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Association of FTO rs9939609 SNP with Obesity and Obesity- Associated Phenotypes in a North Indian Population

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ABSTRACT

Objectives: Obesity is a common disorder that has a significant impact on morbidity and mortality. Twin and adoption studies support the genetic influence on variation of obesity, and the estimates of the heritability of body mass index (BMI) is significantly high (30 to 70%). Variants in the fat mass and obesity-associated (*FTO*) gene have been associated with obesity and obesity-related phenotypes in different populations. The aim of this study was to examine the association of FTO rs9939609 with obesity and related phenotypes in North Indian subjects. ***Methods***: Gene variants were investigated for association with obesity in 309 obese and 333 non-obese patients. Genotyping of the FTO rs9939609 single nucleotide polymorphism (SNP) was analyzed using Restriction Fragment Length Polymorphism Analysis of PCR-Amplified Fragments. We also measured participants fasting glucose and insulin levels, lipid profile, percentage body fat, fat mass and fat free mass. ***Results:*** Waist to hip ratio, systolic blood pressure, diastolic blood pressure, percentage body fat, fat mass, insulin concentration, and homeostasis model assessment index (HOMA-Index) showed a significant difference between the study groups. Significant associations were found for FTO rs9939609 SNP with obesity and obesity-related phenotypes. The significant associations were observed between the rs9939609 SNP and blood pressure, fat mass, insulin, and HOMA-index under a different model. ***Conclusion:*** This study presents significant association between FTO rs9939609 and obesity defined by BMI and also established the strong association with several measures of obesity in North Indian population.

Obesity is a complex disorder with strong genetic components and has an impact on morbidity and mortality. Studies have suggested a genetic cause to variation in body mass index (BMI).[1] Various health risks are related with increasing BMI. An individual's predisposition to obesity is determined by interactions between genetic and environmental factors.[2] Genome-wide association studies (GWAS) identified obesity susceptibility loci at the population level in recent years. Through GWAS at least 52 loci associated with obesity have been identified.[3] The fat mass and obesity-associated gene (*FTO*) was the first obesity-associated locus in cohorts of Europeans, European Americans, and Hispanic Americans.[4,5] Almost all GWAS identified *FTO* as a gene that influences obesity and contributes the maximum to the variance in BMI in Europeans and Asians.[3,6,7] The FTO rs9939609 single nucleotide polymorphism (SNP) variant is of particular interest because it has a known effect on BMI.[4] Subsequent replication studies, confirmed a strong association of the FTO rs9939609 SNP, located in intron 1 of the *FTO* gene, with obesity in various ethnic populations in both children and adults.[8-10] Previous studies in Indian populations have reported an association of the *FTO* gene variants with obesity (defined by BMI).[11-14] However, the relationships between rs9939609 and obesity is inconsistent.[15,16] Since genetic architecture varies across populations and ethnicities; the results could also be different between populations. Thus, the study of different ethnicities may produce new understandings about the genetic factors affecting predisposition of obesity, and could increase our understanding of the results of various populations.

FTO is highly expressed in the hypothalamus region of the brain, which is involved in regulation of food intake and energy expenditure.[17] The association

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studies of *FTO* variants with obesity are additionally supported by subsequent animal studies. Animal studies on mouse models also suggest that the *Fto* is the candidate gene for obesity.[18] Loss of function and/or expression of *Fto* was associated with a lean phenotype, whereas overexpression resulted in obesity.[18] Larder et al,[19] observed that FTO operates as a demethylase, and it has a role in the development of obesity by regulating energy intake.

Obesity is now a common health problem. Both environmental and genetic components may contribute towards an increased risk of obesity. Earlier, we found that MC4R (rs17782313) and POMC (rs1042571) SNPs showed a significant association with obesity.[20]

The aim of our study was to examine the association between the *FTO* rs9939609 SNP with the risk of obesity and obesity-related phenotypes in a North Indian population.

METHODS

All individuals recruited in our study were of North Indian origin, which includes the states of Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, Punjab, and Uttarakhand. Individuals of other backgrounds were excluded and the population was homogeneous with regard to ethnic background (as described in our previous study).[21]

Informed written consent was taken from each participant, and the identity of all participants was kept confidential. The study was carried out with the approval of local ethics committee (IRB number-XXXIV ECM/P6) at King George's Medical University, Lucknow, India. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

All study participants were subjected to a careful screening program that included assessment of personal and family history, physical examination, and determination of anthropometric measurements and biochemical profiles. A total of 821 patients were screened, and 624 were selected based on strict inclusion/exclusion criteria.

