The Lipoprotein Lipase Gene *Hind*III Polymorphism Is Associated With Lipid Levels in Early-Onset Type 2 Diabetic Patients

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Lipoprotein lipase (LPL) plays a central role in triglyceride metabolism, and the LPL gene T495G *Hind*III polymorphism has been associated with variations in lipid levels and heart disease in Caucasians with the more common H+ allele being associated with adverse lipid profiles and increased risk of CHD. We investigated this polymorphism in 785 Chinese subjects with varying components of the metabolic syndrome, including 61.4% with early-onset type 2 diabetes (age at diagnosis ≤ 40 years), and 167 healthy control subjects using a polymerase chain reaction (PCR)-based restriction fragment length polymorphism (RFLP) method. The allele and genotype frequencies were similar in the patients and control subjects. When grouped above or below standard cutoffs for triglyceride levels, the H+ allele was more frequent in hypertriglyceridemic than that in normotriglyceridemic subjects in the total population (81.5% *v* 76.1%) and early-onset type 2 diabetics (84.4% *v* 77.4%, both $P < .05$). Moreover, H+H+ carriers had significantly higher plasma triglyceride and lower high-density lipoprotein (HDL)-cholesterol levels when compared to subjects with the H- allele in the total population, and in patients with early-onset diabetics (both $P < .05$). In the total population and the early-onset diabetic patients, this relationship was confined to males when gender was considered. We conclude that the H+ allele of the LPL gene *Hind*III polymorphism is associated with higher plasma triglyceride and lower HDL-cholesterol levels in Chinese patients with early-onset diabetes.

THE LIPOPROTEIN LIPASE (LPL) enzyme plays a key role in lipid metabolism by hydrolyzing triglyceride-rich lipoproteins and facilitating tissue uptake of triglyceride-rich particles.[1] In type 2 diabetic patients, plasma LPL activity was significantly lower than in healthy subjects, and, in part, may account for the higher triglyceride and lower high-density lipoprotein (HDL)-cholesterol levels observed in these patients, including in Oriental populations.[2-4] Familial, but not spousal, correlations in LPL activity support a genetic contribution to LPL activity.[5] Therefore, defects in the LPL gene can lead to lipid disorders and possibly increased risk of atherosclerosis. The *Hind*III polymorphism, a thymine (T) to a guanine (G) base transition at position +495 in intron 8, which abolishes a *Hind*III restriction enzyme recognition site, is one of the most common polymorphisms in the LPL gene, which is located on the short arm of chromosome 8.[6] Although the LPL *Hind*III polymorphism would not be expected to have any direct functional effect on LPL activity, the H+ allele has been reported to be associated with higher triglyceride and lower HDL-cholesterol levels.[7-10] Several studies also reported that the H+ allele was associated with increased total cholesterol,[11,12] low-density lipoprotein (LDL)-cholesterol,[13] apolipoprotein (apo) C-III,[10] and apo B levels.[11,14] Moreover, several[10,12,15] but not all[7,16,17] studies have reported that the H+ allele is associated with an increased risk of coronary heart disease. Several studies also reported an association between the severity of atherosclerosis and the H+ allele.[7,11,18] The importance of the LPL gene *Hind*III polymorphism in patients with type 2 diabetes mellitus[13,16,17,19] and obesity[20] has also been investigated in several studies, but the results were inconsistent.

In the present study, possible associations between the LPL gene *Hind*III polymorphism and anthropometric and biochemical parameters have been investigated in subjects with varying components of the metabolic syndrome, the clustering of obesity, hypertension, type 2 diabetes, and dyslipidemia, and a group of normal healthy subjects.

MATERIALS AND METHODS

This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All 952 subjects involved in this study gave written, informed consent. They were of Han Chinese origin, without any known ancestors of other ethnic origin living in the Hong Kong Special Administrative Region. The patients had been recruited following referral to the Prince of Wales Hospital outpatient medical clinics for the treatment of hypertension, diabetes, and/or dyslipidemia. The healthy control subjects were recruited from hospital staff and their friends.

