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Lipoprotein lipase variants interact with polyunsaturated fatty acids for obesity traits in women: Replication in two populations

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Abstract *Background and aims:* Lipoprotein lipase (*LPL*) is a candidate gene for obesity based on its role in triglyceride hydrolysis and the partitioning of fatty acids towards storage or oxidation. Whether dietary fatty acids modify *LPL* associated obesity risk is unknown.
Methods and results: We examined five single nucleotide polymorphisms (SNPs) (rs320, rs2083637, rs17411031, rs13702, rs2197089) for potential interaction with dietary fatty acids for obesity traits in 1171 participants (333 men and 838 women, aged 45–75 y) of the Boston Puerto Rican Health Study (BPRHS). In women, SNP rs320 interacted with dietary polyunsaturated fatty acids (PUFA) for body mass index (BMI) ($P = 0.002$) and waist circumference (WC) ($P = 0.001$) respectively. Higher intake of PUFA was associated with lower BMI and WC in homozygotes of the major allele (TT) ($P = 0.01$ and 0.005) but not in minor allele carriers (TG and GG). These interactions were replicated in an independent population, African American women of the Atherosclerosis Risk in Communities (ARIC) study ($n = 1334$).
Conclusion: Dietary PUFA modulated the association of *LPL* rs320 with obesity traits in two independent populations. These interactions may be relevant to the dietary management of obesity, particularly in women.

Abbreviations: LPL, lipoprotein lipase; SNP, single nucleotide polymorphism; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; BPRHS, Boston Puerto Rican Health Study; ARIC, Atherosclerosis Risk in Communities Study; AA, African American; EA, European American; WC, waist circumference; HDL, high density lipoprotein; LD, linkage disequilibrium; HWE, Hardy–Weinberg Equilibrium; CEU, Utah residents with Northern and Western European Ancestry; YRI, Yoruba in Ibadan, Nigeria; FFQ, food frequency questionnaire; BMI, body mass index; PPRE, peroxisome proliferator-activated receptors response element; MAF, minor allele frequency; ASW, African ancestry in Southwest USA; MXL, Mexican ancestry in Los Angeles; LDL, low density lipoprotein; UTR, untranslated region; TSS, transcription start site.

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Introduction

Obesity in the US has reached an overall prevalence of nearly 34% [1], with greater prevalence in some ethnic minorities [2], which might be related to differences in genetic background and behavioral factors [3–5]. The investigation of genetic variants for obesity in conjunction with behavioral factors, especially diet, may benefit development of more specific strategies to ameliorate susceptibility to weight gain.

Lipoprotein lipase (*LPL*) is a candidate gene for obesity, based on its encoded function to absorb fatty acids across tissues [6,7]. *LPL* contributes to fat storage in adipocytes [8], regulation of thermogenesis in skeletal muscle [9]. However, in spite of LPL's demonstrated role in obesity, relevant association studies with *LPL* single nucleotide polymorphism (SNP) have inconsistent findings and show sex-specific differences [10,11].

One hypothesis that may account for the inconsistency is that unexamined factors may modulate *LPL*-associated obesity risk. Dietary fat type (e.g., saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA)) have been evaluated for obesity risk independently of genotype for decades [4]. However, it remains to be explored whether intakes of different fatty acids alter obesity-related traits in the context of *LPL* genotype.

Therefore, we aimed to determine whether dietary fatty acids interact with *LPL* variants for obesity traits in a population of multiple ancestries, stratified by sex. We also aimed to replicate our findings in an independent population.

Methods

Study populations

Discovery population: The Boston Puerto Rican Health Study (BPRHS)

In the BPRHS, there were 1171 participants of Puerto Rican origin, aged 45–75 years, living in the Greater Boston, MA metropolitan area, after excluding those with missing data and implausible energy intake, defined as <2512 kJ (600 kcal) per day or >20093 kJ (4800 kcal) per day. Details for the study have been described previously [12]. Fasting blood were collected for biochemical and genetic analyses. Anthropometric methods were consistent with techniques used by the National Health and Nutrition Examination Surveys. The study protocol was approved by the Institutional Review Board at Tufts Medical Center and Tufts University Health Sciences Campus. Informed consent was received by all participants or their representatives.

Replication population: Atherosclerosis Risk in Communities Study (ARIC)

Participants of replication study in ARIC included 2186 African American (AA) and 8689 European American (EA), considering the multiple ancestry nature of the BPRHS. ARIC was a multi-center study with participants aged 44–66 years from Forsyth County, North Carolina; Jackson, Mississippi; suburban areas of Minneapolis, Minnesota; and Washington County, Maryland [13]. Individuals with implausible energy intakes, defined as in the BPRHS, were excluded from analysis. Body weight was measured using a calibrated scale with subjects in scrub suits without shoes and height was measured using a ruler. Waist circumference (WC) at the umbilicus was measured using a tape measure. Fasting blood was collected from an antecubital vein into a vacuum tube with ethylenediamine tetraacetic acid. Triglycerides and high-density lipoprotein (HDL) were assayed using enzymatic methods and dextran-magnesium precipitation respectively [14]. This study was approved by the Institutional Review Board at each field center, and the University of North Carolina at Chapel Hill. Informed consent was received by all participants or their representatives.

SNP selection, genotyping and linkage disequilibrium (LD) analysis

Four lipids related SNPs (rs2083637, rs17411031, rs13702, and rs2197089) [15–17], and rs320 (common name as *HindIII*) with inconsistent associations with obesity [10,11] were selected as discovery panel tested in BPRHS. Genotyping in BPRHS was performed using the ABI TaqMan SNP genotyping system 7900HT (Applied Biosystems, Foster City, CA). Hardy–Weinberg equilibrium (HWE) was evaluated by Chi-square tests. LD and haplotype was analyzed by HaploView4.2 [18] according to 1000 Genomes Project. Genotypes of replication SNP rs327 in ARIC was imputed by MACH (v1.0.16) [19] with HapMap r22 reference populations, Utah residents with Northern and Western European Ancestry (CEU) and Yoruba in Ibadan, Nigeria (YRI) based on the genome-wide SNP data obtained by the Affymetrix 6.0 chip (Affymetrix, Santa Clara, CA).

Dietary assessment

The BPRHS used a semi-quantitative food frequency questionnaire (FFQ) [20]. The ARIC study used a modified 66-item interviewer-administered FFQ [21]. Dietary fatty acids intake was expressed as a percentage of total energy intake.

Population ancestry admixture

The population admixture of participants in the BPRHS was estimated with reference to three ancestral populations including Native American (15%), Southern European (57%), and West African (27%), and the major principal component estimated by EIGENSTRAT was adjusted in the analysis [22]. The first 10 principal components, estimated using Eigensoft, represent admixture for ARIC EAs. Percentage of European ancestry for ARIC AAs was estimated based on the reference population of CEU using 1350 ancestry informative markers by ANCESTRYMAP [23].

Statistical analysis

Analysis of covariance and general linear models were applied to test genetic associations and interactions between SNPs and different types of dietary fat intake (SFA, MUFA and