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Genetic variant rs9939609 in *FTO* is associated with body composition and obesity risk in Korean females

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ABSTRACT

Introduction The fat mass and obesity-associated (*FTO*) gene is a significant locus in obesity. However, the association between *FTO* genetic variants and body composition has not been fully elucidated.

Research design and methods This observational study examined the associations of *FTO* rs9939609 T>A with obesity and body composition markers in Koreans. A total of 6474 participants from the Korean Genome and Epidemiology Study were analyzed for their general characteristics, body composition and *FTO* genotype with a sex-stratified approach.

Results Females with the obesity risk A allele showed significantly greater body weight, hip circumference, and body mass index and were at a 1.28-fold higher risk of obesity (95% CI=1.088 to 1.507) than those with the TT genotype. Analyses of body composition also showed that females with the A allele had a greater body fat mass and percentage, abdominal fat percentage, and degree of obesity, and this association and *FTO* genetic variation and adiposity was observed in females, especially aged under 50 years. However, the effect of the variant allele on non-fat tissue markers was not evident in females and was not associated with any parameters examined in males.

Conclusions The *FTO* rs9939609 variant is associated with body composition in Koreans, especially body fat markers in females. These results support that the *FTO* rs9939609 variant is a genetic risk factor in the etiology of obesity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *FTO* variation is a key genetic risk locus in the etiology of obesity. The risk allele in the first intron of *FTO* is associated with increased body weight and body mass index. However, precise evidence supporting the association of *FTO* variation with body fat accumulation and its pattern is limited.

WHAT THIS STUDY ADDS

⇒ *FTO* rs9939609 T>A variation is associated with adiposity markers and the risk of obesity. Risk allele A is associated with greater body fat mass and degree of obesity. These associations are only observed in women aged under 50 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study support a better understanding of the role of *FTO* in adiposity: *FTO* is clearly associated with body fat accumulation, mainly in non-abdominal obesity markers, and sexual dimorphism may exist. Differential approaches accounting for an individual's sex and *FTO* genotype should be used in the prevention and management of obesity.

INTRODUCTION

Obesity is an emerging global health problem and the fifth leading cause of death.[1] The WHO defines obesity as a condition in which excessive fat accumulation endangers health and disease.[2] Increased fat tissues release some adipokines, such as leptin, adiponectin and resistin, which are known to be associated with alterations in insulin resistance, glucose and fat/energy homeostasis, and this consequently could result in type 2 diabetes.[3] Furthermore, obesity is also closely associated with an increased prevalence of other chronic diseases, including hypertension, dyslipidemia, coronary artery disease, stroke, and some cancers.[4] According to the Korean Society for the Study of Obesity (KSSO), 36.3% of Korean adults were diagnosed with obesity in 2022.[5] Therefore, it is important to prevent and manage obesity to promote health and increase quality of life.

The fat mass and obesity-associated gene (*FTO*) has been identified as a key genetic risk locus for obesity. The *FTO* gene is located at 16q12.2 and consists of nine exons. Multiple genome-wide association and observational studies suggest that genetic variants present in the first intron of *FTO* are strongly associated with obesity and body mass index (BMI).[6–10] Subsequent studies have also reported the significance of *FTO* in obesity etiology. The *FTO* gene and/or its genetic variation has been suggested to be associated with food intake control,[11] body fat (BF) content regulation via adipocyte degradation,[12] hypothalamic energy homeostasis,[13] insulin control mechanisms,[14] and depression–obesity comorbidity.[15]

The precise biological function and molecular mechanism of FTO in obesity etiology are unclear, although a few studies have suggested the potential mechanism of action. FTO is known to regulate the modification of multiple mRNAs using N6-methyladenosine (m^6A) in obesity and lipid metabolism.[16] The FTO-regulated m^6A level was associated with the accumulation of triglycerides,[17 18] and an association between FTO overexpression and lipid accumulation in animal fat cells has been identified.[16] The regulatory role of FTO was also observed in relation to the adiposity-related hormones ghrelin and leptin. FTO overexpression decreases ghrelin mRNA m^6A methylation and increases ghrelin expression, the hunger hormone.[19] A significant association between FTO mRNA expression and leptin concentrations was reported,[20] and it was observed that FTO mRNA expression in adipose tissue was significantly higher in subjects with obesity than in those without obesity.[21] Therefore, FTO has been proposed to influence the hormones that form the basis of human appetite regulation and thus may influence increases in fat tissue and the development of obesity.

