ARIC Manuscript Proposal #1907

PC Reviewed: 2/14/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1a. Full Title: Genome-wide interaction analysis of SNPs and smoking on obesity traits

b. Abbreviated Title: Obesity gene-by-smoking GWAS interaction

2. Writing Group:
   Anne Justice
   Kari North
   Eric Boerwinkle
   Collaborators with the CHARGE consortium
   Collaborators with the GIANT consortium
   Collaborators with the SHARE consortium

   Other investigators welcome

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

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3. Timeline:
   Statistical analyses: January – February, 2012
   Manuscript preparation: March – June, 2012
4. Rationale:
The relationship between obesity and cardiovascular disease morbidity and mortality is well-documented and widely accepted (Folsom, Kushi et al. 2000; Yusuf, Hawken et al. 2004; McGee 2005; Poirier, Giles et al. 2006; Bogers, Bemelmans et al. 2007; de Koning, Merchant et al. 2007; Whitlock, Lewington et al. 2009; Huxley, Mendis et al. 2010; Yatsuya, Folsom et al. 2010), its effects thought to be largely mediated through numerous cardiovascular risk factors including hypertension (Folsom, Burke et al. 1991; Harris, Stevens et al. 2000; Rainwater, Mitchell et al. 2000; Gregg, Cheng et al. 2005; Guh, Zhang et al. 2009), dyslipidemia (Folsom, Burke et al. 1991; Rainwater, Mitchell et al. 2000; Gregg, Cheng et al. 2005), and diabetes (Folsom, Burke et al. 1991; Rainwater, Mitchell et al. 2000; Gregg, Cheng et al. 2005; Vazquez, Duval et al. 2007; Guh, Zhang et al. 2009). The prevalence of risk factors varies by race-ethnic group, with diabetes prevalence higher and atherogenic dyslipidemia levels lower in African-American (AA) and Hispanic-American (HA) individuals than in European-American (EA) individuals (Rodriguez, Pablos-Mendez et al. 2002; Finkelstein, Khavjou et al. 2004; Kurian and Cardarelli 2007). Behavioral factors also play a key role in cardiovascular disease morbidity and mortality. For example, physical activity has been shown repeatedly to reduce levels of cardiovascular risk factors (Bhargava 2003; Fang, Wylie-Rosett et al. 2003; Hu, Li et al. 2003; Barengo, Hu et al. 2004; Yusuf, Hawken et al. 2004; Warburton, Nicol et al. 2006; Monda, Ballantyne et al. 2009); indeed, physical inactivity is independent of adiposity as a risk factor for cardiovascular morbidity and mortality (Hu, Willett et al. 2004; Hu, Tuomilehto et al. 2004; Weinstein, Sesso et al. 2004; Li, Rana et al. 2006). Additionally, several lines of evidence support an association between cigarette smoke exposure and cardiovascular disease. Cigarette smoke affects the initiation and progression of atherosclerosis through its effects on the vasculature, vasomotor dysfunction, inflammation, and lipid modification (Price, Mowbray et al. 1999; Ambrose and Barua 2004). The association between cigarette smoking and coronary heart disease is well established and consistent across age, sex, race-ethnic, and geographical strata (Doll and Peto 1976; Doll, Gray et al. 1980; Willett, Green et al. 1987; Jonas, Oates et al. 1992; Yusuf, Hawken et al. 2004).

Obesity is one of the leading cardiovascular disease risk factors operating in the population today. While there is a considerable influence of environmental factors on obesity risk, numerous genomic studies have identified well-replicated obesity loci that play a part in an individual’s susceptibility to obesity. What is far less understood is the interaction of genetics and environmental factors such that genetically predisposed individuals may be more susceptible to obesity in an obesogenic environment and, critically, whether adoption of healthy behaviors may attenuate their genetic risk.

Gene-by-smoking interaction analyses on obesity phenotypes from GWAS studies have not been reported to our knowledge. We feel that data from this consortium provides a unique and unprecedented ability to investigate whether the relationships between genetic variants and adiposity measures differ by smoking status. Thus there is a great need for large samples with
documented environmental exposure data, like those available in ARIC, to investigate gene-environment interaction on a genome-wide level.

Note: For analyses of individuals of European-descent, these analyses will be done in collaboration with the CHARGE and GIANT consortia. For analyses of individuals of African-American descent, analyses will be done in collaboration with the SHARE consortium (manuscript proposal currently under review).

5. Main Hypotheses/Study Questions:
To test the interaction effect genome-wide between SNPs and baseline current smoking on baseline adiposity traits (BMI, WC, and WHR).

6. Design and Analysis:
   Subjects and Sample size:
   Individuals with available anthropometric, exposure, and covariate measures. The usual DNA consent restriction and missing data exclusion criteria will be used. Use of GWAS data in African-Americans will follow CARE procedures (see above) and will likely be published as a separate paper.

   Definitions and treatment of variables
   Genotype: Genome-wide genotyping data (~900K SNPs) and available imputed data (~2.8 M SNPs) from the freeze 3 ARIC data. Standard exclusion criteria will be applied.

   Current Smoking: In ARIC, smoking was measured at all visits via questionnaire. We will use current smoking exposure as it has the strongest effect on adiposity phenotypes.

   Phenotype measures: BMI, waist circumference (WC), and waist-hip ratio (WHR) will be defined as quantitative traits. Outcome variables will be transformed as necessary.

   Covariates: Models will be minimally adjusted for age, sex, and field center. Principal components will be controlled for in models to account for population substructure.

   Analysis strategy / statistical analysis
   Additive models will be used to estimate the interaction between SNPs and smoking on adiposity traits. We will run models that (1) contain both the main effects of SNP and smoking and the interaction term for SNP*smoking as well as (2) models stratified by dichotomized smoking. We will seek replication of results within our existing collaboration with the CHARGE and SHARE Consortia. Only summary data including beta coefficients and p-values as well as other necessary data (strand, etc) will be shared with collaborators. No individual-level data will be shared. Meta-analyses based on both effect estimates as well as p-values will be run.

   Multiple testing: We will control for multiple testing using the Bonferroni correction on an overall alpha=0.05.
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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?
   ___ x_ Yes
   ____ 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)* __________ __________)
*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.