In a single visit to the Clinical Pharmacology Studies Unit, blood pressure and anthropometric and biochemical parameters after an overnight fast were measured as described previously.[21] In nondiabetic hypertensives these parameters were measured after 4 to 8 weeks of placebo antihypertensive treatment, whereas in the diabetic subjects trough levels were measured without withdrawing treatment. The nondiabetic hypertensive subjects recruited generally had mild to moderate elevation in blood pressure. During the temporary discontinuation of treatment the patients were monitored on a weekly basis to ensure that their blood pressure did not temporarily exceed systolic/diastolic blood pressure 190/115 mm Hg. If the blood pressure levels were considered too high or the patients complained of symptoms that may be related to elevated blood pressure such as headaches, blood pressure–lowering therapy was resumed immediately. Subjects were defined as hyperten-

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Table 1. Demographic Characteristics of the Subjects in the Healthy Controls, Early-Onset Diabetics, and Nondiabetic Group With Other Components of the Metabolic Syndrome

Characteristic	Healthy Controls	Nondiabetic Patients	Early-Onset Diabetics
No.	167	303	482
Age (yr)	35.9 ± 10.6	46.4 ± 10.9*	38.0 ± 8.6*
Gender (% males)	34.7	48.8	35.5
BMI (kg/m^2)	21.1 ± 2.1	25.8 ± 3.6*	25.2 ± 4.6*
Waist circumference (cm)	69.2 ± 6.3	84.6 ± 9.2*	82.6 ± 11.2*
Systolic blood pressure (mm Hg)	111 ± 9	138 ± 22*	121 ± 19*
Diastolic blood pressure (mm Hg)	64 ± 9	82 ± 15*	77 ± 11*
Mean arterial pressure (mm Hg)	80 ± 8	101 ± 16*	92 ± 13*
Total cholesterol (mmol/L)	4.5 ± 0.8	5.9 ± 1.6*	5.1 ± 1.2*
LDL-cholesterol (mmol/L)	2.7 ± 0.6	3.9 ± 1.5*	3.2 ± 0.9*
HDL-cholesterol (mmol/L)	1.48 ± 0.40	1.22 ± 0.34*	1.26 ± 0.36*
Triglyceride (mmol/L)	0.67 (0.62-0.72)	1.67 (1.54-1.83)*	1.23 (1.17-1.28)*
Glucose (mmol/L)	4.9 (4.8-4.9)	5.1 (5.1-5.2)	7.9 (7.6-8.2)*
Insulin (pmol/L)	30.6 (28.8-33.6)	50.9 (42.3-57.3)*	93.3 (86.8-100.2)*
Insulin-glucose product	148 (134-163)	258 (228-291)*	724 (666-787)*
% with obesity	0	71.4*	59.1*
% with hypertension	0	51.8*	19.9*
% with dyslipidaemia	0	60.9*	31.7*
Mean no. of MES components	0	1.6*	2.1*

NOTE. Values are mean ± SD or geometric mean (95% CI). *$P < .001$ compared with the healthy control group.
Abbreviation: MES, metabolic syndrome (early-onset type 2 diabetes, hypertension, dyslipidemia, or obesity).