Most observational studies on *FTO*, however, mainly rely on BMI for diagnosing obesity. BMI is a well-known index for obesity and BF, but it has some limitations.[22] Because BMI is computed using simple values for height and weight, it does not account for individuals who have excess muscle mass or a short height. Additionally, BMI cannot clearly determine the distribution of body composition compared with direct measurement techniques, including bioelectric impedance.[23] Furthermore, BMI sometimes fails to reflect necessary adjustments due to aging. With age, the BF percentage normally increases, but height and muscle mass tend to be reduced. BMI does not take such changes in BF and muscle mass into consideration.[22] For these reasons, it is difficult to verify the association between increased BF—the critical definition of obesity—and *FTO* genetic variants when relying on BMI as a single indicator.[24]

Earlier studies observed an association between *FTO* genetic variants and BF content and composition. For example, Wählén *et al*[12] and Mehrdad *et al*[20] reported the association between *FTO* genetic variants and BF accumulation, and other studies confirmed similar associations between variations in *FTO* and waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), fat mass (FM), BF%, trunk fat (TF), and BMI.[25 26] However, those studies were conducted in non-Korean populations with limited sample sizes. Few studies have been conducted with Korean participants, and of these, most examined the association between the *FTO* genetic variation and obesity using BMI as a single indicator.[6 24] Given this, further evidence is required to confirm this genetic component in the mechanism of BF accumulation in large populations.

This study aimed to determine whether body composition and the risk of obesity are associated with *FTO* genetic variants in Koreans. The effect of the rs9939609 variant, the most commonly examined genetic marker in *FTO*,[6–8 10] on obesity and body composition, as well as the relationship between this risk allele and BF, was verified using the Korean Genome Epidemiology Study (KoGES), a representative large-scale cohort-based genomic epidemiological study of the Korean population. Since earlier studies reported that the association between *FTO* and obesity varies by sex,[27–29] this study applied a sex-stratified approach.

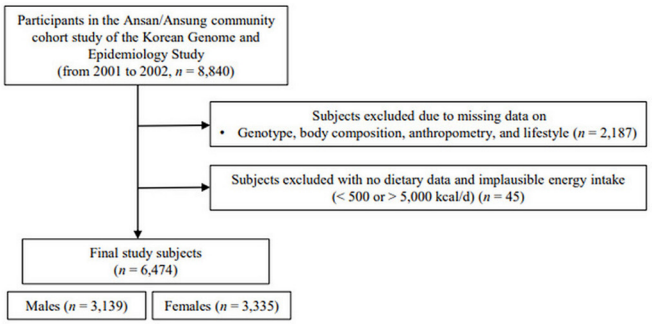

Figure 1 Simplified flow chart of the study subject selection.

METHODS

Cohort description

The KoGES is a project governed by the Korea Centers for Disease Control and Prevention (KCDC) National Institute of Health. The study aimed to identify risk factors for chronic diseases that frequently occur in Koreans and to provide scientific evidence for the prevention and treatment of those diseases. This observational and cross-sectional designed study used a subset of data from the KoGES, comprising a community-based cohort of adult Koreans living in Ansan (urban) and Ansung (rural), for which data were collected in 2001 and 2002. Informed consent was obtained from all participant of KoGES. The details of the KoGES are described elsewhere.[30]

The process of selecting the subjects for this study is shown in figure 1. From the original dataset (n=7011), subjects were excluded if data were missing for genotype information (n=10), anthropometrics (n=9), and lifestyle factors (n=473). Moreover, subjects with implausible total energy intake (<500 kcal or >5000 kcal) were also excluded (n=45). Finally, a total of 6474 participants (3139 men and 3335 women) aged 40–69 years were included in the analysis.

