Monda, ARIC Ms. proposal GIANT

ARIC Manuscript Proposal # 1500

PC Reviewed: 5/12/09   Status: A   Priority: 2
SC Reviewed: _________   Status: _____   Priority: ____

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

b. Abbreviated Title: GWAS and adiposity GIANT

2. Writing Group:
   ARIC authors:
   Kari North, Keri Monda, Eric Boerwinkle

   CHARGE authors:
   Braxton Mitchell, Caroline Fox, Adrienne Cupples, Tamara Harris, Nicole Glazer, Cornelia van Duijn, Ingrid Borecki

   GIANT authors:
   Joel Hirschhorn, Elizabeth Speliotes, Ruth Loos, Cecelia Lindgren, Mike Weedon, Erik Ingelsson, and other members of the GIANT Consortium

   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:
Statistical analyses: February – April, 2009
Manuscript preparation: April – May, 2009
Manuscript revision: June 2009
Manuscript submission: July 2009

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 body mass index (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 require large population-based studies. Linkage analyses of family-based data have identified areas of the human genome that are associated with adiposity traits (Golla, Strauch et al. 2003; Fox, Heard-Costa et al. 2005). In fact, according to the most recently updated ‘Obesity Gene Map’ (Rankinen, Zuberi et al. 2006) 253 quantitative trait locus (QTL) regions for obesity-related phenotypes have been identified in 61 genome-wide scans, and a total of 52 genomic regions that harbor QTLs replicated in two or more studies. Despite this, no specific genetic variants clearly responsible for any of the linkage signals have been identified. It is only with recent major technological advances that we have rapidly expanded options for the evaluation of genetic variation at the level of the single nucleotide polymorphism (SNP).

Genome-wide Association (GWA) studies interrogate whether variation across the human genome in the form of SNPs is associated with given phenotypes. GWAS are now widely recognized as powerful data-driven tools for identifying genetic variants related to common complex diseases such as obesity. Researchers have had notable success using GWAS in discovering genetic variants for anthropometric traits. For instance, a widely-replicated result between FTO and obesity has been reported (Dina, Meyre et al. 2007; Frayling, Timpson et al. 2007; Scuteri, Sanna et al. 2007). More recently investigators from multiple consortia have published findings on numerous loci associated with BMI and obesity (Loos, Lindgren et al. 2008; Thorleifsson, Walters et al. 2009; Willer, Speliotes et al. 2009). Replication of findings is a key ingredient in genetic epidemiology studies and investigators are encouraged to set up collaborations or participate in ongoing consortia to facilitate this. Failure to replicate could be due to many reasons including sample differences, lack of power to find an effect, incomplete phenotype harmonization, among others.

5. Main Hypotheses/Study Questions:
To conduct genome-wide association analyses of adiposity traits (BMI, weight, waist circumference, height, waist-hip ratio) using the ARIC data with replication in the multiple prospective cohort studies comprising the GIANT Consortium.
6. Design and Analysis:

Subjects and Sample size:
Individuals of European ancestry with available anthropometric measures. The usual DNA consent restriction and missing data exclusion criteria will be used. ARIC participants of African American descent will be excluded for these analyses.

Definitions and treatment of variables
Exposure: Genotyped SNPs + imputed HapMap CEU SNPs (approx 2.5 million)

Outcome (phenotypes): Height, BMI, weight, waist circumference (WC), waist-hip ratio (WHR). Height will be transformed into a gender-specific z-score. BMI, weight, WC, and WHR will be transformed using an inverse normal transformation.

Covariates: Age, field center, principal components. Sex will be used as a stratification variable.

Analysis strategy / statistical analysis
Sex-stratified additive models will be used to estimate the association between SNP and adiposity traits accounting for genotype imputation uncertainty, and genomic control. Each cohort is responsible for conducting genome-wide analyses on their data; thus ARIC analyses will be conducted in our group at UNC-Chapel Hill. Beta coefficients and p-values as well as other necessary data (strand, etc) will be shared with collaborators in order to conduct meta analyses.

Meta-analytic strategy: Meta-analysis based on both effect estimates and p-values will be run. The meta analyses will be conducted by multiple GIANT investigators yet TBD.

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 $\alpha=0.05$, a standard approach in GWA analyses, resulting in a significant p-value of approximately $0.05 \times 10^{-8}$.

Listing of participating cohorts in the GIANT Consortium
ADVANCE
ADVANCE_CAD
AGES
Amish
ARIC
B58C part 1
B58C part 2
BRIGHT (WTCCC-HT)
CAHRES
CHD_WTCCC
CHS
CoLaus
CROATIA
DECODE
DECODE
DGI
EGP
EPIC
ERF
Fenland
FHS
FRAM
FTC
FUSION
GASP1
GASP2
GENMETS
GerMiFSI
GerMiFSII
KORA
KORAF4
Migen_Finrisk
Migen_Harps
Migen_Malmo
Migen_MGH
Migen_Regicor
NBS_WTCCC
NFBC
NHS
NSPHS
NTRNESDA
ORKNEY
PICO
PROCARDIS
ROTTERDAM_STUDY
RUNMC
SARDINIA
SEARCH
SHIP
T2D_WTCCC
TWINSUK
TWINSUK 610
TYROL

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://www.cscc.unc.edu/ARIC/search.php
   ___ 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)?
    Ms proposal #1368 (North et al). This is our proposal covering analyses in collaboration with the CHARGE Consotium.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?
    ___ Yes
    ____ No

11.b. If yes, is the proposal
    ___ 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)* __________ __________)

*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


