1.a. Full Title: Carrier test frequencies in a large multi-ethnic sample

b. Abbreviated Title (Length 26 characters): Carrier test frequencies

2. Writing Group:
   Writing group members: Tomek Gambin, Shalini Jhangiani, Amy McGuire, James Lupski and Eric Boerwinkle

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

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3. Timeline: Data are ready and the analysis plan is fully vetted.

4. Rationale: Whole genome and exome sequencing is becoming a more routine component of health care. There is considerable interest in the frequency of carrier test positive individuals (and couples) and secondary findings in the general population.
However, very little data on this topic is available and what is available is on small sample sizes, highly ascertained samples and limited to populations of European descent.

No phenotype data will be presented. No individual level data will be presented. Only those data from participants with full/general consent will be used.

5. **Main Hypothesis/Study Questions:**
   1. To estimate the frequency of autosomal recessive carrier detection positive individuals in a large multiethnic sample.
   2. To estimate the frequency of American College of Medical Genetics (ACMG) secondary findings in a large multiethnic sample.
   3. To estimate the frequency of couples at risk for having an autosomal recessive disorder. (Note: We are not using ARIC spouse data for this analysis. We are simply repeatedly sampling two ARIC study participants.)

   No phenotype data will be presented. No individual level data will be presented. Only those data from participants with full/general consent will be used.

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).**

   ARIC freeze 4 exome data with full consent. Analyses will be carried out in races pooled and stratified by race. Carrier test: 1,423 genes covering 1,493 disorders (source OMIM and MedGen). ACMG: 56 ACMG secondary finding genes curated by the ACMG.

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.cscce.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? __X__ Yes  ____ No

11.b. If yes, is the proposal

__X__ A. primarily the result of an ancillary study (list number* #2009.12)

__   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.cscce.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.

Understood.

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.cscce.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.

Data are already in dbGAP.