Original Article

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The Role of FTO Gene Alleles on the Diet and Metabolic Risk Factors in the Subjects with Diabetes

FTO Gen Alellerinin Diyabetli Kişilerde Diyet ve Metabolik Risk Faktörleri Üzerindeki Rolü

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Abstract

Purpose: To evaluate the effect of differential food intake on metabolic risk markers in Type 2 diabetic individuals with diverse FTO gene alleles.

Materials and Methods: The study was conducted at Baqai Institute of Diabetology and Endocrinology (BIDE) Karachi, Pakistan between March 2011 and May 2013. The present study is based on a previously published case-control study that indicates the association of different FTO gene with type 2 diabetes. The structured questionnaire was used to gather anthropometric, biochemical, and clinical data. Single nucleotide polymorphism (SNP) in FTO gene was analyzed using Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR). The nutritional data were collected using a 24-hour dietary recall questionnaire completed by a trained dietitian. The variations in energy and macronutrient intake of subjects having different FTO gene alleles were investigated and evaluated for correlations between energy and macronutrient intake and metabolic risk variables in three FTO-gene-allele groups.

Results: Overall, 198 adult subjects with type 2 diabetes (T2D) were recruited and categorized into three genotype groups: TT, AA and AT with the mean age of 49.7 ±9.7, 49.3 ±10.6 and 50.2 ±8.8 years, respectively. A close association was observed between the minor allele A at rs9939609 and type 2 diabetes. A linear correlation was observed between diet and metabolic profile markers such as BMI, waist circumference, blood pressure, and lipid profile among high-risk alleles AA. The associations of energy intake and percent level of carbohydrate and protein intake with metabolic syndrome were significantly higher among risk alleles AA (P<0.05). However, the majority of the biochemical parameters and dietary components were found to be statistically insignificant (p>0.05).

Discussion: Genetic profile is likely to affect both dietary habits as well as the association between diet and metabolic syndrome markers. This study concludes that diet-disease associations are more prominent in individuals having risk alleles AA as compared to protective alleles TT and heterozygous alleles AT.

Keywords: Diet, T2DM, FTO, nutrigenomics

Özet

Amaç: Farklı FTO gen alellerine sahip Tip 2 diyabetli bireylerde çeşitli gıda alımının metabolik risk belirteçleri üzerindeki etkisini değerlendirmek.

Gereç ve Yöntemler: Çalışma, Mart 2011 ile Mayıs 2013 arasında Baqai Diabetoloji ve Endokrinoloji Enstitüsü (BIDE) Karachi, Pakistan'da gerçekleştirildi. Bu çalışma, farklı FTO genlerinin Tip 2 diyabet ile ilişkisini gösteren önceden yayımlanmış bir vaka kontrol çalışmasına dayanmaktadır. Antropometrik, biyokimyasal ve klinik verileri toplamak için yapılandırılmış anket kullanılmıştır. FTO genindeki tek nükleotid polimorfizmi (SNP), Amplifikasyon Refrakter Mutasyon Sistemi-Polimeraz Zincir Reaksiyonu (ARMS-PCR) kullanılarak analiz edildi. Beslenme verileri, eğitimli bir diyetisyen tarafından doldurulmuş 24 saatlik bir diyet hatırlatma anketi kullanılarak toplandı. Farklı FTO gen alellerine sahip bireylerin enerji ve makro besin alımındaki değişiklikler araştırıldı ve üç FTO-gen-alel grubundaki enerji, makrobesin alımı ve metabolik risk değişkenleri arasındaki korelasyonlar açısından değerlendirildi.

Bulgular: Genel olarak, Tip 2 diyabetli (T2D) 198 erişkin hasta çalışmaya alındı ve üç genotip grubuna ayrıldı: yaş ortalaması sırasıyla 49.7±9.7, 49.3±10.6 ve 50.2±8.8 olan TT, AA ve AT. Tip 2 diyabet ile rs9939609'daki minör alel A arasında yakın bir ilişki gözlemlendi. Yüksek riskli AA alelleri içinde diyet ve BKİ, bel çevresi, kan basıncı ve lipid profili gibi metabolik profil belirteçleri arasında lineer bir korelasyon gözlemlendi. Metabolik sendrom ile enerji alımı ve karbonhidrat ve protein alımı düzeyleri arasındaki ilişki, AA risk alelleri arasında anlamlı derecede yüksekti (p<0.05). Bununla birlikte, biyokimyasal parametrelerin ve diyet bileşenlerinin çoğunluğu istatistiksel olarak anlamsız bulundu (p> 0.05).

