Association of *FTO* rs9939609 with Obesity in the Kuwaiti Population: A Public Health Concern?

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Significance of the Study

- The common *FTO* gene polymorphism (rs9939609) is found to be associated with overweight/obesity in an obesogenic population. This highlights the role of genetic variants in increasing the risk of obesity in such a population, hence encouraging researchers to further investigate and elucidate the mechanism involved in the development of obesity.

Keywords

Obesity · Kuwait · *FTO* · Polymorphism · Body mass index · Obesogenic population

Abstract

Objective: To investigate the effect of the common fat mass and obesity-associated (*FTO*) gene polymorphism rs9939609 on body mass index (BMI) in one of the most obese populations worldwide. **Subjects and Methods:** Genotypic data for *FTO* rs9939609 were available for 1,034 unrelated Kuwaiti adults obtained from Kuwait's Dasman Diabetes Institute and Kuwait University. The association between the *FTO* polymorphism with BMI as continuous and categorical (normal BMI [<25] vs. overweight/obese [>25]) variables was analyzed using both linear and logistic regression models, re-

spectively, with the assumption of both dominant and additive genetic models performed using the SNPAssoc package from R statistics. **Results:** The A allele was associated with increased BMI ($\beta = 1.21$; 95% CI = 0.16–2.26; $p = 0.023$). In concordance, the categorical BMI (normal vs. overweight/obese) also showed a significant association between the A allele and overweight/obesity (OR = 1.47; 95% CI = 1.01–2.12; $p = 0.041$). However, no association between the *FTO* variant was observed with cardiometabolic traits. **Conclusion:** We observed an association between the common *FTO* rs9939609 polymorphism and increased BMI (overweight/obesity) in Kuwaiti adults, which is consistent with previous research in other populations. Our findings encourage further investigation of genetic variants to elucidate the mechanisms involved in the development of obesity in such an obesogenic population.

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Introduction

Kuwait has been reported as one of the countries with the highest prevalence of obesity with approximately 50% of the population reported as being obese [1]. Obesity and decreased physical activity are factors contributing to the prevalence of type 2 diabetes (T2D). The International Diabetes Federation has recently ranked Kuwait among the top 10 countries with a high T2D prevalence of approximately 20%, which could be attributed to the high prevalence of obesity [2].

Genetic factors increase the susceptibility to obesity [3]. In 2007, Frayling et al. [4] reported the fat mass and obesity-associated (*FTO*) gene as the first genome-wide association study obesity susceptibility gene. Initially, the genome-wide association study showed that the *FTO* variant (rs9939609) was associated with T2D. However, no association was observed when controlling for body mass index (BMI) [4]. It had been reported that the common variant rs9939609, found in the first intron of the *FTO* gene, is one of the most commonly replicated polymorphisms associated with obesity in both children and adults [4]. Although the association has been reported in all age groups and in both genders, inconsistency exists with studies supporting the association as being age- and gender-dependent [5, 6]. The association between *FTO* variants and BMI has also been reported to interact with both physical activity [7] and dietary intake [8], with physical activity attenuating the impact of *FTO* on BMI. *FTO* variants have also been reported to be associated with obesity in different ethnic backgrounds [5, 6]. Hence, the association between *FTO* and obesity could be influenced by multiple factors.

FTO is a nuclear protein that belongs to the α -ketoglutarate-dependent, nonheme iron oxygenase superfamily [9]. The gene encodes a 2-oxoglutarate and Fe(II)-dependent demethylase, an enzyme involved in demethylation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) [10, 11]. Studies have shown that the *FTO* gene is ubiquitously expressed, thereby indicating its involvement in multiple organ systems [11, 12]. These observations were further studied using mouse models that indicated a role for *FTO* in the nervous and cardiovascular systems [12]. Elucidating the genetics of obesity may allow for future predictability of this disease which may help in identifying those at high genetic risk of obesity and preventing it through dietary interventions [13].

Due to the high prevalence of obesity in Kuwait and the obesogenic environment in which the population

lives, the objective of this study was to assess the prevalence and effect of the common *FTO* gene polymorphism (rs9939609) on BMI in a cohort representing a Kuwaiti population.

