ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #204

1. Title:
Apolipoprotein AIV influences carotid artery wall thickness in subjects with a high-risk lipid profile.

2. Writing Group:
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3. Timeline:
Data collection and management for the visit I variables in this sample is already complete. DNA has already been isolated from the study subjects and typing the apolipoprotein AIV polymorphisms can begin immediately. This typing will take approximately 2 weeks. After typing is complete, data analyses will begin immediately.

4. Rationale:
Although the exact function of apo AIV is unknown, it is widely accepted that it has a role in both triglyceride metabolism and reverse cholesterol transport. Unlike the other major apolipoproteins, most apo AIV is found free in plasma, unbound in a lipoprotein particle complex. Apo AIV is dissociated from triglyceride rich particles with the transfer of C-apolipoproteins, and apo AIV is well characterized and we have recently shown that common protein alterations in Apo AIV is well characterized and we have recently shown that common protein alterations in apo AIV are due to substitutions of Ser for Thr at codon 347 and His for Gla at codon 360.

Patients with familial combined hyperlipidemia which account for as much as 10% of premature coronary heart disease may present as elevated cholesterol and/or triglycerides (mixed hyperlipidemia). Mised hyperlipidemia is also associated with altered LDL-subclass patterns, insulin resistance, and hypertension. Previous studies have determined that mixed hyperlipidemia can arise from alterations in the apo AI-CIII-AIV gene cluster in at least some families. However, the mutation responsible for this relationship is not known. In this study we will determine whether amino acid substitutions in the apo AIV gene are associated with mixed hyperlipidemia, its phenotypic expression, or atherosclerosis.

5. Main Hypotheses/Issues to be Addressed:
a) Amino acid substitutions in apo AIV are associated with mixed hyperlipidemia in the ARIC study population.
b) Plasma lipid, lipoprotein and apolipoprotein levels are different among apo AIV genotypes and these differences are consistent across the 4 diagnostic groups (see below).
c) Carotid artery wall thickness is different among apo AIV genotypes and this difference is consistent across the 4 diagnostic groups (see below).

6. Data Requirements:
The data requirements for this manuscript proposal are the same as that for the approved proposal "Restriction fragment length polymorphisms (RFLP) of the AI-CIII-AIV gene cluster: Case-control analysis

of atherosclerosis and established risk factors (MS #113). All data analyses will be performed by E Boerwinkle.

DNA has already been isolated from the study subjects, and the amount of DNA necessary for this proposal will not compromise the objectives of the ARIC project. We have already defined 4 diagnostic groups based on ARIC visit 1 data and identified 268 subjects for this study. The groups are: a) low triglyceride - low cholesterol, b) high triglyceride - low cholesterol, c) low triglyceride - high cholesterol, and d) high triglyceride - high cholesterol, where high triglycerides is defined as a value greater than 250 mg/dl, low triglycerides is defined as a value less than 250 mg/dl, high cholesterol is defined as a LDL-cholesterol less than 160 mg/dl. (Note: if triglyceride levels were greater than 400 mg/dl, then a total cholesterol level of 250 mg/dl was used to categorize this group). The sample sizes are: a) low triglycerides - low cholesterol 50, b) high triglycerides - low cholesterol 48, c) low triglycerides - high cholesterol 47, and d) high triglycerides - high cholesterol 123.