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Apolipoprotein A5 and lipoprotein lipase interact to modulate anthropometric measures in Hispanics of Caribbean origin

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Abstract

Apolipoprotein A5 (APOA5) and lipoprotein lipase (LPL) proteins interact functionally to regulate lipid metabolism, and single nucleotide polymorphisms (SNPs) for each gene have also been associated independently with obesity risk. Evaluating gene combinations may be more effective than single SNP analyses in identifying genetic risk, but insufficient minor allele frequency (MAF) often limits evaluations of potential epistatic relationships. Populations with multiple ancestral admixtures may provide unique opportunities for evaluating genetic interactions. We examined relationships between *LPL* m107 (rs1800590) and *APOA5* S19W (rs3135506) and lipid and anthropometric measures in Caribbean origin Hispanics (n=1019, aged 45–5 years) living in the Boston metropolitan area. Significant interaction terms between *LPL* m107 and *APOA5* S19W were observed for BMI ($P=0.003$) and waist circumference ($P=0.019$). Higher BMI ($P=0.001$), waist ($P=0.011$) and hip ($P=0.026$) were observed in minor allele (G) carriers for *LPL* m107 who also carried the *APOA5* S19W minor allele (G). Additionally, extreme obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) risk was higher (OR=4.02; 95% CI:1.81–.91; global $P=0.008$) for minor allele carriers for both SNPs (*LPL* TG+GG, *APOA5* CG+GG) compared to major allele carriers for both SNPs. In summary, we identified significant interactions for *APOA5* S19W and *LPL* m107 for obesity in Caribbean Hispanics. Population-specific MAFs increase the difficulties of replicating gene-gene interactions, but may support the hypothesis that combinations of frequencies in selected genes could heighten obesity susceptibility in a given population. Analyses of gene-gene interactions may improve understanding of genetically-based obesity risk, and underscore the need for further study of groups with multiple ancestral admixtures.

Introduction

Obesity is a complex, multifactorial condition for which heritability estimates vary widely, and this variability could be related to the large number of potential genetic contributors. Hundreds of obesity candidate loci have been proposed, and genome-wide association studies continue to identify new loci, but each individual locus may account for only a small percentage of the variability in populations (1). Analytic approaches which evaluate combinations of gene variants may improve our understanding of the genetic factors which modulate obesity variation and may help to clarify disparate results in genetic association studies (2).

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Disclosure

The authors have no conflicts of interest to disclose.

Lipoprotein lipase (LPL), an important regulator of lipid and energy metabolism, has been explored as a potential genetic contributor to plasma lipids and obesity. LPL is the rate-limiting enzyme for hydrolysis of circulating triglycerides (TG) that comprise chylomicrons and very low density lipoproteins (VLDL), thereby regulating fatty acids supplied for oxidation in skeletal muscle or for storage in adipose tissue (3). Associations between *LPL* genetic variants and plasma lipids are well-documented (4) and the regulatory function of LPL in fatty acid partitioning and energy metabolism supports a possible additional role in obesity risk. Genetic studies linking *LPL* variants to obesity or altered adipose tissue distribution have reported gene-gene interactions between *LPL* and beta adrenergic receptor (*ADR*) variants or associations involving *LPL* haplotypes (5–7). In addition, the *LPL* promoter single nucleotide polymorphism (SNP), *LPL* m107 (–93 T/G), has been reported to be associated with obesity in Asian Indians in South India (8).

Apolipoprotein A5 (*APOA5*) is another key regulator of TG metabolism and its genetic associations with plasma lipids and cardiovascular disease risk have been replicated in multiple populations (9–12). One mechanism by which *APOA5* regulates plasma lipids is via activation of proteoglycan-bound lipoprotein lipase to augment TG hydrolysis (13). Overexpression of *APOA5* has been shown to increase LPL activity in an animal model (14). A second mechanism by which *APOA5* has been hypothesized to modulate plasma TG is via inhibition of VLDL synthesis (15). Associations between individual *APOA5* SNPs and obesity, as well as lipids, have been reported (10,16) but in another study the association between *APOA5* –1131 T>C and obesity became apparent only when an interaction was considered, that of dietary fat (17).

