ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #104A

1. Title:
Apolipoprotein E Genetic Polymorphism Predicts Carotid Artery Atherosclerosis Houston, TX 77225

2. Writing Group:
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3. Timeline:
Data collection and processing are complete. The manuscript is ready for journal submission subject to ARIC approval.

4. Rationale:
A positive family history of heart disease is a significant risk factor for coronary heart disease (CHD) and genes are known to contribute to interindividual variation in plasma lipid, lipoprotein, and apolipoprotein levels. The virtual explosion in our knowledge of the human genome holds the promise of identifying gene sequences that are also risk factors for CHD. However, little is known about the ability of individual genes to predict disease beyond that afforded by traditional risk factors such as gender, plasma cholesterol levels, weight, and smoking. The null hypothesis dictates that genetic information does not improve prediction of CHD beyond that of traditional risk factors, which are typically cheaper to measure, more accessible to the public, and often lend themself better to intervention.

Allelic variation at the apolipoprotein S (apo E) gene locus is common and its impact on plasma lipid transport has been extensively studied. Apo E is a structural component of circulating chylomicrons, very low density lipoproteins, and high density lipoproteins, and is a ligand for several classes of lipoprotein receptors. Human apo E is polymorphic with three common alleles, e2, e3, and e4. Numerous studies have shown that the average effect of the e2 allele is to lower total serum cholesterol and the effect of the e4 allele is to raise total cholesterol levels. The observed effect of the apo E polymorphism on fasting plasma lipid levels is thought to be attributable to altered receptor binding affinities of the apo E isoforms leading to changes in postprandial chylomicron remnant clearance and subsequent up- and down-regulation of hepatic LDL-receptors.

5. Main Issues/Hypotheses to be Addressed:
1. Ability of the apo E polymorphism to predict case/control status.
2. Ability of the apo E polymorphism to predict case/control status after consider the predictive ability of other (traditional) risk factors.
3. Ability of the apo E polymorphism to predict case/control status after consider the predictive ability of other (traditional) risk factors and the degree of postprandial lipemia.

6. Data Requirements:
Data analyses will be carried out under supervision of Dr. Eric Boerwinkle in the Genetics Center at the

University of Texas Health Science Center. Interpretation of the results of these statistical analyses will be shared jointly by Drs. Patsch and Boerwinkle.

The primary dependent variable is the case/control status as defined by carotid artery wall thickness. Independent variables include, but are not limited to, the apo E polymorphism and the vector of traditional risk factors, such as age, BMI, hypertension status, etc. In addition, we will extend these analyses to include measure of postprandial lipemia such as retinyl palmitate and triglycerides in the top fraction.

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