ARIC Manuscript Proposal #2095

PC Reviewed: 3/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Genome-wide Association Study of vitamin D-Related Traits in ARIC Whites and African Americans

b. Abbreviated Title (Length 26 characters): GWAS of Vitamin D traits


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

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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: Data analyses for GWAS consortia will begin immediately. Final results will not be uploaded until phenotypic information is complete.

4. Rationale:
We are submitting a single, umbrella manuscript proposal for participation in GWAS consortia analyses of vitamin D-related phenotypes, as has been done for some other phenotypes (e.g. diabetes-related quantitative traits; ARIC MS Proposal #1409). Specific phenotypes this proposal pertains to include serum vitamin D2, vitamin D3, total vitamin D (D2 + D3), the vitamin D epimer, fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH). Measurement of these biomarkers is presently taking place through
ARIC Ancillary Study #2009.17, entitled “Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort” (Lutsey PI). All proposed consortia analyses would be eligible for ‘limited review’, as typical for ARIC GWAS consortia manuscripts.

Due to the fluid nature of data analysis and manuscript development within GWAS consortia, it is unclear how many manuscripts will emerge from this work. At the time of submission of this manuscript proposal we are aware of (and hope to contribute to) four GWAS consortia manuscripts that are in planning stages:

1) SUNLIGHT Vitamin D intake interaction project: Looking at dietary intake of vitamin D*SNP interactions on 25(OH)D levels.

2) TRANSEN-D: GWAS of 25(OH)D levels in African Americans. ARIC Caucasian data may also be included as part of the replication cohort.

3) PTH: GWAS using 1000g imputation.

4) FGF23: GWAS using 1000g imputation.

Authorship order and number will be in some ways dictated by the policies of the various consortia. Interested ARIC authors beyond those noted above are welcome to participate.

5. Main Hypothesis/Study Questions:

We propose to study the association of directly genotyped or imputed SNPs from the Affy 6.0 array in ARIC participants and the following vitamin D-related quantitative traits:

1. 25(OH)D – Separate analyses may be conducted for total vitamin D, vitamin D$_2$, vitamin D$_3$, and the vitamin D epimer.

2. FGF23

3. PTH

Furthermore, we propose to study whether behaviors (e.g. dietary vitamin D intake) modify relations between GWAS SNPs and biomarkers levels.

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).

Study design and inclusion/exclusion: subjects and sample size
Both Caucasians and African Americans will be included. Individuals who did not consent to genetic research and those without GWAS data will be excluded.

Publication Strategy
We expect that the publication strategy will largely follow working group specifications of the various GWAS consortia. As noted above, there are at least four manuscripts topics under development. Depending on the timeline for laboratory completion of phenotype measurement and data analysis, ARIC will participate as a full contributor to meta-analyses for some of these traits, and as a replication cohort for others.

The publications committee will be notified by an addendum to this proposal when the publication strategy becomes better developed and additional papers are produced from the science covered in this proposal.

Exposure Measurements and Definitions
This manuscript proposal is concentrated on the analyses of the Affy 6 GWAS data (~1 million) SNPs. Some analyses will use the HapMap imputation, while others will use the 1000g imputation.

Quality Control of Genotyping Data
Standard ARIC exclusions for individuals and SNPs will be applied, including those for missing data and HWE deviations.

Outcome Measurements and Definitions
Serum vitamin D, FGF23, and PTH are presently being measured in stored serum from ARIC visit 2 (1990-1992). At this point in time, all proposed GWAS analyses are utilizing these outcomes as continuous variables. However, in the future analyses employing cut-points may be conducted. All analyses will be cross-sectional.

Statistical Analysis
Analyses will follow unified analysis specifications agreed to by the various GWAS consortia members. Analyses plans for specific projects will be available upon request.

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 ICTDER 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

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
  ____ 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 related proposals exist.

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

2009.17 (Lutsey PI) 
- Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort”

2007.02 (Boerwinkle PI) 
- The National Heart Lung and Blood Institute’s Candidate Gene Association Resource (CARE): Phase I (CARE)

2006.03 (Boerwinkle PI) 
- GWA for loci influencing incident CHD and other HLB phenotypes (NHLBI RFA for large scale genotyping) (STAMPEED) (GEI) || Genome-wide association for loci influencing CHD and other heart, lung and blood phenotypes

  ____ 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/

12a. 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.
12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscu.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.