Fat mass and obesity-associated gene rs11642015 polymorphism is significantly associated with prediabetes and type 2 diabetes subsequent to adjustment for body mass index

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Abstract. The association of the fat mass and obesity-associated gene (*FTO*) rs11642015 polymorphism with prediabetes, type 2 diabetes and obesity in certain populations has not been previously reported. A population-based study was conducted that included 490 type 2 diabetic, 471 prediabetic and 575 normal subjects. The main outcomes of the study were prediabetes, type 2 diabetes and obesity. Binary logistic regression was performed to estimate the association of *FTO* rs11642015 with the risk of prediabetes, type 2 diabetes and obesity following adjustment for the corresponding confounders. A meta-analysis was also conducted to evaluate the association between *FTO* rs11642015 and obesity. *FTO* rs11642015 was significantly associated with prediabetes in the whole sample under the additive model [odds ratio (OR), 1.50; 95% confidence interval (CI), 1.17-1.93; P=0.002], particularly in females. The polymorphism remained consistently significant following adjustment for age and body mass index (BMI), showing an increased prediabetes risk with an additive effect (OR, 1.55; 95% CI, 1.19-2.01; P=0.001). In addition, a significant association was found for rs11642015 with prediabetes and type 2 diabetes under the dominant model. However, under the stringent Bonferroni's correction there was no evidence of positive associations for *FTO* rs11642015 with obesity in the whole sample, females or males. Findings of the meta-analysis showed that *FTO* rs11642015 was not predisposed to obesity. In conclusion, the T allele of *FTO* rs11642015 is positively associated with an increased risk of prediabetes, even after adjustment for age and BMI, particularly in females. Subjects carrying the CT + TT genotype are predisposed to prediabetes and type 2 diabetes. Therefore, results of the population-based study and follow-up meta-analysis suggested that *FTO* rs11642015 is not significantly associated with susceptibility to obesity.

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Introduction

The prevalence of diabetes is on the increase worldwide (1) and the global incidence and prevalence of type 2 diabetes in adolescents varies substantially in different countries and ethnicities (2). The estimated prevalence of diabetes and prediabetes was 11.6 and 50.1%, respectively, in a representative sample of Chinese adults, and these figures may account for up to 113.9 and 493.4 million Chinese adults with diabetes and prediabetes, respectively (3).

The fat mass and obesity-associated (*FTO*) gene is situated on chromosome 16q12.2 and is composed of nine exons (4). *FTO* is highly expressed in rat hypothalamus (5), a brain structure involved in the regulation of energy balance and appetite (5,6). Two independent genome-wide association studies (GWASs) indicated that a number of common variants (including rs9939609) in the first intron of *FTO* have the most significant effect on body mass index (BMI) and susceptibility to obesity, particularly in Europeans (7,8). Since then, the majority of follow-up genetic studies have focused on *FTO* rs9939609, and the positive association between rs9939609 and type 2 diabetes has been shown to be entirely mediated through the effect of *FTO* on obesity (9).

Recently, Sällman Almén *et al* (10) sequenced 412 kilo base pairs of the genome, which covered the complete *FTO* gene in 524 severely obese children and 527 lean controls with massive parallel sequencing, following adjustment for the 44 haplotype blocks in the *FTO* region. Three single-nucleotide polymorphisms (SNPs) (rs55872725, rs11642015 and rs62048402) were

found to be associated with obesity (P<0.0011). rs11642015 and rs62048402 were the top-associated SNPs and had a stronger obesity association (P<0.007) than the frequently studied rs9939609 (P<0.012). The study did not detect any strongly associated variants elsewhere, and therefore it was concluded that intron one was the only obesity-associated region of the *FTO* gene (10). Additionally, it was demonstrated that *FTO* rs11642015 was associated with obesity in Latvia (10), while Kalnina *et al* (11) demonstrated that the rs11642015, rs62048402 and rs9939609 polymorphisms in the first intron of *FTO* contributed to risk of type 2 diabetes, even following the correction for BMI.

