ARIC Manuscript Proposal #2069

1.a. Full Title: GWAS Analysis on the Sense of Smell

b. Abbreviated Title (Length 26 characters): **Smell GWAS**

2. Writing Group:
   Writing group members:

(Currently in alphabetical order): Alonso, Alvaro; Chen, Honglei; Dong, Jing; Franceschini, Nora; Huang, Xuemei; Mosley, Thomas H; for the ARIC analysis

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __DJ___ **[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 submission by July 2014

4. Rationale: Hyposmia (loss of smell) affects up to 25% of the US older adults and adversely impacts their safety and quality of life. More importantly, recent evidence suggests that hyposmia may be one of the earliest symptoms of Parkinson's disease and possibly an early symptom of Alzheimer's disease. It has been hypothesized that research on hyposmia helps to identify high risk populations for neurodegeneration and to understand early disease etiology. However, little is known about the genetic and environmental factors that contribute to hyposmia. Preliminary data showed that carriers of known Parkinson's genes (e.g. LRRK2 and GBA) had abnormal sense of smell [1],

suggesting potential roles of these genetic factors in hyposmia. We therefore propose the first genome wide association study (GWAS) to identify potential susceptibility loci for the sense of smell and hyposmia.

5.   Main Hypothesis/Study Questions: To identify susceptibility loci for the sense of smell using GWAS analysis.

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: GWAS study

Study Description: We will perform GWAS analyses to identify genetic loci that are associated with the sense of smell or hyposmia in the ARIC cohort. We are also contacting other populations for pooled GWAS analysis and confirmation genotyping.

General Analysis Approach: Multiple-stage GWAS analysis including two population-based cohorts: the ARIC and the Health ABC studies (see the "Cohorts Included in Analysis" section below). We will perform GWAS screening using both ARIC and Health ABC studies, and select SNPs that meet the following criteria for further confirmation in an independent sample set: 1) the same direction in both GWAS analysis; 2) $P < 10^{-5}$ in the meta-analysis of these two GWAS. For the sense of smell analysis, we will use linear regression models, and for hyposmia, logistic regression analysis will be applied.

In the analysis, we will exclude individuals with potential dementia defined as MMSE 1) ≤ 22 for less than 7 years of school; 2) ≤ 24 for 8 years of school or some high school education; 3) ≤ 25 for high school graduates; 4) ≤ 26 for those with college education or higher. We will also exclude individuals who did not complete the sense of smell test.

Major Phenotype to Analyze: Sense of smell (continuous, 0-12) or hyposmia (dichotomous: smell score <6). The sense of smell is being measured as part of the ongoing ARIC-NCS examination, using the Sniffin' Stick method. In the clinical visit, participants are asked to smell 12 common odors and total number of correctly identified odor represents the function of smell.

Major Covariate Adjustments: age, sex, education, study site, smoking status (never, ever) and principal components.

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

Cohorts Included in Analysis: In addition to ARIC, we will also propose to the Health ABC Study for pooled GWAS analysis. The Health ABC study (~3000 participants, ~40% African Americans) used the Brief Smell Identification Test (BSIT, score 0-12) to

measure the sense of smell. This method is similar to the Sniffin' Stick and phenotype data will be defined in exactly the same way. GWAS data are available in Health ABC (Illumina Human 1M-Duo). We are also contacting the investigators of other studies which measured the sense of smell as potential replication samples. The analysis will be conducted separately by race (Non-Hispanic Caucasians and African Americans).

- Primary analysis
  - Smell loss as an ordinal outcome.
  - Covariates: age, sex, education, smoking status (never, ever), study site, and principal components.
  - Analysis conducted separately by race

Smell loss = α + β_1 SNP + β_2 age + β_3 Sex + β_4 Education + β_5 ever smoking + β_6 never smoking +β_7 Study site+ β_8 principal components

In secondary analysis, we will define hyposmia as a dichotomous variable (smell score < 6).

Logit (Hyposmia) = α + β_1 SNP + β_2 age + β_3 Sex + β_4 Education + β_5 ever smoking + β_6 never smoking +β_7 Study site+ β_8 principal components

Stratified analyses for positive SNPs with GWAS significant level by using all subjects ($P < 5.0 \times 10^{-8}$)

- Stratified analyses for old and young age

Smell loss/ Logit (Hyposmia) =α + β_1 SNP + β_2 Sex + β_3 Education + β_4 ever smoking + β_5 never smoking + β_6 Study site

- Stratified analyses for female and male sex

Smell loss/ Logit (Hyposmia) =α + β_1 SNP + β_2 age + β_3 Education + β_4 ever smoking + β_5 never smoking + β_6 Study site

- Stratified analyses for ever and never smoking

Smell loss/ Logit (Hyposmia) =α + β_1 SNP + β_2 age + β_3 Sex + β_4 Education + β_5 Study site

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

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)?

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*** 2010.17 Evaluation of olfactory dysfunction in the Atherosclerosis Risk in Communities (ARIC) study **)**
    ___   **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.

Understand

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.

Reference:

1.   Doty, R.L., *Olfactory dysfunction in Parkinson disease.* Nat Rev Neurol, 2012. **8**(6): p. 329-39.