ARIC Manuscript Proposal #2570

1. Full Title: ADiposity EXomechip variants association analysis in INteraction with dietary Fatty Acid intake (ADEXINFA)

b. Abbreviated Title (Length 26 characters): Exonic x fatty acid in adiposity

2. Writing Group:
   Writing group members: Valérie Turcot, Mariaelisa Graff, Kari E North, Guillaume Lettre, other investigators welcome

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

VT

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3. Timeline: ~1 year (June 2015-April 2016)

Replication cohort statistical analyses: June 2015
4. **Rationale:**

Whole body fat and abdominal fat accumulation are complex phenotypes implicating both environment and genetic factors (1): designing efficient prevention, management and treatment strategies requires a deep understanding of these factors, as well as their interactions. Heritability estimates suggest that 40-70% of the variation in obesity phenotypes is attributable to underlying genetic variants (2). While over a hundred of common variants on adiposity phenotypes have been identified in genome-wide association studies (GWAS) (3;4), a substantial proportion of the heritability remains unexplained (5). It has been hypothesized that low-frequency and rare coding variants, as well as gene-environment interactions, may partly explain this “unaccounted for” adiposity genetic risk (5;6). Investigating these variants and environment interactions may help to pinpoint causal adiposity gene and variants. The type of fats consumed is one environmental exposure that was previously associated with adiposity traits (7) and some interactions have also been shown with previously known obesity GWAS hits (8;9). The main objective of this project is to test the interactions between potentially functional coding variants (missense, nonsense, splicing sites; MAF≥1%), available on the ExomeChip (Illumina), with the intake of specific dietary fatty acids on adiposity traits (body mass index [BMI] and waist-hip ratio adjusted for BMI [WHRadjBMI]). The preliminary interaction analyses have been conducted in the Montreal Heart Institute Biobank cohort (MHIBB; N=~4,500) with omega-3 PUFA intake and total saturated fat intake (SFA), which were both associated with adiposity traits in this cohort. Considering the power of our preliminary study, no interaction reached the significant threshold (Bonferroni correction; $P<2.6E-6$), but some interactions were enriched in previously known GWAS loci and OMIM genes. We have thus targeted the two top ($P_{GxE}<0.0001$) ExomeChip variants (potentially functional coding variants) among the known adiposity GWAS loci and OMIM gene for a replication analysis in the ARIC cohort.

**Reference List**


5. **Main Hypothesis/Study Questions:**
Aim: to collect summary statistics of gene-diet interaction analyses for BMI and WHR_{adjBMI} in **unrelated European ancestry individuals part of the ARIC cohort (that have both ExomeChip and dietary fatty acid intake data)**. These analyses will be done in men and women combined. The interaction will be tested between 2 targeted ExomeChip variants and 2 types of fatty acids, namely omega-3 PUFAs (EPA+DHA) and total SFAs.

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).**

**Study design:**
Cross-sectional analysis using data taken from visit 3 in the ARIC population-based cohort

**Inclusion:**
- Adults of ≥ 18 years of age
- European ancestry

**Exclusion:**
- Participants taking omega-3 supplements (excluded in the MHIBB preliminary study because of unknown dosage)
- Participants of another ancestry than European ancestry
- Pregnant women
- Subjects aged < 18 years old
- Important outliers in omega-3 PUFAs (or EPA+DHA), total SFA intake, or implausible daily energy intake (ARIC-specific criteria)
- Missing genotype data
- Missing outcome (BMI, WHR) data
- Missing dietary data (omega-3 PUFAs and SFAs)

**Outcome:**
Body mass index (BMI), waist-to-hip ratio (WHR_{adjBMI}).

The residuals of BMI and WHR will be created when modeling these traits against their covariates (see below). These residuals will then be inverse normally transformed. Residuals and the inverse normal transformation will be done in men and women separately and then combined for the analyses (sex-combined analyses only are requested).

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\text{BMI}_{\text{residuals}} = \text{age} + \text{age}^2 + 10 \text{ first principal components (or MDS)}
\]
\[
\text{WHR}_{\text{residuals}} = \text{age} + \text{age}^2 + 10 \text{ first principal components (or MDS)}
\]

Note: Adjustments for other potential covariates (smoking, physical activity, diet quality scores) are not requested for now in the ARIC analyses since the preliminary study (MHIBB) did not adjust for these covariates (availability issue).
Dietary data:
- Daily intake of total saturated fatty acids [SFA] in gram/day (log$_{10}$-transformed) and expressed as a % of total energy
- Daily intake of eicosapentaenoic [EPA] and docosapentaenoic [DHA] acid in gram/day (log$_{10}$-transformed) and expressed as a % of total energy

Genotype data:
- Illumina ExomeChip (the 2 candidate variants details will be provided along with the analysis plan). QCed using the GIANT ExomeChip Project protocol (CHARGE protocol).

Summary data analysis:
Linear regression models will be used in this replication study to test:

Principal analyses (first round of analyses):
1. The interaction between the 2 candidate exonic variants and fatty acid intake (e.g. inverse normal [BMI$_{residuals}$] = variant + log$_{10}$[fatty acid] + variant*log$_{10}$[fatty acid]; using PLINK software)

Secondary analyses if replicated (second round of analyses):
2. The association between the candidate exonic variant and adiposity traits (outcome) in all individuals, and among individuals in specific fatty acid intake tertiles (e.g. inverse normal [BMI$_{residuals}$] = variant; using PLINK software).
3. The association between dietary fatty acid intake and adiposity traits (e.g. inverse normal [BMI$_{residuals}$] = log$_{10}$[fatty acid]; using any statistical software).
4. The association between the 2 candidate exonic variants and fatty acid intake (e.g. inverse normal [fatty acid(gram/day)] = variant; using PLINK software).

These analyses will be done using the absolute (log$_{10}$[gram/day]) and relative (as a % of total energy) intake of n-3 PUFAs (EPA+DHA) and total SFAs, in men and women combined.

Limitations/challenges:
Dietary fatty acid intake in the preliminary analysis (MHIBB) was estimated based on a 14-item food frequency questionnaire (validated against blood biomarkers; Turcot et al. J Hum Nutr Diet 2014). The ARIC study used a more detailed FFQ and makes it possible to adjust for total energy intake, which was not the case in the preliminary analyses. This is the reason why we are asking to run the analyses for both absolute (gram/day) and relative (% energy) intake of n-3 PUFAs and total SFAs. We also checked that the 2 targeted variants are not associated with intake of n-3 PUFAs and total SFAs in the MHIBB cohort (which could have hidden an association with total energy intake).

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

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.