MS#: 358 (revised)

ARIC Manuscript Proposal
23 January 1997

Pub Comm: Received: 2/26/97 Status: A Priority: 1
Steer Comm: Received: 2/27/97 Status: A Priority: 1
Diabetes genes in African Americans II: Risk of Atherosclerosis and CVD

1. Title:

2. Writing Group: * Brancati (lead), Boerwinkle, Sharrett, Szklo, Kao, Lei, Shuldiner, Watson

3. Timeline: Depends on technical aspects of DNA extraction and processing (1-2 yrs)

4. Rationale: NIDDM is a strong independent risk factor for atherosclerotic cardiovascular disease. It has been hypothesized that much of this risk is conferred prior to the clinical onset of diabetes. Previous studies have identified mutations in a variety of candidate genes which appear to be associated with obesity, insulin resistance, and/or non-insulin-dependent diabetes mellitus (see Diabetes Susceptibility Genes I). It is possible that these diabetes susceptibility genes also confer increased risk of atherosclerosis and cardiovascular disease. No previous study of these susceptibility genes has fully evaluated the cardiovascular risk associated with the genotype, or examined the associated risk of incident cardiovascular disease. The identification of diabetes susceptibility genotypes that predict the development of cardiovascular disease would represent a major advance in our understanding of the excess risk of cardiovascular disease in diabetic persons. These genotypes would also have immediate applications as markers of prognostic risk in observational and interventional studies of persons with NIDDM.

5. Main Hypotheses: A. Cross-sectional: Mutations in the aforementioned genes are associated with increased carotid wall thickness and with an adverse profile of cardiovascular risk factors in whites and African Americans.

6. Design: B. Prospective: Mutations in the these genes are associated with an increased carotid wall thickness and with an increased risk of incident CVD events in whites and African Americans.

7. Data:

Cross-sectional and prospective studies of a representative subsample of the ARIC cohort, stratified by race.

Outcomes: A. Cross-sectional:

8. Sample Size: 1,533 African Americans

9. Power: A. Cross-sectional: Minimal detectable difference = 0.16v for normally distributed variables (e.g. difference of 3/2 minHg for blood pressure, 3 mg/dL for HDL-cholesterol).

B. Prospective: Minimal detectable relative risk of incident CVD =1.75
Weight gain since age 25

B. Prospective: Change in carotid in carotid wall thickness, incident coronary heart disease, incident cardiovascular disease, death

Exposure status: Diabetes susceptibility genotypes to be determined from DNA extracted from existing frozen buffy coat

Covariates: Age, race, gender, education, physical activity, dietary energy intake, medication use (lipid-lowering, anti hypertensive), smoking; (and in prospective study: lipids, blood pressure, BMI, WHR).

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