Obesity is a major predictor of the risk of type 2 diabetes (12). *FTO* was initially identified as a type 2 diabetes susceptibility gene. However, further adjustment for BMI eliminated any significant association with type 2 diabetes (9). The association of the *FTO* variants with type 2 diabetes and BMI has been mostly identified in Europeans (7). However, Meyre (13) examined whether *FTO* was a type 2 diabetes susceptibility gene. Further studies that focus particularly on different ethnicities are required to investigate this hypothesis. As the association between the *FTO* variants and risk of type 2 diabetes varied between ethnicities, conducting relevant future studies in subjects with different ethnic backgrounds is important.

As the association of *FTO* rs11642015 with the risk of prediabetes, type 2 diabetes and obesity in the Chinese population remains unclear, 490 type 2 diabetic, 471 prediabetic and 575 healthy subjects who originated from Shenzhen (China) were recruited. The results were also combined with those from two previously published studies (10,14) to establish the contribution of *FTO* rs11642015 to susceptibility to obesity.

Patients and methods

Participants. The study was a population-based case-control study, in which 1,516 individuals (490 type 2 diabetic, 471 prediabetic and 575 healthy subjects) were consecutively recruited between April 2010 and September 2011. All the subjects were from 16 Community Health Service Centers (Nanshan, China) under the supervision of the Shenzhen Nanshan Center for Chronic Disease Control (Guangdong, China). A two-stage sampling method and a simple random procedure according to the sequence of computer-generated random numbers were applied. The study was approved by the Ethics Committee of Shenzhen Nanshan Center for Chronic Disease Control and all participants provided written informed consent. The BMI was calculated by the weight (kg)/height (m^2). The obesity (BMI≥28 kg/m^2), overweight (24≤BMI<28 kg/m^2) and normal weight (BMI<24 kg/m^2) classes were defined according to the definition proposed by the Working Group on Obesity in China (15). Type 2 diabetes and prediabetes were diagnosed according to the American Diabetes Association guidelines of 2010 (16).

Genotyping. Human genomic DNA was separated from peripheral blood samples using the nucleic acid extraction automatic analyzer (Lab-Aid 820; Zeesan Biotech, Xiamen, China) and all the DNA samples were stored in Tris-EDTA buffer. The DNA concentration was determined using the PicoGreen® double-strand DNA Quantification kit (Molecular Probes Inc., Eugene, OR, USA). All subjects were genotyped for *FTO* rs11642015 using the MassARRAY compact analyzer based on the chip-based matrix-assisted laser desorption ionization time-of-flight mass spectrometry platform (Sequenom Inc., San Diego, CA, USA). Polymerase chain reaction cycles were initiated with an initial denaturation stage at 94˚C for 15 min, followed by 45 cycles at 94˚C for 20 sec for denaturation, 56˚C for 30 sec for annealing, 72˚C for 1 min for primer extension and 72˚C for 3 min for a final extension. DNA amplification for the *FTO* rs11642015 genotyping was performed on 5% of the total samples and were randomly selected for a second genotype. The results remained consistent.

Statistical analysis. Consistency of the genotype frequencies were assessed with Hardy-Weinberg equilibrium (HWE) and percentages were analyzed by the χ^2 test. A one-way analysis of variance was used to compare the continuous variables among the three groups (Table I). Allele and genotype frequencies were compared between cases and controls with the χ^2 test. Binary logistic regression analysis was used to estimate the association of *FTO* rs11642015 with the risk of prediabetes, type 2 diabetes and obesity, subsequent to adjustment for the corresponding confounders. To reduce type I error induced by multiple tests, Bonferroni's adjustment was applied to determine the significance thresholds. This employed the following formula to adjust the significance level and maintain an error rate of 0.05: $1-(1-\partial)^{1/n}$. P<0.008 was adopted as the significant threshold (Tables II and III). Statistical analysis was performed with the SPSS package, version 17.0 (SPSS, Inc., Chicago, IL, USA). All tests were two-tailed and P<0.05 was considered to indicate a statistically significant difference. Power analysis was performed using the Power and Sample Size Calculation software (version 3.0.43) designed by William D. Dupont and Walton D. Plummer Jr (17).

