Original Article

Type 2 diabetes is associated with FTO polymorphism through its effect on increasing the maximum BMI in western region of Saudi Arabia

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ABSTRACT

Background: Several FTO variants have been known to be associated with obesity and typ2 diabetes. Since these variants have been identified in genome-wide association studies (GWAS) in white Europeans, they attracted wide attention for being known to enhance the risk of obesity in different populations. FTO rs9930506 polymorphism was recognized in previous studies as genetic candidate leading to increase obesity measure. Yet it is believed ethnicity variation may cause the differences in response to environment signal.

Objective: The aim of this study is to estimate the genotype and allele frequency in diabetic and healthy individuals in the western region of Saudi Arabia and then investigate the relation of single nucleotide polymorphism to BMI, gender and age in diabetic case compared to control. Genotyping of rs9930506 was performed using TaqMan® OpenArray® Real-Time PCR.

Results: Observation has showed allele A frequency of SNP rs9930506 was 54.9% and 98.3% for DM and healthy control samples respectively. However, alleleG frequency was detected in DM and control subjects as 45.14 % and 1.7% respectively. Evidence indicates that the frequency of allele G is higher in DM case compared to healthy individuals. Also, a strong significant association between FTO SNP rs9930506 and T2DM was reported (P=0.000, U.C. =0.631). Data have shown associations between T2D and BMI, gender and age (P=0.00) suggesting that obese individuals with T2D have a higher frequency 11.138 times compared to obese in healthy control. Additionally, our finding highlighted the impact of the genotype AA of rs9930506 on DM group and determined with a remarkable effect in particular of being obese and male aged from 32 to 53 (P=0.011, OR=56.5).

Conclusion: All together, this study is considered as an initiative to point out to the association of FTO rs9930506 to obesity and T2DM via BMI trait in the most diverse region (western)in Saudi Arabia. This study suggested that male obese are the most affected individuals indicating that FTO SNP exerts different role based on gender and age. Knowing the genetic personal variations will assist in creating strategies to control theses metabolic diseases.

Keywords: BMI trait, FTO, obesity, SNP, type 2 diabetes mellitus

Introduction

complex interplay between the genes and the environment[1]. Earlier it was suggested that variations from person to person observed in response to obsegenic factors owing to a genetic influence to increase fat accumulation in adipose tissues[2]. Thus, predisposition to obesity relies more likely on the individual's genetic variation and the exposure to specific behavior factors, such as diet and physical inactivity[3]. A common variant in FTO (fat mass and obesity-associated) gene was firstly found associated with diabetes mediated by the effect of obesity measure (body mass index; BMI(kg/m^2) in a genome-wide association study (GWAS). It is believed that FTO candidate variants that linked to the imbalance in energy uptake mostly found in FTO intronicregion[4-6]. The FTO gene is located in chromosome segment 16q12.2 and highly expressed in the hypothalamus. It is found to regulate the food intake. Yet the exact role by FTO variants in the energy metabolism leading to obesity is still unrevealed[7-9]. Data from a meta-analysis study of

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white European individuals pointed out to the association of FTO rs9939609 A allele with BMI, increasing in insulin, glucose, and triglyceride levels [10]. Other previous studies have confirmed and replicated the finding of the FTO rs9939609 polymorphism and its impact on BMI [11]. In contrast, various studies did support the involvement of FTO variants in with the accumulation of excess fat [12]. A replication studying African Americans demonstrated incompatible evidence with those in European population as it focused on FTO locus to fine mapping and narrow variants that might implicated in obesity influencing [13].

Beside BMI, it is very advantageous to consider other factors such as age and gender that might alter the individual's risk to obesity and diabetes in the presence of FTO variants. Previous studies have reported the association of FTO SNPs with the increase in BMI and occurred accordingly in males and females [14-16]. Moreover, it was observed from a meta-analysis of 32 GWAS that seven regions known to be associated with BMI have a great impact on waist-hip ratios in women compared in men [17]. Also, a recent study in Mexican population demonstrated a remarkable finding to study the interaction of rs9930506 with BMI, age and gender. Data showed a significant elevation in BMI in women who are a carrier of the minor allele of FTO rs9930506 suggesting the contribution of this SNP to the risk of obesity [18]. Thus, evidence suggested the involvement of FTO SNPs in the distribution of body fat [17] pointing to the differential mechanisms to develop the disease in males and females.

