ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #113

1. Title:
Restriction Fragment Length Polymorphisms (RFLP) of the AI-CIII-AIV Gene Cluster: Case-Control Analysis of Atherosclerosis & Established Risk Factors

2. Writing Group:
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3. Timeline:
A list of subjects, defined below, will be required by mid-June, 1991. We have the opportunity to utilize the RFLP expertise of Dr. Francesco Tuturro, a visiting scientist from Italy, at no expense to the ARIC Study.

4. Rationale:
Familial combine hyperlipidemia (FCHL) is a common disorder of lipid metabolism with a prevalence of 0.5-2.0% and is estimated to cause 10% of premature coronary heart disease. It has recently been shown that a strong association exists between a mutated site of the AI-CIII-AIV gene cluster in a number of families with FCHL [Wojciechowski AP, et.al. Nature 1991; 349:161-3]. RFLP was used to identify the DNA polymorphism on chromosome 11q23-q24. This technique allows for the identification of variation at the DNA sequence level. A site on a chromosome is polymorphic when at least 1 percent of the sequence for a gene product is different from the majority.

This proposed study will examine the frequency of this specific characterized RFLP in different subsets of ARIC case-control subjects, listed below. This will require the identification by the Coordinating Center of the following number and types of subjects required for this study.

At this time only White subjects will be selected as there my be too few Black subjects for all the categories listed below. They are:
1. 100 subjects with hypertriglyceridemia with no disease;
2. 100 subjects with hypertriglyceridemia with disease;
3. 100 subjects with hypertriglyceridemia + hypercholesterolemia with no disease; and
4. 100 subjects with hypertriglyceridemia + hypercholesterolemia and disease.
5. 100 subjects without hypertriglyceridemia, hypercholesterolemia, and disease.

The lipid levels for cutoff points for hypertriglyceridemia and hypercholesterolemia initially are stated below. After approval of this proposal we may have to modify the upper and lower lipid levels dependent on the number of subjects selected by the initial criteria.

Hypertriglyceridemia is defined as triglyceride levels above 700 mg/dL.

Hypercholesterolemia is defined as LDL-chol levels above 160 mg/dL.
The presence of disease is defined by revised B-mode ultrasound determinations.

The frequency of RFLPs in the apoAI-CIII-AIV gene cluster will be examined in these case-control subjects. This investigation will allow for the further evaluation cf this finding in the ARIC population-based study.

5. Main Hypothesis/Issues to be Addressed:
1) Case subjects will have a higher frequency of RFLP at this gene site than controls.
2) There may be a higher RFLP frequency of this site among subjects with phenotypic hypertriglyceridemia and hypercholesterolemia than subjects with either hypertriglyceridemia or hypercholesterolemia alone.

Keywords: AI-CII-AIV gene, lipids, CHD, family, genetics