NOTE

Association of fat mass and obesity-associated and retinitis pigmentosa guanosine triphosphatase (GTPase) regulator-interacting protein-1 like polymorphisms with body mass index in Chinese women

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Abstract. Body mass index (BMI) is the most commonly used quantitative measure of adiposity. It is a kind of complex genetic diseases which are caused by multiple susceptibility genes. The first intron of fat mass and obesity-associated (*FTO*) has been widely discovered to be associated with BMI. Retinitis pigmentosa GTPase regulator-interacting protein-1 like (*RPGRIP1L*) is located in the upstream region of *FTO* and has been proved to be linked with obesity through functional tests. We carried out a genetic association analysis to figure out the role of the *FTO* gene and the *RPGRIP1L* gene in BMI. A quantitative traits study with 6,102 Chinese female samples, adjusted for age, was performed during our project. Among the twelve SNPs, rs1421085, rs1558902, rs17817449, rs8050136, rs9939609, rs7202296, rs56137030, rs9930506 and rs12149832 in the *FTO* gene were significantly associated with BMI after Bonferroni correction. Meanwhile, rs9934800 in the *RPGRIP1L* gene showed significance with BMI before Bonferroni correction, but this association was eliminated after Bonferroni correction. Our results suggested that genetic variants in the *FTO* gene were strongly associated with BMI in Chinese women, which may serve as targets of pharmaceutical research and development concerning BMI. Meanwhile, we didn't found the significant association between *RPGRIP1L* and BMI in Chinese women.

Key words: Fat mass and obesity-associated, Retinitis pigmentosa GTPase regulator-interacting protein-1 like, Body mass index, Single-nucleotide polymorphism

OVERWEIGHT AND OBESITY have been a globally public health crisis, which increase the risk of diabetes,

heart disease, cancer and premature death [1, 2]. At least 2.8 million adults die each year as a result of being overweight or obese. In addition, 44% of the diabetes, 23% of the ischemic heart disease and 7–41% of certain cancer burdens result from overweight and obesity (<http://www.who.int/bmi>). In 2010, the prevalence of overweight and obesity among Chinese adults was 30.6% and 12.0%, respectively [3]. There were 2.1 billion overweight and obese individuals all over the world in 2013 [4]. Trends of overweight and obesity in the Han Chinese population became worrisome during the past thirty

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years [5-8]. Scientists have involved themselves in the exploration of the molecular mechanisms of obesity and obesity-related diseases for a long time. Relevant studies showed that nearly 60% of obesity susceptibility was due to the difference between genotypes [9, 10].

Body mass index (BMI) is one of the most common used index for the diagnosis of obesity. The prevalence of hypertension, diabetes, dyslipidemia and clustering of risk factors is related with the increasing levels of BMI [11]. BMI has a strong heritability ranging from 40% to 80%, including several genes which express in the hypothalamus and play key roles in the regulation of appetite [12, 13]. A meta-analysis showed that both the lower and higher level of BMI contributed to the risk of all-cause mortality in Asian adults [14]. Genome-wide association studies (GWAS) have so far identified 32 loci strongly associated with BMI [12, 15-18].

The fat mass and obesity-associated (*FTO*) gene was firstly reported to be associated with obesity [16, 19, 20]. *FTO* is located on the chromosome 16q12.2 of the human genome and expresses in almost all tissues [21]. It spans more than 4,000 kb of DNA and consists of 9 exons. Previous studies proved that *FTO* played an important role in the nucleic acid demethylation, balance of energy homeostasis and regulation of body fat masses with the help of lipolysis [22, 23]. Its influence on adiposity was supposed to work out through the way of affecting appetite [24]. Take the example of SNP rs9939609, which was mostly widely studied all over the world, adults carried A allele at rs9939609 were substantially obese in Europe (OR 1.67, 95% CI 1.47-1.89, $p = 1 \times 10^{-14}$) [16], Denmark (OR 1.27, 95% CI 1.20-1.34, $p = 2 \times 10^{-16}$) [25], North India (OR 1.3, 95% CI 1.1-1.7, $p = 0.012$) [26] and Japan (OR 1.38, 95% CI 1.20-1.59, $p = 1.2 \times 10^{-5}$) [27]. Meanwhile, rs9939609 was associated with BMI in Chinese girls aged 12-18 years ($\beta = 1.07$, $p = 0.008$) [28], Korean population ($\beta = 0.335$, $p = 1.5 \times 10^{-7}$) [29] and Sorbian population ($\beta = 0.021$, $p = 0.0087$) [30], but this SNP was not significantly associated with BMI in Japanese population (AA 23.22 ± 3.14 vs. AT 22.79 ± 3.25 vs. TT 22.58 ± 3.13 , $p = 0.063$) [27].

