ARIC Manuscript Proposal #1671

PC Reviewed: 7/13/10  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: The association of BMI-, waist circumference-, and height-related SNPs with age at menarche in the Atherosclerosis Risk in Communities (ARIC) Study and Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium.

b. Abbreviated Title (Length 26 characters): Anthropometric SNPs and age at menarche in ARIC and CHARGE

2. Writing Group (ARIC investigators): Lindsay Fernández-Rhodes, Ellen Demerath, Kari North, Nora Franceschini, Jill Dreyfus.

We will pursue collaboration within the CHARGE Reproductive working group for analyses in Caucasians and GIANT Consortium for unpublished SNPs associated with anthropometric measures. CHARGE reproductive working group includes the following studies: ARIC, AGES, FHS, Rotherdam, CHS. If we establish collaborations, we will expand our writing group to reflect this collaboration.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. LR [please confirm with your initials electronically or in writing]

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3. **Timeline:**
Analyses will begin as soon as the manuscript proposal is approved.

4. **Rationale:**
To conduct a genetic association study of body mass index (BMI), waist circumference, and height associated-single nucleotide polymorphisms (SNPs) with age of menarche (AAM) among ARIC and CHARGE population samples.

5. **Main Hypothesis/Study Questions:**

   **Primary Study Questions:**
   1. Do SNPs previously reported to associate with measures of body composition (body mass index and waist circumference) also show associations with AAM?
   2. Do SNPs previously reported to associate with height also show associations with AAM?

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).**

**Introduction:**
Epidemiologic tracking of overweight and obesity only reached global interest after World War II (1). Worldwide there is an estimated increase of 0.5-0.7% in obesity in children per year, and about 1% in adults per year. Even though higher-income countries have historically been at the forefront of this increase, in the last decade Chinese children 6-9 years old have had shocking increases in body mass (20 kg/m² in 1997 to 25 kg/m² in 2006). Kaplowitz reports that among white American children 6-11 years old the prevalence of obesity increased from 5% in 1963-1965 to 12% in 1999-2000 (2).

Age at menarche (AAM) is considered a general marker of hypothalamic-pituitary-driven central pubertal development in girls, but does not capture variation in female breast development, or thelarche, which can occur with or without the activation of the hypothalamic-pituitary-gonadal axis (3). AAM is known to vary between race/ethnic groups in the United States (4, 5) and showed secular trends towards earlier AAM during the late 19th century in European countries (3). The repercussions of early AAM can be psychosocial as well as physiological in nature (3, 6). Early AAM is a known risk factor for adolescent risk taking behaviors, adult obesity, type II diabetes, breast cancer and all-cause mortality. Therefore, understanding the relationship between or the influences of childhood obesity and early AAM, could have a profound impact on global health (3).

Global and local changes in environment (e.g., towards obesogenic) and subsequent gene-environment interactions are hypothesized to be causative of recent shifts in the distribution of AAM (3). In spite of the biologically-plausible links between increased endogenous sex steroid exposure in obese pre-pubertal children and AAM, within the last thirty years reports of secular trends in AAM have been mixed and modest (3). As well the evidence of interaction between
obesity and AAM is mainly associative. For instance, Freedman et al. described a negative association between body mass index (BMI) and AAM, where the incidence of early AAM (menarche before 11 years) among girls in the 75th BMI percentile is 1.8 times that of girls in the 25th percentile of BMI (7), and Ong et al. reported that after adjustment for age and education women with early AAM (before 12 years) are five times as likely to be obese than women with menarche after 14 years of age (OR 5.1, 95% CI 3.4-7.7) (8). In summary, it is currently unclear if the relationship of obesity traits with early age of menarche is causal or if obesity contributes to early menarche.

Given the strong reported associations between obesity and AAM, it is possible that genetic variants involved in growth and body composition may be pleiotropic and play an important role in AAM. As supporting evidence of this, 10 of the 17 currently reported single nucleotide polymorphisms (SNPs) to be associated with AAM have previously been described in studies of obesity phenotypes (Table 1) (9, 10).

Table 1. Known variants associated with age at menarche in genome-wide association studies (GWAS).