Obese and normal-weight patients born in North India, who were aged 20–42 years old, were included in the study. Obese patients were those with a BMI of ≥ 30 kg/m^2 and non-obese patients had a BMI between 18.5 to 29.99 kg/m^2. Pregnant women and patients who did not fulfill the inclusion criteria for obese and non-obese subjects at time of interview and those who had congenital, mental, or endocrine disorders (e.g., Myxoedema and Cushing's syndrome) or metabolic disorders like diabetes mellitus, cardiovascular disease, and congestive heart failure were excluded from the study. Overall, 309 obese subjects (BMI ≥ 30 kg/m^2) and 333 non-obese subjects (BMI < 30 kg/m^2) were enrolled in the study. The participants were recruited from the outpatient department of King George's Medical University, Uttar Pradesh, India, and volunteers from the general population by organizing health awareness camps in Lucknow city. All study subjects' had their height, weight, waist circumferences, and hip circumferences measured to calculate their BMI and waist-to-hip ratio (WHR).

Venous blood samples were taken after an overnight fast. Within one hour of collection, samples were centrifuged to obtain plasma/serum, frozen in aliquots, and stored at −80 °C. Commercially available enzymatic test kits (ERBA Diagnostics Mannheim GmbH, Mannheim, Germany) were used to determine total cholesterol, high-density lipoprotein (HDL), and triglyceride concentrations. Low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol were calculated using the Friedewald equation: LDL-cholesterol = total cholesterol – HDL cholesterol – triglyceride/5 (mg/dL). The inter-assay coefficient of variation was less than 5.0% for HDL-cholesterol and less than 2.5% for triglycerides.[22]

Insulin concentration was determined by the enzyme-linked radio immunosorbent assay (Linco Research, Inc., US). The intra- and the interassay coefficients of variation for the insulin assay were 5.7% and 8.9%, respectively. The lowest detection limit of insulin assay was 0.5 mU/ml.[23] The degree of insulin sensitivity/resistance was calculated according to the homeostasis model assessment index (HOMA-index). Using the HOMA-index, insulin resistance (IR) was calculated as described previously.[24] The fasting glucose concentration was measured using the glucose oxidase-peroxidase (GOD-POD) method.[25] Inter-assay coefficient of variation was less than 5.0%. The Tanita TBF-310 (Tanita Corp., Tokyo, Japan) body fat analyzer was used to assess body composition (i.e., percentage body fat, fat mass). The analyzer has been validated previously.[26] We performed genotyping of the *FTO* rs9939609 SNP by PCR-based restriction fragment

Table 1: Clinical characteristics of study participants.

Variable	Obese n = 309	Non-obese n = 333	*p*-value
Age, years	36.8± 2.4	35.4± 2.2	0.916
Gender*			
Male	153 (49.5%)	194 (58.3%)	
Female	156 (50.5%)	139 (41.7%)	
Diet*			
Vegetarian	175 (56.6%)	185 (55.6%)	
Non-vegetarian	134 (43.4%)	148 (44.4%)	
WHR	0.97±0.10	0.95±0.08	0.015
WC, cm	102.3±12.9	95.6±10.8	0.228
HC, cm	105.6±11.9	100.7±9.3	0.015
Height, cm	159.1±9.9	160.2±10.2	0.764
Weight, kg	79.0±14.2	68.9±13.1	0.169
BMI, kg/m²	33.5±3.6	25.1±3.4	<0.001
SBP, mmHg	128.4±15.2	120.5±11.7	<0.001
DBP, mmHg	86.2±8.1	80.8±7.7	0.027
Adiposity			
Body fat, %	37.3±6.2	27.9 ±6.1	<0.001
FM, kg	30.6±8.3	20.6 ±8.2	<0.001
Fat free mass, kg	48.6±8.0	48.7±12.4	0.834
Insulin sensitivity			
Fasting glucose, mg/dl	109.2±15.9	109.6±18.6	0.065
Fasting insulin, mU/ml	15.0±9.7	10.3±6.0	<0.001
HOMA-index	4.2±2.9	2.8±1.8	<0.001
Lipid profile			
Total cholesterol, mg/dl	213.5±35.7	161.7±44.7	0.003
HDL, mg/dl	42.8±7.1	46.3±10.2	0.001
Triglyceride, mg/dl	130.3±28.9	107.1±19.6	0.008
LDL-C, mg/dl	151.3±30.4	99.7±37.1	<0.001
VLDL-C, mg/dl	26.1±5.8	25.0±4.1	0.008