Interactions between *APOA5* and additional genetic factors, such as *LPL*, may be relevant to modulation of plasma lipids as well as obesity. Demonstrated functional relationships between LPL and *APOA5* proteins in the modulation of plasma lipids lend further support to an analytic approach based on gene-gene interactions. For example, the *APOA5* A139X variant is associated with altered LPL mass and activity in hyperchylomicronemia (18). Further, human carriers of either *APOA5* S16W or *APOA5* m1123 have been demonstrated to exhibit lower LPL activity *in vivo* following an intravenous fat tolerance test (19). Multiple novel *APOA5* variants have been shown to exert variable effects on LPL activation, resulting in varying degrees of impaired lipolysis and hypertriglyceridemia in people (20).

With respect to the obesity phenotype, as opposed to hypertriglyceridemia, potential epistasis between *APOA5* and *LPL* is unexplored. We based selection of specific *APOA5* and *LPL* SNPs on reported phenotypic associations and also on the presence of adequate minor allele frequencies (MAF) in our population. *APOA5* is a strong determinant of plasma TG in many ethnic groups (12,21) but the frequency of SNP *APOA5* S16W (56C>G) is higher in Hispanic Americans compared to non-Hispanic Whites and African Americans (21). The *LPL* SNP m107 (–93 T/G) is of interest in part due to its reported association with increased obesity risk (8), but also because of earlier work reporting its ethnically variable modulation of plasma lipids (22,23). MAF for the *LPL* m107 SNP is highly variable across populations, ranging from undetectable in Chinese and 0.017 in non-Hispanic Whites, to 0.764 in Black South Africans (23). Caribbean Hispanics are characterized by admixture from European, Taíno American Indian and African ancestries, and this provides sufficiently high MAF of both *APOA5* S16W and *LPL* m107 SNPs. In this unique population, we are able to evaluate epistatic relationships which would require much larger sample sizes in other populations. Therefore, in the current study, we examined whether *LPL* m107 and *APOA5* S16W interact to modulate obesity and plasma lipids in Caribbean origin Hispanics.

Methods

Study Design and Subjects

Participants were recruited for a prospective two-year cohort study of men and women of Puerto Rican origin aged 45–74 years and living in the Boston, Massachusetts metropolitan area. Interviews to collect baseline demographic information, medical history, anthropometric and dietary data were conducted between 2004 and 2007 by trained bilingual staff. The Institutional Review Board at Tufts University/New England Medical Center approved the protocol of the current study. Anthropometric data including height, weight, and waist and hip circumference were measured in duplicate consistent with the technique used by the National Health and Nutrition Surveys (NHANES).

Laboratory Methods

Blood was collected for biochemical analyses and genetic analysis. Plasma was separated within four hours in a refrigerated centrifuge and then stored at -70°C . High density lipoprotein cholesterol (HDL-C) was analyzed using EDTA plasma with the enzymatic endpoint reaction with Olympus HDL reagents (OSR6156) and TG were analyzed using EDTA plasma with Olympus TG reagents (OSR6033). HDL-C and TG measurements were performed using the Olympus AU400e (Olympus America Inc., Melville, NY).

Genetic analysis

Genomic DNA was isolated from peripheral blood lymphocytes by standard methods. The SNPs *LPL* m107 (rs1800590) and *APOA5* S16W (rs3135506) were genotyped using the ABI Prism TaqMan multiplex system (Applied Biosystems, Foster City, California).

Population ancestry admixture

The study participants reflect three ancestral populations, European, Taíno American Indian and African, which may be represented in varying proportions for each individual. One hundred ancestral markers were chosen to reduce confounding associated with population stratification. The programs STRUCTURE 2.2 (24) and IAE3CI (25) were used to calculate three admixture values for each subject and similar results were achieved (26). Multivariate regression analysis models incorporate adjustment for population admixture through the addition of two of the three admixture variables as covariates.

