ARIC Manuscript Proposal # 1368r

PC Reviewed: 07/08/08 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1a. Full Title: Analysis of single nucleotide polymorphisms from genome-wide association data for adiposity traits

b. Abbreviated Title: GWAS and adiposity

2. Writing Group:

Kari North
Keri Monda
Ellen Demerath
Linda Kao
Eric Boerwinkle
Braxton Mitchell (with the OOA Study)
Caroline Fox (with the FHS)
Tamara Harris (with the AGES Study)
Nicole Glazer (with the CHS)
Cornelia van Duijn (with the Rotterdam Study)
Ingrid Borecki (with the Family Heart Study)

Other investigators welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. KN

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3. Timeline:

Data arrival: End of June, 2008
Statistical analyses: July – August, 2008
Manuscript preparation: August – September, 2008
Manuscript revision: September – October 2008
Manuscript submission: October – November 2008

4. Rationale:

Several lines of evidence support the role of genetics in the regulation of body mass, including longitudinal family and twin studies which show that BMI, weight, and weight change are all heritable traits (Adams, Hunt et al. 1993; Austin, Friedlander et al. 1997; Lee, Reed et al. 1997; Bouchard, Perusse et al. 1998; Comuzzie and Allison 1998; Hunt, Katzmarzyk et al. 2002; Loos and Bouchard 2003). However, most forms of obesity do not follow simple Mendelian modes of inheritance and thus investigating potential genetic variants that contribute to common forms of obesity will require large population-based studies. Linkage analyses of family-based data have identified areas of the human genome that are associated with

Rankinen, T., A. Zuberi, et al. (2006). "The human obesity gene map: the 2005 update." Obesity (Silver Spring) 14(4): 529-644.
Scuteri, A., S. Sanna, et al. (2007). "Genome-Wide Association Scan Shows Genetic Variants in the FTO Gene Are Associated with Obesity-Related Traits." PLoS Genet 3(7): e115.
van den Oord, E. J. and P. F. Sullivan (2003). "False discoveries and models for gene discovery." Trends Genet 19(10): 537-42.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

____ Yes
__x___ No

11.b. If yes, is the proposal
_X_ A. primarily the result of an ancillary study (AS #2006.03 & #2007.02)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____)

Deleted: list number
Deleted: 1995.07

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. 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.

References

Adams, T. D., S. C. Hunt, et al. (1993). "Familial aggregation of morbid obesity." Obes Res 1(4): 261-70.

Austin, M. A., Y. Friedlander, et al. (1997). "Genetic influences on changes in body mass index: a longitudinal analysis of women twins." Obes Res 5(4): 326-31.

Benjamini, Y., D. Drai, et al. (2001). "Controlling the false discovery rate in behavior genetics research." Behav Brain Res 125(1-2): 279-84.

Bouchard, C., L. Perusse, et al. (1998). The Genetics of Human Obesity. Handbook of Obesity. G. Bray, C. Bouchard and W. James. New York, Marcel Dekker, Inc.: 157-190.

Comuzzie, A. G. and D. B. Allison (1998). "The search for human obesity genes." Science 280(5368): 1374-7.

Dina, C., D. Meyre, et al. (2007). "Variation in FTO contributes to childhood obesity and severe adult obesity." Nat Genet 39(6): 724-6.

Fox, C. S., N. L. Heard-Costa, et al. (2005). "Genomewide linkage analysis of weight change in the Framingham Heart Study." J Clin Endocrinol Metab 90(6): 3197-201.

Frayling, T. M., N. J. Timpson, et al. (2007). "A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity." Science 316(5826): 889-94.

Golla, A., K. Strauch, et al. (2003). "Quantitative trait linkage analysis of longitudinal change in body weight." BMC Genet 4 Suppl 1: S7.

Grant, S. F., M. Li, et al. (2008). "Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP." PLoS ONE 3(3): e1746.

Herbert, A., N. P. Gerry, et al. (2006). "A common genetic variant is associated with adult and childhood obesity." Science 312(5771): 279-83.

Hunt, M. S., P. T. Katzmarzyk, et al. (2002). "Familial resemblance of 7-year changes in body mass and adiposity." Obes Res 10(6): 507-17.

Hunt, S. C., S. Stone, et al. (2008). "Association of the FTO Gene With BMI." Obesity (Silver Spring) 16(4): 902-4.

Lee, J. H., D. R. Reed, et al. (1997). "Familial risk ratios for extreme obesity: implications for mapping human obesity genes." Int J Obes Relat Metab Disord 21(10): 935-40.

Lettre, G., C. Lange, et al. (2007). "Genetic model testing and statistical power in population-based association studies of quantitative traits." Genet Epidemiol 31(4): 358-62.

Loos, R. J. and C. Bouchard (2003). "Obesity--is it a genetic disorder?" J Intern Med 254(5): 401-25.

Lopez-Bermejo, A., C. J. Petry, et al. (2008). "The Association between the FTO Gene and Fat Mass in Humans Develops by the Postnatal Age of Two Weeks." J Clin Endocrinol Metab 93(4): 1501-5.

Nichols, T. E. and A. P. Holmes (2002). "Nonparametric permutation tests for functional neuroimaging: a primer with examples." Hum Brain Mapp 15(1): 1-25.

Price, A. L., N. J. Patterson, et al. (2006). "Principal components analysis corrects for stratification in genome-wide association studies." Nat Genet 38(8): 904-909.

ARIC investigators in the JHU group will run EIGENSOFT and provide principal components for inclusion in regression models.

Multiple testing: The large number of statistical tests these analyses entail will yield false positive results unless appropriate corrections are made for multiple testing. We will control for this using the Bonferroni correction on an overall α=0.05, a standard approach in GWA analyses, resulting in a significant p-value of approximately 0.05×10^{-6}. Secondarily, we will use the false discovery rate (FDR) (Benjamini, Drai et al. 2001; van den Oord and Sullivan 2003) and permutation-based procedures (Nichols and Holmes 2002).

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 ICTDER02 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://www.cscc.unc.edu/ARIC/search.php

__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)?

#795: 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

#814: Association of beta2-adrenergic receptor polymorphisms with asthma and obesity in the Atherosclerosis Risk in Communities Study

#1041: Obesity resistance in an aging population and the effects of two obesity candidate genes in the Atherosclerosis Risk in Communities Study.

#1269r: *FTO*, Obesity and Diabetes.

The above ARIC manuscript proposals all describe studies in which candidate obesity genes will be investigated with adiposity traits. None of these proposals include the use of GWAS data.