Retinitis pigmentosa GTPase regulator-interacting protein-1 like (*RPGRIP1L*) is a ciliary gene located in close proximity to the transcriptional start site of *FTO* and is a transition zone structural component of the primary cilium which is related to human energy homeostasis [31, 32]. *RPGRIP1L* is located on the chromosome 16q12.2 of the human genome and lies in close proximity 5' of and in the opposite direction as *FTO*. It spans

more than 100 kb of DNA and consists of 27 exons [33]. One RT-PCR analysis detected that *RPGRIP1L* was strongly expressed in adult human testis and kidney [34]. Both *RPGRIP1L* and *FTO* belonged to consecutive genes, which were detected on the missing 1.6-Mb chromosome segment in fused-toe mice [35]. *RPGRIP1L* is a component of the basal body of the cilium [36, 37] and might play an important role in the pathway of human energy [38].

We aimed to figure out whether the *FTO* gene and *RPGRIP1L* gene play significant roles in BMI in Chinese female population. Both of them locate in the same pathway and the mechanism of the association among these two genes and obesity remains unknown, so we hypothesized that this pathway composed of *FTO* and *RPGRIP1L* might have some effects on obesity and BMI.

Materials and Methods

We performed the study in 6,102 Chinese female samples totally. Average age, BMI, waist circumference, height and body weight of participants is 19.7 years ($s.d. = 2.9$), 20.4 kg/m² ($s.d. = 2.4$), 70.0 cm ($s.d. = 6.7$), 161.6 cm ($s.d. = 5.5$) and 53.2 kg ($s.d. = 7.1$) respectively. Subjects wore light clothing during the measurement, without shoes. BMI is calculated by dividing weight in kilogram's by height in meters squared. We run the tape measure around the waist with three centimeters above the belly button to get the data of waist circumference. Statistical power was calculated by G-power software (<http://gpower.hhu.de>). A normal distribution of our data is shown in Fig. 1 using the normality test and distribution curve.

The association between the *FTO* gene and BMI has been widely reported. Based on previous reports [39-43], we selected nine variants rs1421085, rs1558902, rs17817449, rs8050136, rs9939609, rs7202296, rs56137030, rs9930506 and rs12149832 for analysis and they were distributed along a 45-kb stretch of intron 1 of *FTO*. Tag SNPs selection of the *RPGRIP1L* gene was performed with the Haploview software (Broad Institute; www.broadinstitute.org), with $r^2 \geq 0.8$ and MAF ≥ 0.05 [44, 45]. Three SNPs rs9934800, rs5005161 and rs35089292 were selected according to the results. The relationship between tag SNPs and the *FTO* gene and the *RPGRIP1L* gene is shown in Fig. 2. In accordance with the study protocol, the Swab DNA Kit (FineGene) was used to extract genomic DNA from saliva samples. We used 1 μ L DNA solution (approximately 20 ng/ μ L) for

Fig. 1 The distribution of the BMI of samples, plotted by BMI on the horizontal axis and probability density on the vertical.

Fig. 2 Relationship between tag SNPs and the *FTO* gene and the *RPGRIP1L* gene.

genotyping. Genotyping was conducted using Affymetrix Axiom® Genome-Wide CHB1/2 Array, as described previously [46].

A linear regression model with BMI as a continuous trait, adjusted for age, was applied to investigate the influence of *FTO* polymorphisms on BMI. Association analysis of SNPs were performed with the SHEsis software [47, 48], including Hardy-Weinberg equilibrium, allelic frequency calculation, pairwise linkage disequilibrium and haplotype analysis. All tests were two-tailed and $p < 0.05$ was considered significant. Correction for multiple-hypothesis testing was adopted with the Bonferroni correction.

Results

Power of statistics equaled 1 finally, indicating strong statistical power. we selected 74 pairs of random repeated samples for genotyping duplicate and the concordance rates of genotyping was 0.996. The average call rate of all SNPs was 0.997, and no deviation from Hardy-

Weinberg equilibrium was found ($p \geq 0.05$). Information of all SNPs in our study is shown in Table 1. Detailed association analysis results of all testing sites are listed in Table 2. It shows the results for the nine polymorphic SNPs, rs1421085, rs1558902, rs17817449, rs8050136, rs9939609, rs7202296, rs56137030, rs9930506 and rs12149832 in the *FTO* gene were significantly associated with BMI after Bonferroni correction, during which rs8050136 showed the strongest association with BMI. Meanwhile, rs9934800 in the *RPGRIP1L* gene showed significance with BMI before Bonferroni correction, but this association was eliminated after Bonferroni correction.

The pairwise linkage disequilibrium among the investigated SNPs in the *FTO* gene and the *RPGRIP1L* gene is shown in Fig. 3. R^2 values of nine *FTO* variants were larger than 0.33 and they were categorized in the same haplotype block. Haplotype analysis of the block, rs1421085-rs1558902-rs17817449-rs8050136-rs9939609-rs7202296-rs56137030-rs9930506-rs12149832, is shown in Table 3.

