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A common variant in the FTO locus is associated with waist–hip ratio in Indian adolescents

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Summary

Background: Common variants in the *FTO* locus, and near *MC4R* locus, have been shown to have a robust association with obesity in children and adults among various ethnic groups. Associations with obesity traits among Indian adolescents have not been determined.

Objective: To study the association of rs9939609 (FTO) and rs17782313 (MC4R) to obesity related anthropometric traits in Indian adolescents.

Methods: Subjects for the current study were recruited from a cross-sectional cohort of 1,230 adolescents (age mean ± SD: 17.1 ± 1.9 years) from South India.

Results: The variant at the *FTO* locus was found to be associated with waist-hip ratio (WHR) but not with overall obesity in this population. No significant association was observed for obesity-traits and Mc4R variant rs17782313.

Conclusion: The common variant of *FTO* (*rs9939609*) is associated with body fat distribution during early growth in Indian adolescents and may predispose to obesity and metabolic consequences in adulthood.

Keywords: Adolescents, *FTO*, Indians, waist–hip ratio.

Variants in the fat mass and obesity-associated (*FTO*) gene, and near melanocortin receptor 4 (*MC4R*) locus, have shown unequivocal association with obesity traits in adults from various ethnic backgrounds. Frayling *et al*. showed a strong effect of a common *FTO* variant with obesity, both in children from the age of 7 years and in adults (1). Genetic variants near *MC4R* were also associated with common obesity (2). Studies that followed showed consistent associations to obesity traits among children and adolescents (3). Evidence from recent genome-wide association studies (GWAS) on childhood obesity further confirmed variants in or near *FTO* and *MC4R* as major obesity-determining genes in younger age groups (4,5). Among Asian ancestries, this effect was observed among Chinese and Japanese (6–8), however, there are no reports among Indian children and adolescents. Previous studies among children and adolescents have used body mass index (BMI) as a surrogate marker of adiposity, despite the fact that BMI represents overall fatness and has a limited value in quantifying body fat distribution, particularly central adiposity, which poses higher risk for metabolic complications among both younger age groups and adults (9). To address the genetic effect on obesity-related traits among Indian adolescents, we investigated the association between two common variants; rs9939609 (*FTO*)

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and rs17782313 (*MC4R*) with BMI, weight, height, waist circumference (WC), hip circumference (HC), waist–hip ratio (WHR), body fat percentage and glucose traits in a cross-sectional cohort of 1230 adolescents [mean (standard deviation) age, 17.1 (1.9) years; men: 917 (75%), women: 309 (25.2%)] from a homogenous population from South India (chiefly Dravidian in origin, with 1.2% being a mixture of Punjabi and Marwari ethnicity).

The institutional ethics committee approved the study and all participants provided informed consent. Subjects with known history of childhood diabetes, age >21 years, treatment with steroids or other medication that would interfere with weight regulation and diabetes were excluded ($n = 32$). Eligible participants underwent a detailed medical evaluation including anthropometric measurements, Tanner's staging for pubertal evaluation and blood sampling by standard procedures as described previously (10). Genotyping ($n = 1217$) was done using TaqMan® SNP genotyping assays (ABI7300, Foster city, California, USA) C_30090620_10 (rs9939609) and C_32667060_10 (rs17782313) as per manufacturer's conditions. Genotyping quality control was tested in 7.2% of the samples (genotyped in duplicate) with 0% difference in genotype. Genotyping failed in 13 samples (1.1%) for rs9939609 and 57 (4.6%) for rs17782313, most probably due to low-quality DNA for the platform used. Linear regression analysis, under an additive model, was used to assess the association between the quantitative traits and the genetic variants. The participants were stratified into normal-weight and obese/overweight based on 85th percentile cut-off for BMI (11) and logistic regression adjusted for age, gender and pubertal staging was used to estimate the obesity risk. Central obesity was assessed at 75th, 85th, 90th and 95th percentile cut-off for WC and WHR. All data were analyzed using STATA (Version 11.0, Texas, USA).

