1.a. Full Title: chr16 dosage effects on blood pressure and BMI

b. Abbreviated Title (Length 26 characters): chr16 CNV

2. Writing Group: Aravinda Chakravarti, Jacqui Beckmann, Kari North, Keri Monda, Rob Scharpf, Georg Ehret, Josef Coresh, Eric Boerwinkle; has also been invited to join: Jim Pankow

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal: GBE for AC

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3. Timeline: mid-2011

4. Rationale:
An exciting dosage effect on chr16 was recently described by members of this group (Beckmann JS and collaborators, Nature. 2010 Feb 4;463(7281):671-5). The inherited variation is a CNV encompassing some 28 genes that seems to be associated with a highly-penetrant dominant form of morbid obesity. According to current data, this deletion is enriched in the morbidly obese. We would like to verify to what extent CNV in this region are present in the general population and to what extent the deletion or duplication are associated with obesity / BMI in this population. Finally, we would like to determine its association with blood pressure/hypertension and glucose/diabetes, two important comorbidities of obesity. In addition, it would be interesting to verify whether smaller rearrangements in this interval can also be identified. Depending on the findings within ARIC, this proposal can be extended to other CHARGE cohorts.

5. Main Hypothesis/Study Questions:
Association of a specific chr16 CNV with BMI, BP/hypertension, and glucose/diabetes. We will also examine the relationship of a BMI x CNV interaction term on the two co-morbidities. The CNV is inferred based on the genome-wide intensity data available. Consecutive runs of loss of heterozygosity could also be used to infer the presence of a deletion.

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).

Phenotypes: SBP, DBP, glucose, diabetes, and BMI, at first visit

a) Model: A dominant genetic model will be assumed for association and a traditional interaction model will be used for the interaction work.

The main analysis will include self-reported whites and blacks from the ARIC study.

b) Transform: no transform, no scaling.

c) Covariates: age, age^2, study-center, sex

d) Exclusions: outliers from the phenotype distribution (>/- +/- 4SD) will be considered separately and together with the main dataset.

e) Control for multiple comparisons: Bonferroni or similar adjustment

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

NA
(This file ICTDER03 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?
Yes

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”?

Yes

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?

Yes

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.cscar.unc.edu/ARIC/search.php
Yes (based on list circulated in July 2008)

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)?
Cf. above.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?
Yes

11.b. If yes, is the proposal
   ___ A. primarily the result of an ancillary study (list number* _________)
   x___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.03
*ancillary studies are listed by number at http://www.cscar.unc.edu/aric/forms/

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.