The meta-analysis was performed by Stata version 11.0 (Stata Corporation, College Station, TX, USA). The Z-test was used to calculate the P-value of the overall effect for the meta-analysis. The combined odds ratios (ORs) together with their 95% confidence intervals (CIs) were assessed with the random-effects method. The between-study heterogeneity was estimated by the χ^2-based Q test (significance level, P<0.10) and I^2 statistics (I^2 values of <25, 25-75 and >75% were defined as low, moderate and high heterogeneity, respectively), which can be interpreted as the percentage of total variation across several studies due to heterogeneity. Publication bias was evaluated by Egger's regression test, Begg's adjusted rank correlation test and a funnel plot. A two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

Characteristics of subjects. The characteristics of individuals included in the study are shown in Table I. A total of 490 subjects with type 2 diabetes, 471 with prediabetes and 575 non-diabetic subjects were involved in the present study. The genotype frequencies were assessed by HWE (Table I).

Comparison of genotype and allele frequencies. A multivariate analysis with covariates of age and BMI revealed that

Table I. Characteristics of the subjects.

Characteristic	Controls	Prediabetes	Type 2 diabetes	P1	P2	P3
Subjects, n	575	471	490			
Female/male, n	289/286	241/230	248/242	0.81	0.91	0.95
Age, years	57.94±10.81	61.39±11.43	62.76±11.14	0.001	0.055	0.001
BMI, kg/m^2	23.52±3.17	25.28±3.82	24.95±3.46	0.001	0.143	0.001
Female						
Age, years	58.50±10.00	61.66±10.43	63.99±10.28	0.001	0.01	0.001
BMI, kg/m^2	23.18±3.09	25.18±4.04	24.69±3.58	0.001	0.12	0.001
Male						
Age, years	57.38±11.56	61.10±12.42	61.51±11.85	0.001	0.70	0.001
BMI, kg/m^2	23.87±3.22	25.37±3.59	25.20±3.32	0.001	0.59	0.001

Groups were compared using one-way analysis of variance. P, P-value; P1, prediabetes vs. controls; P2, type 2 diabetes vs. prediabetes; P3, type 2 diabetes vs. controls; BMI, body mass index.

Table II. Comparison of genotype and allele frequencies between cases and controls in the whole sample, stratified by gender.

FTO (rs11642015)	CC, n	CT, n	TT, n	χ^2	P-value	C, n	T, n	χ^2	OR (95% CI) P-value	OR (95% CI) Unadjusted	OR (95% CI) P-value	OR (95% CI) Adjusted[a]	HWE
Whole sample[b]													
Controls	435	111	7			981	131						
Prediabetes	330	121	18	12.86	0.002[c]	781	157	9.94	0.002[c]	1.50 (1.17-1.93)	0.001[c]	1.55 (1.19-2.01)	0.97
Type 2 diabetes	345	133	9	8.46	0.01	823	151	5.84	0.01	1.37 (1.06-1.76)	0.50	0.91 (0.70-1.18)	
Female													
Controls	218	57	5			493	67						
Prediabetes	162	66	11	7.97	0.01	390	88	7.93	0.005[c]	1.66 (1.17-2.34)	0.006[c]	1.64 (1.14-2.34)	0.57
Type 2 diabetes	174	66	5	3.27	0.19	414	76	2.50	0.11	1.35 (0.94-1.92)	0.55	1.11 (0.77-1.62)	
Male													
Controls	217	54	2			488	58						
Prediabetes	168	55	7	5.38	0.06	391	69	3.94	0.04	1.48 (1.02-2.15)	0.06	1.44 (0.98-2.14)	0.49
Type 2 diabetes	171	67	4	5.67	0.059	409	75	4.99	0.02	1.54 (1.06-2.22)	0.02	1.57 (1.05-2.33)	

