1.a. Full Title:
Low density lipoprotein receptor related protein 1, fatty acids and anthropometric traits

[please note: this a CHARGE working group initiated effort; ARIC is one of several participating cohorts]

b. Abbreviated Title (Length 26 characters):
LRP1, obesity, fatty acids

2. Writing Group:
Writing group members**:
Jennifer Nettleton (ARIC)
Jose Ordovas, Adrienne Cupples, Caren Smith, Caroline Fox (Framingham)
Rozenn Lemaitre, Dariush Mozaffarian, (CHS)
Frank Rooij (Rotterdam)
Jennifer Anderson (Health ABC)
Toshiko Tanaka (InCHIANTI)
Olli Raitakari, Terho Lehtimäki (Young Finns)
Ruth Loos, Zheng Ye (EPIC, Fenland)
Jennifer Anderson (Health ABC)

** 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. _CES_ [please confirm with your initials electronically or in writing]

First author: Caren Smith
Address: 711 Washington St Boston MA 02111
Phone: (617)312-5324 Fax: (617)556-3344
E-mail: caren.smith@tufts.edu

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).
Name: Jennifer Nettleton
Address: E-641 RAS; 1200 Herman-Pressler; Houston, TX 77030
Phone: 713-500-9367 Fax: 713-500-9264
E-mail: jennifer.a.nettleton@uth.tmc.edu

3. Timeline: Provide Data for Meta-analysis: August 20, 2010
4. Rationale:

LDL receptor related protein 1 (LRP1) is a multi-ligand endocytic receptor which mediates lipoprotein remnant uptake and which is highly expressed in several tissues including adipose (Lillis, 2008). Adipocyte-specific knockout experiments by several groups support a role in adipogenesis, and in energy and glucose metabolism (Hofmann, 2007; Masson, 2009; Terrand, 2009). Gene expression studies demonstrate modulation of LRP1 by diet (House, 2005; Llorente-Cortes, 2010) and LRP1 expression predicts weight gain in high saturated fat fed mice (Koza, 2006; GEO database-Edgar, 2002). Fatty acids have been demonstrated to modulate adipocyte LRP1 expression through activation of PPAR-γ (Gauthier, 2003). Although functional evidence is accumulating, population studies for adiposity outcomes related to LRP1 genotype have not been published. However, preliminary evidence for LRP1 SNP rs1799986 (C766T) in US Whites (GOLDN population) suggests association with obesity traits as a main effect and strong interaction with saturated fatty acids in the Boston Puerto Rican Health Study, a population with obesity prevalence of 56% and central obesity of 70%. LRP1 SNP rs1799986 (C766T) also interacted mildly with PUFA in GOLDN for obesity traits. Evaluation of replication in additional populations with larger samples will facilitate interpretation of these preliminary results detected in two genetically and phenotypically disparate populations.

The results from the ARIC study will be combined meta-analytically with other CHARGE studies (FHS, Rotterdam, CHS) in addition to InCHIANTI, EPIC Norfolk, Fenland, Health ABC, MESA and the Young Finns study.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>10,650</td>
</tr>
<tr>
<td>CHS</td>
<td>1800</td>
</tr>
<tr>
<td>FHS</td>
<td>6374</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>4576</td>
</tr>
<tr>
<td>Fenland</td>
<td>1400</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>1124</td>
</tr>
<tr>
<td>Health ABC</td>
<td>1600</td>
</tr>
<tr>
<td>EPIC Norfolk</td>
<td>2000</td>
</tr>
<tr>
<td>Young Finns</td>
<td>2400</td>
</tr>
<tr>
<td>MESA</td>
<td>2382</td>
</tr>
<tr>
<td>Total</td>
<td>34,306</td>
</tr>
</tbody>
</table>

*N’s are approximate

5. Main Hypothesis/Study Questions:

LRP1 is a novel candidate which is associated with anthropometric traits and which interacts with fatty acids to modulate anthropometric traits.
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).

**INTERACTION EXPOSURES:** Intake of saturated fat, polyunsaturated fat, as a percentage of total energy intake, evaluated categorically (based on median intake) and also continuously

**OUTCOME:** BMI, waist circumference, hip circumference

**TRANSFORMATION:** None

**EXCLUSIONS:** Non-white race, improbable dietary intake

**COVARIATES:** age, sex, study-specific covariates

**GENETIC DATA:** 7 LRP1 SNPS shown below, evaluated using an additive model

- rs10876966
- rs715948
- rs1800176
- rs1799986
- rs2306692
- rs12814239
- rs17119494

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

**SIGNIFICANCE THRESHOLD:** P<0.05 with Bonferroni correction

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 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? **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)?
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? ___ X Yes ___ X No

11.b. If yes, is the proposal
_x_ 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/GWAS via STAMPEDE & GENEVA, #2006.03

ARIC is one of ten cohort studies contributing data to the CHARGE Nutrition Working Group -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


4. House RL, Cassady JP, Eisen EJ, McIntosh MK, Odle J. Conjugated linoleic acid evokes de-lipidation through the regulation of genes controlling lipid metabolism in adipose and liver tissue. Obes Rev. 6(3):247-58, 2005


