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The Association of a Rare Variant of -93, -53 Promoter Gene Polymorphisms of Lipoprotein Lipase Gene with Obesity and Insulin Resistance

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ABSTRACT

Objectives: Obesity increases the risk of numerous chronic diseases. Obesity is classified clinically using body mass index (BMI), waist-to-hip ratio, and body fat percentage. The lipoprotein lipase (*LPL*) gene has been linked to lipoprotein metabolism and obesity. We performed a case-control study to determine the association between *LPL* gene polymorphisms and obesity-associated phenotypes such as insulin resistance (IR). ***Methods***: We examined the different *LPL* gene variants for association in 642 individuals segregated by BMI and IR. Genotyping of the *LPL* gene -93 and -53 promoter gene polymorphisms were analyzed using polymerase chain reaction-restriction fragment length polymorphism. ***Results:*** A substantial association was observed for -93 gene polymorphism of the *LPL* gene with obesity, while -53 promoter gene polymorphism showed association with IR. ***Conclusions:*** We found a significant association between -93 and -53 promoter gene polymorphisms of the *LPL* gene with obesity and associated phenotypes in the studied population.

Obesity is the most common non-communicable and public health problem in the world. The magnitudes of obesity include increased risk of developing insulin resistance (IR), cardiovascular disease (CVD), and diabetes mellitus. Previous studies revealed that billions of people suffer from obesity, among them 1.46 billion individuals are overweight, and 502 million are obese.[1] Obesity is strongly associated with all-cause mortality during adulthood due to its correlation with various complex diseases.[2] Obesity is a complex disorder with strong genetic components.[3]

Obesity is commonly related to IR and is often linked with various metabolic irregularities. Indians are considered at a greater risk for development of IR and its complications at a lower degree of adiposity.[4,5] In India, non-obese individuals develop IR during adolescents putting them at risk of vascular diseases.[6] As parallel with the other ethnic groups, for example, Caucasians, phenotypic features of Indians such as body fat, truncal fat, and lean body mass, are significant contributors to IR.[7,8] This risk may be because of a complex interplay of several factors, which includes genetics, nutrition, and environmental factors.

Lipoprotein lipase (*LPL*) gene has emerged as a candidate gene for obesity.[9,10] *LPL* is involved in the regulation of fat storage in adipocytes,[11] and also contribute in the thermogenesis in skeletal muscle.[12] *LPL* gene is significantly associated with lipid metabolism.[13] An association between polymorphisms in the *LPL* gene with lipid levels has been observed in the Indian population.[14] Another study strongly suggests that the *LPL* gene HindIII polymorphism significantly associated with myocardial infarction as an independent risk factor in South Indian populations.[15] *LPL* gene HindIII polymorphism is significantly associated with ischemic stroke risk and elevated levels of plasma triglycerides, reduced high-density lipoprotein (HDL) levels, and intracranial large artery atherosclerosis.[16] Another study also reported significant associations between *LPL* gene polymorphisms, and metabolic syndrome.[17] The same *LPL* gene polymorphism is also associated with IR.[18]

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We sought to estimate the importance of sequence variation in the promoter of the *LPL* gene in association with obesity and obesity-associated phenotypes.

METHODS

All subjects included in the study were north Indians by birth and belonged to the northern states of the country (Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, Punjab, and Uttarakhand). Individuals not associated with the given states by birth were excluded, and the population was homogeneous with respect to ethnicity (as described in a previous study).[19]

The local ethics committee approved the study at King George's Medical University, Lucknow, Uttar Pradesh, India and the study protocol follows the ethical guidelines of the 1975 Declaration of Helsinki. Informed written consent was taken from all subjects willing to participate in the study, and the identity of all participants were kept confidential.

All participants had to follow a careful screening program, which involved individual and family history, physical investigation, determination of anthropometric measurements and biochemical profiles. After screening, a total 642 subjects were selected based on the inclusion/exclusion conditions.

