ARIC Manuscript Proposal # 1672

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

1.a. Full Title: Genome-wide association study of gender

b. Abbreviated Title (Length 26 characters): GWAS of autosomal differences in males versus females

2. Writing Group:

Writing group members: Maja Barbalic, Nora Franceschini, Ellen Demerath

Other ARIC authors will be invited as well as participants from other cohorts included in the study

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

Genotyping is complete. Data analysis will begin immediately.

4. Rationale:

The rationale behind this project is based on the fact that the male-to-female ratio at birth is greater than 1, and has been throughout history and across all populations - typically 51.4 males are born per 50 females. It is presumed this has been selected for, because by reproductive age, the ratio is closer to 1:1 as more males die in infancy and childhood. Male infants are known, for example, have higher respiratory disease mortality rates than female infants. Incompatible genotypes between the autosomes and sex chromosomes could lead to miscarriage, generating gender-specific selection against particular variants. There are likely to be environmental effects driving this ratio distortion as well; for instance, the bias against males increases following war. However it is possible that genetic effects are important, possibly through increasing the number of Y sperm men produce. The absence of any reproducible gender-specific differences in allele frequency will also be useful in guiding genetic association study design, for example for gender-based traits such as menopause and menarche. We will perform GWAS by comparing males versus females as part of the ReproGen genetics consortium (which included the CHARGE Reproductive Aging group); this meta-analysis is being led by the Sanger Institute in UK.

5. Main Hypothesis/Study Questions: Null hypothesis is that there is no difference in allele frequency across the genome between men and women.

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).

The association of genome-wide single nucleotide polymorphism with gender will be performed as a standard case/control association analysis. Females will be coded as 1 and males as 0. Results across cohorts will be combined using inverse-variance meta-analysis.
Exposure: Genetic variants from Affymetrix 6.0 chip
Outcome: Male/female
Exclusions: Those without consent for genetic research

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 ICTDER03 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 ICTDER03 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__X__ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
__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 (list number* 2006.03 (Stampede, genotyping in Caucasians)_________)
___ 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.