General characteristics of the study subjects

Data including lifestyle factors (eg, age, sex, physical activity, alcohol consumption, tobacco smoking, education level, diet, and marital status), body composition, and anthropometric measurements were obtained from the KoGES and the KCDC.[31] The alcohol consumption and smoking status of the study population were categorized as follows: never, past, and current. Education level was classified as follows: 'low' for individuals who graduated elementary school or less, 'medium' for middle

school or high school graduates, and 'high' for those who obtained at least a college graduate degree. Marital status (cohabitation) was classified as follows: 'unmarried' (including bereavement, separation, divorce, etc) and 'married' according to the presence or absence of a spouse or partner. The level of physical activity was assessed using metabolic equivalents of tasks (MET), as described previously.[32]

Genotyping

Genetic data were obtained from the KCDC. The procedure for genotyping followed a previously published protocol.[33] Briefly, DNA samples were extracted from fasting peripheral blood, and genotype was determined using the Affymetrix genome-wide human single nucleotide polymorphism array 5.0 (Affymetrix, Santa Clara, California, USA). Quality control was performed using Bayesian robust linear modeling with the Mahalanobis distance algorithm. Genotypes were excluded if the genotype call rate was less than 95%, the heterozygous frequency was excessively high, and sex and ethnic mismatches or cryptic relatedness were evident. Additionally, markers with a minor allele frequency (MAF)<0.01 and those not in Hardy-Weinberg equilibrium ($p<1\times10^{-6}$) were also excluded.

Anthropometric and body composition measurements

For precise measurement, participants were asked to wear light clothes and to be barefoot. Body composition was assessed by multifrequency bioelectrical impedance analysis (MF-BIA) (InBody 3.0, Biospace, Korea). The MF-BIA technique assumes that the human body comprises five interconnecting cylinders and measures direct impedance in these body compartments using non-fat markers (intracellular fluid, total body water, soft lean mass, lean mass, extracellular fluid, protein, and minerals) and fat markers (FM, BF%, abdominal fat percentage (AF%), and degree of obesity). Although there are few potential issues, including hydration with MF-BIA, the method is considered practical and economic with reliability.[34] Anthropometric measurements were also performed, and BMI was calculated as weight (kg) divided by height (m) squared. WC was measured at the midpoint between the lowest rib and the top of the hipbone, and hip circumference (HC) measured the part of the hip that protruded the most. WHR was calculated by dividing HC (cm) by WC (cm). Following the criteria of KSSO, obesity was defined as a BMI ≥25, and abdominal obesity was defined as a WHR ≥0.9 or WC ≥90 cm in males and WHR ≥0.85 or WC ≥85 cm in females.[35] The WHtR was calculated as HC (cm) divided by height (cm). However, since there is no defined cut-off point of WHtR to diagnose abdominal obesity, a WHtR ≥0.5 was used following earlier studies.[36]

Dietary intake analyses

Dietary intake was measured using a 103-item semi-quantitative Food Frequency Questionnaire developed and validated for the KoGES and assessed by trained dieticians.[37] Consumption frequency for each item was divided into nine categories ('never or almost never,' 'once a month,' 'two to three times a month,' 'one to two times a week,' 'three to four times a week,' 'five to six times a week,' 'once a day,' 'twice a day,' and 'three or more times a day') and three answer options for each food's portion size ('one-half serving', 'one serving' and 'two or more servings'). Daily energy and macronutrient (carbohydrate, protein, and fat) intakes were calculated using data from the Food Composition Table[38] and the Korean Nutrition Society.[39]

Statistical analyses

General characteristics of the study population were analyzed using χ^2 tests or Student's t-tests, accounting for the type of variables. Continuous markers such as age, MET, macronutrient intake, body measurement, and composition data were log-transformed prior to testing. Nutrient intake was adjusted with Willett's residual method.[40] A constant value of 0.001 was added to each observation before log-transformation to account for consumption indicated as zero.

To analyze the association between the *FTO* genetic variant and body components, Student's t-tests were applied for the crude model, and a general linear model was applied to adjust for covariates (age, residential area, physical activity, alcohol and smoking use, education level, marital status, and total energy intake). Linear regression was also used to analyze the association between the *FTO* genetic variant and fat markers, including FM, BF%, AF%, and degree of obesity. Logistic regression was performed to investigate the association between the *FTO* genetic variant and the risk of obesity. Associations were estimated using odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was indicated by p=0.005 using Bonferroni's correction, which accounts for multiple comparisons (calculated as follows: 0.05/11) made for the number of body composition variables. SAS V.9.4 (SAS Institute) and SPSS V.26.0 were used for statistical analyses.