Apparently, it is thought that ethnic variation and race-specific inheritance are mainly attributed for the difference between individuals in responding to the environmental stimuli. The demographic diversity is a compelling reason to assess the genetic variations in Saudi Arabia. Saudi population features variability in social background and religious beliefs widely distributed all over the country; specifically, between the eastern and western provinces. Therefore, it has become more incentive to study each region discreetly. Additionally, there are insufficient data reported in regard to the frequency of genetic variations of FTO SNP rs9930506, nor its linking to obesity-measure (BMI) and the incident of obesity in Saudi society. Therefore, our aim is to assess the frequency of genotypes and alleles of FTO SNP rs9930506 and evaluate the possible association of this SNP to T2DM via BMI in addition to age and gender. Population study was performed by Center of Innovation for Personalized Medicine on diabetic patients in the western region of Saudi Arabia.

Materials and Methods

Participants with Type II diabetes were recruited in collaboration with Endocrinology and Diabetes center at International Medical Hospital (IMC), Jeddah. In addition, healthy human volunteers were participated from king Abdul Aziz University campus. Informed consent and questionnaire forms were completed and signed by each individual joined the study. Clinical parameters were recorded: age, sex, body weight, height, and BMI=weight/height^2 (kg/m^2).

Genomic DNA was isolated from peripheral whole blood samples using QIAampDNA Mini Blood Kit (Qiagen) and from sputum samples using prepIT•L2P Reagent (DNA Genotek, Canada). Genotyping of FTO variant rs9939509 was performed using by Taqman ®OpenArray® Genotyping Real-Time PCR Assays (C__29819994_10, Thermo Fisher Scientific, USA). QuantStudio™ 12K Flex Real- Time PCR System (Thermo Fisher Scientific, USA) was used for SNP detection and allele base calling.

Statistical Analysis

Data analysis was carried out using SPSS Inc. Software, version 24 .0 (SPSS Inc., Chicago.IL, USA). Genotypes and allelic frequencies were estimated within our cohort population to determine the significance differences between diabetes mellitus and healthy control groups.

Chi-Square and Fisher's Exact test were used to observe the difference between the case (diabetic patient) and the control (healthy subjects) groups. The entire data were further classified according to BMI, age, and sex in subgroups to determine the association between rs9930506 variant and these factors for patient and control. Odd ratio (OR) and Uncertainty Coefficient (U.C.) (considered as > 0.7 strong association) were calculated to determine the risk of obesity and development of T2DM. Additionally, logistic regression was performed to estimate the likelihood of having diabetes mellitus between the carrier of rs9930506 AA genotype and the carrier of GG/AG genotype. With Univariate Model unadjusted odds ratio was calculated for predictors separately (BMI, age, and gender) with DM group in regard to control as a dependent variable. Whereas Multivariate Mode, adjusted odds ratio was assessed to determine the impact of the combined factors collectively for each genotype.

Results

Characteristics of the study group: Study subjects were classified by age, gender, and BMI listed in Table 1. To study the association, BMI was further classified into (non-obese, pre-obese and obese). Overall, 235 (49.09%) of the subjects were healthy and 245 (51.0%) subjects have T2D.Normal body weight was found in 119 subjects (41.3%), overweight 78 subjects (27.1%) and obese 56 subjects (19.4 %). The distribution of rs9930506 genotype and allele frequencies was

listed in Table 2. FTO genotypes (AA, AG, and GG) frequencies were calculated for DM group as 12.5%, 84.7% and 2.6% respectively, whereas for control group as 97.2%, 2% and 0.8% respectively. Also allele A and G frequencies were estimated as 54.9% and 45.1% respectively for DM group and 98.3% and 1.7% respectively for healthy individuals.

