ARIC Manuscript Proposal # 1848

PC Reviewed: 10/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Meta-analysis of genome-wide association studies for Forced Vital Capacity in the CHARGE and SpiroMeta Consortia

b. Abbreviated Title (Length 26 characters): GWAS of FVC

2. Writing Group: (co-authors, in no particular order)

Stephanie London, Nora Franceschini, Kari E North, Laura Loehr, Alanna Morrison, David Couper, Bonnie Joubert

And Charge and SpiroMeta collaborators: Daan Loth (leader for CHARGE). Martin Tobin (leader for SpiroMeta)

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]**

F**irst author**: **Nora Franceschini**

Address: 137 E. Franklin St., Suite 306
CB #8050
Chapel Hill, NC 27599-8050

Phone: 919-9661305 E-mail: noraf@unc.edu

3. Timeline: Manuscript submission planned in Fall 2011

4. Rationale: To identify new genetic loci for Force Vital Capacity (FVC), a measure of lung capacity. Although the correlation of the FEV1 and FVC residuals is high (~ 83%), FVC may provide additional insights with regards to restrictive lung syndromes beyond the already identified genetic loci for FEV1/FVC. In a modest size (N=1,114) analysis of GWAS hits for pulmonary function (FEV1 and FEV1/FVC) from our previous CHARGE paper (Hancock et al, 2010), stronger associations were identified for FVC than either FEV1 or FEV1/FVC for some SNPs (Li et al. J Allergy Clin Immunol 2011;127:1457-65). This suggests that we might identify novel loci related to FVC in large scale meta-analysis.

5. Main Hypothesis/Study Questions: To identify new loci associated with Forced Vital Capacity using genome wide association analyses.

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).

Project Description: We will perform GWA studies for Forced Vital Capacity (FVC) in each CHARGE cohort separately and meta-analyze results, comparable to the previous FEV_1 and FEV_1/FVC analyses.

General Analysis Approach: Forced Vital Capacity (FVC) was measured using spirometry during a forced expiratory maneuver. The trait has been already harmonized across CHARGE studies.

Major Phenotype to Analyze: Forced Vital Capacity

Major Covariate Adjustments: age, sex, height, height^2, weight, smoking status (never, former, current) and pack-years of smoking, center/cohort, principal components.

- If deemed necessary/informative we could also analyze Forced Vital Capacity, corrected for FEV1.

Genotyping: We will use already generated genotyping and imputed SNPs from ARIC for white individuals (Affy 6.0).

Cohorts Included in Analysis: ARIC, CHS, FHS, Rotterdam, Ages, Mesa, HealthABC, and CARDIA. We have invited SpiroMeta to participate and they have agreed in principal. At a minimum they will participate via look-up replication in analyses that they have already completed.

We propose a GWA analysis studying FVC as the phenotype and including stratification by ever/never smoking.

- Primary analysis
  - FVC as a continuous outcome
  - Covariates: former smoking, current smoking and pack-years of smoking, age, sex, height, height^2, weight, center/cohort, principle components
  - No exclusion/adjustment for asthma.

Forced vital capacity=$\alpha + \beta_1$ SNP + β_2 current smoking + β_3 former smoking + β_4 smoking pack-years + β_5 age + β_6 height + β_7 height^2 + β_8 weight + β_9 principal components (if appropriate) + β_{10} center (if appropriate)

- Stratified analyses for ever and never smoking

Forced vital capacity=$\alpha + \beta_1$ SNP + β_2 age + β_3 height + β_4 height^2 + β_5 weight + β_6 principal components (if appropriate) + β_7 center (if appropriate)

Note: To exclude height-related SNPs, we will request a look-up replication from the GIANT consortium. This approached worked well in our recent joint meta-analysis with SpiroMeta for FEV1 and FEV1/FVC.

Results

It would be helpful if the results of the analyses will be given in comma delimited files (csv files) with a name including the cohort name, the phenotype FVC and the sub analysis (eversmk, neversmk, all). The following fields are required for each SNP. It would be appreciated if the fields are named following the **bold** titles as below.

- **SNP**: rs number
- **cod_all**: coded allele (effect allele) ("A" "C" "G" "T")
- **noncod_all**: non-coded allele ("A" "C" "G" "T")
- **strand**: the strand of the baseline and the coded alleles ("+" or "-")
- **freq**: allele frequency for **coded allele** (numeric data)
- **Beta**: SNP main effect size for each copy of the coded allele (numeric data)
- **SE**: standard errors of beta_SNP (numeric data)
- **Type**: whether the SNP was genotyped or imputed ("gen" or "imp")
- **Imp_info**: an imputation quality score (numeric data)

Please *do not* apply a genomic control correction, but *please supply the lambda for analyses* so that this correction can be applied by us later if required.

Table 1

Study	**N, total**	**N, males (%)**	**N, females (%)**	**Age (years) [mean (SD)]**	**Height (cm) [mean (SD)]**	**FVC (mL) [mean (SD)]**	**Weight (kg) [mean (SD)]**	**N, never smokers (%)**	**N, ever smokers (%)**	**Pack-years [mean (SD)]**

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 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 ____ 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

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)?

1360- discontinued and folded into 1357
1384 Genome-Wide Association Study (GWAS) of Pulmonary Function and Chronic Obstructive Pulmonary Disease (COPD) – interaction with traffic exposure in ARIC
1357 and 1357r Genome-Wide Association Study (GWAS) of Pulmonary Function and Chronic Obstructive Pulmonary Disease (COPD)
1562 Genome Wide Association Study of interaction with smoking in relation to pulmonary function and COPD

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.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.**