sive if systolic blood pressure was ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or were receiving antihypertensive treatment. Subjects were defined as having type 2 diabetes if they had a fasting plasma glucose concentration ≥ 7.8 mmol/L or oral glucose tolerance test (OGTT) 2-hour glucose concentration ≥ 11.1 mmol/L according to the 1985 World Health Organization (WHO) criteria or receiving hypoglycaemic medication.[22] Only those diabetics with an early onset (age ≤ 40 years) were included in the current study. Patients with obvious secondary hypertension were excluded. Subjects were defined as having hypercholesterolemia if their plasma total cholesterol level was ≥6.2 mmol/L or total cholesterol level <6.2 mmol/L, but ≥5.2 mmol/L and total cholesterol to HDL-cholesterol ratio ≥5.0 or were receiving lipid-lowering treatment. Subjects were defined as having hypertriglyceridemia if their fasting plasma triglycerides were ≥2.3 mmol/L. Subjects were also defined as having higher HDL-cholesterol levels if HDL-cholesterol >1.2 mmol/L in females or >1.0 mmol/L in males. Patients were defined as obese if their body mass index (BMI) was ≥25 kg/m^2.[23] A total of 785 patients with components of the metabolic syndrome were recruited in the study. Of these subjects, in overlapping groups, 32.0% were hypertensive, 61.4% diabetic, 42.7% dyslipidemic, and 45.5% obese.

A total of 167 (17.5%) healthy subjects were recruited. These subjects had no evidence of hypertension, dyslipidemia, or obesity as defined above or diabetes or impaired fasting glycemia (fasting plasma glucose ≥6.1 mmol/L) based on the 1997 American Diabetes Association (ADA) criteria.

The LPL gene *Hind*III polymorphism was screened using a polymerase chain reaction (PCR)-based restriction fragment length polymorphism (RFLP) protocol with *Hind*III digestion.[24] A 12,00-bp fragment in intron 8 of the LPL gene was amplified by using a set of primers 5′ AGT GAT TCA TAC TTT AGC TG 3′ and 5′ TGA GAC ACT TTC TCC CTA GA 3′ as described previously. Digestion in the presence of the restriction sites resulted in 2 fragments of 600 bp (H+ allele), whereas the absence of the restriction site resulted in a fragment of 1,200 bp (H- allele). The heterozygotes for the *Hind*III restriction site showed both 1,200-bp and 600-bp bands. The gels were read independently by 2 investigators blind to the patient's phenotype.

Statistical Analyses

Statistics Package for the Social Sciences (SPSS version 9.0.0, 1998, SPSS Inc, Chicago, IL) was used in the data analyses. The frequencies of the alleles and genotypes among different subgroups were compared by the chi-square test. The independent *t* test and analysis of variance (ANOVA) were performed for investigating the association between the LPL gene *Hind*III polymorphism genotypes and the anthropometric and biochemical parameters. Analysis of covariance (ANCOVA) was used in a similar manner, but allowed for the adjustment of age and gender. The skewed data (fasting plasma triglyceride, glucose, insulin, and insulin glucose product) were logarithmically transformed in the analyses and expressed as geometric mean (95% confidence interval [CI]) while data with normal distribution were expressed as mean ± SD.

RESULTS

Compared to the healthy control subjects, the diabetic and nondiabetic patients all had significantly worse metabolic profiles, with elevated blood pressure, greater obesity and glycemic indices, and an adverse lipid profile (Table 1). The demographic characteristics of the total population divided according to the presence of the H- allele are listed in Table 2. The subjects with the H+H+ genotype had significantly lower plasma HDL-cholesterol and higher triglyceride levels when compared to those with the H-H- or H-H+ genotypes before and after adjustment for age and gender in early onset diabetic and obese subjects and in the total population (Table 2), but not in the healthy controls. No association between the *Hind*III polymorphism and other lipid parameters was found (Table 2). We divided our subjects into the nonoverlapping and overlapping groups with specific metabolic disorders, namely, early-onset diabetes, hypertension, dyslipidemia, and obesity. *Hind*III polymorphism genotypes in the LPL gene were in Hardy-Weinberg equilibrium in each of the groups. The allele

Table 2. Demographic Characteristics of the Subjects in the Total Population Divided According to the Presence of the LPL Gene *Hind*III Polymorphism H- Allele

