

## ARIC Manuscript Proposal # 1042

PC Reviewed: 10/07/04  
SC Reviewed: 10/07/04

Status: A  
Status: A

Priority: 2  
Priority: 2

**1.a. Full Title:** Gene-gene interaction in predicting obesity in the Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters):**

Gene-gene interaction in obesity

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

**First:** Molly S. Bray Ph.D

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**Other Writing Group Members:** Mary Hart, Deanna Hoelscher, Linda Kao, Aaron Folsom, Christie Ballantyne, Jim Pankow

**3. Timeline:**

Genotyping of two polymorphisms in *PPARA* (rs1800206 and rs253778), two polymorphisms in *TNFA* (rs1800629 and rs1800630), two polymorphisms in *RSTN* (rs3219177 and rs3745368), two polymorphisms in *LEPR* (Arg223Gln and Arg309Cys), one polymorphism in *NPY*, and one polymorphism in *POMC* (C7566T) has been completed in African-Americans and Caucasians. Analysis of the single gene and gene-gene effects of these polymorphisms will be completed by December 2004 with the first draft of the paper completed in March 2005.

**4. Rationale:**

Obesity has been attributed to genetic, social, psychological, physiological, nutritional, and socioeconomic influences, implying that not just one variable but combinations, or perhaps multiple, interacting variables affect body size and mass. Studies of related individuals and studies of single gene and multigenic human obesity syndromes support the role of genes in the determination/regulation of body size and mass. Nevertheless, while studies of related individuals provide evidence that genes are important in the determination of overweight and obesity, identification of a causative gene or gene defect for human obesity has proven challenging. Recent years have been an exciting time in the field of obesity research with the discovery of several genes in which mutations that eliminate or greatly diminish the function of their protein products give rise to syndromic forms of obesity in humans very similar to that of animal models. Of the many candidate genes proposed for obesity, these include leptin receptor (*LEPR*), pro-opiomelanocortin (*POMC*), tumor necrosis factor alpha (*TNFA*), resistin (*RSTN*), neuropeptide Y (*NPY*), and peroxisome proliferative activated receptor alpha (*PPARA*), which all are involved in satiety signaling and/or lipid metabolism. The purpose of this study is to investigate the single gene and gene-gene interactions between these polymorphisms and their

association with obesity-related traits, including body mass, BMI, waist-hip ratio, and waist circumference, in African-American and non-Hispanic white participants from the Atherosclerosis Risk in Communities Study.

**5. Main Hypothesis/Study Questions:**

Obesity may be attributed to numerous genes working together to produce obesity-related phenotypes. For this study we propose to investigate the single gene effects of each of the genes listed above, along with the multilocus effects of the genetic polymorphisms, on body size measures.

**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, waist circumference, and body mass. Independent variables include, but are not limited to, polymorphisms in LEPR, POMC, TNFA, RSTN, NPY, and PPARA, 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, non-AA and non-white participants, and AAs from Minneapolis, MN and Washington County, MD. Linear regression will primarily be used to test single gene effects, while other strategies (combinatorial optimization and/or Bayesian belief networks) will be used to test the multi-locus effects. Haplotype analysis will be conducted for genes containing multiple polymorphisms.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**  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?**  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?**  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"?**  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.csc.unc.edu/ARIC/search.php>

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 levels 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: Pranjali 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.**