The minor allele frequencies of the *FTO* and near *MC4R* variant were 0.33 and 0.34, respectively, which were comparable to European adolescents (~40 and 30%) (1,2), but was higher than observed among Chinese children (~12.1%) (4). The genotypes of both variants were not in the Hardy–Weinberg equilibrium (HWE) (rs9939609 $P = 0.036$, rs17782313 $P = 0.022$). No difference in genotype or allele frequencies was observed either for *FTO* or *MC4R* variant when stratified for obesity (Table 1). Homozygous risk allele carriers displayed a 0.007 unit [95% confidence interval (CI) 0.001–0.012) increase in WHR with each copy of the *FTO* risk allele and this remained significant even after BMI adjustment ($\beta = 0.006$, 95% CI 0.001–0.012, $P = 0.021$).

Table 1 Genotype and allele frequencies of *FTO* (rs9939609) and MC4R (17782313) in normal and overweight/obese* participants

	FTO (rs9939609)							MC4R (rs17782313)						
	n	MAF	TT		AT		AA	*P*-value†	*n*	MAF	TT		CT		CC		*P*-value†
Normal	1036	0.33	487	(47.0)	403	(38.9)	146	(14.1)	0.203	998	0.35	489	(49)	321	(32.2)	188	(18.8)	0.077
Overweight/obese	181	0.32	93	(51.4)	58	(32.0)	30	(16.6)		175	0.29	102	(58.3)	46	(26.3)	27	(15.4)	

*Obesity defined based on 85th percentile cut-off for body mass index (International Obesity Task Force recommendation).
†*P*-values derived by Pearson's chi-square test.

Table 2 Association of *FTO* (rs9939609) with obesity-related and glycemic traits

Trait	Total (n = 1217)	TT (n = 580)	AT (n = 461)	AA (n = 176)	Effect size*	P-value†
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	β (95% CI)	
Body mass index (kg m^{-2})	20.7 ± 3.9	20.7 ± 3.9	20.6 ± 4.1	20.9 ± 4.1	0.051 (–0.263, 0.366)	0.75
Height (cm)	163.6 ± 8.6	163.6 ± 8.8	163.6 ± 8.7	163.5 ± 8.2	0.036 (–0.592, 0.520)	0.90
Weight (kg)	55.5 ± 11.6	55.5 ± 11.5	55.2 ± 11.7	56.1 ± 11.9	0.127 (–0.757, 1.011)	0.78
Waist circumference (cm)	68.6 ± 9.4	68.3 ± 9.5	68.5 ± 9.5	69.8 ± 9.2	0.536 (–0.202, 1.274)	0.16
Hip circumference (cm)	84.8 ± 8.9	84.8 ± 8.8	84.8 ± 9.4	84.9 ± 8.6	0.023 (–0.0672, 0.719)	0.95
Waist–hip ratio	0.81 ± 0.07	0.81 ± 0.07	0.81 ± 0.07	0.82 ± 0.09	0.007 (0.001, 0.012)	0.021
Body fat percentage	20.6 ± 8.2	20.6 ± 8.1	20.3 ± 8.3	21.2 ± 8.7	0.181 (–0.321, 0.683)	0.48
Fasting glucose (mmol L^{-1})	5.1 ± 0.5	5.1 ± 0.5	5.1 ± 0.6	5.1 ± 0.5	0.025 (–0.066, 0.016)	0.24
Glucose 120 min (mmol L^{-1})	5.3 ± 0.9	5.2 ± 0.9	5.3 ± 0.9	5.3 ± 1.0	0.059 (–0.014, 0.132)	0.11

*Effect size denotes unit change in the trait for a risk allele.
†Linear regression P-value adjusted for age, gender and Pubertal staging under additive model.
CI, confidence interval; SD, standard deviation.

