ARIC Manuscript Proposal #2185

PC Reviewed: 8/13/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title:

Lipoprotein lipase variant interacts with polyunsaturated fatty acids to modulate obesity traits

b. Abbreviated Title:

LPL interacts with PUFA for obesity

2. Writing Group:

Yiyi Ma, the first author, confirms that all the coauthors have given their approval for this manuscript proposal.

Yiyi Ma, Katherine L. Tucker, Caren E. Smith, Kari E. North , Yu-Chi Lee, Tao Huang, Chao-Qiang Lai, Larry D. Parnell, Kris Richardson, Additional ARIC investigators, to be determined, Jose M. Ordovás

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

J.M. Ordovás

3. Timeline:

Individual cohort statistical analyses: ASAP

Manuscript preparation: ASAP

Manuscript submission: Fall 2013

4. Rationale:

This is a replication study request. Could you please make suggestions of possible ARIC Investigators that would be interested in participating in this paper as an Author?

Lipoprotein lipase (*LPL*) has been evaluated as a candidate gene for obesity based on its functions in several relevant tissues including adipose, skeletal muscle, and the central nervous system. As the rate limiting enzyme in triglyceride hydrolysis, LPL regulates fatty acid uptake and storage in adipocytes [1], and also the uptake of fatty acids for oxidation as an energy source in skeletal muscle [2]. Recently, *LPL* was also shown to regulate body weight and energy balance through central nervous system mechanisms [3].

In spite of the potential relevance of LPL to energy balance and adiposity, research exploring the role of *LPL* variants in obesity-related traits is limited. Three candidate gene studies reported that *LPL* rs320 was associated with obesity, especially in women [4-6]. This association may be related to the *in vitro* finding that the rs320 variant affects gene expression by altering transcription factor binding [7]. In addition, although LPL plays an important role in the disposal of dietary fatty acids [8], whether dietary fat modulates associations between *LPL* rs320 and obesity-related traits is unexplored.

Based on these gaps in knowledge, we conducted a gene-diet interaction study in the Boston Puerto Rican Health Study (n=1171, 70% women, aged 45-75 y), a US Hispanic population with high prevalence of obesity and diabetes [9]. We observed that *LPL* rs320, common name HindIII, interacted with dietary polyunsaturated fatty acids (PUFA) for body mass index (BMI) and waist circumference (WC) in both categorical (*P*=0.01 and 0.02) and continuous analyses (*P*=0.009 and 0.004). Higher intake of PUFA was associated with lower BMI and WC in homozygotes of the major allele (TT) according to both categorical (*P*=0.03 and 0.01) and continuous analysis (*P*=0.01 and 0.004) but not in carriers of the minor allele (TG+GG).

In addition, we found one SNP in high LD (R^2=1) with rs320 in Hapmap CEU population has significant interaction with dietary PUFA intake in the women (P for interaction = 0.03) of Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study (n=1076, 52% women, aged 18-87 y). However this interaction attenuates in the men.

We propose to evaluate replication of these significant interactions with rs320 in ARIC.

5. Main Hypotheses/Study Questions:

To replicate the significant interaction for dietary polyunsaturated fatty acids with *LPL* rs320 modulating obesity traits found in Boston Puerto Rican Health Study (BPRHS).

6. Design and Analysis:

Phenotypic variables: BMI and waist circumference.

Statistical Analyses-

Linear regression model with interaction term between dietary polyunsaturated fatty acids and genotype of *LPL* rs320 will be applied.

<u>Exclusions:</u>

Exclude those with implausible total energy intake, according to cohort-specific definitions.
Ethnicity and gender based analyses: :
Analyses are requested in Whites and African Americans separately, both in the entire population and also stratified by gender.
Genetic model:
Dominant model for SNP rs320, in which homozygote of major allele (TT) are compared to carriers of minor allele (TG/GG). Due to the fact that BPRHS used dominant model, so we would ideally like to see a similar model tested in a replication population.
Dietary exposures:
Polyunsaturated fatty acid intake (% of total energy), modeled as a categorical (dichotomized into high and low based on population median intake) and also as a continuous variable
Covariates:
Study center (categorical, if applicable), gender (categorical, men or women, do not adjust for this for the stratified analysis for each gender), total fat intake (continuous, % total energy), age (continuous, y), physical activity(if applicable), population sub-structure (if applicable), current smoking (binary, yes or no), current drinking (binary, yes or no), total energy intake (continuous, kcal), diabetes status (binary, yes or no), antilipemic medication (binary, yes or no), anti-depressants (binary, yes or no), hormone replacement therapy in women (binary, yes or no), and education level (if applicable).

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

_*__ Yes

_ No

b. If Yes, is the author aware that the file ICTDER02 must be will use to exclude

persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and

for DNA analysis RES_DNA = "CVD Research" would be will use?

_*__Yes

___ No

(This file ICTDER02 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 will use in this manuscript?

_*__ Yes

___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be will use, or the file ICTDER02 must be will use 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

_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)?

This manuscript does not overlap any proposals.

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 (AS #2006.03 & 2007.02)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____)

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.

References:

1. Gonzales, A.M. and R.A. Orlando, *Role of adipocyte-derived lipoprotein lipase in adipocyte hypertrophy.* Nutr Metab (Lond), 2007. **4**: p. 22.
2. Weinstock, P.H., et al., *Lipoprotein lipase controls fatty acid entry into adipose tissue, but fat mass is preserved by endogenous synthesis in mice deficient in adipose tissue lipoprotein lipase.* Proc Natl Acad Sci U S A, 1997. **94**(19): p. 10261-6.
3. Wang, H., et al., *Deficiency of lipoprotein lipase in neurons modifies the regulation of energy balance and leads to obesity.* Cell Metab, 2011. **13**(1): p. 105-13.
4. Corella, D., et al., *Gender specific associations of the Trp64Arg mutation in the beta3-adrenergic receptor gene with obesity-related phenotypes in a Mediterranean population: interaction with a common lipoprotein lipase gene variation.* J Intern Med, 2001. **250**(4): p. 348-60.
5. Chamberland, A., et al., *Association study between candidate genes and obesity-related phenotypes using a sample of lumberjacks.* Public Health Genomics, 2009. **12**(4): p. 253-8.
6. Jemaa, R., et al., *Lipoprotein lipase gene polymorphisms: associations with hypertriglyceridemia and body mass index in obese people.* Int J Obes Relat Metab Disord, 1995. **19**(4): p. 270-4.
7. Chen, Q., et al., *Functional significance of lipoprotein lipase HindIII polymorphism associated with the risk of coronary artery disease.* Atherosclerosis, 2008. **200**(1): p. 102-8.
8. Fielding, B.A. and K.N. Frayn, *Lipoprotein lipase and the disposition of dietary fatty acids.* Br J Nutr, 1998. **80**(6): p. 495-502.
9. Tucker, K.L., et al., *The Boston Puerto Rican Health Study, a longitudinal cohort study on health disparities in Puerto Rican adults: challenges and opportunities.* BMC Public Health, 2010. **10**: p. 107.