Table 1. Demographic of the study population

Variable		Number %
Group	Healthy Control	235 (49.0%)
N (%)	DM Patients	245 (51.0%)
Age	10 – 19	29 (6.7%)
N (%)	20 – 29	147 (34.2%)
	30 – 39	46 (10.7%)
	40 – 49	64 (14.9%)
	50 – 59	79 (18.4%)
	60 and above	65 (15.1%)
Gender	Male	163 (34.9%)
N (%)	Female	304 (65.1%)
BMI	Underweight	35 (12.2%)
N (%)	Healthy	119 (41.3%)
	Overweight	78 (27.1%)
	Obese	56 (19.4%)

* BMI was measured as body weight/height (Kg/m2), underweight: < 18.5, healthy: 18.5 to 25, overweight: 25 to 30, obese: >30

The association of FTO genotype rs9930506 with DM

The relationship between each *FTO* SNPrs9930506 and the case-control group was studied. Result has revealed that there is a strong significant association between FTO SNP rs9930506 (P=0.000, U.C. =0.631) and T2DM (see Table 4). This association is in particular between the genotype AG and T2DM (OR=264.05) in relative to other genotypes of the same SNP (AA/GG). Besides data have suggested that AG genotype is more likely to be present in diabetic patients with a relative risk = 40.333.

Table 2. Genotype and allele frequency

FTO rs9930506	Total =216	DM (n=72)	Control (n=144)
Genotype frequency			
AA	149 (69.0%)	9 (12.5%)	140 (97.2%)
AG	64 (29.6%)	61 (84.7%)	3 (2%)
GG	3 (1.4%)	2 (2.6%)	1 (0.8%)
Allele frequency			
A		79 (54.9%)	283 (98.3%)
G		65(45.14%)	5 (1.7%)

Overview of the relationship between each factor (BMI, age, and gender) with each group (DM and healthy subjects)

Notably, there is an association between increasing in BMI and the presence of T2D (Fisehr's Exact; *P=0.00*, Chi Square; *P=0.000*). However, the association is weak measured by (U.C. = 0.196). Data have shown that obese participants with T2D have a higher frequency by (OR=11.138 times) compared to obese control with a relative risk of getting T2DM in obese participants by 5.649 more than non-obese. Additionally, data analysis has shown a correlation between the age group 54+ and in the presence of T2DM with (*P= 0.00*, OR=25.709, U.C. = 0.498). However, a weak association was found between gender category and T2DM (*P=0.00*, U.C. =0.059). See Table 3.

Effect of each FTO rs9930506 genotype on (BMI, age, and gender) for diabetic and control group

Further the impact of BMI categories on diabetic patient and control in the presence of FTO variants was conducted in depth. Observations showed a significant association between BMI classifications and group categories (Chi square; *P=0.000*, Fisher's Exact; *P=0.007*) for the genotype AA of *FTO* SNP rs9930506; however, the relation was weak (U.C.=0.064). The effect of BMI on obese patients is (OR=18.072) times higher than on obese in healthy control with a relative risk=8.000. The association between age and group categories were examined for the same genotype and found that there is a significant association (Chi square; *P=0.000*, and Fisher's Exact; *P=0.000*), yet it is moderate relationship (U.C. = 0.345).

Particularly, patients at the age of 54 and above are more affected by (OR=18.518) times than those of healthy control at the same age. Subsequently, people aged 54+ with this genotype are more susceptible of getting diabetes mellitus by (Relative Risk=19.231) than young individuals Table 5. Also, there is no impact observed for the genotype AG between BMI, and gender subgroups and diabetes (Chi-square (*P = 0.240*) and Fisher's Exact (*P = 0.201*)), Fisher's Exact, *P=1.000*) respectively. In regards of gender, it is notable to mention that there was a linked between this factor and the groups (Fisher's Exact; *P=0.028*, C.C.= 0.201). The association was significant indicating the odds of male patients are 4.861 times higher than the odds of female patients with a relative risk to have DM for males equal to 1.419 times than females Table 5.

