1.a. Full Title:
Genome-wide GWAS and rare-variant analysis of developmental stuttering risk.

b. Abbreviated Title (Length 26 characters):
genetics of stuttering

2. Writing Group:
Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___JEB__ [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:**
6 months to 1 year for publication of the exome array data, 1-2 years to publication of the 1000 genomes imputation data.

4. **Rationale:**
Developmental stuttering affects ~5% of the population. We have collected one of the largest cohorts of individuals who stutter and have genotyped a subset of 174 for preliminary analysis and exome sequenced 50 cases. We will have an additional 850 genotyped under a funded R03 (1R03DC015329-01) in ~6-8 months. No large scale genomic analyses of developmental stuttering have been undertaken to date, despite high heritability estimates (50-70%).

5. **Main Hypothesis/Study Questions:**
1) What are the contributions of single common variants to stuttering risk? 2) What genes are disproportionately burdened with rare deleterious variants in stuttering cases? 3) Do these risk variants replicate in secondary datasets/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).**
In the short term we propose to analyze our 174 stuttering cases, which have been genotyped on the Exome Chip at the University of Texas SPH against a population based control sample drawn from the ARIC Exome Chip data (which was genotyped identically by the same lab on the same chip). In these analyses we will test for common variant effects as well as enrichment of gene-based burden of rare variants in stuttering cases as compared to population based ARIC controls. When we have the additional 850 stuttering samples genotyped on the Mega Array we propose to use ARIC 1000 Genomes imputation data as population based controls in analyses of common variant effects and in PrediXcan analyses.

7.a. **Will the data be used for non-CVD analysis in this manuscript?**

   **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?**

   **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)?

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/

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes   __x__ No.