1.a. Full Title: Impaired Lung Function Associated with Polymorphisms in Beta-Adrenergic Receptors (ADRB) and Endothelin Receptors (EDNR): The ARIC Study

b. Abbreviated Title (Length 26 characters): Lung Function, ADRB, and EDNR

2. Writing Group: Writing group members:

Matthew B. Schabath, Kelly Volcik, Eric Boerwinkle, and any additional appropriate coauthors from the ARIC study.

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

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3. Timeline:
Manuscript Prep: Dec 2006 to April 2007
Manuscript Revision: May 2007
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4. Rationale:
Beta-adrenergic receptors are members of the seven-transmembrane spanning family of G-protein-coupled receptors. They are expressed in many cell types throughout the body and play a pivotal role in the regulation of a variety of systems including pulmonary, cardiac, vascular, endocrine and central nervous. They are widely
distributed in the lungs and are specifically located in the airways smooth muscle, epithelial cells, mast cells and type II alveolar cells. The beta-adrenergic receptors are involved in a variety of biological actions in the lung including anti-inflammatory, bronchodilation, chemotaxis, and mucociliary clearance (1). The gene encoding the beta-adrenergic receptors is highly polymorphic. In vitro studies have provided evidence that single nucleotide polymorphisms (SNPs) in beta-adrenergic receptors appear to influence receptor function (2). Furthermore, association studies have shown the polymorphisms are associated with bronchial responsiveness (3) and lung function (4).

Like the beta-adrenergic receptors, endothelin receptors also belong to the seven transmembrane-spanning superfamily of G-protein-coupled receptors. Additionally, they are found in a variety of systems and are abundantly distributed in the lungs. The endothelin receptors are involved in a variety of pathophysiological and disease processes in the lungs including airway remodeling, inflammation, neuromodulation, asthma, and COPD (5). Interestingly, there is also evidence of biological interaction between the beta-adrenergic receptors and endothelin receptors in the human lungs (6). Although the endothelin receptor genes are highly polymorphic and are biologically relevant in the pulmonary system, at present there are no data on the role of the endothelin receptor polymorphisms in lung disease or lung function.

The SNPs chosen for the proposed analysis have been genotyped on the entire ARIC Cohort. Furthermore, the beta-adrenergic receptor SNPs are functionally relevant and have been associated with a variety of pulmonary endpoints. On the other hand, the endothelin receptor polymorphisms are novel and have yet to be studied in relation to lung function or any other pulmonary endpoint. Yet, they have been associated with other endpoints including cardiovascular, glaucoma, migranes, and hypertension (7). To our knowledge, this will be the largest study to explore biologically relevant pathway-specific genes for risk of impaired lung function.

References:

5. Main Hypothesis/Study Questions:
1. To estimate the frequency distribution of ADRB and EDNR gene variation in a population-based sample of Caucasians and African-Americans.
2. By ethnic-specific groups, determine the association between individual candidate polymorphisms of the ADRB and EDNR genes and lung function. All analyses will adjusted for, where appropriate, relevant confounding factors such as age, gender, field center, smoking status, pack-years smoked, and prior history of lung disease. Additionally covariates may also be included if deemed statistically and/or biologically relevant.
3. By ethnic-specific groups, evaluate 1) gene-gene interactions among the polymorphisms and 2) gene-environmental interactions for impaired lung function. Smoking is the most important environmental factor that will be explored; other exposures that may be considered include diet, occupation, and physical activity. Again, all analyses will adjusted for, where appropriate, relevant confounding factors such as age, gender, field center, smoking status, pack-years smoked, and prior history of lung disease.

4. Exploratory analyses to describe and characterize the study population, the genotypes, and covariates will be performed before formal analytical methods are applied. Multivariate linear and logistic regression analyses will be performed to describe the association between the risk genotype(s) and lung function. Regression models will be constructed to include statistically significant and biologically relevant variables. The genotypes will be analyzed by main effects, joint effects, haplotypes, and gene-gene interactions. Lung function will be analyzed as a continuous variable, where applicable, and by clinically relevant categories (described briefly below). Environmental factors will also be analyzed as a continuous variable and by distributions (e.g. quartiles of pack-years smoked).

6. Data (variables, time window, source, inclusions/exclusions): The usual DNA restriction, ethnic group and missing data exclusion criteria will be used. Genotypes, environmental exposures (smoking, occupation, physical activity, diet, etc), prior medical history, and covariate data will be required. Additionally, only individuals with the appropriate acceptability code regarding the pulmonary function test (PFT) will be included in the analysis. The main measurement that will be used for this analysis will be the Forced Expiratory Volume at 1 s (FEV₁), which is the volume of gas exhaled in the first second of expiration. However, we will also explore the FVC (i.e., the total volume of gas exhaled), the ratio of FEV₁ to FVC and the combination of FEV₁ and ratio of FEV₁:FVC. Percent predicted FEV₁ (generated from FEV₁) will be analyzed both as a continuous variable and a categorical predictor variable. As a categorical variable, percent predicted FEV₁ will be dichotomized (e.g., by percentile or a clinically important cutpoint [i.e. 80%]) or by generating several levels (e.g., percentile or several clinically important cutpoints).

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?  None

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.

__________________________
Signature

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Date