Subjects with body mass index (BMI) of 18.5 to 29.9 kg/m^2 (non-obese) and ≥ 30.0 kg/m^2 (obese), aged between 20–42 years and born in North India were enrolled in the study. Subjects not fulfilling the above inclusion criteria at the time of interview and/or with congenital disorders, mental disorders, endocrine disorders (e.g., Myxoedema), Cushing's syndrome, and metabolism disorders (diabetes mellitus), CVD, heart failure, and pregnant women were excluded.

Overall 309 obese subjects (BMI ≥ 30.0) and 333 non-obese subjects (BMI < 30.0) were recruited. The subjects were recruited from Lucknow, Uttar Pradesh, India from the general population via health awareness camps in Lucknow city. All study subjects had their body height, waist circumference (WC), and hip circumference (HC) measured. Height and weight were used to calculate BMI, and WC and HC were used to calculate the waist-to-height ratio (WHR).

Venous blood samples collected following overnight fast were centrifuged within one hour of collection to separate the plasma and serum, frozen in aliquots, and stored at -80 °C until investigated. The insulin level was analyzed by enzyme-linked radio immunosorbent assay (Linco Research, Inc.). The insulin assay has 5.7% inter-assay coefficients of variation.[20] The grade of insulin sensitivity/resistance was measured by homeostasis model assessment (HOMA). According to HOMA, IR was considered as described previously,[21] using the following equation:

$$\text{HOMA index (HI)} = [\text{fasting insulin } (\mu U/mL) \times \text{fasting glucose } (mmol/L)/22.5]$$

HI < 3.6 indicates non-IR whereas HI ≥ 3.6 indicates IR.

The fasting concentration of glucose was analyzed by the glucose oxidase-peroxidase (GOD-POD) method.[22] We used a fat analyzer (Tanita–TBF–310, Japan) to estimate body composition, percentage body fat and fat mass (FM). The analyzer was validated formerly by Radley et al.[23]

Phenol-chloroform DNA extraction were used to isolate genomic DNA from whole blood. The fragment of polymerase chain reaction (PCR) containing the single nucleotide polymorphisms (SNP) –T93G and –G53C were amplified using the following primers: forward 50-GCTGATCCATCTTGCCAATGTTA-30; and reverse 50-CCGCGGTTTGGCGCTG AGCAAGT-30. SNPs –T93G, –G53C were distinguished by the enzyme HaeIII and BclI.[9]

Quality control was performed at every step; the ratio of the absorbance at 260 and 280 nm (ratio > 1.75) was used to assess the purity of DNA samples. We used one known genotype sample and one reagent blank for all 25 PCR samples. One-quarter of all samples, including samples of every genotype, were also genotyped by another member of the laboratory.

The independent-samples *t*-test was utilized to confirm whether the means of groups were considerably dissimilar for two independent groups' subjects. Allele and genotype distribution was matched between groups using the chi-square test. The Hardy-Weinberg equilibrium was used to verify the independent segregation of alleles, comparing the observed with those expected genotype frequencies (chi-square tests). Different genetic models: log-additive logistic regression model adjusted

Table 1: Genotype and allele frequency of lipoprotein lipase gene; -93 T<G promoter (rs1800590) polymorphism in study subjects according to body mass index (BMI) and insulin resistance.