Characteristic	Genotype		*P**
	H−H−/H−H+ (n=393)	H+H+ (n=559)	
Age (yr)	40.4 ± 10.6	40.2 ± 10.6	NS
Gender (% males)	36.0	41.0	NS
Total cholesterol (mmol/L)	5.24 ± 1.22	5.29 ± 1.46	NS
LDL-cholesterol (mmol/L)	3.27 ± 1.07	3.30 ± 1.24	NS
HDL-cholesterol (mmol/L)	1.33 ± 0.39	1.26 ± 0.36	.009
Healthy controls (n = 167)	1.54 ± 0.48	1.44 ± 0.33	NS
Early-onset diabetes (n = 480)	1.30 ± 0.34	1.23 ± 0.37	.049
Obesity (n = 356)	1.20 ± 0.30	1.13 ± 0.32	.028
Nondiabetic patients (n = 303)	1.24 ± 0.36	1.21 ± 0.33	NS
Triglyceride (mmol/L)	1.13 (1.06-1.21)	1.25 (1.172-1.34)	.015
Healthy controls	0.64 (0.57-0.71)	0.70 (0.63-0.77)	NS
Early-onset diabetes	1.14 (1.05-1.24)	1.30 (1.20-1.41)	.042
Obesity	1.39 (1.25-1.53)	1.68 (1.53-1.86)	.007
Nondiabetic patients	1.59 (1.42-1.79)	1.73 (1.53-1.96)	NS
BMI (kg/m^2)	24.5 ± 4.0	24.6 ± 4.6	NS
Waist circumference (cm)	80.9 ± 11.0	81.1 ± 11.5	NS
Systolic blood pressure (mm Hg)	124 ± 21	125 ± 21	NS
Diastolic blood pressure (mm Hg)	75.3 ± 13.3	76.8 ± 13.4	*.086*
Glucose (mmol/L)	6.2 (6.0-6.5)	6.4 (6.2-6.5)	NS
Insulin (pmol/L)	62.2 (56.2-68.5)	61.2 (56.1-66.8)	NS
Insulin glucose product	395 (347-447)	380 (342-426)	NS

NOTE. Values are mean ± SD or geometric mean (95% CI),

**P* values from *t* test.

Abbreviation: NS, nonsignificant.

and genotype frequencies in those subgroups are listed in Table 3. In our patients with any aspect of the metabolic syndrome, the frequency of the less common allele H- was 23.4%, with the genotype frequencies being 5.6%, 35.5%, and 58.9% compared with 21.9% and 1.8%, 40.1%, and 58.1% in the controls for the H- allele and H-H-, H-H+ and H+H+ genotypes, respectively. The allele and genotype frequencies were not significantly different between the whole group of patients with any of the

Table 3. The LPL Gene *Hind*III Polymorphism Genotype and Allele Frequencies in the Study Groups With Specific Aspects of the Metabolic Syndrome

Study Group	n	Genotype			Allele Frequency	
		H−H−	H−H+	H+H+	H−	H+
Nonoverlapping groups						
Healthy	167	3 (1.8)	67 (40.1)	97 (58.1)	21.9	78.1
Hypertension alone	66	2 (3.0)	25 (37.9)	39 (59.1)	31.2	68.8
Early-onset diabetes alone	282	19 (6.7)	110 (39.0)	153 (54.3)	26.2	73.8
Dyslipidemia alone	94	2 (2.1)	33 (35.1)	59 (62.8)	19.7	80.3
HT + DM	47	4 (4.1)	28 (29.2)	64 (66.7)	18.8	81.2
HT + DL	87	9 (6.6)	41 (30.1)	86 (63.2)	21.7	78.3
DM + DL	104	6 (3.9)	44 (28.8)	103 (67.3)	18.3	81.7
HT + DM + DL	49	2 (13.3)	9 (18.4)	38 (77.6)	13.3	86.7
Overlapping groups						
Early-onset diabetes	482	27 (5.6)	173 (35.9)	282 (58.5)	23.5	76.5
Hypertension	251	13 (5.2)	87 (34.7)	151 (60.2)	22.5	77.5
Dyslipidemia	335	15 (4.5)	109 (32.5)	211 (63.0)	20.7	79.3
Obesity	357	18 (5.0)	123 (34.5)	216 (60.5)	22.3	77.7
Nondiabetic patients	303	17 (5.6)	106 (35.0)	180 (59.4)	23.1	76.9
Metabolic syndrome*	785	44 (5.6)	279 (35.5)	462 (58.9)	23.4	76.6
Total population	952	47 (5.0)	346 (36.3)	559 (58.7)	23.1	76.9

NOTE. Values are number (%); groups compared with the healthy control group.

