ARIC Manuscript Proposal #992

1. 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):

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   Interested investigators at other ARIC centers/labs

3. Timeline:
   Begin analyses 2/2004
   First Draft 7/2004

4. Rationale:
   The association of cardiovascular disease and obesity has been well documented.\(^2\),\(^9\),\(^11\),\(^12\) Recent studies have shown that African Americans have, overall, higher rates of obesity than Caucasians.\(^1\) The markers POMC, NPY, LEP, LEPR, and MC4R are all related to satiety signaling pathways, which are linked to obesity.\(^2\),\(^4\),\(^10\) Variants of the NPY have been connected to cholesterol metabolism, a major risk factor for CHD.\(^7\) To our knowledge, there are no other publications that have evaluated variants in these obesity candidate genes and the risk of coronary events.
5. Main Hypothesis/Study Questions:

Primary Hypothesis:
Participants who are positive for putative at-risk genotypes in obesity candidate genes POMC, NPY, LEP, LEPR, and MC4R will have higher incidence of CHD. This association may be explained fully or partially by some obesity indicator (eg. BMI).

Secondary Hypothesis:
Associations between variants in obesity candidate genes and incident CHD will differ by gender, race and age.

Note: Genotyping data for the proposed analysis are being generated by Molly Bray’s ancillary study (Gene-Environment Interaction in CHD)

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

The data will be tested in a survival analysis of African American and Caucasian participants from the ARIC study. Data will be stratified by race to reduce the probability of confounding by population stratification. The survival curves for incident CHD of those with and without the at-risk genotypes for obesity POMC, NPY, LEP, LEPR, and MC4R will be compared. Where sample size will allow, separate relative risk estimates will be generated for heterozygotes and homozygotes for the putative at-risk allele. However, data from parallel analyses of these genes and obesity phenotypes in other ARIC manuscripts may provide supplementary data that will justify pooling genotypes and specification of dominant or recessive models.

Incident CHD will be defined as MI, fatal CHD, cardiac procedure, or ECG detected MI. Participants who had a history of CHD at the first visit will be excluded from the analysis. Previous CHD will be defined as MI judged from ECG data at visit 1 or having responded “yes” to any of the following at visit 1: history of MI, heart or arterial surgery, coronary bypass, balloon angioplasty, or angioplasty of coronary arteries.

The data will be minimally adjusted for gender, age, and center and further adjusted for major CVD risk factors (visit 1- LDL cholesterol, HDL cholesterol, triglycerides, hypertension, smoking and diabetes). If positive associations are found, obesity-related variables (BMI, WHR) will be added to the model to evaluate whether gene-CHD associations are mediated by obesity.

Formal tests for interaction with gender and age will be performed. The large sample size (full cohort) will also allow formal testing of gene-gene interactions for genotypes that are relatively common.

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?  
  ___ 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://bios.unc.edu/units/cscc/ARIC/study/studymem.html

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)?

There are no related manuscript proposals in ARIC.

References:


Diabetologia. 1997 (40) 671-675.
