

Common Variation in the *FTO* Gene Confers Risk of Obesity and Modulates Body Mass Index in the Chinese Population

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Objective: Genetic variants in the *FTO* gene have been associated with obesity and type 2 diabetes in European populations. We aimed to test the role of *FTO* genetic variants in obesity and type 2 diabetes in the Chinese population.

Methods: We genotyped 19 single nucleotide polymorphisms (SNPs) spanning from the 3' end of the neighboring *RPGRIP1L* gene to the 5' flanking region of the *FTO* gene. We analyzed their associations with obesity (638 cases and 1,610 controls), type 2 diabetes (759 cases and 784 controls), and obesity-related traits in non-diabetic subjects.

Results: Among the 19 SNPs, the rs9939609 A allele was strongly associated with obesity ($p= 7.0 \times 10^{-4}$) and body mass index (BMI) ($p= 0.0024$) in the Chinese population. The odds ratio for obesity was 2.60 (95% CI: 1.24-5.46; $p=0.011$) for the AA genotype and 1.32 (95% CI: 1.05-1.66; $p= 0.018$) for the AT genotype as compared to the TT genotype. Each additional copy of the rs9936609 A allele was associated with a BMI increase of ~ 0.37 kg/m². The rs9939609 A allele was substantially less common in the Chinese population than in the European population (12.6% vs. 45%). We did not find significant associations of the 19 SNPs with type 2 diabetes or other obesity-related traits.

Conclusions: Genetic variation in the *FTO* gene is strongly associated with obesity and BMI in the Chinese population. The risk variant is less common in the Chinese population but its effect size on BMI is comparable to that in the European population.

Obesity is strongly influenced by genetic factors, with an estimated heritability of > 60% for body mass index (BMI) (1, 2). Genetic susceptibility to the common form of obesity appears to be polygenic. Although theoretical analyses emphasized the power of genetic association study in common polygenic diseases, the search for genes conferring the risk of obesity has thus far not been very successful. A few reported associations with genes such as *GAD2*, *ENPP1*, and *INSIG2* also yielded inconsistent results in replication efforts (3-5).

Recently, several independent studies using different approaches reported strong associations of genetic variants in the *FTO* (fat mass and obesity associated) gene with obesity in populations of European origin (6, 7). Frayling *et al.* initially found the association of *FTO* genetic variants with type 2 diabetes in a genome-wide association (GWA) study for type 2 diabetes (8). However, the association was abolished by adjustment for BMI, indicating that the association with type 2 diabetes was mediated through an effect of obesity (8). They replicated the associations (rs9939609) with obesity in a total of 38,759 individuals (6). Dina *et al.* concurrently reported strong associations of SNPs (rs1421085 and rs17817449) of *FTO* gene with childhood and severe adult obesity (7). Two other GWA studies also independently reported the associations of nearby *FTO* genetic variants

(rs9930506, rs8050136, rs7193144, rs1121980, rs9939973) with obesity and obesity-related traits in European and Hispanic populations (9, 10). All these SNPs fall in a region of strong linkage disequilibrium (LD) in intron 1 of the *FTO* gene. The effect of *FTO* genetic variants on common obesity is also substantial in the European population. Adults who are homozygous for the risk-conferring rs9939609 A allele weighed about 3 kilograms more and had a 1.67-fold increased odds ratio of obesity when compared to those without a risk allele (6). The calculated population attributable risk is ~ 22 % for common obesity in populations of European origin (6).

Reproducibility is essential for reported genetic associations, especially among populations of different ethnic backgrounds. However, studies in an Oceanic population (12), African Americans (10), Han Chinese (13) and Japanese (14) failed to detect associations between previously reported SNPs and obesity or obesity-related traits. Although the limited sample size and power of these studies is the most likely reason for the lack of association, there is emerging evidence showing that other *FTO* SNPs not in LD with rs9939609 may be the causative variant in non-European populations (15). In this study, we aimed to investigate the association of *FTO* genetic variants with obesity and type 2 diabetes in the Chinese population. Instead of testing only a few

variants, we used a gene-based approach (16) by selecting potentially functional and common SNPs from the 3' end of the neighboring *RPGRIP1L* gene to the 5' flanking region of the *FTO* gene. Their associations with obesity-related quantitative metabolic traits were also analyzed.

Methods

Subjects

We recruited 594 young obese cases from the bariatric surgery clinics of En Chu Kong General Hospital in Taiwan. Obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$. 759 type 2 diabetic cases were recruited from the metabolic clinic of National Taiwan University Hospital (NTUH). Type 2 diabetes was diagnosed based on the criteria of the American Diabetes Association (17). We excluded diabetic patients with ages of onset less than 35 years.

We recruited 910 healthy non-obese controls from the health check-up service of NTUH and a community-based health screening program in Taiwan. Non-obesity was defined as $\text{BMI} < 30 \text{ kg/m}^2$. Among them, 784 were confirmed to be normal glucose tolerant after a 75-g OGTT test.

