ARIC Manuscript Proposal # 1041

PC Reviewed: _10/07/04	**Status: __A__**	**Priority: ___2_**
SC Reviewed: __10/07/04	**Status: __A__**	**Priority: __2__**

1.a. Full Title: Obesity resistance in an aging population and the effects of two obesity candidate genes in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
Obesity resistant genes

2. Writing Group (list individual with lead responsibility first):

First: Mary L. Hart Sailors
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Other Writing Group Members: Deanna Hoelscher, Linda Kao, Aaron Folsom, Christie Ballantyne, Jim Pankow

3. Timeline:

Genotyping of the *MC4R* VAL103ILE polymorphism and the *LEP* 19A>G polymorphism are completed in African–Amercians and Caucasians. Analysis will be completed in September 2004 with the first draft of the paper completed in November 2004.

4. Rationale:

Obesity is a highly prevalent disease and has become a major health crisis in the United States and throughout the world. The issue of obesity is important to older Americans because research has indicated that maintaining a lean body mass into maturity is essential for healthy aging. Although a majority of the adult population is now considered overweight, of particular interest are those mature individuals who have maintained a normal weight into late adulthood without excessive caloric restriction or physical activity. Recent research has shown that genetic variation plays a crucial role in the etiology of obesity. Therefore, there may be a genetic mechanism that enables these mature lean, individuals to resist obesity despite an abundance of palatable food and lack of exercise. The human melanocortin-4 receptor gene (*MC4R*) regulates satiety and possibly energy expenditure. Inactivation of the *MC4R* gene in mice results in mature-onset obesity, hyperinsulinaemia, hypergylcaemia, and hyperphagia. The Val103Ile polymorphism of the *MC4R* gene may be linked to body size variation. The human leptin gene (*LEP*) also controls fat stores by influencing feeding and metabolic rate. A common polymorphism, 19A>G, of the *LEP* gene is associated with decreased leptin levels and obesity. The purpose of this study is to investigate the association of the multilocus genotype of these polymorphisms with obesity-related traits, including

BMI, waist-hip ratio, and leptin levels, in African-American and Caucasian participants, ages 45 to 65, from the Atherosclerosis Risk in Communities Study.

5. Main Hypothesis/Study Questions:

Obesity may be attributed to numerous genes working together to produce this phenotype. For this study we propose to investigate a multilocus genotype derived from the *MC4R* VAL103ILE polymorphism and the *LEP* 19A>G polymorphism and its association with obesity-related-measures. The presence of the rare allele in both polymorphism may be protective of obesity.

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

African Americans and Caucasians will be used for these analysis. The dependent variables will be obesity status, BMI, waist-hip ratio, leptin, and intake of total calories per day per kilogram of weight. Independent variables include, but are not limited to, the *MC4R* VAL103ILE polymorphism, the *LEP* 19A>G polymorphism, age at baseline, prevalence of CHD, smoking status, hypertension status, diabetes status, activity level, fasting glucose level, and history of TIA or stoke event. Exclusions will include those who did not allow use of there DNA for research purposes, those who were missing genotype data and blacks from Minneapolis, MN and Washington County, MD. Linear regression will be used to test the effects of the single genes as well as the multilocus genotypes on quantitative traits related to obesity. Logistic regression will be used to test these effects on obesity status.

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**

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

_X_ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to

contact lead authors of these proposals for comments on the new proposal or collaboration)?

1. ARIC MANUSCRIPT PROPOSAL FORM Manuscript #620 1. Full Title: Plasma leptin levels as a predictor of cardiovascular-related morbidity Abbreviated Title: Leptin and cardiovascular disease 2. Writing Group: First: Molly Bray Lead: Eric Boerwinkle Address: Human Genetics Center University of Texas -Houston Health Science Center P.O. Box 20334 Houston, TX 77225 Phone: (713) 500-9816; Fax: (713) 500-0900 Email: eboerwin@gsbs.gs.uth.tmc.edu 3. Timeline: Measurement of plasma leptin levesl in the simult

2. 1 ARIC Manuscript Proposal #992 PC Reviewed: 01/20/04 Status: _ Priority: _ SC Reviewed: _ Status: _ Priority: _ 1.a. Full Title: Obesity candidate genes and incidence of coronary heart disease: The ARIC Study. b. Abbreviated Title (Length 26 characters) CHD and Obesity Genes. 2. Writing Group (list individual with lead responsibility first) Lead: Pranjal Agrawal Address: University of Minnesota 1300 S. Second Street, Suite 300 Minneapolis, MN 55454-1015 Phone: (612) 205-1946 Fax: (413) 622-4640

11. **Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**