	Study subjects classified based on BMI			
	Obese subjects n (%)	Non-obese subjects n (%)	OR (95% CI)	*p*-value*
Genotype				
TT	257 (83.2)	310 (93.1)	Reference	Reference
TG	47 (15.2)	22 (6.6)	2.58 (1.51–4.39)	< 0.001
GG	5 (1.6)	1 (0.3)	6.03 (0.70–51.95)	0.102
TG+GG	52 (16.8)	23 (6.9)	2.73 (1.63–4.58)	< 0.001
Allele				
T	561 (90. 8)	642 (96.4)	Reference	Reference
G	57 (9.2)	24 (3.6)	2.13 (1.55–3.97)	< 0.001
	Study subjects classified based on insulin resistance status (HOMA)			
	Insulin resistant subjects n (%)	Non-insulin resistant subjects n (%)	OR (95% CI)	*p*-value**
Genotype				
TT	208 (88.5)	359 (88.2)	Reference	Reference
TG	24 (10.2)	45 (11.1)	0.92 (0.55–1.56)	0.757
GG	3 (1.3)	3 (0.7)	1.73 (0.35–8.63)	0.506
TG+GG	27 (11.5)	48 (11.8)	0.97 (0.59–1.60)	0.908
Allele				
T	440 (93.6)	763 (93.7)	Reference	Reference
G	30 (6.4)	51 (6.3)	0.98 (0.66–1.48)	0.834

Total number of obese (n = 309) and non-obese subjects (n = 333) (for genotype); total number of chromosomes in obese (n = 618) and non-obese subjects (n = 666) (for alleles); total number of insulin resistant (n = 235) and non-insulin resistant subjects (n = 407) (for genotype); total number of chromosomes in insulin resistant (n = 470) and non-insulin resistant subjects (n = 814) (for alleles).
**adjusted for age and sex.*
***adjusted for age, sex, and BMI.*
HOMA: homeostasis model assessment; OR: odds ratio; CI: confidence interval.

for age and sex, were used to see the differences in genotype distributions.

The dissimilarities between the groups (categorized according to genotypes) were evaluated using one-way ANOVA (continuous variables), variables are expressed by the mean and standard deviation (SD). Association of obesity-associated phenotypes with genotype was attained using the additive model. The additive model is used to determine whether the association of genotype with the studied trait is due to genetic or environmental factors. ANOVA was utilized to analyze the association of phenotype associated with obesity among the different genotypes. The statistical power of the study was > 80%. The power of the study (considered by QUANTO version 1.1 program) takes into account the study type (case-control), disease prevalence, and the minor allele frequency in the control population, 0.05 taken as the level of significance. Statistical analysis was performed using SPSS Statistics (SPSS Inc. Released 2007. SPSS for Windows, Version 15.0, Chicago). A *p*-value < 0.050 was considered statistically significant.

RESULTS

Obese subjects had considerably upper WHR and WC. Fasting insulin ($p < 0.001$), HI ($p < 0.001$), percentage body fat ($p < 0.001$), and FM ($p < 0.001$) were also significantly greater among obese subjects compared to non-obese subjects. Other clinical and biochemical characteristics of study participant are presented in the previous article of our group.[24]

In non-obese subjects the frequency of -93G and -53C variant alleles were 3.6 and 4.8%, respectively. The polymorphisms existed in no linkage disequilibrium. The pooled genotype class TG and GG (TG+GG) and allele frequencies of the sequence variation in the promoter area at -93 bp were significantly different among the non-obese and

Table 2: Physiological parameters and genotypic classes for lipoprotein lipase gene; -93 T<G promoter (rs1800590) polymorphism in obese and non-obese subjects.

	Obese subjects			Non-obese subjects	
	TT (n = 257)	AG (n = 47)	GG (n = 5)	TT (n = 310)	TG+GG (n = 22+1)*
BMI	33.2 ± 1.3	34.4 ± 2.0	38.0 ± 1.7	23.0 ± 3.4	27.0 ± 2.9
p-value		0.001		0.001	
Fasting glucose, mg/dL	109.7 ± 19.1	107.7 ± 15.6	119.2 ± 17.6	109.0 ± 15.8	111.5 ± 17.5
p-value		0.406		0.476	
Fasting insulin, mU/mL	14.5 ± 8.7	16.1 ± 11.5	18.7 ± 11.9	10.2 ± 6.0	11.1 ± 5.6
p-value		0.360		0.490	
HOMA index	4.0 ± 2.7	4.4 ± 3.5	5.4 ± 3.0	2.8 ± 1.8	3.0 ± 1.5
p-value		0.406		0.534	
Percentage body fat	36.4 ± 5.8	40.9 ± 6.1	44.7 ± 6.8	24.6 ± 5.5	29.0 ± 6.1
p-value		< 0.001		0.006	
FM, kg	29.7 ± 7.6	34.1 ± 9.8	43.1 ± 11.6	17.9 ± 9.6	22.6 ± 8.0
p-value		< 0.001		0.007	