Statistical Analyses

All continuous variables were examined for normal distribution. Triglycerides were log transformed in order to normalize the distribution. The relationship between the individual SNPs *LPL* m107 and *APOA5* S16W, and anthropometric measures and plasma lipids were evaluated by analysis of variance techniques. Interactions between the polymorphisms and anthropometric measures or plasma lipids were tested in a multivariate interaction model, with control for potential confounders including age, sex, current alcohol use, current smoking, diabetes, antilipemic medication, energy intake, physical activity and ancestry admixture. Combinations of genotypes were constructed as major-minor allele pairs to evaluate associations of genotype combination with differences in anthropometric measures and lipids. Logistic regression models were fitted to estimate risk (OR and 95% CI) of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) and extreme obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) associated with the presence of one or two genetic variants, as compared with the absence of the genetic variants. SAS (Version 9.1 for Windows) was used to analyze data. A *P* value of 0.05 was considered statistically significant.

Results

Demographic, biochemical, anthropometric and genotypic data are presented in Table 1. Genotype frequencies for the *APOA5* S19W SNP did not deviate from Hardy-Weinberg equilibrium (HWE) expectations but *LPL* m107 deviated from expectations ($P=0.001$). Minor allele frequency (MAF) was 0.128 for *LPL* m107 and 0.104 for the *APOA5* S19W SNP. Anthropometric measures did not differ according to *LPL* m107 genotype, but HDL-C was significantly lower in carriers of the minor allele ($P=0.013$; Table 2). No differences in anthropometric measures were observed for *APOA5* S19W, but TG was significantly higher in carriers of the minor allele ($P<0.0001$; Table 3). Multivariate adjustment for potential confounders included age, sex, current smoking, current alcohol, physical activity, diabetes, antilipemic medication, energy intake and admixture. Lipid measures were also adjusted by waist circumference and hormone use in women.

Genotype combinations for the two SNPs were constructed to evaluate interactions between the genes for lipids and anthropometric measures. No significant interactions were observed between *LPL* m107 and *APOA5* S19W for plasma lipids (data not shown). Significant interaction terms between *LPL* m107 and *APOA5* S19W were observed for BMI ($P=0.003$; Figure 1; panel A) and waist circumference ($P=0.019$; Figure 1; panel B) and marginally significant interaction was observed for hip circumference ($P=0.054$; Figure 1; panel C). Significantly higher BMI was observed in subjects with the minor allele for *LPL* m107 (G) who also carried the *APOA5* S19W minor allele (G) (Figure 1; panel A; $P = 0.001$). Significantly higher waist circumference was observed in subjects with the minor allele for *LPL* m107 (G) who also carried the *APOA5* S19W minor allele (G) (Figure 1; panel B; $P = 0.011$). Similarly, significantly higher hip circumference was present in subjects with the G allele for *LPL* m107 who were also carriers of *APOA5* S19W minor allele (G) (Figure 1; panel C; $P = 0.026$). Differences for BMI, waist and hip were not observed for *LPL* m107 genotype in subjects who lacked the *APOA5* S19W minor allele (G). Total energy intake did not differ according to genotype combination (data not shown). We also evaluated obesity measures and genotype combinations using a second model in which diabetes was not included as a confounder, but this did not alter significant relationships for gene-gene interactions or genotype-associated differences.

Examination of the relationship between *LPL* m107 and *APOA5* S19W genotype combination and extreme obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) revealed an increased frequency of extreme obesity for carriers of the minor allele for both SNPs (*LPL* TG+GG and *APOA5* CG+GG; Table 4). Subjects with extreme obesity for whom genotype data are available for both SNPs are categorized by combined genotype ($n=113$). Compared to the reference group of subjects carrying major alleles for both SNPs, the presence of both *LPL* TG+GG and *APOA5* CG+GG alleles was associated with an odds ratio (OR) of 4.02 for extreme obesity (95% CI of 1.81 to 8.91; global $P=0.008$). The same multivariate adjustments used for the previous analyses were applied.

Discussion

We have observed an interaction between *APOA5* S19W and *LPL* m107 in which the presence of minor alleles for both SNPs was associated with significantly greater measures of obesity, including extreme obesity, compared to subjects with one or no minor alleles. Significant associations for obesity were not observed for either of the individual SNPs, although HDL-C and TG differed according to *LPL* m107 and *APOA5* genotype, respectively. Previous studies have implicated various SNPs of *LPL* and *APOA5*, either individually or in combination with other genes, for obesity and plasma lipids, but interaction between these two genes for obesity has not been reported previously.

