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ORIGINAL ARTICLE

Risk of obesity and metabolic syndrome associated with FTO gene variants discloses clinically relevant gender difference among Turks

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Abstract Gene variations in the fat mass- and obesity-associated gene (FTO) have shown controversial associations with obesity and metabolic syndrome (MetS) in several populations. We explored the association of FTO gene with obesity, MetS, and insulin-related parameters separately in men and women. Two SNPs in the FTO, gene rs9939609 and rs1421085, were genotyped by the Taqman System in 1967 adults (mean age of the whole group 50.1 ± 12.0; 48.4 % male). A random sample of the Turkish Adult Risk Factor cohort was cross-sectionally analyzed. Both SNPs exhibited strong linkage disequilibrium ($r^2 = 0.85$) and minor alleles were associated with risk of obesity in women and of MetS in men. Carriers of the rs1421085 C-allele exhibited higher body mass index (BMI) in each gender. Adjusted fasting insulin and HOMA index were significantly higher in C-allele carriers in men alone. Logistic regression analysis demonstrated significantly increased likelihood for obesity in female C-risk allele carriers (OR 1.61; 95 % CI 1.19–2.18), after adjustment for age, smoking status, alcohol usage, physical activity grade and presence of diabetes mellitus. Male C-allele carriers were at increased risk for MetS (OR 1.44; 95 % CI 1.07–1.95), adjusted for age, smoking status, alcohol consumption, and physical activity. Further adjustment for BMI attenuated the MetS risk, indicating interaction between C-allele, gender and BMI. The FTO gene in Turkish adults contributes independently to obesity in women and—by interacting with BMI—to MetS and insulin resistance in men.

Keywords Abdominal obesity · FTO gene polymorphism · Gender difference · Metabolic syndrome · Obesity · Turkish Adult Risk Factor Study

Abbreviations

FTO	Fat mass- and obesity-associated gene
MetS	Metabolic syndrome
BMI	Body mass index
SNP	Single nucleotide polymorphism
T2DM	Type 2 diabetes
LD	Linkage disequilibrium
CRP	C-reactive protein
HOMA-IR	Homeostasis model assessment of insulin resistance
TARF	Turkish Adult Risk Factor
OR	Odds ratio
CI	Confidence interval
SD	Standard deviation

Introduction

Chronic imbalance between energy intake and expenditure contributes to obesity. Obesity is a significant risk factor for diseases like diabetes mellitus, dyslipidemia, and cardiovascular disease. Genetic, hormonal and environmental

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factors contribute to the development of obesity [1]. Genetic factors have been estimated to control of 30–70 % of the variation in obesity [2].

Obesity is highly correlated with metabolic syndrome (MetS), which may be described as a disorder on energy utilization and storage [3]. MetS comprises the components of abdominal obesity, elevated blood pressure, higher plasma glucose, triglyceride and lower HDL-cholesterol levels and is a risk factor for the development of cardiovascular diseases, heart failure and diabetes [3]. Its prevalence is approximately 34 % in adults in USA, and 53 % in Turkish adults aged 40 years or over [4, 5].

Many genes associated with obesity have been recently identified using genome-wide association studies (GWAS) [6, 7]. The FTO gene which is the first locus unequivocally associated with BMI is of particular interest among the newly detected genes. Possibly, both obesity and MetS, may share genetic backgrounds due to which the FTO gene has been selected as a good candidate gene in studies. The FTO gene is located on chromosome 16q12.2. The gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. It is expressed mainly in liver, muscle, pancreas, adipose tissue, and hypothalamus [8, 9]. It acts its role over lipolysis in regulation of body fat mass, energy homeostasis and nucleic acid demethylation [9].

The FTO gene was first discovered in a GWAS for type 2 diabetes (T2DM) [10], and several research groups independently and almost simultaneously reported that it was associated with obesity (or obesity related traits) in European, Asian and African American populations [6, 11–13, 15]. However, several studies showed inconsistent associations between polymorphisms of FTO gene and obesity in non-European populations [6, 14–16]. Many studies have also examined the association between variants in FTO gene and the risk of MetS in adults but this relationship has been controversial such that an association has been reported in some [17, 18] but not all [18, 19] studies. All the defined FTO polymorphisms associated with T2DM, obesity or MetS are in strong linkage disequilibrium (LD) including rs9939609, rs1121980, rs17817449, rs3751812 and rs1421085 ($r2 > 0.8$) [6, 11, 20].

Obesity, T2DM and MetS are closely linked to elevated levels of insulin, blood glucose, C-reactive protein (CRP) and HOMA-IR (homeostasis model assessment of insulin resistance). The relationship between these variables and FTO polymorphisms remains unclear, though these have been associated with a wider waist circumference in Europeans [21], Asian [15] and Hispanic Americans [16], and higher insulin levels and HOMA-IR in Europeans [21]. Turkish adults, especially women, have a high susceptibility to impaired glucose tolerance and MetS, because of enhanced low-grade systemic inflammation, primarily due to obesity and to the resulting oxidative damage to epitopes of a number of serum proteins [22]. We, therefore, examined herein the association of FTO gene polymorphisms with obesity, MetS, and insulin-related parameters in a large and random sample of the population-based Turkish Adult Risk Factor (TARF) cohort.

Subjects and methods

Study sample

Study subjects were chosen randomly throughout Turkey [23]. They were surveyed biennially up to 2013/2014. Detailed biochemical analyses were performed. All data including the results of physical examination and the genotypes were put together and analysed. Approximately 1967 subjects participated in this study. Unselected 1967 people (1014 female and 953 male) were examined for their FTO genotypes. Approval of the Ethics Committee was obtained in Istanbul Medical Faculty, Istanbul University.

Definitions

The definitions of disease were as follows: Obesity: body mass index (BMI) 30 kg/m^2 or greater; Atherogenic dyslipidemia: joint presence of high triglyceride (>150 mg/dL) and low HDL-C (<40/<50 mg/dL, men/women) [24]; Blood pressure: ≥140 mmHg and/or ≥90 mmHg, and/or use of antihypertensive medication; Diabetes: plasma fasting glucose was ≥126 mg/dL (or 2-h postprandial glucose >200 mg/dL) and/or current use of diabetes medication [25].

Measurement of risk factors

Subjects' body weight was measured using a digital scale. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference (WC), was measured when the subject was standing and wearing only underwear, at the narrowest level between the lower rib margin and the iliac crest using a tape. Cigarette smoking was divided into two categories as current smokers and non-smokers (never and former smokers combined). Anyone who drank once a month or more frequently was considered as user of alcoholic drinks. Four categories were defined for physical activity: 1: walking ≤1 km daily, white-collar worker, sewing-knitting; 2: walking 1–2 km daily, repair worker, house work; 3: walking 4 km daily, mason, carpenter, truck driver, cleaning floors and windows; 4: regular sports activity, heavy labour. Low physical activity was classified as 1+2,

high as 3+4. Blood samples were collected after an 11-h or longer fast in the majority of individuals in this study. Serum were shipped within a few hours on cooled gel packs to Istanbul to be stored at −75 °C, until analyzed at a central laboratory. Serum concentrations of glucose, total cholesterol, fasting triglycerides, and HDL-cholesterol were determined using Hitachi Modular P800 chemistry analyzer (Roche Diagnostic, Germany). Concentrations of apolipoproteins B, A-I and CRP were measured with Behring kits and BN ProSpec analyzer (Siemens Healthcare Diagnostics, Germany). Fasting insulin was determined by electro chemiluminescent immunoassay using COBAS e411 analyzer (Roche Diagnostic, Germany).