[a]Adjusted for age and BMI. [b]Dominant model of rs11642015 (CT + TT vs. CC) showed a significant result for prediabetes vs. controls (P=0.004; OR, 1.55; 95% CI, 1.15-2.09) adjusted for age and BMI; and for type 2 diabetes vs. controls (P=0.002; OR, 1.58; 95% CI, 1.17-2.12) adjusted for age and BMI. [c]Significant results. OR, odds ratio; CI, confidence interval; *FTO*, fat mass and obesity-associated gene; HWE, Hardy-Weinberg equilibrium; BMI, body mass index.

FTO rs11642015 was significantly associated with the risk of prediabetes in the whole sample (T vs. C: OR, 1.55; 95% CI, 1.19-2.01; P=0.001; CC vs. CT + TT: OR, 1.55; 95% CI, 1.15-2.09; P=0.004; Table II). A further breakdown analysis by gender showed that *FTO* rs11642015 was associated with prediabetes, OR, 1.66 (T vs. C: 95% CI, 1.17-2.34; P=0.005), in females. The significant results remained following adjustment of age and BMI (OR, 1.64; 95% CI: 1.14-2.34; P=0.006, Table II).

Statistically significant differences were observed in the genotype frequencies of rs11642015 between subjects with type 2 diabetes and controls in the whole sample, particularly under the dominant model following adjustment for age and BMI (OR, 1.58; 95% CI, 1.17-2.12; P=0.002). Further gender-stratified analysis did not reveal any significant results (Table II). There was no association of rs11642015 with type 2 diabetes for the comparison of the T and C allele and the additional adjustment for age and BMI did not change the results (Table II). According to power calculations, the sample size provided a 67.2% power (∂=0.05) to detect a relative risk for rs11642015.

Breakdown analysis by the BMI categories (14) was then conducted. However, no significant associations were found under the stringent Bonferroni's correction (Table III).

To assess the contribution of *FTO* rs11642015 to obesity, a meta-analysis of the data was performed together with

Table III. Association between *FTO* rs11642015 with obesity and Hardy-Weinberg equilibrium (HWE).

FTO (rs11642015)	CC, n	CT, n	TT, n	χ^2	P-value	C, n	T, n	χ^2	OR (95% CI) P-value	OR (95% CI) Unadjusted	OR (95% CI) P-value	OR (95% CI) Adjusted	HWE
Whole sample													
Normal weight	500	189	18			1189	225						0.97
Overweight	483	137	14	5.13	0.07	1103	165	4.52	0.03	0.79 (0.63-0.98)	0.03	1.55 (1.19-2.01)	
Obese	127	39	2	2.18	0.33	293	43	1.79	0.18	0.77 (0.54-1.10)	0.20	0.91 (0.70-1.18)[a]	
Female													
Normal weight	274	106	7			654	120						0.37
Overweight	218	63	9	3.74	0.15	499	81	0.50	0.47	0.88 (0.65-1.20)	0.47	1.64 (1.14-2.34)	
Obese	60	23	2	0.11	0.94	143	27	0.01	0.99	1.02 (0.65-1.62)	0.80	1.11 (0.77-1.62)[a]	
Male													
Normal weight	226	83	11			535	105						0.33
Overweight	265	74	5	5.00	0.08	604	84	4.44	0.03	0.70 (0.52-0.96)	0.03	1.44 (0.98-2.14)	
Obese	67	16	0	4.96	0.08	150	16	4.21	0.04	0.54 (0.31-0.94)	0.04	1.57 (1.05-2.33)[a]	

[a]Adjusted for age. Subjects were classified as obese if BMI≥28kg/m^2. Normal weight, BMI<24; overweight, 24≤BMI>28; obese, BMI≥28. *FTO*, fat mass and obesity-associated gene; OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table IV. Characteristics of studies assessing the association between *FTO* rs11642015 and obesity.