RESULTS

General characteristics and *FTO* genotype

The distribution of *FTO* rs9939609 and the general characteristics of the study population are presented in table 1. The frequencies of the TT, TA, and AA genotypes were 0.77, 0.22, and 0.02, respectively, which corresponds to an MAF of approximately 0.128 in this Korean population. Due to such a low MAF, all analyses were performed by applying the dominant model (A allele carriers vs the TT genotype). In males and females, genotype was independent of the distribution of age, residential area, physical activity, alcohol use and smoking, educational level, macronutrient intake, and cohabitation.

Table 1 General characteristics of the study population according to *FTO* rs9939609 genotype and sex

	Males (n=3193, 49.3%)			Females (n=3335, 50.7%)		
	TT (n=2414, 76.9%)	TA+AA (n=725, 23.1%)	P value	TT (n=2555, 76.6%)	TA+AA (n=780, 23.4%)	P value
Age (years)	50.82±8.57	49.98±8.24	0.016	51.79±8.86	52.42±9.12	0.083
Region						
Rural (Ansung)	692 (78.5)	190 (21.5)	0.196	942 (76.2)	295 (23.8)	0.630
Urban (Ansan)	1722 (76.3)	535 (23.7)		1613 (76.9)	485 (23.1)	
Physical activity (MET-h)	21.55±14.32	20.49±13.58	0.227	20.56±13.91	20.21±13.76	0.543
Alcohol drinking						
Non-drinker	446 (77.4)	127 (22.6)	0.644	1812 (76.5)	558 (23.5)	0.039
Ex-drinker	216 (74.8)	73 (25.3)		92 (86.8)	14 (13.2)	
Current drinker	1762 (77.0)	525 (23.0)		651 (75.8)	208 (24.2)	
Smoking status						
Non-smoker	486 (77.0)	145 (23.0)	0.112	2430 (76.5)	747 (23.5)	0.349
Ex-smoker	805 (79.0)	214 (21.0)		41 (85.4)	7 (14.6)	
Current smoker	1123 (75.4)	366 (24.6)		84 (76.4)	26 (23.6)	
Education*						
Low	400 (78.9)	107 (21.2)	0.236	1037 (75.6)	334 (24.4)	0.174
Middle	1418 (75.9)	451 (24.1)		1328 (76.8)	402 (23.2)	
High	596 (78.1)	167 (21.9)		190 (81.2)	44 (18.8)	
Cohabitation						
Single†	98 (83.8)	19 (16.2)	0.073	360 (73.9)	127 (26.1)	0.129
Married/partner	2316 (76.6)	706 (23.4)		2195 (77.1)	653 (22.9)	
Macronutrient intake						
Total energy (kcal/day)	2,006.91±564.70	2,005.65±520.83	0.756	1,850.22±594.63	1,850.65±612.77	0.815
Carbohydrate (g/day)	346.27±30.99	347.54±29.67	0.698	334.80±30.46	333.88±30.01	0.511
Protein (g/day)	69.44±11.13	69.26±10.35	0.790	63.02±10.76	63.17±10.56	0.672
Fat (g/day)	35.31±10.68	35.63±9.78	0.160	28.81±10.69	29.22±10.68	0.426

Values are presented as the means and SDs for age, physical activity, and macronutrient intake; other values are presented as the number of subjects with percentages indicated in brackets.
*Education level is divided into three categories: 'low' refers to elementary school graduates or less education; 'middle' refers to middle school graduates or high school graduates; and 'high' refers to junior college graduates or greater education.
†Single refers to individuals reported as unmarried, bereaved, separated, and divorced.
MET-h, metabolic equivalent hours; n, number of subjects.

FTO genotype and anthropometric markers

Statistical analyses were performed to examine whether the *FTO* rs9939609 genetic variant may be associated with anthropometric measurements. Females with the A allele had significantly higher weight, HC, and BMI than those with the TT genotype (adjusted p values were 0.003, 0.001, and 0.001, respectively). There were also significant differences in the distribution of subjects with normal weight, overweight, and obesity by *FTO* genotype (p=0.002). Females with the A allele were more likely to have obesity. However, in males, there was no clear significant difference between the genetic variants in all anthropometric and obesity measurements (table 2).

