ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #622

l. Full title: G-protein ß3 subunit C825T polymorphism predicts the occurrence of atherosclerosis, PAD and incident CHD
Abbreviated Title: GNB3 C825T, Atherosclerosis, PAD and CHD

2. Writing group:
First: Alanna Morrison
Lead: Eric Boerwinkle
Address: Human Genetics Center
University of Texas - Houston Health Science Center
PO Box 20334
Houston, TX 77225
Phone: (713) 500-9816; Fax: (713) 500-0900
Email: eboerwin@gsbs.gs.uth.tmc.edu

Other authors: Christie Ballantyne, Moyses Szklo

3. Timeline:
Measurement of the GNB3 C825T polymorphism will be complete by November, 1998. Analyses will be complete by January, 1999 with a first draft of the paper in June, 1999.

4. Rationale:
Studies on immortalized lymphoblasts from patients with essential hypertension indicate that enhanced sodium-proton exchanger (NHE) activity is genetically fixed and associated with increased cell proliferation (Rosskopf et al.; JCl 92:2553-9, 1993; Cardio Res 29:254-9, 1995). Additional studies suggest that these phenomena are a result of enhanced activation of pertussis toxin (PTX)-sensitive G proteins (Siffert et al.; JCl 96:759-66, 1995; Hypertens 26:649-55, 1995). Siffert et al. (Nat Gen 18:45-8, 1998) reported a novel polymorphism (C825T) in exon 10 of the gene encoding the ß3 subunit of heterotrimeric G proteins (GNB3). An association was observed between the T allele and generation of a splice variant, GNB3-s, in which the nucleotides 498-620 of exon 9 are deleted. The product of this in-frame deletion, GB3-s, was found to be a functional protein, predominantly expressed in cells from individuals carrying the T allele. While analyses performed by Siffert et al. suggest a significant association of the T allele with essential hyeprtension (Nat Gen 18:45-8,1998), to our knowledge no studies have evaluated an association of the C825T polymorphism with risk of atherosclerosis or incident CHD. We propose to evaluate the association of the C825T polymorphism with atherosclerosis and incident CHD in the 3-group, CRS, African-American, PAD and CHD supplement case-control groups of the ARIC study.

5. Main Issues/Hypotheses to be Addressed:
a. Ability of the C825T polymorphism to predict carotid artery disease case status (as measured by wall thickness), both individually and after considering the
predictive ability of traditional risk factors. Analyses for this aim will include the African-American supplement.
b. Ability of the C825T polymorphism to predict PAD case status (as measured by a reduced ankle-arm index), both individually and after considering the
predictive ability of traditional risk factors.
c. Ability of the C825T polymorphism to predict incident CHD case status, both individually and after

considering the predictive ability of traditional risk factors.

6. Data:
The 3-group, CRS, African American, PAD and CHD supplement case-control groups of the ARIC study will be used for these analyses. The primary dependent variable is incident CHD case status. Results from the analysis of carotid artery wall thickness and PAD will be informally compared to incident CHD case status results. Independent variables include, but are not limited to, the C825T polymorphism, age, gender, BMI, smoking status, plasma lipid levels, hypertension status and measures of sodium-proton exchange.