The case-control association analysis for type 2 diabetes included the 759 type 2 diabetic cases and 784 controls with normal fasting glucose and glucose tolerance. They were not matched for age, sex or BMI. The case-control association analysis for obesity included 594 young obese cases and 910

healthy non-obese controls. We further incorporated type 2 diabetic cases with available BMI data ($n=744$) into the analysis. In total, 638 obese cases (594 young obese cases and 44 obese type 2 diabetic cases) and 1,610 non-obese controls (910 healthy non-obese controls and 700 non-obese type 2 diabetic cases) were used in the case-control association analysis for obesity. Association analysis for BMI was performed in all subjects with available BMI data. The association analyses for other obesity-related metabolic traits were performed in all non-diabetic subjects with available metabolic traits. Written informed consent was obtained from every participating subject, and the study was approved by the institutional review board of the NTUH.

Clinical measurements

BMI was calculated as weight in kilograms divided by the square of height in meters. Plasma glucose was determined using a glucose oxidase autoanalyzer (Daikin AntsenseII, Japan) and plasma insulin was measured using a radioimmunoassay (Abbott AXSYM, USA). Fasting total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and uric acid levels were measured using a dry-chemistry autoanalyzer (Fuji FDC-3000, Japan). Serum high-sensitive C-reactive protein (hs-CRP) concentration was measured with a turbidimetric immunoassay utilizing an auto-analyzer (Toshiba

TBA-120FR, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from the product of the fasting insulin concentration (mU/L) and plasma glucose (mmol/L) divided by 22.5 (18). The homeostasis model assessment of beta-cell function (HOMA-beta) was calculated as $20 \times \text{fasting insulin (mU/L)} / [\text{fasting plasma glucose (mmol/L)} - 3.5]$ (18).

Selection of SNPs and genotyping

We selected potentially functional and common SNPs from the 3' end of the neighboring *RPGRIP1L* gene to the 5' flanking region of the *FTO* gene by using FASTSNP (Functional Analysis and Selection Tool for Single Nucleotide Polymorphism) software (19). The FASTSNP software is a web server that allows users to efficiently identify and prioritize SNPs according to their putative functional effects. The prioritization strategy is based on the priority proposed by Tabor *et al.* (20). All SNPs in the *FTO* gene with possible function effects are predicted as "intronic enhancers" which are intronic SNPs with a potential transcriptional factor binding site. We selected only SNPs with known minor allele frequencies > 15 % in the Chinese population. Twenty SNPs were selected. Among them, SNP rs1421092 is located in intron 1 of the *RPGRIP1L* gene. Other SNPs are located in intron 1 (rs11861870), intron 4 (rs2388405), intron7 (rs2287142), intron 8 (rs16952730, rs16952777, rs4784338, rs1107355,

rs12443572, rs13331869, rs12600060, rs16952987, rs918031, rs1008400) and the 5' flanking region (rs1588413, rs11076022, rs11076023, rs12597712, rs2072518, rs2075205) of the *FTO* gene. Because all *FTO* variants (rs7193144, rs8050136, rs9939609, rs9930506, rs1121980, rs17817449) with known associations with obesity and type 2 diabetes in European populations (5-10) are less than 15% in the Chinese population and are in strong LD (mean $r^2 = 0.87$ and mean $D' = 1$) according to the HapMap CHB databank (11), we additionally selected rs9939609 as a tag SNP capturing these SNPs. Genotyping was performed in a total of 21 SNPs using the GenomeLab SNPstream genotyping platform (Beckman Coulter, Fullerton, CA) and its accompanying SNPstream software suite. On average, 97.96% of attempted genotypes were successful except for rs2388405 and rs2287142 in which genotyping failed in all samples. The concordance rate of genotyping duplication was 99.62% based on 40 duplicate samples for each SNP. These 19 SNPs captured 96 of 407 alleles (23%) with frequencies > 5% at an r^2 of 0.8 across a region of 419 kb containing the *FTO* gene from the HapMap CHB database (build 35 release) (11)

Statistical analyses

Genotype data of both case and control groups were used to estimate inter-marker LD by pairwise D' and r^2 . We used the solid spine of LD method implemented in the

Haploview software (<http://www.broad.mit.edu/mpg/haploview/>) to define an LD block with an extended spine of $D' > 0.8$ (21). To compare the LD structures of a 419-kb region containing the *FTO* gene between Chinese and European populations, we used the genotype data from the CHB (Han Chinese) and CEU (Utah residents of northern and western European ancestry) databases in the HapMap (build 35). The LD structures were visualized using the Haploview software.

A Hardy-Weinberg equilibrium test was performed for each SNP for the control group before marker-trait association analysis. The associations of each SNP with obesity and type 2 diabetes were estimated using logistic regression under a log-additive model implemented in the PLINK software (<http://pngu.mgh.harvard.edu/~purcell/plink/>) (22). We tested the model fit for disease association by comparing additive, dominant, and recessive models using logistic regression. Nominal two-sided p -values were reported and were corrected for multiple testing by permutation for 10,000 times.

