

ARIC Manuscript Proposal # 1908

PC Reviewed: 2/14/12
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Replication of a method for estimating the impact of the parent of origin for genetic association.

b. Abbreviated Title (Length 26 characters): Parent of Origin

2. Writing Group:

Georg Ehret, Zoltan Kutalik

Additionally are invited to join: Eric Boerwinkle, Aravinda Chakravarti

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

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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: spring 2012

4. Rationale: Parent of origin (POO) effects have been shown to impact complex genetic traits, but are largely limited to family studies in which related individuals are available. We have explored a method that permits to estimate the impact of the parent of origin in unrelated individuals and this proposal seeks to replicate findings using GWAS data from the ARIC study.

Even if we do not know the origin of the alleles in GWAS studies on unrelated individuals, we know that if a POO effect is acting then

(i) the homozygous individuals (AAs, BBs) carry one paternal and one maternal allele

(ii) about half of the heterozygous (ABs) carry one paternal risk allele and the other half carries one maternal risk allele

If the maternal and paternal effect is different, it follows that the variance in the AA group and the BB group should be similar to each other, but both smaller than the variance in the AB group. It can be shown that

$$\text{Var}(AB) = (\text{Var}(AA) + \text{Var}(BB)) / 2 + (\beta_B(\text{paternal}) - \beta_B(\text{maternal}))^2 / 4$$

where basically $\text{Var}(AA) = \text{Var}(BB)$ in addition. If this is true can be simply tested by an F-test

$$F = (n_{AB} / (n_{AA} + n_{BB})) * ((\text{Var}(AA) * n_{AA} + \text{Var}(BB) * n_{BB}) / \text{Var}(AB))$$

We propose to calculate these statistics genome-wide in ARIC whites and blacks for blood pressure traits (SBP and DBP) and their major co-variate BMI.

5. Main Hypothesis/Study Questions:

A significant parent-of-origin effect can be observed for the selected phenotypes using data from unrelated individuals only.

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).

Genome-wide association statistic. No exclusion by genotype quality because imputed data is going to be used. No exclusion based on the phenotype.

Variables: SBP, DBP, BMI at the first visit.

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.csc.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)?

To our knowledge there is no related manuscript.

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* _____)

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.csc.unc.edu/atic/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.