1.a. Full Title: Assessing the association between mitochondrial DNA copy number and lung function

   b. Abbreviated Title (Length 26 characters): mtDNA CN and lung function

2. Writing Group: Jing Sun (co-first author), Bing Yu (co-first author), Ryan Longchamps, Joe Coresh, Dan E. Arking, Stephanie London, Gregory D. Kirk

*We welcome any other authors who wish to contribute

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

Co-First author:

   Jing Sun  
   Address: Johns Hopkins, 2213 McElderry St, M139, Baltimore, MD 21205  
   Phone: (410) 614-441  
   E-mail: jsun54@jhmi.edu

   Bing Yu  
   Address: UTHealth, 1200 Pressler Street, Suite E-641, Houston, Texas 77030  
   Phone: (713)500-9285  
   E-mail: Bing.yu@uth.tmc.edu

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).

   Name: Dan E. Arking  
   Address: Johns Hopkins, 733 N Broadway, MRB 459, Baltimore, MD 21205  
   Phone: (410) 502-4867  
   Fax: (410) 614-8600  
   E-mail: arking@jhmi.edu

   Name: Stephanie London  
   Address: NIEHS, 111 TW Alexander Drive, RTP NC 27709  
   Phone: 984-287-3688  
   Fax: 301-480-3290  
   E-mail: london2@niehs.nih.gov

3. Timeline: We anticipate that a manuscript will be ready by the end of 2018.

4. Rationale:
   The mitochondria has long been proposed to play a critical role in human disease and aging due to its primary role in energy metabolism [1-4]. As an easily accessible proxy for mitochondrial function, mitochondrial DNA copy number (mtDNA CN) measured
from buffy coat has provided researchers with the ability to assess the role of the mitochondria in disease [5]. Mitochondrial DNA copy number (mtDNA CN) may be associated with lung cancer, especially among smokers [6-8], however, studies on mtDNA CN and chronic obstructive pulmonary disease (COPD) have yielded inconsistent results [9, 10]. We propose to evaluate the association between mtDNA CN and longitudinal change of lung function (e.g. FEV1, FVC, FEV1/FVC ratio), as well as prevalence of COPD in the ARIC cohort.

5. Main Hypothesis/Study Questions:
We hypothesize that mtDNA CN in peripheral blood is associated with lung function decline (e.g. FEV1, FVC, and FEV1/FVC ratio) and prevalence of COPD.

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:** We propose a cross-sectional and a longitudinal study to evaluate the association between mtDNA CN and lung function and COPD. mtDNA CN was previously measured in the ARIC cohort at visit 2 [3]. We will evaluate cross-sectional associations of mtDNA CN with lung function and COPD at the time of visit. We will then evaluate the association of mtDNA CN to longitudinal changes in lung function and prevalence of COPD at visit 5. We will also evaluate the interaction between mtDNA CN and smoking and their joint effect on lung function and COPD in the current study.

**Inclusion/exclusion:** This study will include all participants that have both mtDNA CN data and lung function data available.

**Outcomes and other variables of interest:** For outcomes, the current study will include time varying lung function data (FEV1, FVC, and FEV1/FVC ratio) and COPD status (yes vs. no, defined by pre-bronchodilator spirometry), taken from the visit at which mtDNA CN was measured (study baseline). We will also request information on the following covariates: baseline socio-demographic status (gender, race, age, education, and income), time-varying smoking exposure (smoking status [current smoker vs. former smoker vs. never smoker], smoking intensity [pack-year or pack-day depending on data availability], years since started smoking, and total years of smoking), other behavior information (alcohol use and injection drug use), comorbidities (cardiovascular diseases, renal diseases, HIV infection, HCV infection, etc.)

**Data analysis:** In the cross-sectional analysis, linear regression models will be used to evaluate the association between mtDNA CN and lung function (FEV1, FVC, and FEV1/FVC). Logistic regression models will be used to assess the association between mtDNA CN and COPD (yes vs. no) at the same visit (visit 2) and follow-up visit (visit 5). Longitudinal change of lung function and mtDNA CN will be tested through random effects mixed models. Interaction effects between mtDNA CN and smoking on lung function will also be assessed through all models.
A combined analysis with the ALIVE cohort might be conducted.

**Limitations:** Because mtDNA CN in ARIC is only measured at one time, this study cannot determine whether the association between mtDNA CN and lung function/COPD (if found significant) is a short-term compensatory alteration or a consistent change.

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 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

   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](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)?

   #2173: Lung function decline among adults: the ARIC study

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/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

**References:**