From data analysis using univariate model, unadjusted odds ratio for each predicator (age, BMI and gender) was determined, a significant impact was reported for the genotype AA of *FTO* SNP rs9930506 on BMI and gender but not on age at this model; *P=0.006* and *P=0.025* respectively (Table 6A). The odds of obese category for DM were calculated as 26.7 higher compared to the odds of non-obese for healthy control. However, the odds of males with DM were 4.861 higher compared to the odds of females in healthy subjects. Clearly, when the factors (predictors) were combined using Multivariate Model, the genotype AA of rs9930506 has a significant effect with DM group (*P=0.011*). It can be inferred that the odds ratio of being diabetic, obese, and male who are age ranged from 32 to 53 were 56.5 times increase compared to the odds of non-obese females at the age less than 32 (Table 6B).

Table 3: The relation between study factors (BMI, Gender, and Age) and DM and control groups

Factor		BMI			U.C*.	Test
		Non Obese	Pre Obese	Obese		
Group	Patient	5 (8.1)	23 (37.1)	34 (54.8)	0.196	Fisher's Exact (P=0.000)
	Control	146 (65.9)	55 (24.4)	22 (9.7)		
Odds Ratio Patient		0.046	1.801	11.138		Chi-Square(P=0.000)
Relative Risk		0.123	1.52	5.649		
Factor			Age		0.498	Fisher's Exact (P=0.000)
		≤ 31	**32 – 54**	**54 +**		
Group	Patient	6 (2.7)	122 (53.0)	102 (44.3)		
	Control	172 (86.9)	20 (10.1)	6 (3.0)		
Odds Ratio Patient		0.004	10.08	25.709		
Factor			Gender		0.059	Fisher's Exact (P=0.000)
		Male	Female			
Group	Patient	115 (47.7)	126 (52.3)			
	Control	48 (21.2)	178 (78.8)			
Odds Ratio Patient		3.394	0.295			

Table 4.FTO rs9930506 variant association with each group

Genotype		rs9930506			*U.C	Test
		AA	AG	GG		
Group	Patient	9(12.5)	61(84.7)	2(2.6)	0.631	Fisher's Exact
	Control	140(97.2)	3(2)	1(0.80)		
Odds Ratio Patient		0.004	264.05	4.143		Chi-Square
Relative Risk		0.129	40.333	4		

Table 5. Impact of rs9930506 genotype on BMI, gender, and age for each group

FTO rs9930506			BMI			U.C.	Test	Age			U.C.	Test
			Non Obese	Pre Obese	Obese			-31	32 – 53	54 +		
AA	Group	Patient	1 (20.0)	1 (20.0)	3 (60.0)	0.064	Chi Square (P=0.000)	0	4 (50.0)	4 (50.0)	0.345	Chi Square (P=0.000)
		Control	89 (66.9)	34 (25.6)	10 (7.5)			102 (89.5)	9 (7.9)	3 (2.6)		
	Odds Ratio	Patient	0.123	0.729	18.072		Fisher's Exact (P=0.000)	0	5.814	18.518		Fisher's Exact (P=0.000)
	Relative Risk		0.299	0.781	8			0	6.329	19.231		
AG	Group	Patient	1 (7.1)	7 (50.0)	6 (42.9)	0.146	Chi Square (P=0.000)	3 (5.1)	29 (49.2)	27 (45.7)	0.223	Chi Square(P=0.000)
		Control	1 (33.3)	2 (66.7)	0			3 (100.0)	0	0		
	Odds Ratio	Patient	0.154	0.5	-		Fisher's Exact (P=0.201)	-	-	-		Fisher's Exact (P=0.000)
	Relative Risk		0.213	0.749	-			0.051	-	-		
GG	Group	Patient	-	-	-	-	-	0	1 (50.0)	1 (50.0)	0.274	Chi Square(P=0.386)
		Control	1 (100.0)	-	-			0	1 (100.0)	0		
	Odds Ratio	Patient	-	-	-	-	-	-	-	-		Fisher's Exact (1.00)
	Relative Risk		-	-	-			-	0.5	-		

rs9930506 Genotype	Gender	Group		Odds Ratio	Risk Ratio		C.C.	Test
		Patient	Control		Patient	Control		
AA	Male	5 (15.6)	27 (84.4)	4.861	1.419	0.462	0.201	Fisher's Exact (P=0.028)
	Female	4 (3.7)	105 (96.3)					
AG	Male	31 (96.9)	1 (3.1)	2.067	4.258	0.876	0.074	Fisher's Exact (P=1.000)
	Female	30 (93.8)	2 (6.2)					
GG	Male	-	-	-	-	-	-	-
	Female	2 (66.7)	1 (33.3)					

Table 6A. Unadjusted and adjusted odds ratio (OR) estimates of factors for each genotype (Logistic Regression) for patient in regards to control

FTO rs9930506	Factors	Univariate Model				Multivariate Model			
		B	df	OR	P-Value	B	df	OR	P-Value
AA	Age		2		0.528		2		0.873
	32 – 53	20.392	1	N	0.996	19.627	1	N	0.996
	54 +	21.491	1	N	0.996	18.645	1	N	0.996
	BMI		2		0.012*		2		0.249
	Pre Obese	0.962	1	2.615	0.501	1.735	1	5.67	0.368
	Obese	3.285	1	26.7	0.006*	3.092	1	22.032	0.095
	Gender								
	Male	1.581	1	4.861	0.025*	2.416	1	11.206	0.124
AG	Age		2		1		2		1
	32 – 53	21.203	1	N	0.998	73.621	1	N	0.997
	54 +	21.203	1	N	0.998	76.662	1	N	0.999
	BMI		2		0.743		2		1
	Pre Obese	1.253	1	3.5	0.441	-37.058	1	0	0.998
	Obese	21.203	1	N	0.999	0.44	1	1.553	1
	Gender								
	Male	0.726	1	2.067	0.562	36.802	1	N	0.998

Discussion

Since FTO gene was identified in genome wide screening of European populations as obesity- related traits, it brought a lot of attention to the importance of this locus (16q12.2). Several FTO variants were previously recognized and showed association and type 2 diabetes suggesting the growing in adiposity have led to adverse metabolic consequences[5, 19, 20]. Up to date, the precise function of FTO is not certain. Yet evidence has suggested that it has a role in regulating energy intake, particularly controlling the individual's behaviors in response to food[21, 22]. Most of the studies conducted were restricted to European white population, which might lead to misleading results. The FTO- related obesity trait or type 2 diabetes associations' studies are required further investigation in non-Caucasian ancestry.

In this study, we reported a strong association of FTO SNP rs9930506 with obesity and the incidence of T2DM mellitus in diabetic-healthy cohort performed at King Abdulaziz University with IMC hospital. Our findings have revealed that G-allele frequency of this SNP was 45.14% higher in diabetes mellitus group compared to those in their counterpart in healthy group (1.7%). Further, our data analysis has indicated a strong association between FTO rs9930506 genotype AA with DM group specifically for obese, male aged between 32 and 53 compared to who are non-obese, female and age < 32 (P= 0.011, OR= 56.5)). Also, our study pointed out to a remarkable association between rs9930506 AG polymorphism and T2DM among other genotypes of the same SNP (P=0.000,

OR= 264.05). Previous study performed on Polish adults has indicated that this genotype has a strong relationship on BMI and obesity[23]. Another study in Italian population demonstrated a robust association of rs9930506 G-allele with increased BMI[24].

