ARIC Manuscript Proposal # 1664

1.a. Full Title: Genome-wide association study of Il-6 in European-Americans: CHARGE Consortium

b. Abbreviated Title (Length 26 characters): GWAS of Il-6

2. Writing Group for ARIC:

Writing group members: Maja Barbalic, Ron C. Hoogeveen, Christie Ballantyne
The coauthors from the other cohorts

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MB__ [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:**

Circulating Interleukin-6 (IL-6) is a cytokine marker of inflammation and a risk factor for cardiovascular events. IL-6 protein levels are highly heritable and are considered to be under significant genetic influence. We will conduct a meta-analysis of genome-wide association results for IL-6 levels from ARIC and eight other large cohort studies in the setting of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium.

5. **Main Hypothesis/Study Questions:** To investigate the association of genome-wide genetic variation with inter-individual variation in IL-6 levels in adults of European ancestry

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).**

Additive genetic effects on IL-6 levels will be assessed by linear regression using ProbABEL software. All ARIC European-American participants with biomarker levels measured and genotype data available will be included. IL-6 was measured for a subset of ARIC. In order to account for the case status that could be related to IL-6 levels, we will include the case status as a covariate in the model. The covariates will include sex and age in addition. We will run a weighted analysis based on the inverse of the sampling fractions for the top SNPs from the GWAS results to validate our results from the initial non-weighted analyses. Metaanalysis combining the results from individual CHARGE studies will be performed using inverse variance weighting with a fixed effects model.

**Exposure:** 2.5 million HapMap genetic variants identified in CEPH trios

**Outcome:** IL-6

**Exclusions:** Those without consent for genetic research

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