Table 1 Information of twelve SNPs in *FTO* and *RPGRIP1L* gene

SNP ID	Position	Function	Polymorphism	Call Rate	H-W <i>p</i> value
rs9934800	Chr16:53654582	intron	C/T	1.000	0.762
rs5005161	Chr16:53664764	intron	C/T	0.999	0.483
rs35089292	Chr16:53692910	intron	C/A	0.995	0.361
rs1421085	Chr16:53767042	intron	C/T	1.000	0.789
rs1558902	Chr16:53769662	intron	A/T	0.998	0.644
rs17817449	Chr16:53779455	intron	G/T	0.996	0.438
rs8050136	Chr16:53782363	intron	A/C	1.000	0.744
rs9939609	Chr16:53786615	intron	A/T	0.999	0.627
rs7202296	Chr16:53787778	intron	A/G	0.996	0.457
rs56137030	Chr16:53791993	intron	A/G	0.998	0.394
rs9930506	Chr16:53796553	intron	A/G	1.000	0.926
rs12149832	Chr16:53808996	intron	A/G	0.990	0.221

Table 2 Linear regression analysis of SNPs, adjusted for age

Locus	SNP	Allele Frequency		Beta	<i>p</i>	Bonferroni <i>p</i>
<i>PRGRIP1L</i>	rs9934800	C 1648 (0.135)	T 10550 (0.865)	0.144	0.021	0.252
	rs5005161	C 5125 (0.420)	T 7065 (0.580)	-0.003	0.939	1
	rs35089292	C 1470 (0.121)	A 10676 (0.879)	-0.06	0.362	1
<i>FTO</i>	rs1421085	C 1644 (0.135)	T 10560 (0.865)	0.334	1.16×10^{-7}	1.39×10^{-6}
	rs1558902	A 1630 (0.134)	T 10548 (0.866)	0.332	1.49×10^{-7}	1.79×10^{-6}
	rs17817449	G 1614 (0.133)	T 10538 (0.867)	0.329	2.03×10^{-7}	2.44×10^{-6}
	rs8050136	A 1646 (0.135)	C 10558 (0.865)	0.334	1.08×10^{-7}	1.30×10^{-6}
	rs9939609	A 1619 (0.133)	T 10569 (0.867)	0.326	2.66×10^{-7}	3.19×10^{-6}
	rs7202296	G 1606 (0.132)	A 10554 (0.868)	0.316	6.56×10^{-7}	7.87×10^{-6}
	rs56137030	A 1608 (0.132)	G 10572 (0.868)	0.318	5.10×10^{-7}	6.12×10^{-6}
	rs9930506	G 2289 (0.188)	A 9915 (0.812)	0.208	1.73×10^{-4}	2.08×10^{-3}
	rs12149832	A 1636 (0.135)	G 10440 (0.865)	0.296	2.92×10^{-6}	3.50×10^{-5}

Bold font denotes significant *p*-values (<0.05) after Bonferroni correction.

Discussion

In this study, we examined the associations of SNPs within the *FTO* gene and the *RPGRIP1L* gene with BMI in Chinese women.

Although the *FTO* region harbors the strongest genetic association with BMI, the mechanistic basis remains unclear. Previous reports have widely studied the association between the *FTO* gene and BMI in various populations [16, 25-30]. We therefore postulated that this

association would still exist in Chinese women and selected nine SNPs for further replication experiments during these reports. Our study confirmed that nine SNPs in the *FTO* locus, rs1421085, rs1558902, rs17817449, rs8050136, rs9939609, rs7202296, rs56137030, rs9930506 and rs12149832, were associated with BMI in a quantitative traits study with large sample sizes of a Han Chinese origin, which may serve as targets of pharmaceutical research and development concerning BMI.

The *FTO* protein is part of the AlkB family of non-home

Fig. 3 The pairwise linkage disequilibrium among the investigated SNPs in the *FTO* gene and the *RPGRIP1L* gene. The pairwise LD r^2 values were illustrated in the matrices. The deep color indicated relatively strong linkage disequilibrium, and *vice versa*.