Data presented as mean±SD.
HOMA index: homeostasis model assessment index; FM: fat mass; BMI: body mass index.
**TT vs. TG+GG.*

obese subjects [Table 1]. Stratification of the study subjects based on IR revealed that the frequency of the pooled genotype and allele of -93 T<G variant was not different among IR subjects (27/235, 11.5%) compared with non-IR subjects (48/407, 11.8%).

We observed statistically significant differences in the dispersal of genotypes and alleles among obese and non-obese subjects. Analysis of regression discovered the odds ratio (OR) for the studied trait, for the subjects having the pooled genotype (TG+GG) was 2.73 (95% confidence intervals (CI): 1.63–4.58, $p < 0.001$) adjusted for age and sex.

The relationship of -93 T<G SNPs with obesity were additionally sustained by its

Table 3: Physiological parameters and genotypic classes for lipoprotein lipase gene; -93 T<G promoter (rs1800590) polymorphism in insulin resistant and non-insulin resistant subjects.

	Insulin resistant			Non-insulin resistant		
	TT (n = 208)	TG (n = 24)	GG (n = 3)	TT (n = 359)	TG (n = 45)	GG (n = 3)
BMI	30.4 ± 4.5	33.3 ± 5.7	39.6 ± 7.0	27.7 ± 5.4	30.3 ± 5.7	33.5 ± 6.6
p-value		< 0.001			0.003	
Fasting glucose, mg/dL	119.0 ± 18.8	117.1 ± 18.8	123.0 ± 18.8	103.8 ± 13.7	104.8 ± 14.2	109.4 ± 7.1
p-value		0.829			0.701	
Fasting insulin, mU/mL	20.0 ± 6.6	24.7 ± 7.9	27.0 ± 8.8	5.7 ± 3.7	8.6 ± 3.4	9.1 ± 2.3
p-value		< 0.001			0.004	
HOMA index	4.8 ± 2.1	6.5 ± 0.9	8.7 ± 2.4	1.8 ± 0.1	2.9 ± 0.8	3.1 ± 0.6
p-value		< 0.001			0.004	
Percentage body fat	34.0 ± 6.5	40.6 ± 9.5	48.2 ± 4.9	30.5 ± 7.4	33.3 ± 8.4	38.1 ± 5.2
p-value		< 0.001			0.018	
FM, kg	27.9 ± 8.7	34.5 ± 12.5	46.0 ± 9.3	22.8 ± 8.7	26.8 ± 10.7	34.5 ± 14.2
p-value		< 0.001			0.002	

Data presented as mean±SD.
HOMA index: homeostasis model assessment index; FM: fat mass; BMI: body mass index.

Table 4: Genotype and allele frequency of the lipoprotein lipase gene; -53 G<C promoter polymorphism in study subjects according to body mass index (BMI) and insulin resistance.

