

ARIC Manuscript Proposal # 1472

PC Reviewed: 02/10/09
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Genome-wide association analysis of age of menarche: the CHARGE Consortium

b. Abbreviated Title (Length 26 characters): Genomewide association of age at menarche

2. Writing Group (ARIC investigators): Ellen Demerath, Nora Franceschini, Aaron Folsom, Eric Boerwinkle

CHARGE participating studies:

Framingham Heart Study, Rotterdam Study I and II, TwinsUK, InCHIANTI, HAPI Heart Study

Other CHARGE WG collaborators and affiliations:

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

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3. Timeline: Analyses will begin when all genotyping and QC is completed.

4. Rationale:

To conduct a genome-wide association analyses of age of menarche among ARIC participants and a meta-analysis across CHARGE cohorts.

5. Main Hypothesis/Study Questions:

Our goal is to explore the contribution of genetic factors to variation in the age at first menses (menarche) in women of European ancestry. We propose to perform a genome-wide association analyses of age of menarche using the set of genotyped and imputed SNPs in ARIC and to conduct a meta-analysis of the results across 7 CHARGE cohorts.

We also plan to expand our analyses to African Americans as the genotyping data is available. Use of GWAS data in African-Americans will follow CARE procedures, and a CARE DAC on this topic is in preparation.

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 methodologic limitations or challenges if present).

Introduction: While age at menarche is significantly influenced by genetic factors (heritability ~ 0.50), no specific genetic variants have yet been identified to be associated with this important reproductive health trait. As girls with earlier menarche tend also to be or become obese and of short stature, identification of SNPs associated with age at menarche may point to regulatory mechanisms involved in growth, obesity and chronic disease risk.

Subjects: Women of European ancestry with available measures of age of menarche. Use of GWAS data in African-Americans will follow CARE procedures.

Variables (phenotype): Self reported age at first menses (menarche), which was collected in ARIC at the baseline visit

Exclusions: Age at menarche < 9 years or >17 years, which correspond to approximately the 1st and 99th percentiles of age at menarche among older women of European Ancestry. Exclusions based on participant consent for use of DNA and non-CVD related outcomes will be made. SNPs that failed QC and subjects for whom population stratification PC estimates are not available will be excluded.

Exposure: 2.5 million imputed and measured SNPs included in the Affymetrix 6.0 SNP chip.

Model: Linear regression for analysis of continuous variables, additive genetic model. Due to significant secular trends in age at menarche, analyses will be conducted using birth year as a covariate. We will perform analysis using all available SNPs that pass QC. We will adjust for population stratification using principal components if required.

Transform: Age of menarche is normally distributed so no transformation of the data will be performed.

Covariates: Basic model: birth year and study center adjusted. Age at baseline is highly correlated with birth year (>0.95), so we will not adjust for v1age01 variable.

Statistical significance: Bonferroni correction adjustment (1/ number of tests performed) ($\sim 10^{-7}$)

Meta-analyses: We will perform meta-analysis of parameter estimates and p-values across the 7 cohorts engaged in the CHARGE Aging and Longevity-Reproductive Health Working Group, using fixed effects and the program METAL.

We also explore pleiotropic genetic effects of age of menarche and anthropometric measures in coordination with the anthropometric CHARGE WG, if applicable.

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

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?

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.csc.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)?

no paper proposals related to menarche or genetics of menarche

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 (list number*2006.03 (Stampede and Geneva genotype funding in Caucasians) and 2007.02 (CARE, genotyping in African Americans).

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.csc.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.