Fe (II)/dioxygenases, which belongs to the Escherichia coli AlkB and human ABH enzyme family [49, 50]. A meta-analysis indicated that the connection between *FTO* SNPs and BMI could be modified by physical activity (PA). It showed that physically active adults with risk allele homozygous SNP of rs9939609 reduced the odds of obesity by 27% [51]. The interaction between the rs1421085 and PA in six ethnic groups was also identified in another study [52], which included East Asian, South Asian, African, Native American, Latin American and European. Several studies explored the link between *FTO* SNPs and food intake to figure out the mechanisms for variants in *FTO* and the risk of adiposity. The BMI-increasing allele of rs1421085 was found to be associated with higher protein intake [53]. The risk allele of rs8050136 was found to be related to the percentage of calories from fat and negatively related to the percentage of energy from carbohydrates [54]. The risk allele of rs9939609 was also verified to decrease fiber intake and increase protein intake [55]. One breakthrough found that the rs1421085 T-C alteration disrupted a conserved motif for the regulatory gene *ARID5B*, causing derepression of a potent preadipocyte enhancer that ultimately resulted in a cell-autonomous developmental shift from energy-dissipating beige adipocytes to energy-storing white adipocytes, with a 5-fold reduction in mitochondrial thermogenesis and an increase in lipid storage [56]. It meant that the *FTO* SNP rs1421085 represented the

Table 3 Haplotype analysis of *FTO* gene

Haplotype	Beta	SE	<i>p</i>	Bonferroni <i>p</i>
TTTCTAGAG	-0.226	0.055	4.30×10^{-5}	1.29×10^{-4}
CAGAAGAGA	0.341	0.065	1.98×10^{-7}	5.94×10^{-7}
TTTCTAGGG	-0.103	0.103	0.315	0.945

Haplotypes with frequency <0.03 were ignored.

Bold font denotes significant *p*-values (<0.05) after Bonferroni correction.

causal variant that disrupted a pathway for adipocyte thermogenesis, providing a mechanistic basis for the genetic association between *FTO* and BMI.

Previous studies confirmed the role *RPGRIP1L* gene played in obesity and indicated that *RPGRIP1L* linked to obesity-associated variants in the *FTO* gene functionally [57-59]. We therefore supposed that *RPGRIP1L* might also connect with BMI. To our knowledge, the association analysis between the *RPGRIP1L* gene and BMI has rarely been noted. We found that rs9934800 of *RPGRIP1L* showed significance with BMI before Bonferroni correction. However, the association was too weak and it was eliminated after Bonferroni correction. The other two SNPs in the *RPGRIP1L* locus, rs5005161 and rs35089292, weren't found association with BMI.

Some researchers focused on the transcription factor the cut-like homeobox 1 (*CUX1*), which displaced acti-

vators and recruited histone deacetylase 1 to transcribe repressor. The obesity-protective allele of rs8050136 in *FTO* advanced the DNA-binding of CUX1 isoform P110, which catalyzed the expression of *FTO* and *RPGRIP1L* [18, 19]. Reversely, the obesity-risk allele of rs8050136 tended to act on CUX1 isoform P200, which was a transcriptional repressor of *FTO* [19]. This study showed that 70% reduction in cutl1 mediated by siRNA contributed to 90% decrease in *FTO* expression and 65% decrease in *RPGRIP1L* expression. Both of them could be identified as *cux1* protein binding sites, so it seemed that *FTO* variation changed *RPGRIP1L* expression indirectly. Hemizygous *RPGRIP1L* mice with function reduced, were used for further research to explore the relationship between *RPGRIP1L* and obesity. Results indicated that the *RPGRIP1L*^{+/-} mice consumed more food and increased higher weight than normal ones. Deficiency of leptin receptor signaling in *RPGRIP1L*^{+/-} mice was identified in subsequent studies and *RPGRIP1L* was speculated to deliver the formation of leptin receptor clustering.

Haplotype association analysis identified a protective haplotype in *FTO* locus, T-T-T-C-T-A-G-A-G, carrying the major allele of nine SNPs in this block (rs1421085-rs1558902-rs17817449-rs8050136-rs9939609-rs7202296-rs56137030-rs9930506-rs12149832) with BMI. Additionally, we found a risk haplotype C-A-G-A-A-G-A-G-A carrying the minor allele of these SNPs with BMI. The results of haplotype association verified the analysis of single polymorphism sites.

In conclusion, our main finding was a significant association between *FTO* and BMI, although not between *RPGRIP1L* and BMI, in Chinese women. Both of them locate in the same pathway and *RPGRIP1L* lies upstream of *FTO*. If this pathway is connected with obesity or BMI, knocking out *RPGRIP1L* may disorder its function and lead to the fat phenotype of mice. In other words, we speculated it's *FTO*, not *RPGRIP1L*, contributing to obesity. Despite our sample size was relatively large and we achieved association significance of common variants, further evidence from functional experiments was needed to support our findings and to show the role of

FTO, *RPGRIP1L* or related pathways in the mechanism of BMI.

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Disclosure

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All participants signed written informed consent. Our study was approval of the Ethics Committee of Human Genetic Resources in Bio-X Institutes at Shanghai Jiao Tong University and corresponded to the 'Guidance of the Ministry of Science and Technology for the Review and Approval of Human Genetic Resources'.

The authors declare no competing financial interests.

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