Authors (year)	Ethnicity	Case/ control, n	BMI Case[a]	BMI Control[b]	Case, n CC	Case, n CT	Case, n TT	Control, n CC	Control, n CT	Control, n TT	OR (95% CI)	HWE	Refs.
Sällman Almén *et al* (2013)	Swedish	524/527	-	-	-	-	-	-	-	-	1.29 (1.15-1.46)[c]	-	(10)
Rovite *et al* (2014)	Latvian	380/380	44.5±5.0	22.9±1.6	107	184	89	80	192	108	1.27 (1.04-1.56)[c,d]	0.75	(14)
Present study (2014)	Chinese	188/712	31.09±3.61	21.76±1.63	127	39	2	500	189	18	0.79 (0.56-1.13)[c,e]	0.97	

[a]Case, obesity; [b]Control, normal weight; [c]Additive model; [d]OR was estimated following adjustment for age and gender; and [e]OR was estimated following adjustment for age. -, not available. *FTO*, fat mass and obesity-associated gene; BMI, body mass index; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

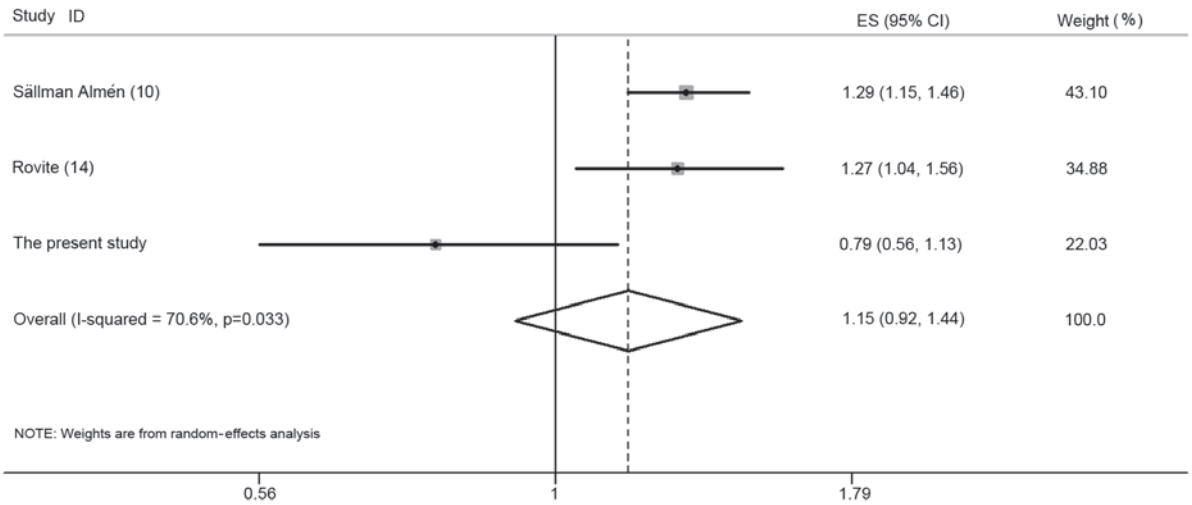

Figure 1. Meta-analysis plot for the association between fat mass and obesity-associated gene rs11642015 and obesity.

data from two previous publications (10,14). A meta-analysis suggested that the association between *FTO* rs11642015 and obesity under the additive model was not significant with high heterogeneity (OR, 1.15; 95% CI, 0.92-1.44; P=0.21; $P_{heterogeneity}$=0.03; I^2=70.6%; Fig. 1). There was no evidence of any publication bias observed (Begg's test = 0.29 and Egger's test = 0.32).

Discussion

The association between the *FTO* rs11642015 polymorphism with prediabetes, type 2 diabetes and obesity was examined in the present study, and to the best of our knowledge, the association has not been reported previously in the Chinese population. The association of the *FTO* locus with type 2 diabetes may vary in different populations.