Evidence for LPL as a regulator of energy balance and potential modulator of obesity is extensive, although inconclusive. One previous study reported an increased risk of obesity associated with the individual SNP *LPL* m107 in a population of Asian Indians (8), but the tendency towards an association with obesity for this SNP alone did not reach significance in the current study. Consideration of LPL as a potential modulator of obesity is based on the role of LPL in regulating the supply of TG-derived fatty acids to skeletal muscle for oxidation or to adipose for storage (3). LPL sensitivity to energy balance is reflected in its tissue-specific responses to feeding, fasting and exercise (3,27). The effect of weight loss on adipose LPL activity varies among individuals, and may predict subsequent weight regain. In the 6 months following a hypocaloric intervention, human subjects whose adipose LPL had decreased during the intervention demonstrated less weight regain than those whose LPL had increased during the intervention, suggesting that LPL may play a regulatory role in ongoing weight maintenance (28). Whether this variability in LPL response to energy deficit is related to genetic variants, or to additional factors acting to regulate LPL, is unknown. In another study of adipose LPL and obesity, leptin-deficient (ob/ob) mice lacking adipose LPL but expressing skeletal muscle LPL demonstrated reduced weight and fat mass compared to ob/ob mice which did not lack LPL, although the apparent resistance to obesity conferred by adipose LPL knockout was not observed in non-ob/ob mice (29). Animal studies demonstrating that the LPL activator NO-1886 (ibrolipim) is associated with decreased fat accumulation and increased uncoupling protein 3 (*UCP3*) mRNA in high-fat-induced obese animals suggest a role for LPL in energy balance, possibly through stimulation of increased fatty acid oxidation by skeletal muscle (30).

Collectively, the preceding physiologic studies provide a framework by which LPL may modulate obesity, but do not address the question of whether single SNP genetic variation in *LPL* is sufficient to influence obesity or whether variation in other regulators of energy and lipid metabolism is also required. Obesity association studies for *LPL* often report interactions between *LPL* and other potential obesity candidates, such as *ADR* and glucocorticoid receptor variants, and suggest an interplay between *LPL* and other genetic factors in modulating obesity (6,7). These results support observations in our population, in which neither *LPL* nor *APOA5* variants alone were associated with obesity, but in which the presence of both minor alleles was associated with higher anthropometric measures.

In order to better characterize the nature of the increased measures of obesity associated with genotype, we also examined the risk of extreme obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) by genotype combination. Extreme obesity prevalence was 12% in this Caribbean-origin Hispanic population, which exceeds estimates for prevalence in Hispanic Americans of unspecified origin, aged 50–79 years (31). While obesity risk ($\text{BMI} \geq 30 \text{ kg/m}^2$) did not differ according to genotype combination, the OR of extreme obesity was four times greater in subjects carrying both minor alleles. This observation represents a potentially important clinical finding, as $\text{BMI} \geq 40 \text{ kg/m}^2$ is associated with more co-morbidities and higher mortality than less severe obesity (31).

In addition to the interactions observed for obesity, *APOA5* S16W was associated with higher TG in our population. An association between *APOA5* and altered TG is consistent with previous studies in other groups (32). While we detected no association between *LPL* m107 and TG, previous studies have produced conflicting results in which the *LPL* m107 minor allele has been associated with unchanged, higher or with lower TG in different ethnic groups (23, 33). One source of apparent conflict in associations for *LPL* m107 and lipids may be the differential LD patterns between *LPL* m107 and other *LPL* SNPs. For example, LD between *LPL* D9N and m107 is strong in non-Hispanic Whites and the D9N SNP has been shown to be associated with high TG (23,34). LD between *LPL* m107 and *LPL* D9N is weak in Africans, and in the current study of subjects with African as well as European admixture, weak LD

between *LPL* D9N and *LPL* m107 may account for the lack of an association for *LPL* m107 with TG. Alternatively, *APOA5* may be a more important modulator of plasma TG in this population, and may modulate TG via inhibition of VLDL synthesis in addition to its interaction with *LPL* (15).