FTO genotype and body composition markers

Table 3 shows the association between *FTO* rs9939609 genetic variants and body composition. In females, there was no significant difference between genotypes in non-fat components, including intracellular and extracellular fluid, total body water, soft lean mass, lean mass, protein, and minerals. However, significant differences according to genotype were observed among markers for fat tissues such as FM, BF%, AF%, and degree of obesity (adjusted p values were 0.001, 0.003, 0.001, and 0.001, respectively). In males, there was no significant difference between genotypes in all variables examined.

Table 2 Association between anthropometric markers and the *FTO* rs9939609 genotype

	Males (n=3139, 49.3%)				Females (n=3335, 50.7%)			
	TT (n=2414, 76.9%)	TA+AA (n=725, 23.1%)	P value$_{crude}$	P value$_{adjusted}$	TT (n=2555, 76.6%)	TA+AA (n=780, 23.4%)	P value$_{crude}$	P value$_{adjusted}$*
Height (cm)†	167.29±5.83	167.03±5.41	0.308	0.055	154.07±5.52	153.88±5.49	0.397	0.863
Weight (kg)	68.26±9.67	68.80±9.39	0.155	0.385	58.78±8.39	59.80±8.54	0.003	0.003
WC (cm)	83.47±7.56	84.04±7.25	0.053	0.051	80.40±9.50	81.46±9.48	0.006	0.024
HC (cm)	94.27±5.62	94.66±5.35	0.078	0.233	93.93±5.89	94.68±6.10	0.002	0.001
WHR	0.89±0.06	0.89±0.06	0.298	0.056	0.86±0.09	0.86±0.08	0.187	0.566
BMI (kg/m²)	24.34±2.87	24.62±2.87	0.022	0.040	24.75±3.22	25.24±3.30	<0.001	0.001
Normal/underweight‡	762 (78.9)	204 (21.1)	0.213	N/A	770 (80.0)	193 (20.0)	0.002	N/A
Overweight	646 (76.2)	202 (23.8)			686 (77.4)	200 (22.6)		
Obesity	1006 (75.9)	319 (24.1)			1099 (74.0)	387 (26.0)		
WHtR	0.50±0.05	0.50±0.04	0.026	0.009	0.52±0.07	0.53±0.07	0.004	0.018
Normal	1136 (78.8)	305 (21.2)	0.018	N/A	953 (79.4)	247 (20.6)	0.004	N/A
Abdominal obesity	1287 (75.3)	424 (24.7)			1602 (75.0)	531 (25.0)		

*Adjusted models considered residence area, age, alcohol consumption, smoking status, educational level, physical activity, cohabitation, and total energy.
†Data are presented as the means±SDs.
‡Data are presented as the number of subjects (%).
BMI, body mass index; HC, hip circumference; n, number of subjects; N/A, not applicable; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

Table 3 Association of body composition with the *FTO* rs9939609 genotype in Koreans

	Males (n=3139, 49.3%)				Females (n=3335, 50.7%)			
	TT (n=2414, 76.9%)	TA+AA (n=725, 23.1%)	P value$_{crude}$	P value$_{adjusted}$	TT (n=2555, 76.6%)	TA+AA (n=780, 23.4%)	P value$_{crude}$	P value$_{adjusted}$*
Intracellular fluid (L)	24.68±3.08	24.79±3.01	0.332	0.975	18.43±2.11	18.52±2.17	0.358	0.128
Total body water (L)	36.79±4.48	36.88±4.30	0.507	0.881	27.59±3.10	27.74±3.16	0.254	0.103
Soft lean mass (kg)	50.20±6.04	50.32±5.89	0.583	0.742	37.64±4.23	37.83±4.34	0.302	0.128
Lean mass (kg)	53.09±6.32	53.23±6.17	0.609	0.773	39.96±4.47	40.17±4.52	0.287	0.119
Extracellular fluid (L)	12.12±1.47	12.10±1.40	0.773	0.372	9.16±1.07	9.21±1.08	0.232	0.150
Protein (kg)	13.40±1.61	13.43±1.57	0.591	0.731	10.05±1.13	10.10±1.15	0.262	0.106
Minerals (kg)	2.89±0.28	2.89±0.27	0.603	0.722	2.32±0.19	2.32±0.20	0.256	0.105
Fat mass (kg)	15.12±4.83	15.53±4.76	0.030	0.033	18.84±5.21	19.62±5.40	<0.001	0.001
Fat mass (%)	21.78±4.90	22.23±4.80	0.024	0.011	31.57±5.14	32.35±5.35	0.001	0.003
Abdominal fat (%)	0.90±0.04	0.90±0.04	0.101	0.018	0.90±0.05	0.91±0.06	<0.001	0.001
Degree of obesity (%)	113.75±13.41	115.27±13.50	0.008	0.010	122.61±16.43	125.17±16.81	<0.001	0.001

All data are presented as the means±SDs.
*Adjusted models considered residence area, age, alcohol consumption, smoking status, educational level, physical activity, cohabitation, and total energy.
n, number of subjects.