	Study subjects classified based on BMI			
	Obese subjects n (%)	Non-obese subjects n (%)	OR (95%CI)	*p*-value*
Genotype				
GG	283 (91.6)	304 (91.3)	Reference	Reference
GC	14 (4.5)	26 (7.8)	0.57 (0.29–1.12)	0.105
CC	12 (3.9)	3 (0.9)	2.93 (0.92–9.32)	0.068
GC + CC	26 (8.4)	29 (8.7)	0.89 (0.51–1.55)	0.678
Allele				
G	580 (93.9)	634 (95.2)	Reference	Reference
C	38 (6.1)	32 (4.8)	0.78 (0.58–1.43)	0.823
	Study subjects classified based on insulin resistance status (HOMA)			
	Insulin resistant subjects n (%)	**Non-insulin resistant subjects n (%)**	**OR (95% CI)**	***p*-value****
Genotype				
GG	190 (80.9)	397 (97.5)	Reference	Reference
GC	37 (15.7)	3 (0.7)	40.01 (9.55–167.60)	< 0.001
CC	8 (3.4)	7 (1.7)	2.41 (0.860–6.74)	0.094
GC + CC	45 (19.1)	10 (2.4)	10.76 (5.16–11.45)	< 0.001
Allele				
G	417 (88.7)	797 (97.9)	Reference	Reference
C	53 (11.3)	17 (2.1)	2.78 (1.56–3.55)	< 0.001

Total number of obese (n = 309) and non-obese subjects (n = 333) (for genotype); total number of chromosomes in obese (618) and non-obese subjects (n = 666) (for alleles); total number of insulin resistant (n = 235) and non-insulin resistant subjects (n = 407) (for genotype); total number of chromosomes in insulin resistant (n = 470) and non-insulin resistant subjects (n = 814) (for alleles).
**adjusted for age and sex.*
***adjusted for age, sex, and BMI.*
OR: odds ratio; CI: confidence interval.

Table 5: Physiological parameters and genotypic classes for lipoprotein lipase gene; -53 G<C promoter polymorphism in obese and non-obese subjects.

	Obese subjects			Non-obese subjects			
	GG (n = 283)	GC (n = 14)	CC (n = 12)	GG (n = 304)	GC (n = 26)	CC (n = 3)	GC+CC* (n = 26+3)
BMI	33.2 ± 3.3	34.7 ± 4.4	36.7 ± 5.6	22.8 ± 3.3	23.8 ± 2.6	24.8 ± 3.0	26.7 ± 2.9
p-value		0.002			0.017		0.004
Fasting glucose, mg/dL	109.2 ± 18.5	116.9 ± 20.2	111.4 ± 16.9	112.4 ± 15.6	112.1 ± 15.5	116.4 ± 34.3	115.4 ± 17.7
p-value		0.297			0.078		0.083
Fasting insulin, mU/mL	13.7 ± 8.2	18.7 ± 11.3	33.9 ± 1.5	8.2 ± 4.8	9.3 ± 5.0	20.8 ± 6.6	19.5 ± 7.4
p-value		< 0.001			< 0.001		< 0.001
HOMA index	3.8 ± 2.6	5.1 ± 3.1	9.8 ± 1.7	2.5 ± 1.5	2.8 ± 2.4	5.9 ± 2.0	5.6 ± 2.2
p-value		< 0.001			< 0.001		< 0.001
Percentage body fat	36.9 ± 6.1	40.2 ± 5.1	41.3 ± 5.8	26.6 ± 6.1	29.8 ± 5.9	31.7 ± 4.7	30.9 ± 5.7
p-value		0.008			0.014		0.022
FM, kg	30.2 ± 8.1	34.3 ± 9.7	34.2 ± 10.0	20.3 ± 8.2	20.3 ± 7.2	20.3 ± 4.7	22.9 ± 7.0
p-value		0.059			0.250		0.111

Data presented as mean±SD.
HOMA index: homeostasis model assessment index; FM: fat mass; BMI: body mass index.

Table 6: Physiological parameters and genotypic classes for lipoprotein lipase gene; -53 G<C promoter polymorphism in insulin resistant and non-insulin resistant subjects.