Abbreviation: HT, hypertension; DM, early-onset diabetes; DL, dyslipidemia.

*Metabolic syndrome group includes any patient with at least 1 component of the syndrome (DM, HT, DL, or obesity). The genotype and allele frequencies did not differ between controls and any patient groups.

Table 4. LPL Gene *Hind*III Polymorphism Genotype and Allele Frequencies in Groups With Serum High and Low Triglyceride and HDL-Cholesterol Levels in the Total Population and Groups With Early-Onset Diabetes or Obesity

Study Group	n	Genotype (%)			Allele Frequency (%)	
		H−H−	H−H+	H+H+	H−	H+
Total population						
Low triglyceride	779	40 (5.1)	292 (37.5)	447 (57.4)	23.9	76.1
High triglyceride	165	6 (3.6)	49 (29.7)	110 (66.7)*	18.5	81.5*
Low HDL-cholesterol	343	15 (4.4)	115 (33.5)	213 (62.1)	21.1	78.9
High HDL-cholesterol	578	31 (5.4)	216 (36.1)	328 (57.0)	24.6	75.4
Early-onset diabetes						
Low triglyceride	405	26 (6.4)	151 (37.3)	228 (56.3)	22.6	77.4
High triglyceride	77	1 (1.3)	22 (28.6)	54 (70.1)*	15.6	84.4*
Low HDL-cholesterol	194	7 (5.6)	65 (35.6)	122 (58.8)	20.4	79.6
High HDL-cholesterol	286	20 (7.0)	106 (37.1)	160 (55.9)†	25.5	74.5‡
Obesity						
Low triglyceride	271	15 (5.5)	101 (37.3)	155 (57.2)	24.2	75.8
High triglyceride	86	3 (3.5)	22 (25.6)	61 (70.9)*	16.3	83.7*
Low HDL-cholesterol	184	10 (5.4)	55 (29.9)	119 (64.7)	20.4	79.6
High HDL-cholesterol	172	8 (4.7)	68 (39.5)	96 (55.8)	24.4	75.6

*$P < .05$ for the genotype or allele distribution between the high (≥2.3 mmol/L) and low triglyceride groups. †$P = .065$, ‡$P = .076$ for the genotype and allele distribution, respectively, between the high (>1.2 or 1.0 mmol/L for females and males, respectively) and low HDL-cholesterol groups.

features of the metabolic syndrome or any subgroup and the controls.

We further a priori divided our subjects into subgroups according to plasma triglyceride and HDL-cholesterol levels (Table 4). The frequency of the H+ allele was significantly higher in hypertriglyceridemic subjects than in those with normal triglyceride levels in the total population (81.5% *v* 76.1%, $P = .04$), in subjects with early-onset diabetes (84.4% *v* 77.4%, $P = .014$), or in all patients with obesity (83.7% *v* 75.8%, $\chi^2 = 4.25$, $P = .039$), but not in the nondiabetic obese subgroup. In the subjects with early-onset diabetes, the H+H+ genotype frequency was also more common in those with high triglycerides compared to those with lower levels (70.1% *v* 56.3%, $P = .038$). In the diabetic subjects, there was a nonsignificant tendency for the H+ allele frequency to be higher in those with lower HDL-cholesterol compared to those with higher HDL-cholesterol (Table 4, 79.6% *v* 74.5%, $P = .076$). No gender-specific effects were found in the distribution of allele and genotype frequencies.

