1.a. **Full title:** Resistin gene polymorphisms and association with obesity and body size measures in African Americans, Mexican Americans, and non-hispanic Whites from two community-based studies

1.b. **Abbreviated title:** Resistin variation and obesity

2. **Writing group:**
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3. **Time line:**
   Resistin will be sequenced in 24 samples each from African American, Caucasian, and Mexican American populations. The individuals to be resequenced will be selected based on the availability of transformed cell lines. Subsequently, all identified variation within the coding and promoter regions of the gene will be genotyped in the ARIC African Americans from Jackson, MS and Forsyth County, the incident CHD and (new) cohort random sample (stratified by age and sex) from the ARIC study, and a random sample of Mexican Americans from Starr County, Texas in collaboration with Dr. Craig Hanis at UT. As the gene has exciting potential and has not yet been analyzed in the context of the effects of genetic variation at the population level, we plan to sequence the gene to look for variation and genotype the identified variants in Caucasians, African Americans, and Mexican Americans. Dr. Hanis’ lab will conduct the sequencing work (it is already underway, in fact), and Dr. Bray’s lab will develop a multiplex mass spec genotyping protocol that will allow genotyping to be completed quickly.

4. **Rationale:**
   Obesity, the most prevalent chronic disease in the United States today, is associated with a number of co-morbidities, primary among them insulin resistance and diabetes. Though much has been learned about the mechanisms that may relate these conditions, no single factor has yet been identified to explain the connection between increased adiposity and aberrant insulin response. Recently, a newly discovered gene, resistin, has been identified that has been hypothesized to be one
link between obesity and insulin resistance (Steppan et al. (2001) Nature, 409:307-312). The resistin gene is expressed almost exclusively in adipose tissue and is downregulated in response to treatment with a class of anti-diabetic drugs called thiazolidinediones (TZDs). Resistin protein is secreted from white adipose tissue and is increased in obesity. Administration of resistin to mice resulted in impaired glucose tolerance and decreased sensitivity to the effects of insulin, making it a prime candidate for obesity-induced insulin resistance. The molecular target of resistin has not yet been identified, and studies identifying genetic variation and gene structure are yet to be completed. The discovery of resistin provides a unique opportunity to characterize the presence and effect of variation within this gene as it relates to obesity, body mass and fat, and incident disease in multiple populations.

5. Main Issues/Hypotheses to be addressed:
   a. Influence of variation in the resistin gene on obesity and measures of body mass/fat topography (weight, BMI, waist circumference, hip circumference, waist/hip ratio, weight at age 25) at baseline. Analyses will be done univariately and after controlling for a vector of traditional risk factors (age, gender, smoking, diabetes, HDL and LDL cholesterol).
   b. Influence of variation in the resistin gene on obesity and measures of body mass/fat topography (weight, BMI, waist circumference, hip circumference, waist/hip ratio, weight at age 25) over time. Analyses will be done univariately and after controlling for a vector of traditional risk factors (age, gender, smoking, diabetes, HDL and LDL cholesterol).
   c. Tests of interaction between variation in the resistin gene and environmental factors such as activity level and caloric intake as they relate to obesity and measures of body mass/fat in multivariate models that include traditional risk factors (age, gender, smoking, hypertension, diabetes, HDL cholesterol, and LDL cholesterol).

6. Data:
   In the ARIC study, variants within the resistin gene will be analyzed in all African Americans residing in Jackson, MS (n = 3506) and Forsyth County, NC (n = 479) from the ARIC cohort, as well as the incident CHD and (new) cohort random sample (stratified by age and sex). ARIC baseline anthropometric data will be used in these analyses. Logistic regression will be used to predict prevalent obesity (BMI ≥30 kg/m²). Multivariate ANCOVA analyses will be conducted for weight, BMI, waist circumference, hip circumference, and waist/hip ratio, as quantitative outcome measures. Covariates will include age, gender, and menopausal status/hormone use (for women only). This work is being conducted using funding from the CDC grant “Gene-Environment Interaction in Cardiovascular Disease”.

   When an assay becomes available, resistin protein will be measured in the above groups as well. Future analyses would consider the relationship between resistin variation and resistin protein levels as well as possible interactions between resistin and leptin, both at the level of genetic sequence variation and protein quantity variation.

7.a. Will the data be used for non-CVD analysis in this manuscript? __ Yes  _X_ 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
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 ICTDER01 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://bios.unc.edu/units/cssc X Yes  ___ No