Minor allele frequency (MAF) of FTO rs9930506 (allele G) estimation in our study was similar to that observed in European, nevertheless genotype AA was more likely to be associated with T2DM through BMI measure. In contrast, inconsistent findings were observed in Asian population when such association between FTO genotype and obesity measure or T2DM was conducted. It has been reported that the minor allele frequencies for rs9939609 and rs9930506 (0.12 and 0.20 respectively) in Chinese Han population were substantially lower than those observed in white people (0.48 and 0.45)[25]. Additionally unlike European population, there was no support evident for the association between FTO genotype and BMI[26]. Differences observed in genotype association between DM compared to healthy control might be attributed to ethnic diversity, sample size and collection and exposure to the environmental signal. Moreover, gender and age differences were observed as obesity and T2DM were associated with FTO variant. Similarly, it was reported by Jacobsson et al. that rs9939609 SNP might have an obesity effect based on gender among girls[15].

Looking for insights into FTO function was attempted by several researches before its variants were identified in 2007 as obesity-associated trait. Common SNPs among the entire genome were correlated with complex diseases. Successfully, genome wide association study was conducted to identify variants in FTO region that leading to the risk to develop T2DM through linking of BMI. Finding has suggested that individuals with the homozygous risk allele of FTO have a modest effect on BMI with 3 Kg more than homozygous for those with the protective allele, However, FTO SNPs effect on adiposity are still elusive because lack of knowledge whether of this effect is directly by FTO or collectively with other genes in the same locus[5, 6, 27, 28]. Indeed, the first two intronic region and exon 2 of FTO as well as other elements of the neighbor genes harbor the association signal of BMI-related SNPs. It was found that the retinitis pigmentosa GTPase regulator-interacting protein 1-like (RPGRIP1L) gene is in a proximal distance to the 5` end of FTO[5]. Primarily FTO gene was discovered when homozygous deletion of the genes located within a 1.6 mega base on chromosome 8 was created in the mouse causing developmental defects in the nervous system and deformity in the head and face[29, 30]. Similar profound observations were reported in human patient who suffer with anisomastia. Chromosomal duplications at the region 16q11-q13, a region harboring FTO gene, have been described in those patients resulting into disruption of genes positioned on this segment. Mental retardation, facial abnormalities and obesogenic behavior are more likely to be manifested[31]. Moreover, since FTO protein is related to dioxygenases family that plays a role in DNA repair mechanism, demathylation of 3-mthylthymine it was asserted that a homozygous FTO SNP at position (c.947G>A) is responsible for polymalformation syndrome affecting Palestinian Arab family. Genetic analysis of the family pedigree suggested that non-synonymous mutation results in amino acid substitution (P.R316Q; arginine toglutamine) at 316 position of FTO protein with loss of function[32]. Obviously, association of variants does not mean these variants are the causative of the disorder. Therefore, attempting continues to elucidate the correlation between FTO variants the obesity epidemic by examining the clinical involvement FTO function interrupted. Accordingly, it has been demonstrated by a study in china that the overexpression of FTO mRNA has a potential to increase liver enzymes (ALT and AST) in Non-alcoholic fatty liver diseases (NAFLD)[33]. Interestingly, genotyping of FTO rs17817449 T/G, rs9939609 T/A, and rs8050136 C/A, in African American population has revealed a significant association between this SNP and the risk to develop colorectal adenomas[34]. Further, multivariate analysis has postulated that diabetic individuals who are carrier of heterozygote T/A variant of FTO rs9939609 are more likely to be susceptible of having pancreatic cancer in comparing to those with T/T homozygote[35]. In summary, FTOrs9930506 is associated with higher BMI and it is gender and age dependent. The results also demonstrated that the increase in fat mass attributable to FTO variants leading to the risk of obesity and developing type 2 diabetes. It is apparent that the effect of FTO focused mostly on the individual's appetite. Therefore, identifying FTOSNPs that link to obesity might provide a deep insight to understand the mechanisms underlie the correlation between obesity and T2D to facilitate the individual's management of diet behavior. However, further powered studies are required to assess the effects of FTO variants on other metabolic traits correlated with both conditions.

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Abbreviation

BMI – Body Mass Index

DM – Diabetes Mellitus

OR – Odd Ratio

U.C. – Uncertainty Coefficient
FTO – Fat Mass and Obesity-Related
NAFLD - Non-alcoholic fatty liver diseases

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