Previous studies examining *LPL* m107 and HDL-C are similarly mixed. While we observed a significant association for *LPL* m107 minor allele with lower HDL-C, an earlier study reported no differences in HDL-C for *LPL* m107/D9N haplotypes in a small, combined African-American/Hispanic American population (35). Similarly, no associations between *LPL* m107 and plasma lipids were reported for Asian Indians (8). However, lower HDL-C was associated with the *LPL* m107 minor allele in two non-Hispanic White populations (34,36). Ethnic-specific LD patterns may underlie differential associations for HDL-C as well as for TG. Alternatively, the lower HDL-C observed in *LPL* m107 carriers in the current study may be related to the non-significant tendency for increased obesity and increased abdominal obesity in minor allele carriers.

Several limitations for the current study must be addressed. One question relating to *LPL* m107 is the deviation from HWE observed in the current population, because deviation may indicate genotyping error. Laboratory procedures in place to detect error include blinded no-template controls and DNA sample replicates. Further, genotype clusters were re-checked visually to confirm that genotyping error did not occur. Genotype error rate was estimated at less than 0.5%. Previous studies which have evaluated HWE have not reported deviation for this SNP; however, HWE analysis has not been reported in all studies. In one previous study for which *LPL* m107 allele frequencies were reported but HWE not evaluated, we calculated a slight deviation from HWE [$P=0.03$] (22). HWE deviation may reflect population substructure or selection, or may support an association between genotype and disease (37). A second consideration is the relatively small number of subjects ($n=47$) carrying minor alleles for both SNPs. Ideally, a larger population with a greater number of minor allele carriers would be preferable.

In summary, we observed an interaction between *LPL* m107 and *APOA5* S19W for obesity in Caribbean origin Hispanics. Replication is critical for validating association and interaction studies, and the observations reported for a single population in the current study must therefore be considered hypothesis-generating rather than definitive. However, replication of gene-gene interactions may be more difficult than replication of single SNP studies due to the requirement for adequate MAF for both SNPs. *LPL* m107 MAF is highly variable, ranging from 0.76 in South African Blacks (23), 0.28 in African Americans (35), 0.128 in the current population, 0.05–0.06 in Asian Indians (8), and 0.017 in non-Hispanic Whites (23). In addition, groups in which *LPL* m107 frequency may be sufficient for testing, such as Asian Indians, may exhibit a relatively lower MAF (0.03) for *APOA5* S19W, which is substantially less than that reported for the current Caribbean origin Hispanic population (0.104) or other Hispanic populations [0.15](21). Population differences in allelic frequencies increase the difficulties of replicating gene-gene interactions, but also support the hypothesis that combinations of allelic frequencies in multiple genes may heighten genetic susceptibility for disease risk in a given population, such as Hispanics of Caribbean origin. Increasing understanding of gene-gene interaction may provide a more realistic picture of genetically-based obesity risk, and underscores the need for further study of groups with multiple ancestral admixtures.

