The association between variation within the human perilipin gene and both obesity-related quantitative traits and plasma lipid profiles in the Atherosclerosis Risk in Communities (ARIC) Study.

Perilipin, obesity-related quantitative traits, and lipid panel.

First: Cristina S. Barroso
Lead: Molly Bray, PhD
Address: Human Genetics Center
U.T. Houston Health Science Center
P.O. Box 20186
Houston, TX  77225
Phone: 713-500-9891; Fax: 713-500-0900
E-mail: Molly.S.Bray@uth.tmc.edu

Other authors: Darin Tessier, Linda Kao, Aaron Folsom, Jim Pankow

Measurement of the perilipin variants will be complete by December 2003 and statistical analyses are expected to be complete by March/April 2004. A draft manuscript is projected to be distributed for internal circulation by June/July 2004.

Adipocytes have the ability to expand and contract in response to stored lipid energy changes. Agents that influence the formation of lipid droplets or the storage of triglycerides may modify the viability of adipose tissue. Abnormalities in lipid droplet formation may lead to type 2 diabetes, obesity, and atherosclerosis (Londos et al., 1999; Murphy & Vance, 2000). Perilipin (PLIN) is found on the surface triacylglycerol-rich lipid droplets in adipocytes (Londos et al., 1999) and cholesterol ester-rich droplets in steroidogenic cells (Servetnick et al., 1995). Expression of the PLIN gene has also been found in ruptured plaques, suggesting that PLIN in atherosclerotic plaques may result in increased lipid retention and plaque destabilization (Faber et al., 2001). To date no studies have investigated the association between PLIN and obesity phenotypes and/or lipid panels. The purpose
of this investigation will be to evaluate the association between interindividual variation within the PLIN gene and both obesity-related quantitative traits (i.e., body mass index [BMI], waist circumference, and waist-to-hip ratio), plasma lipid profiles (i.e., total cholesterol, HDL-C, LDL-C, and triglycerides), and incident CHD.

5. **Main Issues/Hypotheses to be addressed:**
   a. Influence of the *PLIN* variants on obesity and obesity-related measures.
   b. Influence of the *PLIN* variants on plasma lipid profiles.
   c. Influence of the *PLIN* variants on incident CHD. Analyses will be done univariately and after controlling for a vector of traditional cardiovascular disease risk factors.
   d. Influence of dietary intake of total calories, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, trans fatty acids, the Keys equation, and animal fat on the relationship between the *PLIN* variants and obesity-related measures (i.e., BMI, waist circumference, waist-to-hip ratio).
   e. Influence of dietary intake of total calories, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, trans fatty acids, the Keys equation, and animal fat on the relationship between the *PLIN* variants and lipid panel (i.e., total cholesterol, HDL-C, LDL-C, triglycerides).
   f. Influence of dietary intake of total calories, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, trans fatty acids, the Keys equation, and animal fat consumption on the relationship between the *PLIN* variants and incident coronary heart disease (CHD). Analyses will be done univariately and after controlling for a vector of traditional cardiovascular disease risk factors.
   g. For all analyses, race-specific effects will be explored. To prevent misclassification resulting from measurement error in dietary intake, the lowest and highest tertiles of each dietary intake measure will be used in the analysis.
   h. The PHASE haplotype reconstruction program, version 2.0.1 (Summertown, Oxford, UK) will be used to reconstruct haplotypes from the *PLIN* variants.

6. **Data:**
   The *PLIN* variants will be genotyped in all individuals in the ARIC cohort. Exclusion criteria for participation in this study will be positive diagnosis of type 2 diabetes, use of cholesterol lowering medications, and prevalent CHD or stroke. Incident CHD will be defined as CHD cases occurring subsequent to visit 1 through 2000. ARIC baseline nutrition, physical activity level, body size data, and plasma lipid level data will be used in these analyses. Multivariate linear regression analyses will be conducted for BMI, waist circumference, waist-to-hip ratio, plasma total cholesterol, HDL-C, LDL-C, and log-transformed total triglycerides as outcome measures. Multivariate logistic analyses will be conducted for obese (BMI $\geq 30$ kg/m$^2$), non-obese (BMI $< 30$ kg/m$^2$), centrally obese (waist circumference $\geq 102$ cm and $\geq 88$ cm for men and women, respectively) and non-centrally obese (waist circumference $< 102$ cm and $< 88$ for men and women, respectively) as outcome measures. Cox proportional hazard survival analyses will be conducted for the incident CHD cases. Analyses will be stratified by gender. Significant gene-diet interactions will be
included. Covariates will include age and physical activity for obesity outcomes and age, physical activity, and BMI for lipid panel and incident CHD outcomes.

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

7b. 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 ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

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

8b. 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