Table 4 Association between the *FTO* rs9939609 genotype and fat markers in Koreans

			B	SE	Adjusted r^2	P value*
Males	rs9939609	Fat mass (kg)	0.392	0.196	0.081	0.046
	A allele	Fat mass (%)	0.497	0.199	0.083	0.012
		Abdominal fat (%)	0.004	0.002	0.140	0.014
		Degree of obesity (%)	1.483	0.558	0.049	0.008
	<48 years†					
	rs9939609	Fat mass (kg)	0.473	0.282	0.053	0.093
	A allele	Fat mass (%)	0.425	0.276	0.062	0.125
		Abdominal fat (%)	0.004	0.002	0.057	0.116
		Degree of obesity (%)	1.992	0.775	0.027	0.010
	≥48 years					
	rs9939609	Fat mass (kg)	0.240	0.276	0.094	0.385
	A allele	Fat mass (%)	0.456	0.289	0.070	0.115
		Abdominal fat (%)	0.003	0.002	0.064	0.238
		Degree of obesity (%)	0.915	0.805	0.056	0.256
Females	rs9939609	Fat mass (kg)	0.713	0.212	0.027	0.001
	A allele	Fat mass (%)	0.664	0.205	0.075	0.003
		Abdominal fat (%)	0.006	0.002	0.239	0.001
		Degree of obesity (%)	2.261	0.663	0.043	0.001
	<50 years†					
	rs9939609	Fat mass (kg)	0.871	0.301	0.015	0.004
	A allele	Fat mass (%)	0.702	0.295	0.025	0.017
		Abdominal fat (%)	0.007	0.003	0.035	0.017
		Degree of obesity (%)	2.953	0.952	0.029	0.002
	≥50 years					
	rs9939609	Fat mass (kg)	0.609	0.296	0.037	0.040
	A allele	Fat mass (%)	0.700	0.283	0.047	0.014
		Abdominal fat (%)	0.007	0.003	0.049	0.006
		Degree of obesity (%)	1.784	0.918	0.013	0.052

*Linear regression models were adjusted for residence area, age, alcohol consumption, smoking status, educational level, physical activity, cohabitation, and total energy.
†Median age of each sex group.
B, regression coefficient.

FTO variant allele and adiposity markers

Regression models were used to further examine the association between genotype and fat markers (table 4). In females, the *FTO* rs9939609 A allele was associated with an increase in FM by 713 g (B=0.713, adjusted r^2=0.027, p=0.001), BF% by 0.664% (B=0.664, adjusted r^2=0.075, p=0.003), AF% by 0.006% (B=0.006, adjusted r^2=0.239, p=0.001), and the degree of obesity by 2.261% (B=2.261, adjusted r^2=0.043, p=0.001). However, there was no decisive association between the genotype and these variables when assessed in males.

Earlier studies have suggested that the effect of the *FTO* genotype differs by age.[41] Therefore, our study populations were grouped into two groups by median age, men (48 years old) and women (50 years old), and analyses were performed to examine whether the significant association between *FTO* genetic variation and adiposity markers, FM, BF%, AF%, and the degree of obesity remained. The findings revealed that, again, the *FTO* genotype showed limited association with those fat tissue markers in men under or over 48 years of age. Interestingly, the significant effect of the *FTO* genotype was clearly evident in women only under the median age of 50 years old. Indeed, women under 50 years of age with the *FTO* rs9939609 A allele showed increased FM (B=0.871, adjusted r^2=0.015, p=0.004) and degree of obesity (B=2.953, adjusted r^2=0.029, p=0.002). These adiposity markers only showed putative associations with the A allele in women ≥50 years old.

