Manuscript #604

1. Full title: Effect of Two New DNA Polymorphisms in the apoE/C1/CII Gene Locus on lipoprotein levels and apolipoprotein levels.
   Abbreviated title: (length 26) Two new apoE/apoC1 RFLPs.

2. Writing Group:
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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 apoC1 (apoC1 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 apoC1 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

ARIC MANUSCRIPT PROPOSAL FORM
(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.