Subjects and Methods

Study Subjects and Ethics Statement

A total of 1,034 subjects with *FTO* rs9939609 genotypic data were obtained from 2 institutions: Kuwait University and Dasman Diabetes Institute, Kuwait. Exclusion criteria were children aged <18 years and non-Kuwaitis. Hence, a total of 888 subjects were available for analysis. All the subjects were requested to participate in the study during outpatient visits to Mubarak Al Kabeer Hospital, Kuwait, and the Dasman Diabetes Institute's Genetic Clinic. The Ethics Committees at the Ministry of Health, the Faculty of Medicine, and the Office of Research Affairs at Dasman Diabetes Institute approved the study which adheres to the Declaration of Helsinki on ethical principles for medical research involving human subjects. The study was explained to all participants, and both written and oral informed consents were obtained for this study. Similarly, consents from parents were provided for subjects <18 years of age. Only subjects who gave consent to participate in the study were included and requested to provide two 5-mL fasting EDTA blood samples. All T2D patients ($n = 294$) were under treatment with oral hypoglycemic agents, and none were on insulin or insulin-sensitizing drugs (thiazolidinedione compounds) or lipid-lowering medication at the time of recruitment.

Anthropometric Measurements

Every participant in this study underwent a detailed history and medical examination for anthropometric assessment (Table 1). All anthropometric measurements were made by trained observers and/or clinical research coordinators using standard techniques with the participants wearing light clothes without shoes. Height was measured to the nearest 0.1 cm using a stadiometer and weight to the nearest 0.1 kg using a standardized standing beam balance. Then, BMI was calculated as weight (kilograms) per squared height (square meters) and categorized based on WHO standards (underweight: >18.5, normal: <25, overweight: ≥ 25 , and obese: ≥ 30) [14]. In addition, the 2 fasting EDTA blood samples collected from each participant were used for biochemical analysis using plasma, and for genomic DNA extraction. Standard routine fasting plasma glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol were analyzed on an automated analyzer (Beckman Unicel DxC 800, Beckman Corporation, Brea, CA, USA). Low-density lipoprotein cholesterol was calculated using the Friedewald formula [15].

DNA Isolation and Genotyping

DNA was extracted from 200 μ L of whole blood using a Qiagen DNA mini kit (Qiagen, CA, USA) according to the manufacturer's instructions [16]. The TaqMan genotyping assay (Life Technologies, CA, USA) was used to determine the *FTO* variant rs9939609 genotypes according to standard manufacturer protocols [17]. Allelic discrimination was performed and analyzed using ABI 7500 fast real-time PCR system SDS software (Life Technologies, CA, USA).

Table 1. Anthropometric and metabolic characteristics, and *FTO* rs9939609 genotype frequencies, according to body mass index category

Variable	Normal weight (<i>n</i> = 214)	Overweight/obese (<i>n</i> = 674)	All participants (<i>n</i> = 888)	<i>p</i>
Age, years	29.3±15.5	45.5±16.3	41.6±17.6	<0.0001
Subjects (female)	142 (66%)	417 (62%)	559 (63%)	0.256
BMI	21.9±2	33.3±6.8	30.5±7.7	<0.0001
Total cholesterol, mmol/L	4.5±1.3	4.8±1.06	4.7±1.14	0.009
LDL-C, mmol/L	2.8±1.34	2.9±0.95	2.9±1.04	0.752
Triglyceride, mmol/L	0.7±0.48	1.5±1.44	1.3±1.33	<0.0001
HDL-C, mmol/L	1.3±0.34	1.1±0.35	1.1±0.35	0.0003
FPG, mmol/L	7.2±3.9	7.6±3.6	7.6±3.6	0.419
T2D (yes)	24 (11%)	270 (40%)	294 (33%)	<0.0001
<i>FTO</i> subtypes				0.147
TT	71 (33%)	187 (27.5%)	258 (29%)	
TA	101 (47%)	325 (48.5%)	426 (48%)	
AA	42 (20%)	162 (24%)	204 (23%)	