*Data presented as mean± standard deviation. *Data presented as n (%). SBP: systolic blood pressure; DBP: diastolic blood pressure; FM: fat mass; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; HOMA index: homeostasis model assessment index; HDL: high-density lipoprotein-cholesterol; LDL: low-density lipoprotein-cholesterol; VLDL: very low-density lipoprotein-cholesterol; BMI: body mass index. Obese patients = BMI ≥30. Non-obese patients = BMI <30.*

length polymorphism analysis as previously described.[27] Genomic DNA was extracted from the peripheral blood leukocyte pellet using the standard salting-out method and blinded genotyping of the *FTO* rs9939609 SNP was performed. A 10% masked, random sample of cases and controls were tested twice by different laboratory personnel, and the reproducibility was 100%.

The independent-samples *t*-test was used to assess differences between the obese and non-obese patients. Genotype and allele distribution was compared between the two groups using the chi-square test. The independent segregation of alleles was tested for the Hardy-Weinberg equilibrium (HWE), comparing the observed genotype frequencies with those expected (chi-square test). For case-control studies, differences in genotype distributions were calculated applying different model like log-additive, recessive and dominant logistic regression model adjusted for age and sex (for regression analysis wild-type genotype was taken as a reference).

The differences among the three groups were assessed by one-way ANOVA for continuous variables and data presented as the mean ± standard deviation (SD). A post hoc test was used for pairwise multiple comparisons between means. Tukey's post hoc test used studentized range statistics to make all of the pairwise comparisons between groups. Association of genotype with obesity-associated phenotypes was performed assuming different genetic models. The additive and recessive models were used to detect the association of different FTO rs9939609 variants with the obesity-associated phenotype, to ensure that the effect of the genotype with the condition were due to the genetic variation or other factors. For the additive model, ANOVA was used and for the recessive model *t*-statistics were used. The statistical power of the study was > 80%. This was calculated by the QUANTO program (USC Biostats, California, US) version 1.1, which considered the study type (case-control), disease prevalence (prevalence of obesity), and frequency of the minor allele in the control population at the level of significance 0.050. All analysis of the association between genotype and phenotype were conducted using the SPSS Statistics (SPSS Inc., Chicago, US), version 15. A p-value < 0.050 was considered statistically significant.

RESULTS

Anthropometric and clinical characteristics of the 642 participants of the present study are provided in Table 1. WHR, systolic blood pressure, diastolic blood pressure, percentage body fat, fat mass (FM), insulin concentration, and HOMA-Index showed a significant difference between obese and non-obese study participants. *FTO* SNP variant genotypic data for 333 obese and 309 non-obese patients were also analyzed, and the results are presented in Table 2. The distribution of the studied SNP genotypes followed the HWE (p = 0.455, non-obese patients).

The analyzed genotypic data expressed that *FTO* SNP AA genotype (p = 0.015; odds ratio (OR) 1.7

Table 2: Genotype and allele frequency of FTO rs9939609 gene polymorphism in obese and non-obese subjects.

	Frequency		OR (95%CI)	*p*-value
	Obese n = 309	Non-obese n = 333		
Genotype				
TT	97 (31.4)	128 (38.4)	Reference	Reference
TA	138 (44.7)	148 (44.5)	1.23 (0.87–1.75)	0.247
AA	74 (23.9)	57 (17.1)	1.713 (1.11–2.65)	0.015
Allele				
T	332 (53.7)	404 (60.7)	Reference	Reference
A	286 (46.3)	262 (39.3)	1.33 (1.06–1.66)	0.012
TT+TA	235 (76.1)	276 (82.9)	Reference	Reference
AA	74 (23.9)	57 (17.1)	1.53 (1.04–2.25)	0.033*
TT	97 (31.4)	128 (38.4)	Reference	Reference
TA+AA	212 (68.6)	205 (61.6)	1.37 (0.99–1.89)	0.062**

Data expressed as n (%). p-value derived from regression analysis using best genetic model, sex adjusted.
OR: odds ratio
**Recessive indicates AA vs. TA, TT.*
***Dominant indicates TT vs. TA, AA.*

95% CI 1.1–2.7) and A allele (p = 0.012; OR 1.3 95% CI 1.1–1.7) were significantly associated with risk of obesity. Similar results were found in the recessive model (AA vs. TA, TT) (p = 0.033; OR 1.53 95% CI 1.0–2.3).

