ARIC Manuscript Proposal #2158

PC Reviewed: 6/11/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: GWAS follow-up for lung function using expression quantitative trait locus analysis

b. Abbreviated Title (Length 26 characters): **eQTLs and lung function.**

2. Writing Group:

Writing group members: This is a paper from two consortia being lead by a junior (Maen Obeidat) and senior author (Peter Pare) outside investigators (Univ. of British Columbia) who have the lung eQTL database (see description). They are using only the meta-analyzed data from CHARGE-SpiroMeta meta-analysis. The plan with the consortium is for two authors per cohort to be included. This would be Stephanie London and Alanna Morrison. If the plan changes we can add more authors.

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

Manuscript submitted within 12 months.

4. Rationale:

The SpiroMeta-CHARGE meta-analyses of GWAS for lung function measures in the general population have identified a total of 27 novel loci (1-3). The exact molecular mechanisms underlying these associations are not fully understood. Moreover, most of the associated SNPs are intronic or intergenic with no obvious functional role. Integrative genomics is a powerful tool to unravel the molecular signals in genetic associations by integrating the trait associated SNPs with expression quantitative trait loci (eQTL) in relevant tissue types.
By integrating gene expression and whole-genome genotyping in lung tissues from ~12,00 individuals, investigators at the Lung eQTL study participating centers (University of British Columbia and University of Laval in Canada, and University of Groningen in the Netherlands) have built a rich and unique lung tissue specific eQTL resource which is valuable to study the genetic contribution to lung related phenotypes (4).

5. Main Hypothesis/Study Questions:

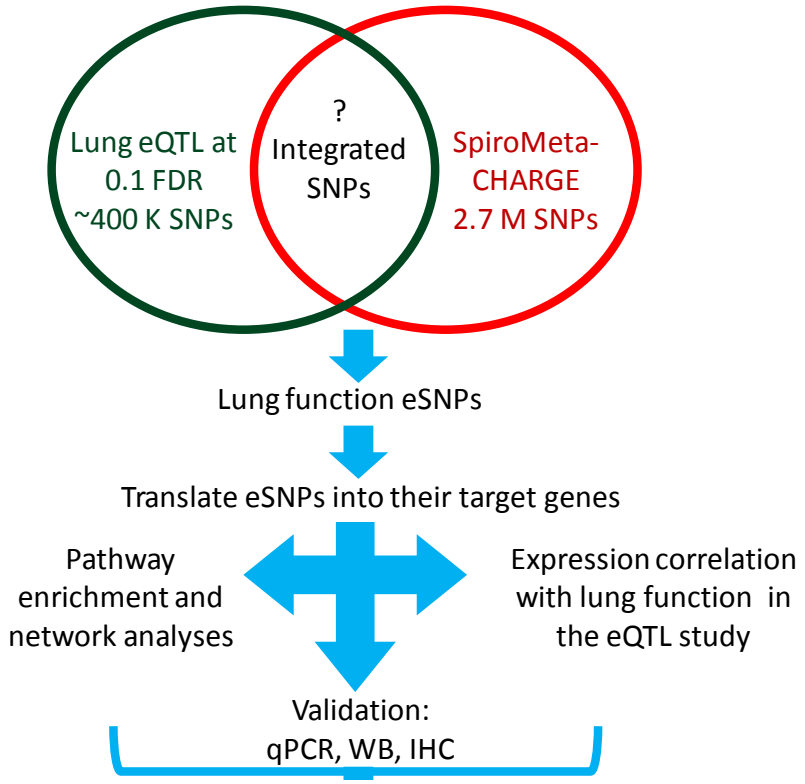
We hypothesize that s subset of SNPs which influence lung function do so by acting as eQTL in the lung to change the level of expression of their gene product.

Specific study questions are:

1. From the SpiroMeta-CHARGE GWAS results, which SNPs influence both lung function and gene expression in the lung ?
2. What are the genes that are being regulated by these SNPs?
3. What is the direction of effect of the SNP on lung function and mRNA?
4. What pathways these genes are involved in?

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 study design is summarized in the figure below. The project involves the integration of the SpiroMeta-CHARGE lung function meta-analyzed GWAS results with lung specific eQTL dataset.
The traits are FEV1 and FEV1/FVC. Only the meta-analysis results file will be used. SNPs that are associated with both lung function and mRNA levels are prioritized as being potentially causal for variation in lung function and will be followed up in a number of analyses none of which cohort data.
First, the mRNA levels of genes regulated by the integrated SNPs will be correlated with lung function in individuals from the eQTL study (n~850). Second, these genes will be tested for enrichment in Gene Ontology process and networks. Finally, a number of genes that show strong evidence across the multiple datasets will be validated at the protein level using immunohistochemsitry.



7.a. Will the data be used for non-CVD analysis in this manuscript? __x__ Yes ____ No

Only meta-analysis results that already exist will be used. From ref 3.

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 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

Only meta-analyzed results will be used – from ref 4.

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

Only meta-analyzed results will be used – from ref 4.

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).

This proposal is highly related to a pathway analysis manuscript proposal that I am submitting at the same time. It is called "Pathway analysis based on meta-analysis of genome wide association studies of FEV_1 and FEV_1/FVC". That other MS proposal does not use this eQTL database. Both use the same CHARGE-SpiroMeta meta-analyzed results. The plan is to publish the pathway manuscript first and then submit this one which has a different type of pathway analysis –based only on the eQTL SNPs.

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/

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.cscc.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.

References

1. Repapi et al. Nature Genetics 2010
2. Hancock et al. Nature Genetics 2010
3. Maria Soler Artigas et el. Nature Genetics 2011.
4. Ke Hao et al. PLoS Genetics 2012.