Table 5 OR of obesity risk according to the *FTO* rs9939609 genotype in Koreans

				OR (95% CI)	
		Without obesity, n (%)	With obesity, n (%)	Crude model	Adjusted model*
Males	TT	1408 (77.6)	1006 (75.9)	Ref	Ref
	TA+AA	406 (22.4)	319 (24.1)	1.100 (0.930 to 1.300)	1.084 (0.914 to 1.285)
	P value			0.266	0.356
	<48 years†				
	TT	635 (56.1)	496 (43.9)	Ref	Ref
	TA+AA	184 (50.3)	182 (49.7)	1.266 (1.000 to 1.604)	1.256 (0.990 to 1.594)
	P value			0.050	0.061
	≥48 years				
	TT	773 (60.2)	510 (39.8)	Ref	Ref
	TA+AA	222 (61.8)	137 (38.2)	0.935 (0.735 to 1.190)	0.932 (0.729 to 1.161)
	P value			0.586	0.571
Females	TT	1456 (78.7)	1099 (74.0)	Ref	Ref
	TA+AA	393 (21.3)	387 (26.0)	1.305 (1.111 to 1.532)	1.281 (1.089 to 1.507)
	P value			0.001	0.003
	<50 years†				
	TT	795 (63.8)	451 (36.2)	Ref	Ref
	TA+AA	205 (55.0)	168 (45.0)	1.359 (1.071 to 1.723)	1.374 (1.081 to 1.748)
	P value			0.011	0.010
	≥50 years				
	TT	661 (50.0)	648 (50.0)	Ref	Ref
	TA+AA	188 (45.1)	229 (54.9)	1.243 (0.996 to 1.550)	1.228 (0.983 to 1.533)
	P value			0.054	0.070

*Adjusted models considered residence area, age, alcohol consumption, smoking status, educational level, physical activity, cohabitation, and total energy.
†Median age of each sex group.
n, number of subjects; Ref, reference.

FTO genotype and risk of obesity

Finally, table 5 shows the association between *FTO* rs9939609 and the risk of obesity, as assessed by logistic regression. In females, the risk of obesity increased 1.31-fold (95% CI=1.111 to 1.532, p=0.001) in the crude model. After a further statistical model accounting for various covariates was applied, females with the A allele were at 1.28 times higher risk of obesity (95% CI=1.089 to 1.507, adjusted p=0.003). However, in males, the *FTO* rs9939609 A allele was not associated with the risk of obesity. Additional analyses by age group were also performed. The results from the logistic regression analyses still showed an increased risk of obesity of approximately 1.37 times in women under 50 years old, though the statistical significance was limited.

DISCUSSION

This study investigated the association between body composition and *FTO* genetic variants, which are significant genetic markers of obesity, in a Korean population. The findings suggested that the *FTO* rs9939609 genetic variant is associated with an increased risk of obesity and BF tissues in females but not males.

FTO is known to be a decisive risk locus in the pathophysiology of obesity.[20] As described above, multiple studies have suggested that *FTO* genetic variation is associated with the risk of obesity, yet most of those studies have relied on a single phenotype marker BMI. A few studies have confirmed an association between the *FTO* risk allele A and the BF-related markers WC, HC, TF, BF, and FM; however, evidence was from a small study group.[12 24 25 28] The present study provides evidence from a large cohort of Korean adults to support that *FTO* rs9939609 is associated with various body sizes and BF tissue markers. Weight and BMI were significantly higher in individuals with the *FTO* rs9939609 A allele, and this association was clearly indicated by the differences in BF volume.

Interestingly, however, there were no significant differences between some indicators of abdominal obesity, supporting the findings of earlier studies. Previously, the *FTO* rs9939609 genetic variant was only significantly

associated with BF%.[25] The *FTO* rs9939609 A allele was found to influence weight and BMI but not other abdominal obesity markers, such as the WHR.[42] In females with obesity, *FTO* mRNA expression levels in subcutaneous fat tissue were significantly higher than those in females without obesity.[12] Furthermore, *FTO* mRNA expression levels in subcutaneous adipose tissue were threefold higher than those in visceral adipose tissue.[43] Given these findings, *FTO* mRNA expression appears to be more abundant in subcutaneous fat tissue than in visceral fat tissue, influencing overall fat volume accumulation rather than visceral fat. Additionally, such a tissue-specific mechanism of action of the obesity risk gene might be related to the sex-dimorphic association of the *FTO* genotype identified in this study.

