ARIC Manuscript Proposal #772

PC Reviewed: 02/ 15 /01	**Status: A**	**Priority: 1**
SC Reviewed: 03/01/01	**Status:A**	**Priority: 1**

1.a. Full title: GNB3 gene-obesity interaction in predicting hypertension in African Americans from the Atherosclerosis Risk in Communities Study

1.b. Abbreviated title: GNB3, obesity and hypertension

2. Writing group:

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3. Time line:

Measurement of the GNB3 C825T polymorphism has been completed in the African American portion of the ARIC cohort. A draft manuscript will be distributed for internal circulation by February 2001.

4. Rationale:

The C825T polymorphism located in exon 10 of the G protein 3 subunit gene (GNB3) was first discovered in human hypertensive cell lines that displayed an increase in activity of the sodium-proton exchanger (Siffert et al., 1998). The 825T allele has been associated with generation of a splice variant, GNB3-s, in which the nucleotides 498-620 of exon 9 are deleted, and the product of this in-frame deletion, Gβ3-s, was found to encode a functional protein, predominantly expressed in cells from individuals carrying the T allele. Subsequent to this finding, researchers have shown an association between the 825T allele and hypertension in two German populations and an Australian white population (Siffert, 1998; Schunkert, 1998; Benjafield, 1998). In addition to its role in sodium processing and total body fluid homeostasis, intracellular signaling via G-proteins is critically important in adipocyte formation (Siffert et al., 1999). Obesity has been established as a major risk factor for hypertension, and studies have demonstrated that the 825T allele is associated with obesity in both hypertensive (Siffert et al., 1999; Siffert et al, 1999) and normotensive individuals (Hegele et al., 1999). An additional investigation of a hypertensive and normotensive cohort showed elevated measures of sodium-proton exchanger activity in obese persons, but not lean individuals (Delva et al., 1993), suggesting that the effect of the GNB3 C825T polymorphism may be modified by obesity

status. The objectives of this investigation are to determine the association of the C825T allele polymorphism in relation to hypertension status, obesity, and measures of body size/fat in the ARIC African American cohort from Jackson, MS and Forsyth County (n=4,212). Based on these analyses, we will investigate the hypothesis that hypertension may be mediated by the association between the C825T polymorphism and obesity status.

5. Main Issues/Hypotheses to be addressed:

a. Influence of the GNB3 C825T polymorphism on hypertension status. Analyses will be done univariately and after controlling for a vector of traditional risk factors (age, gender, BMI, smoking, diabetes, and total cholesterol).

b. Influence of the GNB3 C825T polymorphism on obesity status and body size measures (BMI, waist circumference, hip circumference, waist/hip ratio, percent body fat). Analyses will be done univariately and after controlling for a vector of traditional risk factors (age, gender, smoking, hypertension, diabetes, and total cholesterol)

c. Tests of interaction between the GNB3 C825T polymorphism and both obesity and hypertension in multivariate models that include traditional risk factors (age, gender, smoking, hypertension, diabetes, HDL cholesterol, and total cholesterol).

d. For all analyses, gender-specific effects will be explored. Comparison of the results obtained in b and c above may indicate whether the effects of this C825T polymorphism on hypertension (if any) are mediated through its effects on obesity or body mass/fat topography or through alternative pathways.

6. Data (variables, time window, source, inclusions/exclusions):

The C825T variant has been measured in the African American portion of the ARIC cohort, as part of our ARIC ancillary study looking at gene-environment interaction. Relationships between C825T genotype and hypertension, obesity, and physical activity will be tested using logistic regression and relationships between C825T and body size measures will be tested using multiple regression. A draft manuscript will be distributed for internal circulation by February 2001. All non-African Americans and African Americans from Minnesota and Washington County will be excluded from the study.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X_ Yes ___ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __X_ Yes ____ No

(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _X_ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X_ Yes ____ No