Determination of the FTO genotyping

Genomic DNA isolation from peripheral blood was performed using QIAmpR DNA Maxi KIT (Qiagen, Germany). Two common SNPs of FTO gene; rs1421085 (T/C) and rs9939609 (A/T) were genotyped using TaqMan allelic discrimination technology on ABI prism 7900 HT Sequence Detection System (Applied Biosystems, CA). Genotyping quality was checked using blind DNA duplicates. The genotyping accuracy was 100 % for each SNP.

Data analysis

Chi-square test and Hardy–Weinberg equilibrium were used to observe the expected genotype distribution. Genotype-phenotype associations were examined with dominant genetic models. Because the number of individuals with the CC genotype was low, homozygotes for the C allele and heterozygotes were grouped as FTO rs1421085-C allele carriers (dominant model) for statistical comparisons. Analyses were performed in men and women separately. Due to the skewed distribution, values derived from log-transformed (geometric) means were used for serum lipoprotein (a), triglycerides, insulin, HOMA-IR, CRP. Sixty individuals (23 men and 37 women) who used lipid-lowering medication were excluded in analyses related to lipid levels. In order to compare continuous variables expressed as means and standard deviation (SD), the two-tailed t test and analysis of variance test were used. Categorical variables were compared by chi-square test. To adjust confounding variables logistic regression models were used to generated maximum likelihood estimates of odds ratios (ORs) and 95 % confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. All statistical analyses were performed by using Windows SPSS version 10.0 software. LD between sites was estimated using Encyclopedia for Genetic Epidemiology studies (http://www.oege.org/software/cubex), with the data presented as D′.

Results

Study characteristics

General characteristics of the study sample (n = 1967) of the TARF cohort which represents middle-aged and elderly Turks, are shown in Table 1. Obesity prevalence was higher in women (43 %) than men (22.2 %), while the prevalence of atherogenic dyslipidemia was higher in men (31.4 %) than in women (24.8 %). But the prevalence of the MetS was similar in women (47.4 %) and men (46.4 %). Of 1014 females, 346 (34.1 %) were postmenopausal. Current smoking and physical activity were higher in men.

Functional annotation of FTO rs9939609 T>A and rs1421085 T>C polymorphisms

We used the RegulomeDB online database (http://regulome.stanford.edu/) to extract information regarding the possible regulatory effects of SNPs that were signicantly associated with obesity phenotype. Rs1421085 polymorphism was located in FTO genomic sequences that were predicted to have some regulatory implication. The majority of associated SNPs belongs to category 5, as classified in Pirim et al., that there was minimal evidence that these variants broke the transcription factor (TF) binding sites or disrupted the regulatory motifs, but supporting expression quantitative trait loci (eQTL) data were not available [26]. Rs9939609 was not classified in that category because functional data have not been found.

Frequencies of FTO rs9939609 T>A and rs1421085 T>C polymorphisms

Genotypes for rs9939609 T>A and rs1421085 T>C polymorphisms of FTO gene were obtained for 1967 participants of the TARF study population. The distribution of the rs9939609 polymorphism was 36.0 % (n = 709), 48.3 % (n = 950) and 15.7 % (n = 308) for the TT, AT and AA genotypes, respectively. The genotype distribution of the rs1421085 polymorphism was 33.6 % (n = 660), 48.8 % (n = 960) and 17.6 % (n = 347) for TT, TC and CC genotypes, respectively. The minor allele frequencies observed for the two SNPs in the adult Turkish population were 39.8 % for the rs9939609-A allele and 42.0 % for the rs1421085-C allele. Genotype frequencies for the total sampled population were evaluated in accordance with Hardy–Weinberg equilibrium ($p = 0.728$ for rs9939609, $p = 0.948$ for rs1421085) and LD. The analyses showed that the rs9939609 T>A and rs1421085 T>C loci of FTO

Table 1 Baseline characteristics of the TARF study participants by gender

Characteristic	Men (n = 953)	Women (n = 1014)	*p*-value
Age (years)	50.1 ± 12.0	49.2 ± 11.8	NS
Waist circumference (cm)	94.0 ± 11.0	90.6 ± 12.2	<0.001
Body mass index (kg/m^2)	27.7 ± 4.0	29.3 ± 5.4	<0.000
Total cholesterol (mg/dL)	184.6 ± 37.6	192.6 ± 39.9	<0.000
HDL-cholesterol (mg/dL)	38.7 ± 11.4	46.0 ± 12.4	<0.000
LDL-cholesterol (mg/dL)	113.2 ± 31.5	119.2 ± 34.3	0.001
Fasting triglyceride[a] (mg/dL)	125.8 ± 1.7	100 ± 1.6	<0.001
Fasting glucose (mg/dL)	98.0 ± 29.4	97.5 ± 27.8	NS
Insulin[a] (uU/mL)	7.94 * 1.9	7.94 * 1.5	NS
HOMA-IR[a]	1.90 * 1.9	1.81 * 1.9	NS
Lipoprotein(a)[a]	9.54 * 2.5	11.4 * 2.5	0.022
C-reactive protein[a]	1.99 * 2.51	2.51 * 3.16	<0.001
Apolipoprotein A-I (mg/dL)	128.9 ± 27.1	145.3 ± 30.1	<0.001
Apolipoprotein B (mg/dL)	114.3 ± 35.6	113.2 ± 35.7	NS
Systolic BP, mm Hg	127.3 ± 22.1	133.4 ± 26.5	<0.000
Diastolic BP, mm Hg	81.5 ± 12.9	83.2 ± 14.3	0.007
Diabetes mellitus, % (n)	8.0 (76)	6.8 (69)	NS
Hypertension, % (n)	37.9 (361)	48.8 (495)	<0.000
Metabolic syndrome, % (n)	46.4 (442)	47.4 (481)	NS
Obesity, % (n)	22.2 (195)	43.0 (410)	<0.000
Atherogenic dyslipidemia, % (n)	31.4 (286)	24.8 (244)	0.002
Smoking status, % (n)	71.1 (650)	20.2 (201)	<0.000
Physical activity grade III or IV, % (n)	46.3 (860)	19.2 (920)	<0.000
Alcohol consumption % (n)	17.3 (157)	0.6 (6)	<0.000
Lipid lowering drug usage, % (n)	2.4 (23)	3.6 (37)	0.111
Menopause status, % (n)	–	34.1 (346)	–

Continuous variables are presented as mean ± SD and dichotomous variables as percentages. A two-tailed *t* test was used for comparison of means, and χ^2-test for percentages

NS not significant, *BP* blood pressure

* 1 SD is denoted by a factor to be multiplied or divided

[a] log-transformed values

were in LD ($D' = 0.967$, $r^2 = 0.85$). Because of linkage disequilibrium between these SNPs was high, we chose rs1421085 for further analysis depending on its strong association with obesity and MetS (Table 2).

Effects of the FTO rs1421085 T>C polymorphism on obesity and MetS

The frequency of the rs1421085 T>C polymorphism was significantly higher in individuals with elevated BMI and waist circumference. The presence of the rs1421085 C allele was related to increased BMI in each gender ($p = 0.002$ and $p = 0.009$, for men and women, respectively) but increased waist circumference and polymorphism relationship was found only in men ($p = 0.039$). The differences between the TT and TC+CC genotypes in men and women were 0.9 and 1 kg/m^2 for BMI, 1.29 cm and 1.35 for waist circumference, respectively. Figure 1 shows mean values of BMI, adjusted for age, smoking status, alcohol consumption, physical activity and diabetes mellitus stratified by the FTO rs1421085 genotypes. Higher BMI in each gender was observed in carriers of the rs1421085 C allele after the stated adjustments. The significant relationship of the C allele to waist circumference attenuated in men after adjustments, but still tended to wider waist girth.

The frequencies of subjects carrying the rs1421085 T>C 'minor' allele were significantly different among the obese and non-obese groups in both sexes, the genotypes TC+CC being more common in obese than in non-obese individuals (Table 2). Table 3 shows significant association between the rs1421085 C allele and obesity in logistic regression analysis, after adjustment for diabetes mellitus, physical activity, alcohol consumption, smoking status and age

Table 2 The genotypic frequency distribution of rs1421085 and rs9939609 polymorphisms in the presence of obesity and MetS

Genotypic distribution						
Gender	Non-obese % (n)	Obese % (n)	*p*	Non-MetS % (n)	MetS % (n)	*p*
Rs1421085						
Women						
TT	37.5 (198)	27.6 (107)	0.002	34.2 (180)	31.6 (145)	0.49
TC+CC	62.5 (330)	**72.4** (281)		67.8 (346)	68.4 (306)	
Men						
TT	36.0 (241)	28.2 (53)	0.046	38.1 (193)	29.8 (126)	0.008
TC+CC	64.0 (428)	**71.8** (135)		61.9 (314)	**70.2** (297)	
Rs9939609						
Women						
TT	39.4 (208)	31.7 (123)	0.017	36.5 (192)	35.3 (159)	0.69
TA+AA	60.6 (320)	**68.3** (265)		63.5 (334)	64.7 (292)	
Men						
TT	39.0 (261)	28.7 (54)	0.010	40.0 (203)	32.4 (137)	0.016
TA+AA	61.0 (408)	**71.3** (134)		60.0 (304)	**67.6** (286)	

Values are in % and unadjusted

Subjects using drugs (5 % of sample) were excluded

Associations are considered significant when $p < 0.05$ and are indicated in bold

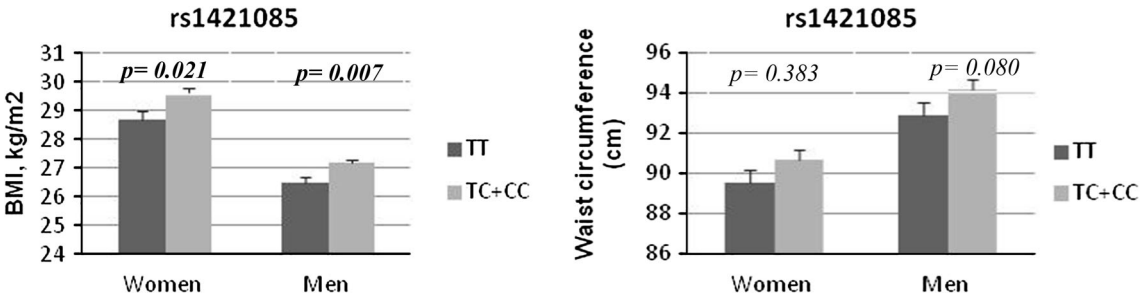

Fig. 1 Estimated mean (*SE) values for BMI and waist circumference across the genotypes of rs1421085 in women and men, after adjustment for smoking status, alcohol consumption, physical activity and age. Note significant associations among carriers of the rs1421085 TC+CC and BMI in each gender. In contrast to women, the C allele in men is associated with increased BMI and tends also to wider waist girth

stronger in women (OR 1.61, $p = 0.002$) than men. Regarding MetS risk in men, the C-allele exhibited interaction with BMI insofar as the significant OR of 1.44 attenuated to substantially below unity when BMI was included in the adjustment (∼obesity largely overlapped with abdominal obesity). Associations between rs1421085 and MetS in women were not significant.

Effects of the FTO rs1421085 T>C polymorphism on metabolic variables

We further investigated the association between this polymorphism and certain metabolic variables. Mean values controlled for age, smoking status, alcohol consumption, physical activity, were similar regarding fasting TG and glucose, total-C, LDL-C, HDL-C, Lp(a), apoB, apoA-I levels in either gender ($p > 0.05$), nor were meaningful differences noted between the rs1421085 genotypes and systolic and diastolic blood pressure (data not shown).

Significant difference existed in the adjusted mean values across rs1421085 genotypes relative to HOMA index, fasting insulin and CRP levels only in men (Table 4). The minor allele carriers had higher insulin levels and HOMA index than common allele carriers. Significance of this association was retained regarding insulin concentrations after adjustment for BMI as well. At variance, the HOMA index attenuated with the BMI adjustment to borderline significance. Adjusted mean CRP values were similar across the genotype groups in men.

Table 3 Adjusted association by logistic regression of the FTO rs1421085 genotypes with obesity and MetS

Gender	Risk of obesity		Risk of MetS			
	Adjusted OR (95 % CI)	p^a	Adjusted OR (95 % CI)	p^a	Adjusted also for BMI OR (95 % CI)	p^b
Women						
TT	1		1		1	
TC+CC	**1.61** (1.19–2.18)	0.002	1.15 (0.86–1.54)	0.339	1.05 (0.75–1.48)	0.76
Men						
TT	1		1		1	
TC+CC	1.34 (0.92–1.94)	0.122	**1.44** (1.07–1.95)	0.015	0.76 (0.53–1.07)	0.12

Associations are considered significant when $p < 0.05$ and are indicated in bold

OR odds ratio, *CI* confidence interval

[a] Indicate p-values, adjusted for smoking status, alcohol consumption, physical activity and age and, in the analysis for obesity risk, diabetes mellitus

[b] Indicate p-values, adjusted for smoking status, alcohol consumption, physical activity, age and BMI

Table 4 Adjusted insulin, HOMA and CRP values in men, by FTO rs1421085 genotypes

Genotypes	Mean ± S.E. (n)[a]	*p*	Mean ± S.E. (n)[b]	*p*
Insulin[c] (mIU/L)				
TT	6.77 * 1.07 (106)	0.016	6.83 * 1.07 (97)	0.047
TC+CC	**8.35** * 1.05 (218)		**8.10** * 1.05 (197)	
HOMA IR[c]				
TT	1.58 * 1.08 (104)	0.013	1.60 * 1.08 (95)	0.065
TC+CC	**2.01** * 1.05 (210)		1.91 * 1.05 (189)	
CRP[c] (mg/L)				
TT	1.76 * 1.09 (140)	0.083	1.77 * 1.09 (133)	0.111
TC+CC	2.13 * 1.07 (231)		2.11 * 1.07 (220)	

Associations are considered significant when $p < 0.05$ and are indicated in bold

* 1 SE is denoted by a factor to be multiplied or divided

[a] Adjusted for smoking status, alcohol consumption, physical activity and age

[b] Adjusted for smoking status, alcohol consumption, physical activity, age and BMI

[c] Log-transformed values

Discussion

Main findings of this relatively large population-based study on the influence of the FTO gene rs1421085 T>C among middle-aged and elderly Turks were as follows. The minor allele was significantly more frequent in obese than in non-obese individuals, regardless of gender, but was more frequent only in men with than without MetS. Second, the C-allele was significantly associated with multi-adjusted risk of obesity in women alone but with that of MetS in men alone. The C-allele interacted in men with BMI in the risks of both MetS and HOMA index. These findings, collectively, offer a plausible explanation to the previously reported observations [27–29] on gender difference regarding overall and central obesity among Turkish adults.

Racial distribution of FTO genotypes, relation to adiposity and explanation of reported controversial findings

We found that rs1421085 polymorphism had stronger association with obesity and MetS than did the rs9939609 polymorphism, a relationship previously shown in four studies on Caucasians [20, 30–32]. We, therefore, chose the rs1421085 for further analyses.

The minor allele frequencies for the FTO gene rs1421085 and rs9939609 polymorphisms observed in the present study (39.8 and 42 % (for rs9939609 and rs1421085, respectively)) is similar to that observed in different European populations (38–45 %) [6, 10, 11, 20] and non-Hispanic White Americans (42 %) [16, 33]. However, in Asian populations (10–18 %), [34, 35], African Americans (8–14 %) [13, 16, 32] and Hispanic Americans (20–25 %) [16, 33] the frequency of the minor allele is lower than in our population. The reported SNPs in FTO are located in a strong LD block in the first intron of FTO [15] as also confirmed herein among Turks.

Small and large-scale studies have reported associations between rs1421085 T>C polymorphism of FTO gene and obesity or BMI in Caucasian populations of European ancestry [11, 20, 21, 33, 36], Americans [6, 13, 16, 33] and Asians [15, 34, 35]. An association between this polymorphism and increased BMI and obesity was reported in some [13, 15, 34] but not all [6, 14–16] studies in African-

Americans and Asians. Minor allele frequency was nearly 40 % among Whites, somewhat lower in Hispanic Americans and South Asians, but as low as 11–18 % in East Asians and African Americans (Table 5). Both the minor allele frequency and the strength of the FTO genotype effect on BMI and obesity in our study was concordant with reports on white populations. Genetic variants in the FTO gene with controversial relationship to obesity and BMI may be due to lower minor allele frequencies in African American and East Asian populations than in Europeans. In addition, these races differ in their environmental risk profiles and body composition.

Gender modulation of the genotype effect on BMI

Meta-analyses on the rs1421085 carriage in Caucasians, Asians and Americans, disclosed an association between FTO rs1421085 T>C polymorphism and obesity risk at ORs 1.43 and 1.48, respectively [36, 37]. Stratified analysis by sex showed that 25 FTO SNPs were related to obesity only in females [38]. Initial studies on Europeans observed no gender difference in association of the FTO common variant with obesity [10, 20]. Yet an important role of the FTO common variant for gender-specific development of obesity in children was pointed to by Jacobsson [39]. On the other hand, genetic effect of the rs1421085 polymorphism was more apparent among male Koreans [34] Furthermore, sex dependent genetic effect on fat composition was published as well [40]. In the Turkish population, it had been recognized that gender differences are important in the development of diabetes and cardiovascular disease from obesity or MetS [41]. Independent influence of the C-allele on BMI in women likely leads to the preferential diabetes pathway, whereas need of interaction between the C-allele and BMI in men preferentially yields abdominal obesity and MetS on the way to cardiovascular disease (Fig. 2). We report here an independent association with obesity of the rs1421085 polymorphism in women at an OR 1.61. These studies suggest that the FTO gene may influence the commonly observed sex-dimorphism in adiposity.

(In)dependent association with MetS

Two meta-analyses had shown that FTO gene polymorphisms were associated with increased risk of MetS in adults at an OR 1.89. [17, 18]. However, as indicated by Zhou et al., most previous studies did not adjust for BMI

Table 5 Data on FTO gene rs1421085 polymorphism affecting obesity in different races

	Reference	Effect on adiposity		Minor allele frequency (%)
		Yes	No	
Whites				
White Americans	6	BMI		0.25
White Americans	13	Obesity, BMI		0.41
White Americans	30	Obesity		0.37
French	21	Waist		–
Belgians	20	Obesity, BMI		0.40
Norwegians	31	Obesity		0.41
Portuguese	32	Obesity, BMI, Waist		0.45
Turks	Present study	Obesity, BMI		0.42
Hispanic Americans				
	6	BMI		0.25
	16	BMI, Waist		0.20
African Americans				
	6		BMI	
	16		BMI	0.14
	13	Obesity		0.11
Asians				
Japanese	35	Obesity		0.18
Koreans	34	BMI		0.14
Chinese	15	BMI		0.12
Malays	15	BMI		0.29
Malays	14		Obesity	0.30
Asian Indians	15		BMI	0.35

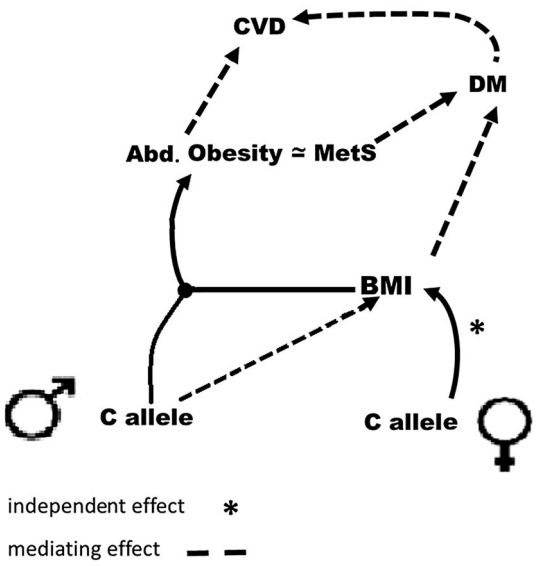

Fig. 2 Schematic representation of pathways for independently affecting or mediating adiposity in rs1421085 C-allele carriage by males and females. Independent influence on BMI in women likely leads to the preferential diabetes pathway, whereas need of interaction between the C-allele and BMI in men preferentially yields abdominal obesity and MetS on the way to cardiovascular disease

[18]. In Chinese children, association between FTO variants and MetS was lacking, even without adjusting for BMI [19]. Hence, it was unclear whether FTO variants are risks for MetS.

Abdominal obesity is a key component of MetS. The mutant C-allele of the FTO rs1421085 polymorphism has been associated with a wider waist in Europeans [21], South Asians [15] and Hispanic Americans [16], though not in African-Americans [16] and Belgians [20]. We found an association between the FTO variant and abdominal obesity in men which attenuated slightly after adjustments. Gender, beyond race, influences this relationship of the minor allele with adipose tissue distribution, as schematized in Fig. 2. In addition, with the purpose of obtaining an overview, a summary of the association of the rs1421085 polymorphism with obesity and the distribution of minor allele frequency in different populations is presented in Table 5.

FTO genotype, gender and adiposity phenotypes among Turks

The results of this study have a corollary in gender-dependent variability of adiposity distribution among Turks previously reported in the TARF study. Computerized tomographically-assessed visceral adipose tissue (VAT) area In 157 middle-aged adults was linearly associated in men at a steeper slope with BMI increments than in women [27], indicating that accumulation of fat tissue was closely accompanied by abdominal obesity in men. Whereas age-adjusted VAT area alone significantly predicted a composite endpoint of cardiometabolic risk in men, body fat mass defined by body composition analyzer or VAT predicted it in women [29]. Thus gender-modulated fat distribution interacted with the dynamics of cardiometabolic risk. Finally, women tended to be less susceptible to accumulation of VAT per kg body fat mass [28]. Both, insulin resistance and inflammation, are differentially related to visceral fat in men and women. Atherogenic dyslipidemia in men is correlated more with visceral fat than with fat mass [28].

Limitations and strength

Minor limitations of this study includes the focusing on rs1421085 polymorphism without assessing the combined effect of functional SNP(s) located in other regions of the gene that are in high LD with the SNPs, and other interacting genetic factors on analyses. Lacking analysis of FTO mRNA and protein expression might be a further minor limitation. Rs1421085 is located in a transcription factor binding site and thus could have regulatory role in affecting the expression of FTO.

On the other hand, the large-sized cohort representing both sexes of a general population having a high prevalence of MetS, life-style and insulin resistance data and adjustments for BMI, as well as stratified analysis for sex, yielding genotype-phenotype corollary for cardiometabolic risk constitute important strengths.

In conclusion, the present study not only confirmed in Turkish adults the association of the FTO rs1421085 genotype with BMI, but also revealed a clinically significant gender difference. The minor allele was associated with increased risk of obesity in females and, by interacting with BMI in males, with the risk of MetS and hyperinsulinemia. Future functional studies of the FTO gene are needed to explore the basic mechanism of the development of the obesity. For example, rs1421085 was classified in category 5, however evidence that these variants interrupt the binding sites of the transcription factor is still lacking.

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Compliances with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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