Acid Dimorphism (Ala455val) In Ischemic Stroke and MRI Cases: The ARIC Study

1.b. Abbreviated Title (Length 26): TM dimorphism in stroke and MRI

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

   Lead: Aleksic N.; Wang Yao-Wei; Folsom A.; Ahn C.; Juneja H., Wu K.K.
   Address: UT Houston, Internal Medicine-Hematology, M.S.B. 5.243 6431 Fannin Houston Tx 77030
   Phone: (713) 500-6807 Fax: (713) 500-6810
   Electronic Mail Address: aleksic@heart.med.uth.tmc.edu
                        kkwu@heart.med.uth.tmc.edu
                        chulahn@heart.med.uth.tmc.edu
                        folsom@epivax.epi.umn.edu

3. Timeline:
   Determination of TM A455V gene polymorphism has been completed in the ARIC visit 1 incident ischemic stroke and MRI cases and cohort random DNA samples as approved by the CC.
   Preliminary analysis 06/2000
   Manuscript preparation 07/2000
   Circulation to co-authors 08/2000
   Submission to Publication Committee 09/2000

4. Rationale:

   Thrombomodulin is an integral endothelial cell membrane receptor for thrombin (1). Thrombin binding to TM results in a conformation change of thrombin which activates the protein C (PC) anticoagulant pathway. The impairment of the PC pathway is likely to contribute to risk factors for thrombosis. The ARIC study showed that a possession of 455V allele increased risk for developing CHD in African-Americans, but not in Caucasians. TMA455V dimorphism is located in the region of TM responsible for thrombin binding and PC activation. At present, it is unknown what impact Ala455Val substitution has on TM function, but the possibility that dimorphism is an additional predictor of early arterial thrombosis deserves additional attention. Stroke is the single leading cause of severe disability and the third leading cause of death in the U.S.(2). The development of stroke is known to be related to vascular risk factors, but besides conventional risk factors little is known about contribution of hemostatic genetic polymorphisms to the risk of developing cerebrovascular thrombotic event (3).
We propose to analyze the frequency of thrombomodulin C/T dimorphism (Ala455 to Val replacement) in the ARIC incident ischemic stroke cases and cohort random samples and its association with disease. We also want to analyze the association of TMA455V polymorphism with visit 3 MRI cases who had an infarction by MRI. There is no information and no prospective data regarding TMA455V polymorphisms and stroke/MRI. We will analyze the relation between TMA455V polymorphism and plasma level of soluble TM in MRI group. We also propose to perform analysis in relation to ethnic origin. It has been indicated that the incidence of stroke is higher in African-Americans than in Caucasians (4). The ARIC study offers great opportunity for such analysis.

5. **Main Hypothesis:**
Presence of 455C/T dimorphism in TM gene is associated with an increased risk for incident ischemic stroke/MRI.

6. **Data (variables, time window, source, inclusions/exclusions):**
Data will be sent to the CC and also analyzed locally by Dr Chul Ahn.

References: