RESEARCH ARTICLE

The FTO genetic variants are associated with dietary intake and body mass index amongst Emirati population

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Abstract

Background

The risk of obesity is determined by complex interactions between genetic and environmental factors. Little research to date has investigated the interaction between gene and food intake. The aim of the current study is to explore the potential effect of fat mass and obesity-associated protein gene (FTO) rs9939609 and rs9930506 single nucleotide polymorphism (SNP) on the pattern of food intake in the Emirati population.

Methods

Adult healthy Emirati subjects with Body mass index (BMI) of 16–40 kg/m² were included in the study. Genotyping for FTO rs9939609 (A>T) and rs9930506 (A>G) was performed using DNA from saliva samples. Subjects were categorized according to the WHO classification by calculating the BMI to compare different classes. Dietary intake was assessed by a sixty-one-item FFQ that estimated food and beverage intakes over the past year. The daily energy, macronutrient, and micronutrient consumption were computed.

Results

We included 169 subjects in the final analysis (mean age 30.49± 9.1 years, 57.4% females). The mean BMI of the study population was 26.19 kg/m². Both SNPs were in Hardy Weinberg Equilibrium. The rs9939609 AA genotype was significantly associated with higher BMI (p = 0.004); the effect was significant in females (p = 0.028), but not in males (p = 0.184). Carbohydrate intake was significantly higher in AA subjects with a trend of lower fat intake compared to other genotypes. The odds ratio for the AA was 3.78 in the fourth quartile and 2.67 for the A/T in the second quartile of total carbohydrate intake, considering the first quartile as a reference (95% CI = 1.017–14.1 and 1.03–6.88, respectively). Fat intake was significantly lower in the FTO rs9930506 GG subjects. The presence of FTO rs9930506 GG genotype decreased the fat intake in subjects with FTO rs9939609 AA (p = 0.037).
Conclusions

The results of this study highlight the interaction of the FTO risk alleles on the food intake in Emirati subjects. The FTO rs9939609 AA subjects had higher carbohydrate and lower fat intake. The latter was accentuated in presence of rs9930506 GG genotype.

Introduction

The consequences of the obesity epidemic have been a great burden on the health systems worldwide; including an increased risk of serious chronic conditions; such as heart diseases, cancer, and diabetes [1]. The interplay between the environmental changes and the genetic factors has led to a significant increase in obesity prevalence worldwide [2]. Gene-environment interaction is defined as a response or adaptation to an environmental agent, a behavior, or a change in behavior, conditional to the genotype of the individual [3]. Such interaction can give new insight into the variation of body mass index (BMI) and obesity susceptibility among individuals [4]. Mathematical models have predicted that even a small energy excess or deficit (around 1%) may result over time in weight gain or loss [5]. Obviously, environmental differences may mask the genetic effect on BMI [6].

The fat mass and obesity-associated (FTO) gene [chromosome 16 (16q12.2a)] has shown the largest effect on BMI, although the increase is modest [7]. The link of FTO rs9939609 A allele to high BMI was described in many previous studies all over the world [8,9] and in the Middle East; including Saudi Arabians [10], Kuwaitis [11], Emiratis [12] and diabetic Palestinians [13]. It has been also identified as a genetic risk of metabolic syndrome in Egyptians [14]. The FTO rs9930506 (G>A) is the most strongly linked neighboring SNP to rs9939609 and was reported to be highly associated with a high BMI, especially in European Americans and Hispanic Americans who showed strong links[9]. Homozygotes of the “G” allele of this SNP experienced an additional 1.3 BMI units compared to homozygotes of the common “A” allele [15].

The UAE is at the top of the list of countries with high obesity prevalence [16]. The prevalence has dramatically increased in the last few decades due to the changing lifestyle and eating habits[17]. In the current study, the aim is to explore the potential effect of two FTO SNPs rs9939609 and rs9930506, strongly linked to obesity, on the pattern of food intake in the Emirati population. We hypothesize that those SNP’s are affecting predilection to certain types of food, that leads to more significant weight gain.

Subjects and methods

Subjects

This study is a cross-sectional study of two FTO SNPs. The sample size was calculated according to the following formula: S = [(1.96)^2 \ p (1-p)] / d^2, where p = expected prevalence of FTO SNPs in the population based on previous studies, and d = absolute error or precision (i.e. the difference between the calculated prevalence and the true prevalence). This formula applies for a type I error of 5% (p<0.05 is considered statistically significant).

We recruited healthy adult Emirati subjects from the University of Sharjah and primary health care centers.
Our inclusion criteria are adult healthy Emirati subjects, competence to give an informed consent and to complete the questionnaire. Exclusion criteria are body mass index (BMI) below 16 or above 40 kg/m$^2$, inability to give a consent or to complete the questionnaire. Ethical approval was obtained before the study started. All participants gave informed consent according to the study protocol approved by the Research and Ethics Committee, University of Sharjah. We excluded subjects with hypertension, diabetes mellitus, and other chronic diseases. All were non-smokers and do not drink alcohol. Subjects who followed strict dietary changes in the past 2 years were also excluded. We made sure that the participants did not eat before 30 minutes of collecting 2 ml of saliva samples. They were asked to give saliva without phlegm. The samples were preserved at -20 °C and DNA extraction using the QIAamp extraction kit (cat# 51306) was performed within 7 days.

**Anthropometry**

Anthropometric measurements were taken using standardized techniques and calibrated equipment. Participants were weighed to the nearest 0.1 kg wearing light clothing. Using a stadiometer, height was measured without shoes and recorded to the nearest 0.5 cm. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m$^2$). BMI was categorized according to the WHO classification: BMI less than 18.5 kg/m$^2$ as underweight, BMI 18.5 to 24.9 kg/m$^2$ as normal weight, BMI 25.0 to 29.9 kg/m$^2$ as overweight, and BMI 30.0 kg/m$^2$ or greater as obese [18]. BMI was also expressed in quartiles for further analysis.

**Dietary survey**

Dietary intake was assessed by a sixty-one-item FFQ that estimated food and beverage intakes over the past year [19]. It included information on consumption of commonly consumed food items and beverages in the UAE. The subjects were asked to record the frequency of consumption either per day, per week, per month, per year or never. Each listed food item had a standard portion, expressed in household measures. A reference portion, representing one standard serving expressed in household measures, was defined for each food item. Participants were assisted with the reference portions of the two-dimensional food portion visual (Millen and Morgan, Nutrition Consulting Enterprises, Framingham, Massachusetts, United States), as well as supplementary visual aids about portion sizes of common items in the traditional Gulf and Middle Eastern cuisine meals [Abu Dhabi Food Control Authority. A Photographic Atlas of Food Portions for the Emirate of Abu Dhabi. User’s Guide. Abu Dhabi: 2014. Abu Dhabi Food Control Authority] to help to estimate ingested quantities. The reported frequency of each food item and beverage was then converted to a daily portion intake. The daily energy, macronutrient, and micronutrient consumption by participants were computed using the food composition tables provided by the NUTRITIONIST PRO™ diet analysis software (Axxya Systems LLC., USA, version 5.1.0, 2014, First Fata Bank, Nutritionist Pro, San Bruno, CA).

**Genotyping**

Genotyping for *FTO* rs9939609 (A>T) and rs9930506 (A>G) was performed as described in our previous study [20]; using StepOne Real-Time PCR Systems (Thermo Fischer Scientific, USA) using TaqMan® Drug Metabolism Genotyping Assay (Applied Biosystems, USA). Context sequence is shown in Box 1. Allele-1 (wild) is bound to VIC, allele-2 is bound to FAM. We used the Chi-square test through the online tool http://www.oeye.org/software/hwe-mr-calc.shtml; to estimate Hardy–Weinberg equilibrium and the allele frequency [21].
Statistical analysis

We described data in terms of mean ± standard deviation (SD), frequencies (number of cases) and percentages when appropriate. Categorical data were compared using Chi-square ($X^2$). Independent-samples t-test was used to compare the homozygous risk genotype group to other genotypes for each SNP. The odds ratio was used to describe the effect size when there is a significant difference. Correlation between various continuous variables and when significant, multiple regression was used. p-value $\leq 0.05$ was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 23 for Microsoft Windows.

Results

In the current study, we initially recruited 215 healthy adult Emiratis. We excluded 10 subjects with a BMI above 40 kg/m$^2$ and 9 subjects below 16 kg/m$^2$; 27 subjects were further excluded.

### Table 1. Participant characteristics.

|                                | Mean ± SD (range)         |
|--------------------------------|---------------------------|
| Age (years)                    | 30.49 ± 9.19 (18–54)     |
| Gender                         |                           |
| Male (n,%)                     | 97 (57.4%)                |
| Female (n,%)                   | 72 (42.6%)                |
| Total carbohydrate intake (g/d)| 395.46 ± 142.73 (113.49–811.29) |
| Total protein intake (g/d)     | 150.60 ±58.12 (37.12–346.59) |
| Total fat intake (g/d)         | 126.45 ±56.52 (30.48–296.10) |
| BMI (Kg/m$^2$)                 | 26.19 ± 4.63 (17.58–37.11) |

**BMI**

| BMI               | n (%)          |
|-------------------|----------------|
| BMI <24.9         | 69 (40.8%)     |
| BMI = 25–29.9     | 60 (35.5%)     |
| BMI = 30 or more  | 40 (23.7%)     |

**FTO rs9939609**

| Genotype | n (%) |
|----------|-------|
| A/A      | 27 (16.0%) |
| A/T      | 76 (45.0%) |
| T/T      | 66 (39.1%) |

**FTO rs9930506**

| Genotype | n (%) |
|----------|-------|
| G/G      | 35 (20.7%) |
| A/G      | 74 (43.8%) |
| A/A      | 59 (34.9%) |

*168 subjects were genotyped for FTO rs9930506.
due to extreme values provided for any single food item. The data of only 169 subjects were considered for further analysis. The normality of data was checked by QQ-plot. Table 1 shows the baseline characteristics of the study group. Mean age of the study population was 30.49 ± 9.1 years, range 18–54 years, 57.4% females. The mean BMI of the population was 26.19 kg/m², which indicates overweight. Males had higher mean BMI as compared to females (25.65 and 26.90 kg/m², respectively).

Both SNPs were in Hardy-Weinberg equilibrium (using Chi square test, the p-value = 0.52 for rs9939609 and 0.19 for rs9930506). Minor allele frequency was 0.38 for rs9939609 and 0.43 for rs9930506. The frequencies of BMI quartiles and different genotypes in male and female participants are presented in Table 2. BMI significantly correlated with age (Pearson correlation = 0.308, p = 0.0001). With every year increase in age, there is 0.156 kg/m² increase in BMI.

![Clustered Boxplot of Fat_TOTAL by FTO9939609 by FTO rs_9930506](https://doi.org/10.1371/journal.pone.0223808.g001)

**Fig 1. Interaction of FTO rs9939609 and rs9930506 on fat intake.** In the group of subjects carrying FTO rs9939609 A/A risk allele (n = 27), we explored the additive effect of rs 9939506 risk allele G, using independent samples t-test to compare the two subgroups. If homozygous for both risk alleles, the subject intake of fat is significantly lower. The presence of FTO rs9930506 GG genotype significantly decreased fat intake in subjects with FTO rs9939609 AA (n = 3 and 24 respectively, p = 0.037, using Mann–Whitney non-parametric test). This was not noticed in other FTO rs9939609, (p-value = 0.32).

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Association of SNPs to BMI

The FTO rs9939609 AA genotype, detected in 15.9% of the study population, was significantly associated with high BMI (\(>25\)kg/m\(^2\)), (Pearson’s Chi-square \(p = 0.004\), Effect size: \(\Phi = \text{Cramer’s } V = 0.257\)). Females had a significantly higher BMI according to FTO rs9939609 genotype (\(p = 0.028\)), but not males (\(p = 0.184\)). This was not observed when comparing FTO rs9930506 GG (detected in 20.7%) with others (\(p = 0.215\)).

Multinomial logistic regression showed a significant decrease in weight in T/T genotype of rs993609 with a 0.95 kg/m\(^2\) decrease in BMI (\(p = 0.02\)) in subjects between 25–29.9 kg/m\(^2\). This effect was not detected in subjects with a BMI of 30 or more.

Association of SNPs to macronutrient intake

Carbohydrate intake was significantly higher in the FTO rs9939609 AA subjects. They also had a trend of higher protein and lower fat intake compared to other genotypes. Fat intake was significantly lower in the FTO rs9930506 GG subjects and they had a trend of higher carbohydrate and higher protein intake, Table 2. We explored the additive effect of rs9939506 risk allele G.

Fat intake was significantly lower in the FTO rs9930506 GG rs9939609 AA subjects (subjects homozygous for both risk alleles, \(n = 3\), Fig 1.

Quartiles of total carbohydrate intake were compared, setting the first quartile as a reference. The odds ratio for the AA genotype was 3.78 in the fourth quartile and 2.67 for the A/T in the second quartile of total carbohydrate intake, Table 3.

We investigated which carbohydrate-rich food items correlated significantly to total carbohydrate intake, in the FTO rs9939609 AA group compared to other genotypes. White bread, rice, and rice-based products were highly correlated with carbohydrate intake in the AA group, whereas intakes of high carbohydrate with higher fat food items including pies, fried potato, chips were significantly correlated with other genotypes of this SNP.

There was no significant difference between food intake of different macronutrients and BMI.

Association of SNPs to micronutrient intake

FTO rs9939609 AA was associated with a significantly higher intake of Vitamin D, B1, B2, B6, and selenium, (\(p<0.05\)). Subjects in various BMI quartiles did not differ significantly regarding the intake of vitamins and trace elements. However, there was a significant but weak correlation between BMI and intake of B3 (Pearson = 0.165*, \(p = 0.032\)), Calcium (Pearson = 0.180*, \(p = 0.018\)), Magnesium (Pearson = 0.193*, \(p = 0.012\)) and potassium (Pearson = 0.180*, \(p = 0.019\)).

Discussion

The current study was conducted on the Emirati population to explore the effect of FTO variants on food predilection. It provides a distinct effect of the FTO risk alleles in Emiratis' food

| Tertile of total carbohydrate intake | N  | OR     | 95% CI      | P     |
|-------------------------------------|----|--------|-------------|-------|
| First*                             | 44 | -      | -           | -     |
| Second                             | 43 | 2.67 [A/T] | 1.03–6.88  | 0.042*|
| Third                              | 42 | 1.51   | 0.62–3.7    | 0.36  |
| Fourth                             | 40 | 3.78 [A/A] | 1.017–14.1 | 0.047*|

*First quartile is the reference, OR = Odds ratio, CI = Confidence interval.

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intake in comparison to that of other ethnicities. Variants of both rs9939609 and rs9930506 showed highly significant association with high BMI in the database of The Genetic Investigation of ANthropometric Traits (GIANT) [22]. In our study, the homozygous risk genotype of rs9939609 and rs9930506 genotypes, were detected in 16% and 20.7% of the study population. This is close to our previous study that showed a prevalence of 20.5% and 21.9% of those genotypes, respectively in the Emirati population [20].

The wide variation of the FTO rs9939609 prevalence was observed among several populations, for instance, the minor allele frequency (MAF) was 26.6% in Pakistanis [23], and 42.3% in Russians [24]. In regard to the FTO rs9939506 prevalence, the MAF was documented as 45% among Europeans [22], compared to 20% in the Chinese population [25].

The FTO rs9939609 AA genotype was significantly associated with high BMI, in line with other studies [8,9]. Females showed a significant difference in BMI according to genotype, in line with the study of Khan et al., 2018 [12]. In our previous study on a cohort from the National Diabetes Project, we could not detect an association with BMI in the Emirati subjects with the A allele. This may be due to the lower percentage of female subjects in the previous study. Such gender difference was previously described in Swedish and Chinese children and adolescents with obesity [26,27]. However, this was not found in non-Hispanic whites and African Americans [28].

Our study showed that carbohydrate intake was significantly higher in the FTO rs9939609 AA subjects and they had a trend of higher protein and lower fat intake compared to other genotypes. In their study on gene-environment interactions, Young et al. showed that the diet score with high protein, food weight, and saturated fat showed a strong positive association with BMI. They found that the effect of FTO on BMI is enhanced in individuals with a higher diet score [29].

Previous studies showed that obesity susceptibility genes may interact with saturated fatty acids, but not mono- or poly-unsaturated fatty acids, to promote weight gain [30]. As a consequence, high-fat diets, with an enhanced palatability and high energy content, may have a primary role for the obesity epidemic. Moreover, increased intake of refined carbohydrates, and sugar-sweetened beverages, over the past few decades led to an increased prevalence of obesity [31]. In contrast to previous studies, our results showed that the AA allele is associated with higher carbohydrate and lower fat intake [32,33]. It should be noticed that the previous studies were performed on Caucasians. Age may play a role in food preference. The weather difference may explain the predilection to a high-fat diet in Caucasians carrying the risk allele. The results in children may be more robust, as the social desirability and underreporting is probably less than that in adult [34]. However, it is generally difficult to accurately estimate energy intake and expenditure in children [35]. It should be noticed that the environmental changes over time may modify the effect of FTO genotype on BMI by modifying the penetrance of genetic risk factors, leading to diverse phenotypes [36]. Such environmental changes may also include micro-nutrients; e.g. Vitamin D was shown to significantly modify the FTO effects on weight gain, with a more prominent effect of the genotype among children with insufficient vitamin D levels [37].

Noteworthy, there was a significant correlation between high carbohydrate intake and high-fat items in the A/T and the T/T genotype of rs9939609 compared to the AA genotype, although the latter was significantly correlated with high carbohydrate lower fat foods. If combined with rs9939506 G/G genotype of the rs9939506, there is significantly less fat intake in the AA genotype group. Such SNP interaction is first to be reported in the current study.

Dietary intake and total energy consumption are one of the major environmental players in obesity. The FTO A allele was proved to raise the risk of increasing food intake through impairing central processing of satiety [38], as the FTO gene is highly expressed in the hypothalamus.
Many studies showed that dietary intake plays a significant role in the development of obesity [40]. The relationship between specific dietary nutrient intake and gene variations on obesity was recently investigated. The high-energy intake has been associated with high consumption of protein, carbohydrate, fat and added sugars [41]. On the other hand, diets high in micronutrients such as vegetables, fruits, and whole grains were inversely related to the prevalence of obesity [42]. There is increasing evidence for the importance of micronutrients in genome stability and health. Even small damages caused by micronutrient deficiencies in the genome can produce serious consequences [30].

The FTO is a 505 amino acid protein with Alpha-ketoglutarate-dependent dioxygenase. It repairs alkylated DNA and RNA by oxidative demethylation. In higher eukaryotes, it specifically demethylates N(6)-methyladenosine (m⁶A) RNA, the most prevalent internal modification of messenger RNA (mRNA), [43]. The FTO transcripts containing the A (risk) allele of rs9939609 were more abundant than those with T allele in blood and fibroblasts [44]. Interestingly, subjects homozygous for the FTO rs9939609 AA allele have dysregulated orexigenic hormone acyl-ghrelin within brain regions that regulate appetite; thus, modulating the neural responses to food images in homeostatic and brain reward regions as evidenced by functional MRI. Furthermore, overexpression of FTO in cell models reduces methylation of ghrelin mRNA N⁶-methyladenosine, leading to increased ghrelin mRNA and peptide levels. The effect was also shown in the blood of AA subjects [45].

In addition to the central effect, FTO variants may exert an effect on cellular metabolism. The rs9939609 is in linkage disequilibrium with rs1421085 (T>C), which may lead to obesity through the disruption of ARID5B-mediated repression of Irx3 and Irx5. This leads to a shift from browning to whitening programs in the mitochondria with reduced mitochondrial thermogenesis[46]. A direct interaction exists between the promoters of Iroquois homeobox gene 3 (Irx3) and the FTO in humans (and other species). Up to 30% weight loss may be due to genetic deficiency in Irx3. Thus, Irx3 is a key determinant of body mass and composition, probably by its interaction with FTO [47]. Interestingly, the partial deletion of Irx3 in the hypothalamus may lead to an opposite effect [48]. The interaction between Irx3 and FTO may vary according to the genotype and explain the effect on appetite [49].

The FTO interacts with several other proteins. To achieve full validity of the enrichment test, we added an entire set of proteins to the STRING interactive database, with 'first shell' and 'second shell' are both set to 'none' in the Data Setting box (protein-protein interaction 'PPI' enrichment, p-value = 0.0111). This lowered down the PPI enrichment p-value:< 1.0e⁻¹⁶. The FTO and Melanocortin receptor 4 (MCR4) are co-expressed in other species, but not in humans. The MCR4 plays a central role in energy homeostasis and somatic growth. The FTO is also co-expressed with ALKBH2, another DNA oxidative demethylase [50].

The UAE is located at a geographic hub between Africa, Europe and Asia and was thus exposed to human dispersal waves (e.g. the Paleolithic “Out of Africa” migrations and the exodus of Neolithic pastoral agriculturalists from the Fertile Crescent and Northern Africa around 11,000 years ago [51]. UAE population is genetically highly heterogeneous [32]. Genetic characteristics of Emiratis are in common with the rest of Arabian Peninsula populations [53]. However, the Emirati population has a relatively high Asian component due to admixture with immigrants from geographically close countries [54]. Following an initial pilot study, it was feasible to recruit subjects from the University of Sharjah and primary health care centers to include variable age groups. University students and visitors attending the primary health care centers come from all over the country, although mainly from the city of Sharjah. This may be a limitation to our study, as it may not equally represent Emirati population from various backgrounds, nevertheless, the study includes a good representation of indigenous Emirati population.
This study is first of its kind to explore the effect of FTO SNPs on food predilection in the Emirati population. It showed interesting interactions among the two SNPs notorious for their link to obesity. In the future, we would like to replicate our results on an independent large cohort of subjects.

Conclusion
The FTO genotype plays a significant role in determining the predilection and preference of macro- and micronutrients. The results of the current study highlight the effect of the FTO risk alleles interaction on Emiratis’ food intake. In contrast to previous studies in other ethnicities, we showed that the FTO rs9939609 AA subjects have higher carbohydrate and a trend of lower fat intake. The latter is accentuated in presence of rs9930506 GG genotype. Further investigations are required to elucidate potential interactions of SNPs and food preference, and to unleash the mechanistic link.

Supporting information
S1 File. Genotyping of study population. The file includes genotyping of two SNPs saved as "$\text{.sav}$ file.
(SAV)

S2 File. Food item intake of study population. The file includes daily intake of different food items saved as "$\text{.xl}$ file.
(XLS)

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