For quantitative trait analyses, all metabolic traits including BMI were logarithmically transformed and standardized to the Z -score units. The associations of each SNP with metabolic traits and the per-allele effect size on metabolic traits were estimated using linear regression in an additive genetic model in

PLINK. We tested the model fit for metabolic traits association by comparing additive, dominant, and recessive models using linear regression. Nominal two-sided p -values were reported and were corrected for multiple testing by permutation for 10,000 times.

In the case-control association study for obesity and association analysis for quantitative metabolic traits, we combined samples from different study populations. We used the Cochran's Q test for heterogeneity and the I^2 statistics to estimate heterogeneity between study populations. Meta-analysis of obesity association for the combined samples was performed using the fixed effects Cochran-Mantel-Haenszel method implemented in PLINK. The combined odds ratio and significance level was estimated using the study population as strata. For quantitative metabolic traits association analyses in the combined samples, we used inverse variance methods implemented in the Comprehensive Meta-analysis Software Version 2 (Biostat, Englewood NJ) to estimate the combined effect size on BMI and significance level.

To provide approximate estimate of the per-allele effect size in BMI units (kg/m^2), we used the methods adopted by Frayling *et al.* (6). The Z -score unit differences were translated into BMI units using the standard deviation of the BMI in general Chinese population (3.01 kg/m^2 in healthy controls of this study).

The population attributable risk fraction

(PAF) was estimated with data from the control group, calculated as follows: $1 - (1 - [p^2 \text{OR}_{\text{homo}} + 2p(1-p)\text{OR}_{\text{hetero}} + (1-p)^2])$, where p is the risk-allele frequency, OR_{homo} is the odds ratio for homozygotes, and $\text{OR}_{\text{hetero}}$ is the odds ratio for heterozygotes. Power calculations were performed using Genetic Power Calculator (<http://pengu.mgh.harvard.edu/~purcell/gpc/>) (23).

Results

Basic demographic data, SNP information, and structure of LD

The baseline characteristics of participants are shown in Table 1. The basic information of the 19 genotyped SNPs is summarized in supplementary Table 1. Graphical representation of SNPs in relation to the exon-intron structure and the LD pattern between markers are depicted in Fig. 1. We compared the structures of LD across a 419-kb region containing *FTO* gene using genotype data from the CHB and CEU HapMap samples. The LD structures across this region shared high similarity between the two populations (supplementary Fig. 1).

Association analysis of genetic variants of *FTO* gene with obesity and BMI

The rs9939609 A allele was identified as the risk variant for obesity in populations of European ancestry (6). Among the 19 SNPs in this study, the rs9939609 A allele was strongly associated with obesity ($p = 7.0 \times 10^{-4}$, Table 2, Fig. 2). The per-A allele increase of odds ratio

for obesity was 1.43 (95% CI: 1.16-1.75, Table 2, supplementary Fig. 2). The association remained significant after correction for multiple testing. The genotypic odds ratio for obesity was 2.60 (95% CI: 1.24-5.46, $p = 0.011$) for the AA genotype and 1.32 (95% CI: 1.05-1.66, $p = 0.018$) for the AT genotype. The genetic model was best fit with an additive model ($p = 7.0 \times 10^{-4}$, 0.0098, and 0.014 for additive, recessive, and dominant model respectively). When different criteria for obesity were applied (24), the associations were also significant (allelic $p = 7.6 \times 10^{-4}$ for obesity defined as $\text{BMI} \geq 28 \text{ kg/m}^2$ and 0.0081 for $\text{BMI} \geq 27 \text{ kg/m}^2$). The frequency of the rs9939609 A allele (12.6 %) was substantially lower in our study than that of European populations (~45 %) (6), corresponding to a lower PAF of 8.7% in the Chinese population.

The rs9939609 A allele was also associated with increased BMI ($p = 0.0024$, Fig. 2) and weight ($p = 0.0065$). In our study cohort, carriers with AA genotype (mean BMI \pm SD: $31.52 \pm 8.76 \text{ kg/m}^2$) and AT genotype (mean BMI \pm SD: $28.75 \pm 7.89 \text{ kg/m}^2$) were heavier than those with TT genotypes (mean BMI \pm SD: $28.08 \pm 8.45 \text{ kg/m}^2$) ($p = 0.0088$ and 0.048, respectively) (Fig. 3). The genetic model was best fit with an additive genetic

model ($p= 0.0024, 0.0091, 0.073$ for additive, recessive, and dominant models respectively). Each additional copy of the rs9939609 A allele was associated with a BMI increase of a mean 0.124 Z-score units, equivalent to $\sim 0.37 \text{ kg/m}^2$ or 1.07 kg in body weight for a person 1.7 m tall (supplementary Fig. 2). The extent of variance in BMI explained by rs9939609 was $\sim 0.5\%$ in the Chinese population.

There was no heterogeneity in the per-A allele increase of odds ratio for obesity and effect size on BMI among different study populations (supplementary Fig. 2). We did not detect any significant interaction between rs9939609 genotype and age or sex on the risk of obesity or BMI (data not shown).

Association analysis of genetic variants of *FTO* gene with type 2 diabetes

We did not observe significant association between rs9939609 and type 2 diabetes. Two SNPs (rs16952777 and rs1107255) in LD block 1 were nominally associated with type 2 diabetes (Table 3). SNPs in the same block were also nominally associated with fasting glucose concentrations in non-diabetic subjects (supplementary Table 2). However, none of these associations remained significant after adjustment for multiple testing.

Association of *FTO* genetic variants with obesity-related metabolic traits

Results from the association analysis with other obesity-related metabolic traits are shown in supplementary Table 2. We did not observe significant association between

rs9939609 and obesity-related metabolic traits including fasting glucose, insulin, cholesterols, triglycerides, uric acid, CRP and blood pressure. We found 9 hypotheses with $P_{\text{nominal}} < 0.05$ but none of them remained significant after permutation testing. A borderline significant association result was obtained between HOMA- β and rs1421092 after permutation testing ($P_{\text{permuted}} = 0.054$).

Discussion

Genetic polymorphisms of the *FTO* gene are the only genetic variants that have been reproducibly associated with obesity in populations of European ancestry (6, 7, 9, 10). However, these associations were controversial in Asian populations. Li *et al.* found no association of *FTO* variants with obesity and BMI in the Chinese population. Horikoshi *et al.* also found no association of *FTO* variants with BMI in the Japanese population. In contrast, another group reported that rs9939609 was associated with BMI in the Japanese population (25). A recent study also found strong associations of rs9939609 and other SNPs located in the intron 1 LD block with severe obesity in the Japanese population (26). In this study, we confirmed the strong association of *FTO* genetic variants with obesity and BMI in a Han Chinese population. This is one of the first studies that successfully replicated the association of *FTO* genetic polymorphisms

with obesity in the Chinese population. Furthermore, we found that the effect size of the rs9939609 A allele on obesity risk and BMI are comparable to that in European populations (6, 7). However, the risk allele was much less common in the Chinese population than in European populations (12.6% vs. 45%), leading to a lower PAF (8.3% vs. 22%). Only ~1.7 % of the Chinese population were homozygotes of the A allele, in contrast to 16 % in European populations. The variance of BMI explained by rs9939609 was also lower (~0.5%) when compared to European populations (~1%). Previous analyses suggested that purifying selection (negative selection) has operated on the *FTO* gene since the divergence of chimpanzee and human (12). It will be of interest to reconstruct the phylogenic relationship between *FTO* genetic variants and to explore possible adaptive evolution to environmental changes.

Li *et al.* recently reported no association of *FTO* genetic polymorphism in the intron 1 block (rs9939609, rs8050136, rs9930506) with obesity in the Chinese population. The reason for the discrepancy is not known. The sample size and design of the study by Li *et al.* was comparable to our study and was sufficiently powered. However, our study recruited mainly young obese cases. This approach may increase the genetic load and decrease the interference of environmental effects. It is also possible that unrecognized difference in population structure existed

between two study populations. Li *et al.* also proposed that other *FTO* variants outside the intron 1 block might be associated with obesity. Therefore, instead of testing only few variants, we adopted a gene-based approach by selecting common and potential functional SNPs across the *FTO* and nearby *KIAA1005* gene. Although the coverage of *FTO* genetic variation was far from sufficient using this approach, the highest association signal appeared in the intron 1 of *FTO* gene. Consistent with our findings, Hotta *et al.* also found highest association signals with severe obesity in the intron 1 block of *FTO* gene (26). These data indicate that the underlying causative variant is located in the intron 1 block or is in strong LD with SNPs in the intron 1 block in the Chinese or Japanese populations, similar to the findings in European populations (6,7,9,10).

We did not detect an association of rs9939609 with type 2 diabetes in our study. Only nominal associations of two SNPs located in a nearby LD block were found with type 2 diabetes and fasting glucose. However, assuming an allele frequency of 12.5 %, an allelic relative risk of 1.17 (8,27,28) and diabetes prevalence of 8 % in the Chinese population in Taiwan, enrollment of approximately 2,300 cases would be necessary for the case-control study to have 80 percent power (23). A sample size of at least threefold of the present study would be needed to detect the effect. Therefore, our study is underpowered to

detect such association. Furthermore, the type 2 diabetic cases in our study cohort was comprised of mostly non-obese subjects (mean BMI= 24.66 kg/m²). This is in contrast to the type 2 diabetic cases in the Wellcome Trust Case Control Consortium (WTCCC) and United Kingdom Type 2 Diabetes Genetic Consortium (UKT2D) (mean BMI= 30.95 kg/m²) (8, 27, 28). The lower BMI of type 2 diabetic cases in our study would weaken the genetic contribution of *FTO* to type 2 diabetes. In accord with our study, two studies in Japanese and Chinese populations also yielded insignificant associations of rs9939609 with type 2 diabetes (13, 25). Horikoshi *et al.* reported nominal association of rs8050316 with type 2 diabetes but no association was found with rs9939609 in Japanese (14). The mean BMI of type 2 diabetic cases in these studies were similar to our study. Given the lower risk allele frequency and the relatively leaner body build of type 2 diabetic patients in the Chinese and Japanese population, larger sample size is needed to detect the association with type 2 diabetes and the genetic contribution of *FTO* to type 2 diabetes may be of less importance in these populations.

We did not observe significant associations of obesity-related metabolic traits with SNPs near the *FTO* gene. Three studies in Chinese and Japanese population also failed to detect significant associations with obesity or type 2

diabetes-related metabolic traits including fasting glucose, insulin, lipids, and blood pressure (13, 14, 26). However, a meta-analysis in 17,037 Caucasians found significant associations with *FTO* genotype with fasting glucose, insulin, triglyceride, and HDL-C (29). Again, the most probable reason for lack of association in the Chinese and Japanese population is the lack of adequate power. A similar meta-analysis combining all studies in these populations may be needed to improve the power.

In summary, we confirmed the association of *FTO* genetic polymorphisms with obesity and BMI in the Chinese population. The risk allele is much less common in the Chinese population but its effect size obesity risk and BMI were comparable to those in European populations. We did not observe significant association of *FTO* genetic polymorphism with type 2 diabetes, probably due to inadequate power. Given the lower risk allele frequency and the leaner body build of type 2 diabetic patients in the Chinese population, the genetic contribution of *FTO* gene to type 2 diabetes in the Chinese population may be less than that in European populations.

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Table 1. Basic characteristics of the study subjects.

	<i>N</i>	Males: females	Age (years)	BMI (kg/m ²)
Obesity case-control study				
Cases	638	219: 419	37.00±0.56	38.86±8.19
Controls	1,610	822: 788	61.08±0.33	24.04±2.89
Type 2 diabetes case-control study				
Cases	759	381: 378	60.03±11.85	24.66±3.40
Controls	784	438: 346	63.37±14.0	23.63±3.08

Data were presented as means ± SD.

Table 2. Association analysis of *FTO* sequence variants and obesity.

#	SNP name	Major/ minor allele	Genotype distribution*		Genotypic $P_{nominal}$	MAF		Odds ratio for obesity (95%CI)	Allelic $P_{nominal}$ (adjusted P^{**})	Allelic $P_{permuted}^+$
			Case	Control		Case	Control			
1	rs1421092	G/A	(172:280:179)	(356:775:428)	0.018	0.494	0.476	1.08 (0.94-1.26)	0.26 (0.70)	0.96
2	rs11861870	T/C	(119:308:206)	(282:766:534)	0.81	0.432	0.421	1.04 (0.90-1.20)	0.60 (0.83)	1.0
3	rs9939609	T/A	(18:167:425)	(20:347:1158)	0.0028	0.166	0.126	1.43 (1.16-1.75)	7×10⁻⁴ (0.034)	0.0087
4	rs16952730	A/G	(52:268:310)	(136:651:784)	0.81	0.297	0.294	1.02 (0.87-1.19)	0.82 (0.69)	1.0
5	rs16952777	C/G	(142:313:159)	(342:786:425)	0.97	0.485	0.472	1.01 (0.88-1.17)	0.84 (0.32)	1.0
6	rs4784338	T/G	(41:315:165)	(338:785:432)	0.99	0.481	0.470	1.01 (0.87-1.16)	0.96 (0.27)	1.0
7	rs1107355	G/A	(74:312:228)	(273:756:542)	0.15	0.393	0.415	0.88 (0.76-1.02)	0.098 (0.42)	0.67
8	rs12443572	C/G	(12:171:426)	(50:443:1047)	0.16	0.160	0.176	0.85 (0.70-1.03)	0.097 (0.55)	0.67
9	rs13331869	T/A	(11:166:44)	(47:436:1046)	0.080	0.152	0.174	0.84 (0.69-1.02)	0.077 (0.33)	0.58
10	rs12600060	G/T	(119:323:168)	(307:766:462)	0.61	0.460	0.450	1.08 (0.93-1.25)	0.31 (0.84)	0.98
11	rs16952987	G/A	(80:299:249)	(208:707:647)	0.58	0.366	0.360	1.04 (0.89-1.21)	0.64 (0.73)	1.0
12	rs918031	T/C	(86:309:233)	(246:719:603)	0.38	0.383	0.386	0.97 (0.84-1.13)	0.68 (0.72)	1.0
13	rs1008400	C/T	(87:310:231)	(249:718:605)	0.34	0.385	0.387	0.97 (0.83-1.12)	0.65 (0.73)	1.0
14	rs1588413	C/T	(54:275:297)	(118:611:855)	0.029	0.306	0.268	1.23 (0.98-1.31)	0.011 (0.46)	0.12
15	rs11076022	G/A	(142:330:159)	(324:811:448)	0.28	0.486	0.462	1.13 (0.98-1.31)	0.10 (0.63)	0.68
16	rs11076023	T/A	(117:311:190)	(272:744:514)	0.31	0.441	0.422	1.11 (0.96-1.29)	0.16 (0.60)	0.85
17	rs12597712	C/G	(119:315:186)	(280:771:500)	0.40	0.446	0.429	1.11 (0.96-1.28)	0.16 (0.65)	0.86
18	rs2072518	G/A	(137:319:170)	(334:801:442)	0.65	0.474	0.466	1.07 (0.92-1.24)	0.36 (0.73)	0.99
19	rs2075205	A/T	(153:303:133)	(364:776:374)	0.36	0.483	0.503	0.91 (0.89-1.06)	0.22 (0.49)	0.93

* Genotype distribution are shown as the counts of three genotypes (aa, Aa, AA): a present the minor allele and A represent the major allele.

**adjusted for age, sex and BMI; ⁺ Permutation for 10,000 times; MAF, minor allele frequency.

Table 3. Association analysis of *FTO* sequence variants and type 2 diabetes.

#	SNP name	Major/ minor allele	Genotype distribution*		Genotypic <i>P</i> _{nominal}	MAF		Odds ratio for type 2 diabetes (95%CI)	Allelic <i>P</i> _{nominal} (adjusted <i>P</i> [*])	Allelic <i>P</i> _{permuted} ⁺
			Case	Control		Case	Control			
1	rs1421092	G/A	(178:356:219)	(164:376:208)	0.50	0.473	0.469	1.01 (0.88-1.18)	0.83 (0.92)	1.0
2	rs11861870	T/C	(136:358:259)	(131:377:256)	0.77	0.419	0.420	1.00 (0.86-1.15)	0.95 (0.80)	1.0
3	rs9939609	T/A	(11:172:55)	(10:166:550)	0.94	0.132	0.127	1.05 (0.84-1.31)	0.67 (0.86)	1.0
4	rs16952730	A/G	(61:316:380)	(71:314:371)	0.65	0.289	0.302	0.94 (0.80-1.10)	0.44 (0.64)	1.0
5	rs16952777	C/G	(154:366:219)	(180:384:188)	0.095	0.456	0.493	0.86 (0.75-0.99)	0.038 (0.056)	0.43
6	rs4784338	T/G	(153:370:220)	(175:378:194)	0.20	0.455	0.488	0.88 (0.76-1.01)	0.071 (0.14)	0.58
7	rs1107355	G/A	(115:369:270)	(146:369:246)	0.092	0.397	0.435	0.86 (0.74-0.98)	0.033 (0.044)	0.36
8	rs12443572	C/G	(19:216:50)	(23:214:50)	0.82	0.172	0.176	0.97 (0.77-1.18)	0.75 (0.61)	1.0
9	rs13331869	T/A	(16:211:499)	(23:214:501)	0.55	0.167	0.177	0.94 (0.77-1.14)	0.49 (0.49)	1.0
10	rs12600060	G/T	(157:354:223)	(139:379:218)	0.37	0.455	0.446	1.04 (0.89-1.20)	0.63 (0.71)	1.0
11	rs16952987	G/A	(96:350:308)	(101:339:311)	0.86	0.559	0.561	0.99 (0.86-1.16)	0.93 (0.99)	1.0
12	rs918031	T/C	(114:344:289)	(114:358:285)	0.88	0.483	0.486	0.99 (0.85-1.18)	0.86 (0.90)	1.0
13	rs1008400	C/T	(115:344:29)	(115:357:284)	0.86	0.383	0.387	0.98 (0.85-1.14)	0.82 (0.86)	1.0
14	rs1588413	C/T	(56:295:40)	(52:290:423)	0.78	0.269	0.259	1.05 (0.89-1.24)	0.52 (0.55)	1.0
15	rs11076022	G/A	(156:386:213)	(148:397:223)	0.79	0.462	0.453	1.04 (0.90-1.20)	0.61 (0.60)	0.87
16	rs11076023	T/A	(140:351:243)	(114:362:25)	0.21	0.430	0.405	1.11 (0.96-1.29)	0.15 (0.17)	0.93
17	rs12597712	C/G	(141:366:235)	(120:375:249)	0.33	0.437	0.413	1.10 (0.95-1.28)	0.19 (0.21)	0.91
18	rs2072518	G/A	(167:378:205)	(150:388:228)	0.35	0.475	0.450	1.10 (0.95-1.28)	0.18 (0.16)	0.99
19	rs2075205	A/T	(183:367:178)	(162:375:185)	0.48	0.503	0.485	1.07 (0.93-1.25)	0.31(0.36)	1.0

* Genotype distribution are shown as the counts of three genotypes (aa, Aa, AA): a present the minor allele and A represent the major allele.

**adjusted for age, sex and BMI; ⁺ Permutation for 10,000 times; MAF, minor allele frequency.

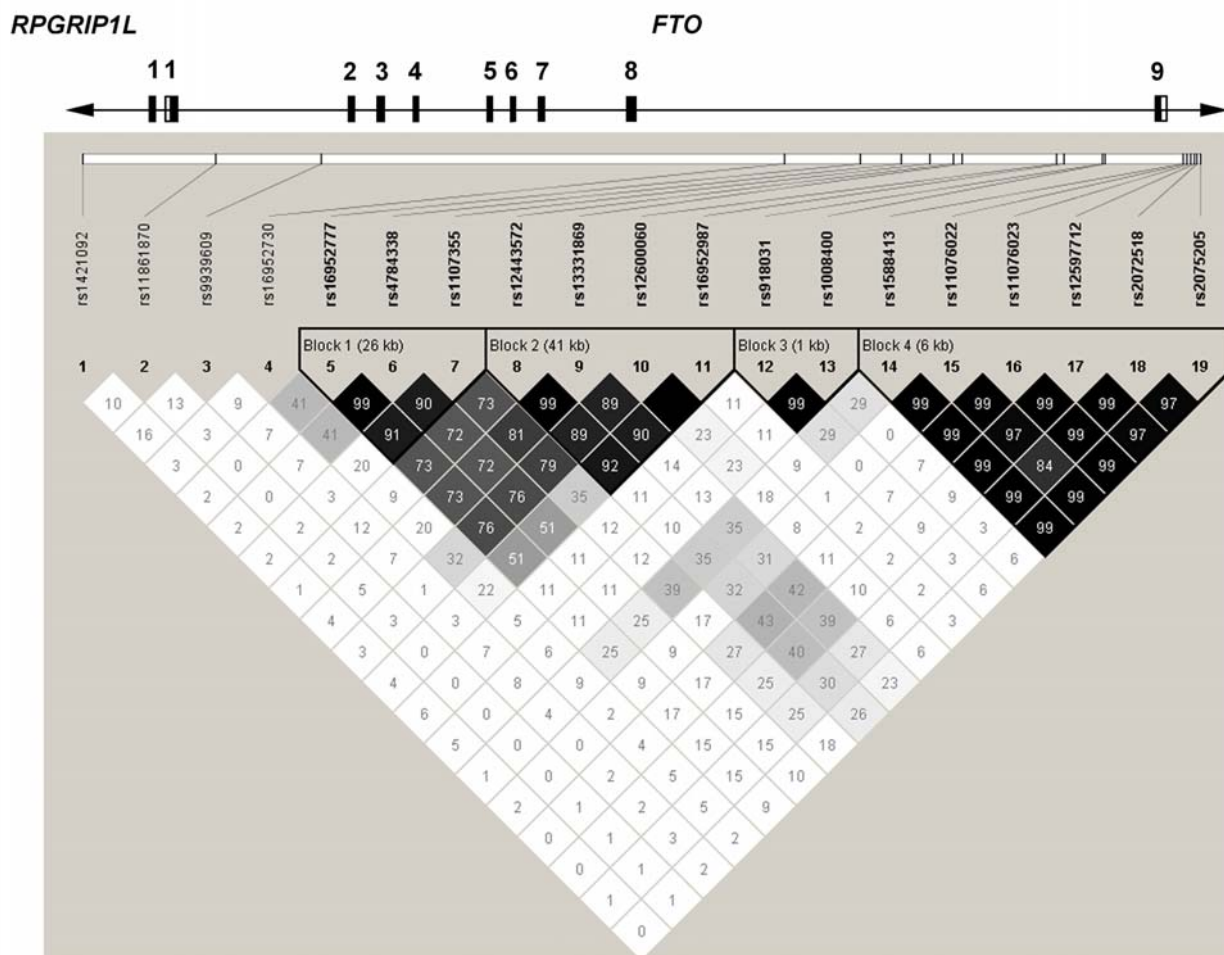


Figure 1. Graphical representation of SNPs in relation to the exon-intron structure (upper part) and Haploview LD graph of *FTO* gene (lower part). The exon regions are shown with filled rectangles and numbered in order. Pairwise LD coefficients $D' \times 100$ was shown in each cell (D' values of 1.0 were not shown). Alternative D' /LOD color scheme of Haploview was applied for LD color display (high LOD score and high D' in black; high LOD score and low D' in white; low LOD score and high D' in shade of gray; low LOD score and low D' in white).