The present study found that the *FTO* rs9939609 genetic variant is associated with BF-related markers (FM, BF%, AF%, and degree of obesity), though this association was more clearly observed in females, especially younger than 50 years. Earlier studies reported a similar sex-specific association of *FTO* variation with obesity and body fatness. In a study of Chinese children, the *FTO* rs9939609 genetic variant was only associated with an increase in weight, BMI, WHtR, and BF in girls.[44] Marcadenti *et al* also reported that females with the A allele had more BF than those with the TT genotype, but with no significant difference in males.[27] Furthermore, in a study of premenopausal women, those with the AA genotype showed significantly higher values for weight, BMI, and FM than those with the TT genotype.[28 29] These findings provide evidence that sex differences in BF distribution are related to variations in *FTO*. It is known that males and females have differential body fatness mechanisms. Sex hormones, including estrogen, are clearly involved in regulation of adipose tissue function and distribution.[45] Females also have a higher BF% than males, and their distribution of adipose tissues differs from that of males. For instance, females accumulate fat mainly in the areas of the hip and thighbone, whereas men mainly accumulate visceral fat in the abdominal region.[46] As described above, the effect of the *FTO* variant was mainly evident in non-abdominal fat tissues, and *FTO* mRNA was more highly expressed in subcutaneous adipocytes than in visceral tissue. Given these sex-based differences in adiposity and the mechanisms by which *FTO* influences fat accumulation, it is possible that *FTO* variation is more clearly defined in non-abdominal fat markers among females, as observed in the current study. Moreover, findings from stratified analyses by age group also may support this sex-specific association between *FTO* genetic variation and adiposity. Further analyses regarding the *FTO* genotype and adiposity markers in males and females grouped by median age were performed, and the significant effect of genetic variation was retained only in women under 50 years old. There were unknown factors that could not be considered in the analyses, the results may be associated with females' menopausal status. Although we were not able to obtain information on menopausal status in this female population, the average age of menopause is 49.3 years in the Korean population,[47] which was similar to the median age of this study population. Few studies could be referenced to understand the age-specific and sex-specific findings of the current study. The influence of *FTO* genetic variation was not observed in a population including women at age 70 years,[41] but the association of the *FTO* genotype with increased fat tissues was detected in premenopausal women.[28 29] Due to the lack of such information, the current findings must be interpreted with caution. Regardless, we should not dismiss the potential sex-specific association of *FTO* genetic variation related to female hormones in obesity etiology.

This study is the first to analyze the association between *FTO* rs9939609, a significant genetic marker of obesity, and body composition using large-scale genetic epidemiological data from a Korean population. The results of this study could be used to understand the role of *FTO* in the pathophysiology and body composition metabolism of obesity in Koreans. However, this study has some limitations. First, data were collected from 6500 subjects aged 40–60 years from the Ansan/Ansung Community Cohort Study, KoGES. KoGES is a representative large study cohort in Korea; however, these subjects may not represent all Koreans. Further studies on Korean populations with a wider range of ages, including those younger than 40 or older than 70 years of age, could provide more insights on *FTO* genetic variation in obesity etiology. Second, the impact of menopause on female adiposity is important. However, menopausal status could not be considered due to the lack of information. Third, obesity is a complex multifactorial disease involving a wide range of socioeconomic, psychological and dietary variables. Although the statistical analyses accounted for multiple covariates, many variables may not have been considered. Fourth, this study mainly examined the *FTO* rs9939609 variation, the most commonly known genetic risk locus in obesity etiology. However, other genes and genetic variants and their interactions may also be associated with obesity etiology. These limitations must be considered in the interpretation of the study findings.

The findings of this study suggest that the *FTO* rs9939609 genetic variant is associated with increased obesity risk and BF-related markers in Korean adults. This risk effect associated with the *FTO* rs9939609 A allele was more clearly evident in non-abdominal fat markers and females, especially aged under 50 years. The findings of this study may improve the understanding of the role of *FTO* in the pathophysiology of obesity and may contribute to the further treatment and prevention of obesity and related diseases.

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Contributors H-GP performed data analyses, curation and writing of the original draft. J-HC conceptualized, designed, and performed writing, review, editing the draft and supervised the study. J-HC was responsible for the final content as the guarantor of this study. All authors have read and approved the final version of draft.

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