The *FTO* rs9939609 SNP showed significant association with different obesity-associated phenotypes including percentage body fat, FM, insulin concentration and HOMA-index. The strongest associations were observed with FM, fasting insulin and HOMA-index under additive and recessive models [Table 3]. The risk allele (A) of *FTO* rs9939609 shows a positive association with systolic and diastolic blood pressure.

Table 3: Metabolic parameters and genotypic classes for rs9939609 (n = 642).

Metabolic profile	Genotypic			Additive *p*-value$	Recessive *p*-value *
	TT n = 225	TA n = 286	AA n = 131		
SBP, mmHg	123.0 ±13.8	123.7±14.3	127.9±13.2	0.004	0.001
DBP, mmHg	83.0±8.3	83.0±8.3	85.0±8.2	0.046	0.013
Adiposity					
Body fat, %	31.4±4.8	32.2±5.9	34.6±6.5	0.013	0.005
FM, kg	23.8±5.0	25.0±6.4	29.3±8.6	<0.001	<0.001
Insulin sensitivity					
Fasting glucose, mg/dl	109.0±16.3	108.8±16.9	111.6±19.4	0.504	0.303
Fasting insulin, mU/ml	11.2±5.1	12.6±6.8	14.8±6.9	<0.001	<0.001
HOMA-index	3.1±2.1	3.4±2.5	4.3±2.8	<0.001	<0.001
Lipid profile					
Total cholesterol, mg/dl	182.9±48.0	189.0±46.9	188.2±48.2	0.260	0.345
HDL, mg/dl	45.0±9.9	44.7±8.6	43.8±8.1	0.321	0.150
Triglyceride, mg/d	116.8±26.4	119.2±28.7	118.8±24.6	0.339	0.374
LDL-C, mg/dl	121.3±41.5	127.1±41.9	124.5±46.3	0.316	0.608
VLDL-C, mg/dl	23.4±5.3	23.8±5.7	23.8±4.9	0.339	0.231

*Data represent mean±SD for genotypic classes based on unrelated individuals; n = 642. $p-value between wild genotype vs. heterozygous genotype vs. variant genotype by Tukey's post hoc test. *Recessive value indicates AA vs. TA, TT for rs9939609. Recessive p-value calculated by t-statistics.*
SBP: systolic blood pressure; DBP: diastolic blood pressure; FM: fat mass; HOMA index: homeostasis model assessment index; HDL: high-density lipoprotein-cholesterol; LDL: low-density lipoprotein-cholesterol; VLDL: very low-density lipoprotein-cholesterol.

DISCUSSION

The *FTO* gene is a genetic risk factor for obesity, and variants in the first intron of the *FTO* gene have the most prominent polygenic effect on obesity. These variants were discovered in a GWAS.[4] We investigated the association of the *FTO* rs9939609 SNP with obesity in a North Indian population. Previous studies are comparable to our study, which shows significant association of FTO with obesity.

The *FTO* rs9939609 variant showed association with increased BMI adjusted for age, sex, and ethnicity/population structure.[28] In addition to this, Kopelman et al,[29] observed an association between the *FTO* rs9939609 genotype and increased BMI. A large-scale study exposed the association of the minor allele (A allele) of the *FTO*-rs9939609 variant with a higher BMI.[30] Dwivedi et al,[31] also showed an association between obesity and variant rs9939609.

Significant associations were observed between the *FTO* gene and obesity (as defined by BMI) in different East Asian and South Asian populations.[32,33] Previous studies also noted and established the association between *FTO* rs9939609 with obesity in Asian populations.[2,34,35]

In contrast, some studies found no association between *FTO* rs9939609 SNP and the risk of obesity in Pakistani, Korean, and Chinese populations.[36-38] The frequency of the A allele at the rs9939609 variant in our population was 0.39, which is comparable to other studies in North Indian (0.31), Pakistani (0.40), and European (0.45) patients. In contrast, a low frequency was reported in Japanese (0.18) and Chinese (0.12) populations. This suggests that the distribution of the *FTO* rs9939609 SNP has a noticeable ethnic variation.[2,36,38,39] *FTO* rs9939609 SNP was significantly associated with obesity in western and south Indian populations.[14,40] While in North Indian populations *FTO* rs9939609 SNP showed association with type 2 diabetes, this association was not completely mediated by BMI.[39] Yajnik et al,[41] also observed the same findings in the south Indian population (2009).