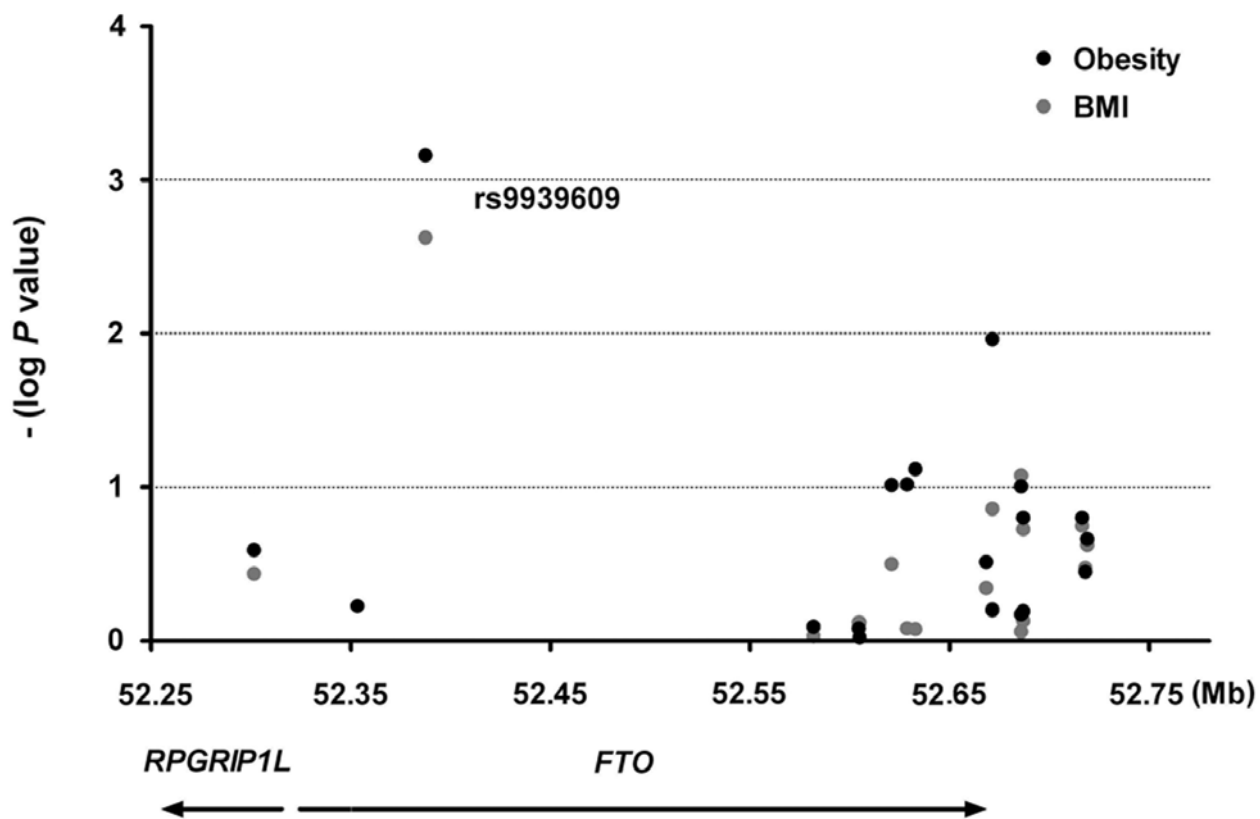


Figure 2. Associations of SNPs near the *FTO* and *RPGRIP1L* gene regions of chromosome 16 with obesity and BMI in the Chinese population.

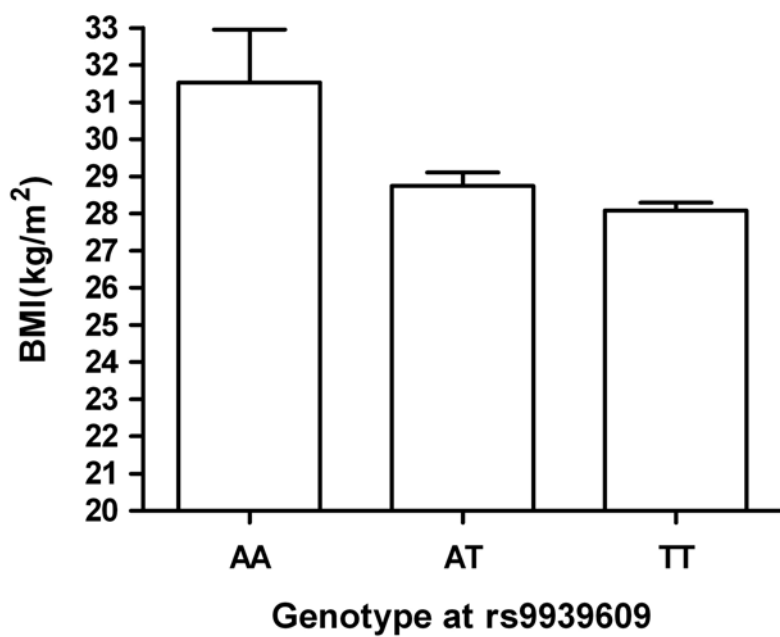


Figure 3. BMI according to genotype at rs9939609. Data were expressed as means \pm SE (error bars).