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References

1. Perusse L, Rankinen T, Zuberi A, et al. The human obesity gene map: the 2004 update. *Obes Res* 2005;13(3):381–490. [PubMed: 15833932]
2. Bouchard L, Tremblay A, Bouchard C, Perusse L. Contribution of several candidate gene polymorphisms in the determination of adiposity changes: results from the Quebec Family Study. *Int J Obes* 2007;31(6):891–899.
3. Lithell H, Boberg J, Hellsing K, Lundqvist G, Vessby B. Lipoprotein-lipase activity in human skeletal muscle and adipose tissue in the fasting and the fed states. *Atherosclerosis* 1978;30(1):89–94. [PubMed: 678312]
4. Chen W, Srinivasan SR, Elkasabany A, Ellsworth DL, Boerwinkle E, Berenson GS. Influence of lipoprotein lipase serine 447 stop polymorphism on tracking of triglycerides and HDL cholesterol from childhood to adulthood and familial risk of coronary artery disease: the Bogalusa heart study. *Atherosclerosis* 2001;159(2):367–373. [PubMed: 11730816]
5. Goodarzi MO, Taylor KD, Guo X, et al. Haplotypes in the lipoprotein lipase gene influence fasting insulin and discovery of a new risk haplotype. *J Clin Endocrinol Metab* 2007;92(1):293–296. [PubMed: 17032721]
6. Li S, Chen W, Srinivasan SR, Boerwinkle E, Berenson GS. Influence of lipoprotein lipase gene Ser447Stop and beta1-adrenergic receptor gene Arg389Gly polymorphisms and their interaction on obesity from childhood to adulthood: the Bogalusa Heart Study. *Int J Obes* 2006;30(8):1183–1188.
7. Ukkola O, Perusse L, Chagnon YC, Despres JP, Bouchard C. Interactions among the glucocorticoid receptor, lipoprotein lipase and adrenergic receptor genes and abdominal fat in the Quebec Family Study. *Int J Obes Relat Metab Disord* 2001;25(9):1332–1339. [PubMed: 11571596]
8. Radha V, Vimalaswaran KS, Ayyappa KA, Mohan V. Association of lipoprotein lipase gene polymorphisms with obesity and type 2 diabetes in an Asian Indian population. *Int J Obes* 2007;31(6):913–918.
9. Chandak GR, Ward KJ, Yajnik CS, et al. Triglyceride associated polymorphisms of the APOA5 gene have very different allele frequencies in Pune, India compared to Europeans. *BMC Med Genet* 2006;7–76. [PubMed: 16464259]
10. Elosua R, Cupples LA, Fox CS, et al. Association between well-characterized lipoprotein-related genetic variants and carotid intimal medial thickness and stenosis: The Framingham Heart Study. *Atherosclerosis* 2006;189(1):222–228. [PubMed: 16430904]
11. Hubacek JA, Skodova Z, Adamkova V, Lanska V, Poledne R. The influence of APOAV polymorphisms (T-1131>C and S19>W) on plasma triglyceride levels and risk of myocardial infarction. *Clin Genet* 2004;65(2):126–130. [PubMed: 14984471]
12. Lai CQ, Tai ES, Tan CE, et al. The APOA5 locus is a strong determinant of plasma triglyceride concentrations across ethnic groups in Singapore. *J Lipid Res* 2003;44(12):2365–2373. [PubMed: 12951359]
13. Merkel M, Loeffler B, Kluger M, et al. Apolipoprotein AV accelerates plasma hydrolysis of triglyceride-rich lipoproteins by interaction with proteoglycan-bound lipoprotein lipase. *J Biol Chem* 2005;280(22):21553–21560. [PubMed: 15774484]
14. Fruchart-Najib J, Bauge E, Niculescu LS, et al. Mechanism of triglyceride lowering in mice expressing human apolipoprotein A5. *Biochem Biophys Res Commun* 2004;319(2):397–404. [PubMed: 15178420]
15. Weinberg RB, Cook VR, Beckstead JA, et al. Structure and interfacial properties of human apolipoprotein A-V. *J Biol Chem* 2003;278:34438–34444. [PubMed: 12810715]
16. Niculescu LS, Fruchart-Najib J, Fruchart JC, Sima A. Apolipoprotein A-V gene polymorphisms in subjects with metabolic syndrome. *Clin Chem Lab Med* 2007;45(9):1133–1139. [PubMed: 17635078]
17. Corella D, Lai CQ, Demissie S, et al. APOA5 gene variation modulates the effects of dietary fat intake on body mass index and obesity risk in the Framingham Heart Study. *J Mol Med* 2007;85:119–128. [PubMed: 17211608]