The findings demonstrated that the *FTO* rs11642015 T allele was associated with the risk of prediabetes, particularly in females, and the association retained its significance following correction for age and BMI. Subjects carrying the CT + TT genotype were predisposed to prediabetes and type 2 diabetes following correction for age and BMI. This was consistent with the study by Kalnina *et al* (11), in which *FTO* rs11642015 was linked with a higher type 2 diabetes prevalence and the significance was retained subsequent to correction for BMI.

Notably, a significant association was not observed between the *FTO* rs11642015 polymorphism and obesity in the whole sample, females and males under the stringent Bonferroni's correction. Under the stringent Bonferroni's correction, the correction may be extremely conservative and may increase the likelihood of type II error. In contrast to the present study, Sällman Almén *et al* (10) observed a stronger association of *FTO* rs11642015 with obesity compared to rs9939609 by massive parallel sequencing in Latvia. The minor allele frequency (MAF) observed in the present study was 0.18 for rs11642015, whereas the corresponding MAF in the study by Sällman Almén *et al* (10) was 0.48. The differences among the studies may be due to the differences in the risk allele frequencies and linkage disequilibrium structure across different ethnicities. Other reasons include the varying study designs, different sample sizes and ethnic differences in genetic background and environmental factors (18). Whether there was an association of the *FTO* rs11642015 with obesity was not clear, and therefore a meta-analysis was also conducted with available studies to provide more definitive evidence. The meta-analysis, including a total of 2,711 subjects, provided evidence that *FTO* rs11642015 is not associated with obesity.

Obesity is one of the most important risk factors for the development of type 2 diabetes (19). The most common genetic variant of the *FTO* gene is rs9939609, and the first GWAS detected the contribution of rs9939609 to type 2 diabetes. However, the significant association was not apparent following adjustment for BMI (9), indicating that the association between the *FTO* locus and type 2 diabetes was mediated by BMI and that *FTO* is a susceptibility locus for obesity instead of type 2 diabetes. Several studies have reported that the association between the *FTO* locus and risk of type 2 diabetes remained significant following adjustment for BMI (20-22). However, a recent study showed a significant association between the *FTO* rs9939609 polymorphism and type 2 diabetes in a Vietnamese population, independent of obesity-related measurements, socio-economic status and lifestyle factors (23). Findings of that study showed that the association between the *FTO* locus and type 2 diabetes was not completely moderated through BMI, as the accurate estimates may not be revealed in particular populations.

There have been fewer studies reported in South Asians. Of three studies that have been reported, there were two that confirmed the association between the *FTO* locus and obesity susceptibility (24,25) and one that did not (26). The association of the *FTO* variants with type 2 diabetes and BMI has been independently identified in a number of Caucasian European populations. However, Asians and Europeans have differences in body composition, and therefore, *FTO* may have a smaller effect on obesity in Asians compared to Europeans. A population-based homogeneous population with 100% Han Chinese was determined, which eliminated the ethnical heterogeneity. A group of prediabetes subjects were also included. The majority of the previous studies only focused on two groups (type 2 diabetes and non-diabetic subjects). Including the group of prediabetes subjects is useful for identifying high-risk individuals at early stages and providing improved early prevention. Identification of the *FTO* variations in multi-ethnic groups is useful for understanding the diverse genetic backgrounds in different ethnicities. Additionally, the P-values are also corrected for multiple comparisons to avoid false-positive associations.

However, there are certain limitations that require highlighting. Firstly, due to the cross-sectional design, the selection bias cannot be neglected. In addition, the sample size was relatively small and the power at 67.2% to detect the association. Thirdly, there is a possibility that the interaction between gene-gene or gene-environment factors may conceal the true effect of specific genetic variants.

In conclusion, a significant association of the *FTO* rs11642015 T allele was observed with prediabetes following correction for age and BMI, particularly in females. Subjects carrying the CT + TT genotype are predisposed to a prediabetes and type 2 diabetes risk. Future investigation is required to elucidate the molecular function of *FTO*, downstream pathways and interactions, as well as the biological pathways that are fundamental for the independent association between the *FTO* variation with obesity and type 2 diabetes (27).

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