However, these associations did not hold for Bonferroni adjustment for multiple testing. Significant associations were not observed for other regional measurements (WC, HC, skin-fold thickness) (Table 2). Logistic regression under an additive model displayed a marginally significant *FTO* risk with abdominal obesity at 95th percentile cut-off for WHR (Odds ratio (OR) 1.46; 95% CI 1.03–2.04, P = 0.031) and this risk remained significant even after adjustments with height (OR 1.45; 95% CI 1.03–2.04, P = 0.031) or BMI (OR 1.52; 95% CI 1.06–2.17, P = 0.022). No significant association was observed at cut-offs between the 75th and 95th percentile for BMI or WC. We further tested if these associations could be replicated by excluding consanguineous individuals and observed both the *FTO* association with obesity risk and WHR remained consistent. The *MC4R* variant, rs17782313 did not display an association with any of the obesity traits (Supporting information Table S1). No gender differences were observed.

Our results demonstrate that the *FTO* rs9939609 variant is associated with body fat distribution in Indian adolescents and may predispose to future metabolic risk in adulthood, since WHR correlates strongly with insulin resistance and dyslipidemia among Indians and other ethnic groups independent of overall obesity (12). Another variant of *FTO* (rs8050136) was previously shown by GWAS to be associated with WHR after adjustment for BMI in adults (13). The linkage disequilibrium between rs8050136 and rs9939609 is very high (r^2 = 0.97, D = 1) in GIH HapMap population (http://hapmap.ncbi.nlm.nih.gov/). Both the variants showed strong association with BMI and WHR among North Indian adults (14) and rs8050136 was shown to increase obesity risk twofolds among South Indian Adults (15). Although, genetic loci that regulate body fat distribution are distinct from those that influence BMI and obesity, we speculate that rs9939609 may exhibit differential phenotypic effects during early growth (central adiposity) and the effects in the adulthood (overall obesity) may be modified by environmental influence. This warrants future studies with longitudinal design and larger sample size. We did not find an association between *MC4R* genotypes and obesity traits in this cohort and this is most likely due to low statistical power. Although statistically significant associations have been reported in cohorts of similar size (16–18), the difference could be in the low mean body fat content in this cohort; which likely makes it more difficult to observe an association. Similarly, we did not find an association between *MC4R* genotype with any obesity-related traits in childhood, adolescence and adulthood in another longitudinal cohort from the same geographical region (18). We speculate that the observed differences in the effect sizes of *MC4R* variants in this population might be due to modulation of adiposity effects by population specific environmental factors, which may have a stronger influence during adulthood, than younger age groups.

To our knowledge, this is the first replication study of these loci among Indian adolescents. Further, our cohort is well-characterized and drawn from a homogenous population, allowing for assessment of the genetic variants in relation to multiple measures of obesity.

The study does have several limitations. The participants of the study were drawn from schools in semi-urban India and may not be representative of the whole community. Our study has a power of 60% to detect a SNP that significantly increased the variance explained (r^2) by the BMI-adjusted models by at least 0.1%, calculated at an alpha level of 0.05 and sample size of 1226 using '*powerreg*' command of STATA 11. A low power (60%) may explain the non-significant association with BMI; however, it should be emphasized that BMI is not a reliable indicator of obesity in young Indians, who are known to have a lower lean body mass and higher subcutaneous fat (19). Deviations from HWE could probably be due to enrichment of homozygosity, which is the case in consanguineous parentage (26%). Exclusion of individuals born to consanguineous parentage also showed deviations from HWE, which probably could be related to the enrichment of homozygosity since inter-familial marriages might have been practised in the earlier generations in this population.

We conclude that a common variant in the *FTO* locus is associated with WHR, a measure of body fat distribution, in young Indians. Our results imply that obesity genes may affect body fat distribution during early growth leading to overall obesity and other metabolic consequences in adulthood.

Conflict of interest statement

None.

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Author contribution

NT, KB and FK designed the study. SKV, VJ and HFG carried out the experiments. SKV, TF and EI did data analysis, interpretation, generation of tables and literature search. All authors were involved in the writing the paper and approved the final version of the manuscript.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Association of MC4R (rs17782313) with obesity-related and glycemic traits. ‡Linear regression *P*-value adjusted for age, gender and Pubertal staging under additive model. §Effect size denotes unit change in the trait for a risk allele. CI, confidence interval; SD, standard deviation.