	Insulin resistant			Non-insulin resistant			
	GG (n = 190)	GC (n = 37)	CC (n = 8)	GG (n = 397)	GC (n = 3)	CC (n = 7)	GC+CC* (n = 3+7)
BMI	29.7 ± 5.4	30.8 ± 4.5	35.4 ± 6.6	27.4 ± 2.0	28.0 ± 5.4	34.0 ± 6.8	32.0 ± 6.4
p-value		0.009			0.016		0.022
Fasting glucose, mg/dL	119.3 ± 18.6	116.1 ± 16.8	119.8 ± 27.8	103.7 ± 13.7	120.2 ± 23.8	109.0 ± 7.5	112.4 ± 13.9
p-value		0.624			0.071		0.048
Fasting insulin, mU/mL	19.4 ± 6.4	24.2 ± 9.9	27.0 ± 6.1	4.2 ± 1.6	7.7 ± 3.3	8.9 ± 2.7	7.1 ± 2.7
p-value		< 0.001			0.005		0.013
HOMA index	5.6 ± 2.0	6.8 ± 2.4	7.7 ± 2.1	1.4 ± 0.5	1.9 ± 0.8	2.8 ± 0.7	2.3 ± 0.7
p-value		<0.001			0.006		0.027
Percentage body fat	34.8 ± 7.1	34.2 ± 8.0	39.8 ± 6.7	30.8 ± 7.6	29.3 ± 8.7	36.6 ± 5.8	34.4 ± 7.2
p-value		0.137			0.125		0.135
FM, kg	28.9 ± 9.5	27.7 ± 9.6	33.3 ± 10.8	23.3 ± 9.0	19.1 ± 8.3	29.4 ± 10.9	26.3 ± 10.9
p-value		0.315			0.148		0.296

Data presented as mean±SD.
HOMA index: homeostasis model assessment index; FM: fat mass; BMI: body mass index.
**GG vs. GC+CC.*

association with obesity-related traits [Table 2 and 3]. The non-obese subjects with pooled genotype (TG+GG) of -93 T<G SNP had greater BMI (TT, 23.0±3.4 kg/m^2 vs. TG+GG, 27.0±2.9 kg/m^2, p = 0.001), percentage body fat (TT, 24.6±5.5 vs. TG+GG, 29.0±6.1, p = 0.006), and FM (TT, 17.9±9.6 vs. TG+GG, 22.6±8.0, p = 0.007) values compared to individuals with the TT genotype.

Correspondingly, in obese subjects, genotypes of -93 T<G SNP showed different BMI, percentage body fat, and FM in obese and non-obese subjects.

The allele and genotype frequencies of -53 G<C promoter polymorphism of the *LPL* gene were statistically significant between non-IR and IR subjects and non-significant in non-obese and obese subjects [Table 4]. Analysis of regression showed the OR (adjusted for age, sex, and BMI) for IR subjects for pooled genotype (GC+CC) genotype was 10.76 (95% CI: 5.16–11.45, p < 0.001).

The association of -53 G<C variant with IR was further supported by its association with IR-related traits [Table 5 and 6]. The non-IR subjects with pooled genotype (GC+CC) of -53 G<C SNP had higher insulin (GG, 4.2±1.6 vs. GC+CC, 7.1±2.7, p = 0.013), and HI (GG, 1.4±0.5 vs. GC+CC, 2.3±0.7, p = 0.027) values matched by subjects with TT genotype [Table 6].

DISCUSSION

The -93 T<G SNP showed a significant association with higher risk of obesity. The -53 G<C SNP showed an emerging risk of IR in the North Indian population. Previously, we reported a significant association between the *FTO* gene polymorphism with IR.[24] To the best of our knowledge, this is the first report to consider the association of these polymorphisms with obesity and associated phenotypes like IR in the North Indian population.

Subjects with the pooled genotype (TG+GG) of -93 T<G SNP were at 2.73-fold increased risk of obesity compared to subjects with the TT genotype. Additionally, subjects with pooled genotype (TG+GG) had considerably increase BMI, percentage body fat, and FM values compared to non-obese subjects with the TT genotype.