When gender-specific effects were investigated in the total population, the associations between this polymorphism and plasma HDL-cholesterol and triglyceride levels were confined to males (n = 377). The male subjects with the H+H+ genotype had significantly lower plasma HDL-cholesterol (1.16 ±0.32 mmol/L, n = 220) when compared to those with the H-H+ (1.21 ± 0.36 mmol/L, n = 139) or H-H- (1.26 ± 0.34 mmol/L, n = 18) genotype before ($P = .033$) and after adjustment for age and BMI ($P = .013$). Moreover, in males, the plasma triglyceride levels were significantly higher in those homozygous for the H+ allele [1.40 (1.26 to 1.56) mmol/L, n = 220] when compared to the subjects with the H- allele [1.18 (1.07 to 1.30) mmol/L, n = 157] before ($P = .014$) and after adjustment for age and gender ($P = .037$). However, in the diabetic males, no relationship between the polymorphism and triglyceride levels were identified. In females, the polymorphism did not appear to be associated with lipid levels in either the total populations or the subgroups analyzed. In early-onset diabetics, the relationship of this polymorphism and plasma HDL-cholesterol was also confined to males, with levels significantly higher in the subjects with the H-H- or H-H+ genotypes (1.30 ± 0.34 mmol/L, n = 70) than in those with the H+H+ genotype (1.23 ± 0.37 mmol/L, n = 101, $P = .049$). No gender-specific effects were found in the obese subjects.

DISCUSSION

This study was based on a large group of patients either with varying components of the metabolic syndrome or healthy subjects. In agreement with previous studies, the more common H+ allele of the LPL gene *Hind*III polymorphism was associated with higher triglyceride and lower HDL-cholesterol levels. Positive associations with these lipid parameters were identified in the early onset type 2 diabetic patients and in patients with obesity, but were not apparent in the healthy controls. The lack of an association in the healthy controls may, in part, be due to the truncation of the distribution of the lipid levels during selection. However, the genotype distributions in the groups in which the relationship was identified and the controls were similar, suggesting that there was no preferential selection of a particular genotype. The associations between the *Hind*III polymorphism and triglyceride and HDL-cholesterol levels were confined to the diabetic males when genders were considered separately. Similar gender-specific effects have been reported previously, including with this polymorphism.[7,8,10,11,25] However, in other studies, the H+ allele was associated with increased total cholesterol and LDL-cholesterol in females, not in males,[13] or with triglyceride levels in both genders.[8] We suggest that hormonal factors may play an important role in modulating the relationship between the LPL gene *Hind*III polymorphism and lipid levels in different genders. Some evidence shows that the LPL gene could be regulated at a transcriptional level by progesterone[26] and growth

hormone[27] in mice, whereas LPL activity appeared to be regulated by endogenous testosterone[28] and oestradiol[29] in humans, supporting our hypothesis. Although most studies describing positive gender-specific associations agree with the current study, differences are likely to arise as a result of differences in study design and the population demographics. For example, Larson et al[13] examined the associations in much older subjects than the current study (mean age, 57 *v* 40 years), meaning a significant proportion of the females would likely be postmenopausal, which would impact on the proposed effects of hormonal factors on the regulation of the LPL gene. Additionally, other confounding factors such as different smoking status and lifestyle of subjects in different genders should also be considered in interpreting varying results.

