1a. **Full title:** Resistin gene polymorphisms and association with insulin resistance and diabetes in the Atherosclerosis Risk in Communities Study

1b. **Abbreviated title:** Resistin variation and human disease

2. **Writing group:**
   
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3. **Time line:**
   All identified variation within the coding and promoter regions of the resistin gene will be genotyped in the ARIC African Americans from Jackson, MS and Forsyth County, and the incident CHD and (new) cohort random sample (stratified by age and sex).

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 measures of fasting insulin and glucose at baseline. Analyses will be done univariately and after controlling for a vector of traditional risk factors (age, gender, smoking, hypertension, diabetes, HDL and LDL cholesterol).
   b. Influence of variation in the resistin gene on measures of fasting insulin and glucose over time. Analyses will be done univariately and after controlling for a vector of traditional risk factors (age, gender, smoking, hypertension, diabetes, HDL and LDL cholesterol).
   c. Relationship between variation in the resistin gene and both prevalent and incident diabetes. These analyses will be done univariately and after controlling for a vector of traditional disease risk factors.
   d. Tests of interaction between variation in the resistin gene and environmental factors such as activity level and caloric intake as they relate to diabetes and measures of insulin resistance in multivariate models that include traditional risk factors (age, gender, smoking, hypertension, diabetes, HDL cholesterol, and LDL cholesterol). For all analyses, race- and gender-specific effects will be explored.

6. Data:
  Variants within the resistin gene will be genotyped 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) from the ARIC study. ARIC baseline insulin and glucose data will be used in these analyses. The effect of genotype as a predictor of incident diabetes will be evaluated using Cox proportional hazards modeling. Logistic regression will be used to predict prevalent diabetes (defined by variable DIABTS02). Multivariate ANCOVA analyses will be conducted for fasting insulin and glucose, as quantitative outcome measures. Covariates will include age, gender, and menopausal status/hormone use (for women only).

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
   (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 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/csc
   ___ X  Yes  ___ No