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>SNPs</th>
<th>Implicated Gene</th>
<th>Population</th>
<th>Adjustments*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs2815752‡</td>
<td>NEGR1</td>
<td>European descent</td>
<td>birth year or birth cohort</td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>rs2568958‡</td>
<td>NEGR1</td>
<td>European</td>
<td>birth year</td>
<td>(10)</td>
</tr>
<tr>
<td>2</td>
<td>rs6548238‡</td>
<td>TMEM18</td>
<td>European descent</td>
<td>birth year or birth cohort</td>
<td>(9)</td>
</tr>
<tr>
<td>3</td>
<td>rs7647305‡</td>
<td>ETV5</td>
<td>European</td>
<td>birth year</td>
<td>(10)</td>
</tr>
<tr>
<td>4</td>
<td>rs10938397‡</td>
<td>GNPDA2</td>
<td>European descent</td>
<td>birth year or birth cohort</td>
<td>(9)</td>
</tr>
<tr>
<td>5</td>
<td>rs13357391</td>
<td>SPOCK</td>
<td>European and Chinese</td>
<td>age (among Chinese)</td>
<td>(11)</td>
</tr>
<tr>
<td>6</td>
<td>rs314276</td>
<td>LIN28B</td>
<td>European</td>
<td>Age</td>
<td>(6)</td>
</tr>
<tr>
<td></td>
<td>rs314277</td>
<td>LIN28B</td>
<td>European, European-American,</td>
<td>none, birth year</td>
<td>(12), (10)</td>
</tr>
<tr>
<td></td>
<td>rs314280</td>
<td>LIN28B</td>
<td>European</td>
<td>birth year</td>
<td>(10)</td>
</tr>
<tr>
<td></td>
<td>rs7759938</td>
<td>LIN28B</td>
<td>European descent</td>
<td>birth year or birth cohort</td>
<td>(9)</td>
</tr>
<tr>
<td>9</td>
<td>rs2090409</td>
<td>intergenic</td>
<td>European descent</td>
<td>birth year or birth cohort</td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>rs7861820</td>
<td>intergenic</td>
<td>European-American</td>
<td>none</td>
<td>(12)</td>
</tr>
<tr>
<td>11</td>
<td>rs4074134‡</td>
<td>BDNF</td>
<td>European descent</td>
<td>birth year or birth cohort</td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>rs4923461‡</td>
<td>BDNF</td>
<td>European</td>
<td>birth year</td>
<td>(10)</td>
</tr>
<tr>
<td>12</td>
<td>rs7138803‡</td>
<td>BCDIN3D</td>
<td>European</td>
<td>birth year</td>
<td>(10)</td>
</tr>
<tr>
<td>16</td>
<td>rs3751812‡</td>
<td>FTO</td>
<td>European</td>
<td>birth year</td>
<td>(10)</td>
</tr>
<tr>
<td></td>
<td>rs9939609‡</td>
<td>FTO</td>
<td>European descent</td>
<td>birth year or birth cohort</td>
<td>(9)</td>
</tr>
</tbody>
</table>

*The adjustments reported, not including those for population stratification.
‡These obesity-associated SNPs were part of a panel of previously reported obesity SNPs investigated separately in the GWAS at an adjusted significance level of p<0.05.

For these reasons, we propose to conduct genetic association analyses of the effects of body mass index (BMI), waist circumference, and height associated-SNPs with AAM in ARIC and the CHARGE samples of European descent. We will only examine SNP-AAM associations in the
population of SNP discovery (i.e. Caucasians), due to race differences in haplotype block length. However, we may expand our analyses to include other ancestry populations as novel variants are discovered in these populations.

**Subjects:**  
Women of European ancestry with available measures of AAM.

**Variables (phenotype):**  
Self reported age at first menses (menarche).

**Exclusions:**  
AAM < 7 years or >18 years, which correspond to observations beyond three standard deviations from the mean AAM among older women of European Ancestry. As there maybe differences between populations, observations beyond three standard deviations from the mean AAM for that specific population will also be excluded.

Additionally, exclusions based on participant consent for use of DNA and non-CVD related outcomes will be made. The SNPs, which failed quality control and subjects for whom population stratification (principal component) estimates are not available, will be excluded.

**Exposure:** At the beginning of the analysis, selection of BMI-, waist circumference-, and height-associated SNPs genotyped in ARIC (Affymetrix 6.0 SNP chip, IBC Chip, or as part of other consortia) and in the other studies of the CHARGE Consortium.

**Model:** Linear regression for analysis of continuous variables will be conducted with an additive genetic model, but recessive or dominant models will also be considered, as appropriate. The SNP selection will be race-specific for SNPs associated with BMI, waist circumference, or height. As new genome-wide association studies (GWAS) are conducted in African-Americans or other populations, newly discovered variants may be included in our analysis.

Due to significant secular trends in AAM, analyses will be conducted using birth year or birth decade as a covariate. We will perform analysis using all available SNPs that pass quality control. In ARIC, we will adjust for population stratification using principal components in samples of European descent, and ancestry-informative markers or principal components in African Americans (if applicable). In CHARGE, adjustments for population stratification will be done using the method available for the study (AIMs, principal component or others).

**Transform:**  
AAM is normally distributed. Therefore, no transformation of the data will be performed.

**Covariates:**  
In modeling the effect of the SNP on AAM, the confounders birth year or birth decade, study center (if applicable), and measures of population stratification will be included.
Statistical significance: Bonferroni correction adjustment (1/ number of tests performed)

Secondary analyses: The participating studies have collected anthropometric data in middle-aged or older women. Therefore, we will not be able to study the effects of pre- and post-pubertal anthropometric measures in our analyses. However, the ARIC study has collected self-report weight at age 25. Therefore, as secondary analyses, we will consider exploring the change in effect estimates of associations of SNPs and age of menarche by adjusting for the weight at age 25. These analyses may not be feasible in the other CHARGE cohorts, which may not have comparable measures of weight at earlier ages.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes    ____ 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? __X__ 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

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.csecc.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)?

No paper proposals related to previously described anthropometry associated SNPs and age at menarche were found.

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

b. If yes, is the proposal
A. primarily the result of an ancillary study (list number)* 2006.03 (Stampede and Geneva genotype funding in Caucasians), 2007.02 (CARe, genotyping in African Americans), 2007.14 (Genetic Epidemiology of Causal Variants Across the Life Course), and 2009.12 (Building on GWAS for NHLBI-disease: the CHARGE consortium).

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
1 Popkin BM. Recent dynamics suggest selected countries catching up to US obesity. Am J Clin Nutr;91:284S-8S.