18. Marçais C, Verges B, Charrière S, et al. ApoA5 Q139X truncation predisposes to late-onset hyperchylomicronemia due to lipoprotein lipase impairment. *J Clin Invest* 2005;115(10):2862–2869. [PubMed: 16200213]
19. Kovar J, Adamkova V. Lipoprotein lipase activity determined in vivo is lower in carriers of apolipoprotein A-V gene variants 19W and -1131C. *Physiol Res* 2008;57(4):555–561. [PubMed: 17705673]
20. Dorfmeister B, Zeng WW, Dichlberger A, et al. Effects of six APOA5 variants, identified in patients with severe hypertriglyceridemia, on in vitro lipoprotein lipase activity and receptor binding. *Arterioscler Thromb Vasc Biol* 2008;28(10):1866–1871. [PubMed: 18635818]
21. Pennacchio LA, Olivier M, Hubacek JA, Krauss RM, Rubin EM, Cohen JC. Two independent apolipoprotein A5 haplotypes influence human plasma triglyceride levels. *Hum Mol Genet* 2002;11(24):3031–3038. [PubMed: 12417524]
22. Hall S, Chu G, Miller G, et al. A common mutation in the lipoprotein lipase gene promoter, -93T/G, is associated with lower plasma triglyceride levels and increased promoter activity in vitro. *Arterioscler Thromb Vasc Biol* 1997;17(10):1969–1976. [PubMed: 9351361]
23. Ehrenborg E, Clee SM, Pimstone SN, et al. Ethnic variation and in vivo effects of the -93t->g promoter variant in the lipoprotein lipase gene. *Arterioscler Thromb Vasc Biol* 1997;17(11):2672–2678. [PubMed: 9409241]
24. Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. *Genetics* 2003;164:1567–1587. [PubMed: 12930761]
25. Tsai HJ, Choudhry S, Naqvi M, Rodriguez-Cintron W, Burchard EG, Ziv E. Comparison of three methods to estimate genetic ancestry and control for stratification in genetic association studies among admixed populations. *Hum Genet* 2005;118(3–4):424–433. [PubMed: 16208514]
26. Lai CQ, Tucker KL, Choudry S, et al. *Hum Genet*. 2008 [Epub ahead of print]. Population admixture associated with disease prevalence in the Boston Puerto Rican health study.
27. Ruge T, Svensson M, Eriksson JW, Olivecrona G. Tissue-specific regulation of lipoprotein lipase in humans: effects of fasting. *Eur J Clin Invest* 2005;35(3):194–200. [PubMed: 15733074]
28. Nicklas BJ, Rogus EM, Berman DM, Dennis KE, Goldberg AP. Responses of adipose tissue lipoprotein lipase to weight loss affect lipid levels and weight regain in women. *Am J Physiol Endocrinol Metab* 2000;79(5):E1012–E1019. [PubMed: 11052955]
29. Weinstock PH, Levak Frank S, Hudgins LC, 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 USA* 1997;94:10261–10266. [PubMed: 9294198]
30. Kusunoki M, Tsutsumi K, Iwata K, et al. NO-1886 (ibrolipim), a lipoprotein lipase activator, increases the expression of uncoupling protein 3 in skeletal muscle and suppresses fat accumulation in high-fat diet-induced obesity in rats. *Metabolism* 2005;54(12):1587–1592. [PubMed: 16311090]
31. McTigue K, Larson JC, Valoski A, et al. Mortality and cardiac and vascular outcomes in extremely obese women. *JAMA* 2006;296(1):79–86. [PubMed: 16820550]
32. Lai CQ, Demissie S, Cupples LA, et al. Influence of the APOA5 locus on plasma triglyceride, lipoprotein subclasses, and CVD risk in the Framingham Heart Study. *J Lipid Res* 2004;45(11):2096–105. [PubMed: 15342688]
33. Hall S, Talmud PJ, Cook DG, et al. Frequency and allelic association of common variants in the lipoprotein lipase gene in different ethnic groups: the Wandsworth Heart and Stroke Study. *Genet Epidemiol* 2000;18(3):203–216. [PubMed: 10723106]
34. Samuels ME, Forbey KC, Reid JE, et al. Identification of a common variant in the lipoprotein lipase gene in a large Utah kindred ascertained for coronary heart disease: the -93G/D9N variant predisposes to low HDL-C/high triglycerides. *Clin Genet* 2001;59(2):88–98. [PubMed: 11260209]
35. Talmud PJ, Hall S, Holleran S, Ramakrishnan R, Ginsberg HN, Humphries SE. LPL promoter -93T/G transition influences fasting and postprandial plasma triglycerides response in African-Americans and Hispanics. *J Lipid Res* 1998;39(6):1189–1196. [PubMed: 9643350]
36. Kastelein JJ, Groenemeyer BE, Hallman DM, et al. The Asn9 variant of lipoprotein lipase is associated with the -93G promoter mutation and an increased risk of coronary artery disease. The Regress Study Group. *Clin Genet* 1998;53(1):27–33. [PubMed: 9550358]

37. Wang J, Shete S. A test for genetic association that incorporates information about deviation from Hardy-Weinberg proportions in cases. *Am J Hum Genet* 2008;83(1):53–63. [PubMed: 18589394]

Figure 1.

