ARIC Manuscript Proposal #2163

PC Reviewed: 7/9/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Title: Genetic determinants of reproductive traits in CHARGE: menarche and menopause timing
   
   b. Abbreviated Title (Length 26 characters): reproductive and genetics

2. Writing Group: Nora Franceschini, Ellen Demerath, Eric Boerwinkle, Megan Grove, Alanna Morrison and other interested ARIC Authors.
   
   Other authors from the CHARGE consortium will be included.
   
   I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. NF [please confirm with your initials electronically or in writing]

   First authors: Nora Franceschini and Ellen Demerath

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   Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

3. Timeline: Analyses will begin upon approval of this manuscript proposal.

4. Rationale: Menarche and menopause are fundamental biologic events during a woman’s lifetime. The timing of both age at menarche (AAM) and age at natural menopause (ANM) is associated with a range of significant health conditions later in life that extend beyond
reproductive health to obesity\(^{(1)}\), T2DM\(^{(2,3)}\), osteoporosis\(^{(4-6)}\), cardiovascular disease\(^{(7-9)}\), breast\(^{(10)}\) and ovarian cancer\(^{(11)}\), and mortality\(^{(8,12,13)}\).

We have conducted GWAS for AAM and ANM within the international CHARGE and ReproGen consortia and have identified and replicated 32 genetic loci for AAM\(^{(14)}\) and 17 genetic loci for ANM\(^{(15)}\) from diverse biologic pathways. Our strongest association for AAM was in a SNP in \textit{LIN28B} a gene associated with adult height. The allele associated with earlier AAM was associated with decreased height (girls with early menarche are shorter as women). Subsequent work established that \textit{LIN28B} has sex specific effects on childhood growth\(^{(17)}\) and prolonged effects on body mass index (BMI) from adolescence to adulthood in women\(^{(18)}\). These studies demonstrate how further investigation into genetic associations may provide insights into the effects of puberty timing on human growth and obesity risk over the lifecourse. For ANM a \textit{UIMC1} SNP\(^{(19,20)}\) was among the top associations. The protein encoded by \textit{UIMC1} interacts with BRCA1 and estrogen receptor \(\alpha\) and is thought to recruit BRCA1 to DNA damage sites\(^{(21)}\). Many of the novel associations for ANM function in pathways important to somatic aging (DNA repair and immune response) and suggest mechanistic links between reproductive aging and senescence. Insights into the genetic basis of sexual maturation and reproductive aging may not only improve our understanding of disorders of puberty and menopause but also advance our understanding of how AAM and ANM confer risk for serious health conditions and provide new strategies for prevention and treatment.

In this study we propose to extend this work by conducting a meta-analysis of Exomechip genotyping data for AAM and ANM to identify low frequency and rare variants associated with these phenotypes that are more likely to be functional.

5. Main Hypothesis/Study Questions:
1. Common and low frequency variants in the exome are associated with menarche and menopause timing.
2. Genome wide common and low frequency variants are associated with menarche and menopause timing.

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).

Subjects and sample sizes:

Phenotype harmonization across CHARGE cohorts and collaborating studies has been already done.

Multiple cohorts participated in joint calling of the Exomechip including: AGES, ARIC, CHS, CARDIA, Rotterdam, Fam HS, FHS, HABC, JHS, MESA (CHS and MESA do not have menarche; CARDIA does not have many menopausal women; FamHS does not have reproductive traits; JHS has only AA women)

In addition the following cohorts outside the CHARGE joint calling effort are interested in participating in this project:
Estonia: \(n=2500\)
KORA F4
SardiNIA
WGHS
WHI
Finally, the European Exomechip Consortium has agreed to exchange top associations for replication.

**Genotypes**: All samples in CHARGE have exome chip data and 1000G imputed data. Genotype calling has been standardized across studies. Quality control has been already done.

**Inclusion/exclusion Criteria**: Only women with available trait will be used for analysis. For menopause, we will restrict the data to natural menopause by excluding women with hysterectomy or menopause due to chemical/drug therapy. We propose analysis of European and African ancestry individuals.

**Quality Control**: Quality control has been standardized across participating studies.

**Primary Phenotypes**

- Age of menarche(14): self-reported between ages of 9 and 17 years
- Age of natural menopause(15): self-reported between ages of 40 and 60 years

**Covariates**: adjustments for birth year, measures of population stratification and region will be done for age of menarche analysis. For age of menopause, we will only adjust for measures of population stratification and region.

**Analysis**: Analysis protocols have been developed by the CHARGE statistical working group for single variant analysis and burden test using gene-based units. Meta-analysis of data across studies has also been standardized.

We will implement two burden tests. First, a Variable Threshold Combined Multivariate and Collapsing count method, where the number of rare alleles is counted in each gene, then the gene is tested for association. Second, we will use SKAT for all rare variants (MAF < .05) within a gene. SKAT allows for variants with opposite directions of effect within the same gene, whereas the variable threshold combined multivariate and collapsing method does not.

**Other Analysis Considerations**

**Genotype Annotation**: this has been already provided by the CHARGE consortium

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? _____ 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.cscu.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?  _____ Yes  __X__ No

11.b. If yes, is the proposal

_____ A. primarily the result of an ancillary study (list number*)

_____ 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.cscu.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.
Reference List