Additionally, we investigated the association between *FTO* rs9939609 with various obesity-related phenotypes. We observed a significant association with different obesity-associated phenotypes.

We observed a positive association of *FTO* rs9939609 with systolic and diastolic blood pressure. A meta-analysis comprising of 57,464 hypertensive cases and 41,256 controls reported a significant association between FTO rs9939609 and blood pressure, which disappeared on adjustment for BMI.[42] In stratified analysis, a significant association was observed between FTO rs9939609 and risk of hypertension in obese subjects only. Subgroup analysis based on ethnicity showed a significant association between FTO rs9939609 and blood pressure in both European and Asian populations. Previous studies suggest that the A allele carriers of FTO 9939609 have higher systolic and diastolic blood pressure.[43,44]

The mechanism by which the *FTO* genetic variant regulates the susceptibility to hypertension is currently unknown. FTO protein is highly expressed in the hypothalamus and controls energy homeostasis and metabolism.[45] The hypothalamus is also a potent regulator of blood pressure. One study found that FTO increases the risk for hypertension, which was related, in part, to higher sympathetic modulation of vasomotor tone modulated by the paraventricular and dorsomedial nuclei of the hypothalamus.[43] Therefore, FTO-hypertension association might correlate with the regulation of sympathetic vasomotor tone. Additionally, FTO also regulates weight gain principally by hypothalamic control of food intake and energy homeostasis.[17] Therefore, FTO may play a significant role in regulating obesity (weight gain) and blood pressure through the hypothalamus.

A significant association was observed between the FTO rs9939609 SNP and body fat mass and percentage body fat. Lear et al,[46] also reported a positive association between the rs9939609 SNP and greater FM and percentage body fat. Another study observed a significant association with increased body fat as assessed by bioelectrical impedance.[47] Vasan et al,[40] also observed a significant association with body fat distribution in a south Indian population. Hotta et al,[48] noted that FTO was associated with more subcutaneous tissue (SAT) and visceral adipose tissue (VAT). *FTO* mRNA expression was higher in SAT than in VAT in a study on lean and obese men.[49] Subcutaneous FTO expression correlated with visceral FTO expression. These results suggest that FTO may have a role in the distribution of body fat. The functional role of the *FTO* gene is not yet clearly understood, nor is it clear how the variants influence body size.

Insulin resistance is commonly associated with obesity.[50] In our study, a significant positive

association was found between FTO rs9939609 and fasting insulin, insulin resistant traits, and HOMA-index. Shahid et al,[51] also reported that the rs9939609 variant allele showed association with insulin level and HOMA-index. Association of *FTO* rs9939609 variant with plasma insulin and HOMA-index indicates that this SNP may disturb metabolism and prompt obesity and obesity-related phenotypes. Previous studies reported that the *FTO* gene variant was significantly associated with predisposition to diabetes through an effect on BMI.[4,38,52] Additionally, fasting insulin could function as physiological factors that affect metabolic syndrome,[53] which aggregates in families.[54]

The association of FTO with BMI and other obesity-related measurements have important clinical implications since increased risk of cardiometabolic diseases have been reported in Indians.[55]

It is reported that the rs9939609 SNP significantly associated with obesity and with other obesity measurements (waist, hip circumference, and WHR).[14,41] A strong association of FTO variants with type 2 diabetes was observed in other studies, but this association became non-significant when adjusted for BMI.[14,39,42] We observed a significant association of rs9939609 SNP with obesity and risk allele shows significant association with obesity and obesity-related phenotypes. The difference reported in the studies conducted in European and Indian populations may be explained by a link between body size and type 2 diabetes.[55]

Our small sample size may have reduced our capability to identify certain associations. Lack of data, in particular, lifestyle factors such as education, occupation, per capita income, population social background, and daily activity patterns, are also limitations of the study. Another limitation of the study is multiple comparisons. However, the majority of literature to date suggest that the rs9939609 SNP is associated with measures of blood pressure, body fat, insulin, and the insulin resistance index. Lastly, as our study nature is cross-sectional, so we are limited to identifying associations only and longitudinal studies are required to identify and understand the role of FTO.

CONCLUSION

The *FTO* gene rs9939609 variant is associated with obesity and obesity-associated phenotypes in the adult North Indian population. We also established that the rs9939609 SNP is associated with several measures related to obesity especially with blood pressure, percentage body fat and FM, plasma insulin, insulin resistance. Therefore, functional studies needed to explain further the role of FTO.

Disclosure

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