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; T2D, type 2 diabetes. If percentages are not indicated, the values given indicate means ± standard deviations.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 23; SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± standard deviation, and percentages where appropriate. Hardy-Weinberg equilibrium was tested using the web-based calculator available at <http://www.oege.org/software/hwe-mr-calc.shtml> (accessed on December 18, 2017) [18]. Analysis of variance was used to assess the association between the *FTO* variant and continuous variables. The Pearson χ^2 test was used for the analysis of categorical variables. The association of the *FTO* variant and categorical BMI was assessed by binary logistic regression represented as odds ratio (OR) and 95% confidence intervals (CI) after adjusting for both age and gender. Linear regression was used to assess the association between the *FTO* variant and BMI as a continuous variable represented by the β -coefficient and 95% CI after adjusting for both age and gender. We considered 2 genetic models: a dominant model (TT vs. TA and AA) to assess the impact of carrying at least 1 A allele compared to none and an additive model to assess the dose-dependent association of the A allele using the SNPAssoc package from R software [19]. Significance was set as $p < 0.05$.

Results

Population Characteristics

Our population sample included 888 Kuwaiti nationals, of whom 559 were females and 329 were males. The characteristics of the population studied are given in Table 1. Analysis was based on subjects being split into 2

Table 2. Body mass index category distribution according to gender

	All participants, <i>n</i> (%)	Males, <i>n</i> (%)	Females, <i>n</i> (%)	<i>p</i>
Underweight	14 (1.6)	2 (0.6)	12 (2.1)	0.006
Normal	200 (22.5)	70 (21.3)	130 (23.3)	
Overweight	260 (29.3)	117 (35.6)	143 (25.6)	
Obese	414 (46.6)	140 (42.5)	274 (49.1)	

binary categories representing normal weight subjects with BMI <25 and overweight/obese subjects with BMI ≥25. Overweight and obese subjects represent $n = 674$ (76%) as opposed to $n = 216$ (24%) being normal. Increase in age was significantly associated with overweight/obesity. Cardiometabolic traits were significantly different between normal and overweight/obese subjects ($p < 0.01$). The *FTO* rs9939609 genotype frequencies were in Hardy-Weinberg equilibrium ($p > 0.05$) and are presented in Table 1. The frequency of the A allele was found to be 47%. T2D is significantly more common in overweight and obese subjects (40%) compared to normal BMI subjects (11%), with $p < 0.0001$. We did not observe any difference between males and females when categorically comparing normal versus overweight and obese BMI ($p = 0.256$).

Table 3. Relation between *FTO* genotypes and anthropometric and metabolic characteristics

Variable	TT (<i>n</i> = 258)	TA (<i>n</i> = 426)	AA (<i>n</i> = 204)	<i>p</i>
Age, years	42.6±18.3	40.7±16.8	42.4±18.1	0.307
Subjects (female)	153 (27%)	273 (49%)	133 (24%)	0.342
BMI category				
≤24.9	71 (27.5%)	101 (24%)	42 (20%)	0.501
25–29.9	71 (27.5%)	124 (29%)	65 (31%)	
≥30	116 (45%)	201 (47%)	97 (49%)	
Mean BMI ± SD	29.8±7.1	30.8±8.1	31.1±7.7	0.08
Total cholesterol, mmol/L	4.6±1.1	4.8±1.2	4.7±1.1	0.113
LDL-C, mmol/L	2.81±0.9	2.97±1.1	2.88±0.8	0.186
Triglyceride, mmol/L	1.47±1.2	1.4±1.5	1.24±0.6	0.197
HDL-C, mmol/L	1.15±0.3	1.19±0.3	1.19±0.3	0.432
FPG, mmol/L	7.8±3.7	7.6±3.8	7.5±3.2	0.807
T2D (yes)	92 (31%)	137 (47%)	65 (22%)	0.508

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; T2D, type 2 diabetes. If percentages are not indicated, the values given indicate means ± standard deviations.