Anthropometric measures by *LPL m107/APOA5 S19W* genotype combination. (A) BMI (kg/m²); (B) Waist; (C) Hip. Means adjusted for age, sex, smoking, alcohol, antilipemic medication, physical activity, diabetes, energy, admixture. Error bars indicate standard error of means.

Table 1

Demographic, biochemical, lifestyle and genotypic characteristics.¹

Age,y	57.8±7.3
Female,n (%)	714(71.9)
BMI,kg/m ²	32.2±6.8
Obese,n (%) ²	574(59%)
Extreme obesity, n(%) ³	119(12%)
Waist,cm	102±15
Hip,cm	110±14
HDL-C, mmol/L	1.16±0.33
Triglyceride, mmol/L	1.86±1.4
Total energy intake (kcal)	2106±861
Diabetes, n(%) ⁴	408(41.2)
Antilipemic medication, n(%)	383(38.6)
Current alcohol use, n(%)	379(38.4)
Current smoker, n(%)	227(23.1)
LPL m107, n(%)	
TT	787(77.2)
TG	204 (20)
GG	28(2.8)
APOA5 s19w, n(%)	
CC	810(80)
CG	193(19.1)
GG	9(0.9)

¹ Values are mean±SD or n(%)² Obesity=BMI ≥30 mg/kg²³ Extreme obesity=BMI ≥40 mg/kg²⁴ Diabetes=Fasting glucose≥126 mg/dL or taking antidiabetic medication.

Table 2

Associations between *LPL* m107 genotype, anthropometric measures and lipids in Caribbean Hispanics.

	TT (n=787)	TG+GG (n=232)	P value
BMI(mg/kg ²) ¹	30.8±0.3	31.5±0.5	0.161
Waist(cm) ¹	101±1	103±1	0.250
Hip(cm) ¹	107±1	109±1	0.147
HDL-C(mmol/L) ²	1.21±0.04	1.15±0.04	0.013
Triglycerides(mmol/L) ²	1.80±0.01	1.84±0.01	0.698

¹ Meansadjusted for age, sex, alcohol, smoking, diabetes, antilipemic medication, physical activity, energy, admixture.
² Meansadjusted for age, sex, alcohol, smoking, diabetes, antilipemic medication, physical activity, admixture, hormone use(women), waist.

Table 3
Associations between *APOA5* S19W genotype, anthropometric measures and lipids in Caribbean Hispanics.

	CC (n=810)	GC+GG (n=202)	P value
BMI (mg/kg ²) ¹	30.9±0.3	31.3±0.5	0.451
Waist (cm) ¹	102±1	102±1	0.894
Hip (cm) ¹	107±1	108±1	0.811
HDL-C (mmol/L) ²	1.20±0.04	1.18±0.04	0.333
Triglycerides (mmol/L) ²	1.71±0.01	2.05±0.01	<0.0001

¹ Meansadjusted for age, sex, alcohol, smoking, diabetes, antilipemic medication, physical activity, energy, admixture.
² Meansadjusted for age, sex, alcohol, smoking, diabetes, antilipemic medication, physical activity, admixture, hormone use(women), waist.

Table 4

Odds ratios for extreme obesity by combined *LPL* m107 and *APOA5* S19W genotype.^{2,3}

	BMI≥40,n(%)	OR	95% CI	Lower	Upper	P value
<i>APOA5</i> S19W CC/ <i>LPL</i> m107 TT	64(11.1)	1 ¹				
<i>APOA5</i> S19W CC/ <i>LPL</i> m107 TG+GG	20(11.9)	1.24	0.70		2.19	0.469
<i>APOA5</i> S19WCG+GG/ <i>LPL</i> m107 TT	17(12.1)	1.02	0.55		1.89	0.946
<i>APOA5</i> S19W CG+GG/ <i>LPL</i> m107 TG+GG	12(26.7)	4.02	1.81		8.91	0.0006

¹ Reference genotype combination

² Maximum likelihood estimates, global genotype effect: Chi square statistic=11.96, 3 DF, $P=0.008$

³ Multivariate adjustment for age, sex, alcohol, smoking, diabetes, antilipemic medication, physical activity, energy, admixture.