ARIC Manuscript Proposal # 1656

1.a. Full Title:
Genome-wide association analysis of macronutrient intake
[please note: this a CHARGE working group initiated effort; ARIC is one of several participating cohorts]

b. Abbreviated Title (Length 26 characters):
GWAS - macronutrient intake

2. Writing Group:
Writing group members**:
Jennifer Nettleton & Jim Pankow (ARIC)
Jose Ordovas, Adrienne Cupples, Julius Ngwa (Framingham)
Rozenn Lemaitre, Dariush Mozaffarian, (CHS)
Frank Rooij (Rotterdam)
Kenneth Rice (CHARGE)
George Dedoussi, Stavroura Kanoni (GENDAI, GHRAS)
Paul Franks (GLACIER)
Mary Feitosa (Family Heart Study)
Melissa Garcia (Health ABC)
Toshiko Tanaka (InCHIANTI)
Olli Raitakari (Young Finns)
Ruth Loos (EPIC, Fenland)

** The full author list will include multiple members from each of the cohorts participating in the CHARGE Nutrition Working Group

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **[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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E-mail: jennifer.a.nettleton@uth.tmc.edu
3. **Timeline:**

<table>
<thead>
<tr>
<th>Stage 1 GWAS</th>
<th>July 1, 2010</th>
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<tbody>
<tr>
<td>Meta-analysis</td>
<td>July 15, 2010</td>
</tr>
<tr>
<td>Stage 2 Replication</td>
<td>August 15, 2010*</td>
</tr>
<tr>
<td></td>
<td>If we recruit studies that have funding to conduct genotyping, this will likely be extended to September 1, 2010</td>
</tr>
<tr>
<td>Manuscript</td>
<td>October 15/November 15 2010</td>
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</table>

4. **Rationale:**

In many modern societies, metabolic diseases such as diabetes, cardiovascular disease and hypertension are highly prevalent. Nutrition is one of the main modifiable risk factors for many such conditions, thus understanding the factors that contribute to eating behavior has important public health implications. While human eating behavior is driven by many psychological and social factors such as culture, economics, and health beliefs, there is evidence from family studies that food intake, in particular, macronutrient intake has a significant genetic component (1).

Family studies have reported suggestive linkage near genes such as proopiomelanocortin (POMC) and neuromedin B (NMB) (1-5). Similarly, candidate gene studies have shown association with polymorphisms in gene such as fat mass and obesity related (FTO), melanocortin 4 receptor (MC4R) and 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A) with macronutrient intake (6-8).

Taken together, these studies support the notion that there is a genetic component to food consumption in humans. However, the differences in study population, dietary assessment methods as well as statistical methodologies between the studies make the results difficult to compare. In addition, each of the studies had relatively small sample sizes limiting the power of the studies. The CHARGE consortium provides an ideal opportunity to investigate whether there are other genetic loci associated with food consumption in a large number of individuals. As such, we propose conducting a genome-wide association analysis using ~2.5 million genotyped and imputed SNPs with macronutrient intake. The results of the ARIC macronutrient intake results will be combined with the other CHARGE studies (FHS, Rotterdam, CHS) in addition to Family Heart Study, InCHIANTI, EPIC, Fenland, Health ABC, MESA and Young Finns study in a meta-analysis. Replication of top hits will be replicated in the GHRAS, GENDAI, MalmoDC, ULSAM, PIVUS and GLACIER. (see Table, page 3)

*For cited references, see page 5.*
Table*

<table>
<thead>
<tr>
<th>GWAS STUDY NAME</th>
<th>N</th>
<th>Replication STUDY NAME</th>
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<tbody>
<tr>
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<td>GHRAS</td>
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<td>Young Finns</td>
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<td>MESA</td>
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<td>GWAS total</td>
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</table>

*N’s are approximate;

5. Main Hypothesis/Study Questions:

Common genetic variants are associated with macronutrient intake.

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).

TRAITS: Intake of fat, carbohydrate, protein as a fraction of total energy intake

TRANSFORMATION: None

EXCLUSIONS: Non-white race, improbable dietary intake

COVARIATES: age, sex, study specific covariates

GENETIC DATA: ~2.5 million genotyped or imputed SNPs

GENOME-WIDE ASSOCIATION ANALYSIS: Multiple linear regression using imputed SNP dosages (1df) to assess additive associations

META-ANALYSIS: Meta-analysis of summary statistics for each analysis will be performed using inverse variance weighted method.

SIGNIFICANCE THRESHOLD: A threshold of p-value 5x10⁻⁸ will be used to determine genome-wide statistical significance.
7.a. Will the data be used for non-CVD analysis in this manuscript? ___ 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? ___ Yes ___ No
(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 ___ 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”? ___ 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

___ 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)?

We are not aware of any overlap

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes ___ No

GWAS via STAMPEDE & GENEVA, #2006.03

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/

(AS 2006.03)

ARIC is one of 12 cohort studies contributing data to the CHARGE/MAGIC-based meta-analysis.

Since this work is a product of CHARGE which utilizes GWA data, ancillaries related to STAMPEDE & GENVA are also acknowledged.
12. 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, and we will meet this deadline
References

1. Rankinen T, Bouchard C. Genetics of food intake and eating behavior phenotypes in humans. Annu Rev Nutr 2006;26:413-34.