(Table 1); however, differences in the distribution of all BMI categories between males and females were observed ($p = 0.006$; Table 2). There was no difference in mean age between males (42.2 ± 17.7 years) and females (41.2 ± 17.5 years): $p > 0.05$. Obesity was more prevalent in females compared to males, with $n = 274$ (49.1%) and $n = 140$ (42.5%), respectively, whereas prevalence of overweight in males was higher compared to that in females, with $n = 117$ (35.6%) and $n = 143$ (25.6%), respectively, $p = 0.007$. Similarly, when the BMI was used as a continuous variable, a significant difference was observed with females showing a mean BMI of 30.9 ± 8.4 compared to a mean BMI of 29.9 ± 6.4 in males, with $p = 0.04$.

Relationship between FTO rs9939609 and BMI, Cardiometabolic Traits, and T2D Risk

A χ^2 test showed no statistical significance in the distribution of the *FTO* variant between both normal and overweight/obese BMI categories ($p = 0.147$; Table 3). However, the distribution of the AA genotype was found to be higher (24%) in the overweight/obese group compared to the normal BMI group (19.6%). The TT genotype distribution was found to be higher in the normal BMI group (33.2%) compared to the overweight/obese group (27.2%). Using BMI as a continuous variable, we observed a dose-dependent trend with the A allele showing an increased BMI; however, results were not significant ($p = 0.08$) (Fig. 1). The relationships between the *FTO* variant and cardiometabolic traits and T2D risk

Fig. 1. Boxplot demonstrating the distribution of mean BMI (weight/height²) for the 3 *FTO* genotypes (TT, TA, and AA) with an unadjusted p value.

were also evaluated (Table 3). Our results showed no association between the *FTO* variant and any of the cardiometabolic traits along with T2D prevalence even after controlling for age and gender ($p > 0.05$).

Table 4. Logistic regression to predict factors associated with categorical BMI (overweight and obese vs. normal BMI)

Variable	OR (95% CI)	<i>p</i>
Age (+1 year)	1.06 (1.05–1.08)	<0.0001
Sex (female)	0.81 (0.57–1.16)	0.265
<i>FTO</i> (dominant model)		
TT	1	0.041
TA + AA	1.47 (1.01–2.12)	

Table 5. Linear regression model to predict factors associated with BMI

Variable	β (95% CI)	<i>p</i>
Age (+1 year)	0.15 (0.08–0.15)	<0.0001
Sex (female)	1.18 (0.19–2.16)	0.019
<i>FTO</i> (dominant model)		
TT	1	0.023
TA + AA	1.21 (0.16 – 2.26)	

Logistic regression analysis adjusted for age and gender under a genetic dominant model showed carriers of the A allele were associated with the overweight/obese group (OR = 1.47; 95% CI = 1.01–2.12; p = 0.041) (Table 4). Similarly, an additive genetic model showed a significant trend of the A allele with overweight/obesity (OR = 1.29; 95% CI = 1.02–1.64; p = 0.036). Nevertheless, linear regression analysis using BMI as a continuous variable showed the A allele to be associated with increased BMI (β = 1.21; 95% CI = 0.16–2.26; p = 0.023) under a dominant genetic model after adjusting for age and gender (Table 5). Although a trend was observed when an additive genetic model was used, results did not reach significance (β = 0.62; 95% CI = –0.031 to 1.29; p = 0.062). Age was found to be a significant predictor (p < 0.05) in both logistic and linear regressions; however, only gender (female) was found to be a predicting factor of a higher BMI in the linear regression analysis (Table 5).

Discussion

Our results indicate an association between the common *FTO* rs9939609 gene polymorphism with overweight/obesity. Prevalence of the high-risk genotype (AA) was found to be higher in the overweight/obese group compared to the normal BMI group. Moreover, the

A allele was associated with increased BMI when used as a continuous variable. We did not observe an association between the *FTO* rs9939609 with T2D risk. Similarly, we did not find an association with cardiometabolic traits.