The TG replacement at nucleotide -93 lies two bases 5' to a preserved reversed GA box in the *LPL* gene.[25] This essential motif binds the transcription factors and is important for *LPL* promoter action. The simple recognition unit of the specificity protein (Sp) family transcription factors, known as a GC

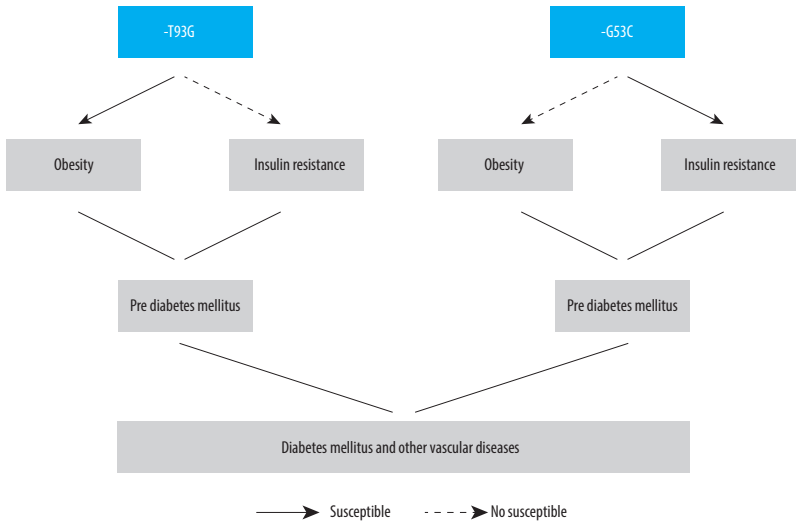

Figure 1: Schematic representation of association of the studied polymorphisms of lipoprotein lipase gene.

box. Furthermore, GA and GT boxes can similarly bind Sp proteins in the *LPL* gene's promoters. The nucleotides flanking this preserved component may stimulate the binding affinity of Sp1 and Sp3.[25]

Previous functional experiments using the rat smooth muscle cell line revealed the -93G promoter had increased activity in vitro than the -93T promoter.[26] In the human adrenal cell line, NCIH295, similar observations were obtained using the luciferase assay with the G allele.[26] The association of -93T<G variant also observed with other measures of obesity-associated phenotypes, especially percentage body fat and FM, suggests it could be a significant contributor to obesity and obesity-associated comorbidities. A sex-specific association of the *LPL* gene polymorphisms with body fat has been suggested.[27] Even though the -93G promoter polymorphism is not associated with IR this promoter variant showed association with different measures of IR phenotypes especially fasting insulin, HI, percentage body fat, and FM in IR and non-IR subjects with almost the same intensity.

In different populations, -53 G<C promoter polymorphism was established as a rare variant.[9,28] However, these studies showed a significant association with less risk of increasing obesity and other vascular diseases. In our study, -53 G<C promoter polymorphism showed a significant association with IR but no association with obesity. Significant association of clinical and biochemical parameters of IR (like fasting insulin and HI) were observed with the genotypes of this promoter SNP in IR and non-IR subjects.

In previous studies, *LPL* gene polymorphisms were shown to be related to different features of dyslipidemia, CAD, and MI but these studies are mostly based on South Indian populations.[14–16,29]

These studies explain the significance of the *LPL* gene association with vascular disease including obesity and associated phenotypes in the Indian population. Thus, the findings of present study support that the *LPL* gene polymorphism is associated with obesity and obesity-associated phenotypes especially IR which may stimulate the development of other vascular diseases in North Indian populations [Figure 1].

CONCLUSION

Genetic variants in the *LPL* gene might play a significant role in predisposing obesity and obesity-associated phenotypes risk, especially IR, in the North Indian population, signifying them as important genetic determinants of obesity and obesity-associated phenotypes.

Disclosure

The authors declared no conflicts of interest. The study was funded by the Indian Council of Medical Research, New Delhi, India [SAN No - 45/14/2008-HUM-BMS].

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