ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #604

1. Full title: Effect of Two New DNA Polymorphisms in the apoE/CI/CII Gene Locus on lipoprotein levels and apolipoprotein levels.
Abbreviated title: (length 26) Two new apoE/apoCI RFLPs.

2. Writing Group:
Lead: Neil S. Shachter
Address: Columbia University
630 W. 168th Street
PH 10-305
New York, NY 10032
Phone: (212) 305-9893
Fax: (212) 305-3213
Email Address: nss5@columbia.edu

Members: Eric Boerwinkle, Rajasekhar Ramakrishnan, Richey Sharrett, Woody Chambless

3. Timeline (From date of approval):

Receipt of samples for PCR by Shachter Lab:	1 month
Completion of PCR:	4 months
Submission of data for analysis by center	5 months
Completion of data analysis	8 months
First Draft of manuscript	9 months
Manuscript submission	10 months

4. Rationale:
1) The Shachter lab has determined in two relatively small populations that a common regulatory region polymorphism in apoCI (apoCI HpaI) has a large and
statistically significant effect on plasma levels of apoB (AHA submitted abstract attached). Because of ethnic variation in the linkage disequilibrium of this
polymorphism with the allelic variants of apoE, this effect is most readily observed in African-Americans of apoE 3/3 genotype.
2) This lab has acquired similar data on a common regulatory region polymorphism of apoE (-491 A/T). This polymorphism significantly affects the plasma
triglyceride level (see attached abstract). Ethnic differences in the linkage disequilibrium of this polymorphism with the allelic variants of apoE are less
pronounced.

5. Main Hypothesis:
We propose that the HpaI-positive (H2) allele of apoCI polymorphism will correlate with lower apoB levels in individuals of apoE 3/3 genotype. We further propose that the overexpressing (A) allele of apoE –491 A/T will correlate with higher triglyceride levels because of the effect of increased apoE.

6. Data (variables, time window, source, inclusions/ exclusions):
We propose to perform PCR genotyping for both new polymorphisms in the ARIC simultaneous batch including the African-American supplement. Since the various disease categories included in this batch

(coronary cases, carotid Atherosclerosis cases, and others) are not of interest for the purposes of this analysis, the sampling design will be taken into account to permit generalization of our results to the entire eligible ARIC cohort. The sample will be used appropriately so that inference to a defined population is straightforward. Initial statistical analysis will be performed at Columbia after the genotype data are sent to the ARIC Coordinating Center, and Woody Chambless will provide guidance regarding the appropriate analysis of this complex sample. A time window for these studies appears above.