Our findings are in concordance with previous studies reporting the association of the *FTO* A allele with increased BMI and that the frequency of the A allele in our study was similar to that observed in other populations ranging from 45 to 48% [4, 20]. This may suggest that the effects of environmental factors on obesity in Kuwait are larger than genetic factors. In addition, this may also suggest that other variants within *FTO* or other genes may explain the high prevalence of obesity seen in our studied population. It is reported that multiple neighboring single-nucleotide polymorphisms within the first intronic region of the *FTO* gene are associated with BMI [21]. This is consistent with recent findings showing that different variants within the *FTO* gene are associated with different classes of obesity [6]. Moreover, a study by Sentinelli et al. [20] showed an association between the common *FTO* rs9939609 polymorphism with BMI in an Italian population; however, a stronger association was observed with another polymorphism, rs9930506, within the *FTO* gene suggesting the impact of other polymorphisms on BMI. This also supports findings that the impact of *FTO* on obesity is population-dependent [20, 22]. These findings may explain our borderline association of the rs9939609 with the BMI; however, this needs to be replicated further in other cohorts in the population. The *FTO* variant has been reported to be involved in weight regain after bariatric surgery [23] which is considered a common obesity intervention in the Kuwaiti population [24], and therefore identifying patients at high risk of weight regain prior to intervention may help in planning the course of treatment.

On the other hand, we did not find any association of *FTO* rs9939609 with the T2D risk. A recent study by Kamura et al. [25] suggested that the association between *FTO* variants and T2D is mediated through the lifetime maximum BMI at the time of or before diagnosis of T2D. Nevertheless, our lack of association with the T2D risk has also been reported in populations of similar genetic background to the Kuwaiti population [26, 27]. It is apparent that ethnicity plays a role in *FTO* rs9939609 and T2D risk among different populations, possibly under the influence of other T2D susceptibility factors of stronger effect.

The relation between the *FTO* variants and *FTO* gene expression has been investigated; however, results indicate a lack of correlation [28]. The study by Smemo et al.

[28] demonstrated the connection between *FTO* variants and the regulation of the homeobox gene *IRX3*. *Irs3*-deficient mice demonstrated a 20–25% reduction in body weight. The study suggests that *FTO* acts as a transcriptional factor involved in regulating the expression of *IRX3* through its interaction with the promoter region of the *IRX3* gene which is found to be nearly a megabase away. The relation of the 2 genes is also supported by the high linkage disequilibrium between variants in the *FTO* and *IRX* genes [29], suggesting that the *FTO* gene is a regulator of the *IRX3* gene [30]. Moreover, the *FTO* encodes a 2-oxoglutarate and Fe(II)-dependent demethylase, an enzyme involved in the demethylation of DNA and RNA [9–11]. Physical activity and dietary intake have been shown to alter epigenetic mechanisms [31]. A limitation of our study is the lack of data regarding physical activity which may have influenced the impact of *FTO* on BMI. A recent study by Awad et al. [32] reported low levels of physical activity in both males and females of the Kuwaiti population with about 40% reported as being physically inactive. The study by Celis-Morales et al. [7] demonstrated that physical activity attenuates the effect of *FTO* on BMI, which may suggest an impact of physical inactivity on the association of *FTO* with overweight/obesity in our cohort; however, such a claim needs further investigation.

Although our study was not designed to assess the prevalence and distribution of obesity, our secondary findings suggest a similar prevalence of obesity and overweight rates to previous studies of the Kuwaiti population, with results showing females have higher rates of obesity [1, 32]. Such findings may be attributed to genet-

ic or lifestyle differences; however, further investigation on our population is required for adequate assessment.

Conclusion

We observed an association between the common *FTO* gene polymorphism (rs9939609) with overweight/obesity. To the best of our knowledge this is the first reported association between *FTO* and BMI in the Kuwaiti population. Further replication studies in our population investigating the *FTO* rs9939609 are required to validate our findings. Other variants within the *FTO* gene and related genes regulated by the *FTO* should be investigated to further measure the impact of genetic factors on obesity. Studying the genetics of obesity in extremely obese populations can help us better understand the factors and mechanisms underlying the development of obesity in populations with similar obesogenic environments.

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Disclosure Statement

There is no conflict of interest.

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