The effect of the LPL gene *Hind*III polymorphism in type 2 diabetes has only been investigated in a few studies.[8,16,17] It has been reported that acquired LPL deficiency contributes to severe hypertriglyceridemia in diabetic subjects.[30] We speculate that type 2 diabetes provides a condition which causes decreased sensitivity of the *Hind*III H+ allele to insulin regulation, leading to reduced LPL activity. Low muscle LPL activity has been suggested to account for the elevated triglyceride levels in patients with diabetes.[31] This could explain the elevated triglyceride levels observed in our diabetic subjects with the H+H+ genotype. However, data from one study showed that the LPL gene *Hind*III polymorphism did not appear to be associated with lipid and lipoprotein levels[17] in a diabetic Caucasian population (n = 240). In the Caucasian study, the mean age of patients was 58 ± 6.0 years whereas in the present study early-onset type 2 diabetic patients had a mean age of 38 ± 8.0 years. This suggests that the LPL *Hind*III polymorphism is more likely to be associated with higher plasma triglyceride and lower HDL-cholesterol levels in the patients with early-onset type 2 diabetes rather than in older diabetic patients, possibly also resulting from age-related differences in the hormonal regulation of the gene. To our knowledge, this is the first report examining the relationship between the LPL gene *Hind*III polymorphism and hyperlipidemia in early-onset diabetes. Racial differences and sample size should also be taken into account when interpreting the varying results between these 2 studies. We found the prevalence of the less frequent allele H- to be 21.9% in our control population, similar to another report of Chinese subjects (21%),[32] which is lower than the frequencies of 30 and 32% in Caucasians[7,10] and a US black population, respectively.[33]

In a group of normoglycaemic Caucasian subjects, the LPL gene *Hind*III polymorphism H+H+ homozygotes had higher fasting plasma insulin levels when compared to the H-H+ heterozygotes, supporting the association between the *Hind*III polymorphism and the metabolic syndrome.[34] However, our present study failed to find any relationship between this polymorphism and fasting glucose, fasting insulin, and insulin resistance, which was similar to most previously published studies.[9,13,35] The role of genetic variants of LPL in patients with type 2 diabetes needs to be further investigated.

In obese subjects, the responsiveness of LPL in adipose tissue to glucose or insulin stimuli is either delayed or blunted.[36] However, in formerly obese women who have lost weight, the responsiveness of the LPL to intravenous glucose and insulin increases markedly.[37] Therefore, it is assumed that obesity represents a condition that may enhance an underlying genetic susceptibility to hyperlipidaemia and diabetes. The present study showed that the H+ allele of the *Hind*III polymorphism was associated with higher triglyceride and lower HDL-cholesterol levels in obese subjects. Similar to our study, the *Hind*III H+H+ genotype was also previously reported to be associated with hypertriglyceridemia and low HDL-cholesterol levels in subjects with visceral obesity.[20] However, in the current study this relationship is likely driven by the diabetic subjects that form 63.9% of the obese group. Such results indicate that dyslipidemia associated with obesity may be modulated by the LPL gene *Hind*III polymorphism.

How the LPL gene *Hind*III polymorphism may modulate the levels of plasma triglyceride and HDL-cholesterol is not well understood. The intronic LPL gene *Hind*III polymorphism does not alter the LPL amino acid sequence. However, this polymorphism and lipid levels may be related by linkage disequilibrium with a functional mutation either in the LPL gene such as the Serine447-Stop substitution or the *Pvu*II polymorphism, which were reported to be associated with plasma total cholesterol and triglyceride levels.[7-10,15,16,25,38]

Previous studies have associated the H+ allele with increased total cholesterol,[11,12] LDL-cholesterol,[13] apo C-III,[10] and apo B.[11,14,18] Although we did not measure the latter 2 parameters, no association between the LPL gene *Hind*III polymorphism and lipids other than triglyceride and HDL-cholesterol was found in present study. As described earlier a number of factors resulting form differences in population demographics and methodology may, in part, account for these differences. For instance many of the studies that reported positive associations with total or LDL-cholesterol levels examined patients with overt vascular disease[11,12] or after the introduction of lifestyle modifications, such as low-calorie[14] or low-cholesterol diets[13] and exercise interventions,[13] which may affect these associations.

In summary, the LPL gene *Hind*III polymorphism may modulate the magnitude of dyslipidemia in early-onset diabetes and obesity. The underlying mechanisms are not well understood. Further studies on the role of the LPL gene *Hind*III polymorphism are required to address these points.

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