Tartışma: Genetik profilin hem beslenme alışkanlıklarını hem de diyet ile metabolik sendrom belirteçleri arasındaki ilişkiyi etkilemesi muhtemeldir. Bu çalışmada, koruyucu alel TT ve heterozigot alel AT'ye kıyasla, risk aleli AA olan bireylerde diyet-hastalık ilişkisinin daha belirgin olduğu sonucuna varılmıştır.

Anahtar kelimeler: Diyet, T2DM, FTO, nutrigenomikler

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Introduction

As reported by GWAS (Genome-wide Association Studies), the FTO gene (fat mass and obesity associated gene) and obesity are correlated (1,2).

Several independent studies in different ethnic European individuals have also recognized a strong association between that the FTO gene and obesity (2,3). The association between FTO and BMI has also been reported in non-European inhabitants including South Asians (4–6). In a previous work, the correlation between FTO single nucleotide polymorphisms (SNPs) and obesity was found to be non-significant (7,8). However, it was found that translation of FTO SNPs accounts dissimilar variations in BMI (0.16–0.20%) in Asian populations than in Europeans (9).

Earlier studies have reported an association between FTO SNPs and increased risk of type 2 diabetes (T2DM), and in the majority of the cases, it is affected by obesity. However, there are some reports indicating an independent association of SNPs with the risk of diabetes (10). Although a significant association of FTO (rs 9939609) variant with T2DM among South Asians has been reported, its link with obesity, metabolic syndrome and T2DM is still not clear (11). The FTO variant for allele 'A' (rs 9939609) is linked to the high risk of developing diabetes, which is strongly arbitrated by BMI. However, the results vary among South Asians (12).

The effect of genetic polymorphisms on nutrient metabolism has also been described in the epidemiological studies showing a direct relation of unhealthy diet with chronic diseases including cancer, diabetes, rheumatoid arthritis, osteoporosis, and cardiovascular diseases. The genetic variations having an impact on nutrient metabolism can be understood by having the knowledge of the processes involved in digestion, absorption, transport, biotransformation, uptake, and elimination. A more specific understanding can be generated by studying the metabolism of ingested bioactive food ingredients (13).

The adults having high-risk alleles have been reported to have higher requirements for energy, macronutrients intake, and unhealthy eating habits (14). The genetic variants have also been shown to have an influence on metabolic response to food components (15). It implies that the higher risk for diabetes among AA allele is probably mediated through the impact of genes on food intake or differential impact of dietary variations on the metabolic profile. The present study explored variations in dietary intakes and links between diet and metabolic risk markers in T2DM having various risk alleles.

Material and Methods

A total of 198 subjects (110 males and 88 females) visiting the outpatient department (OPD) of Baqai Institute of Diabetology and Endocrinology (BIDE) were enrolled in the study. The study period was from March 2011 to May 2013. Ethical approval was taken from the Institutional Review Board (IRB) of BIDE. The present study is based on a previously published case-control study that described the association of different FTO genes with T2DM; where TT represents a homozygous protective allele, AA is homozygous risk allele and AT is heterozygous allele (16). The basic clinical, demographic, and genetic data were taken from a previous study. The dietary data for this study were specifically collected through a 24-hour dietary recall questionnaire (17).

The study subjects were grouped on the basis of BMI and waist circumference, obesity traits, and hypertension among FTO gene variants. The measurements of weight, height and blood pressure were obtained by the paramedical staff. Body mass index (BMI) was calculated by measuring weight in kilogram and height in meter square. According to the Asian guidelines, BMI $\geq$ 23 kg/m^2 is considered as overweight (18). The standard measurement for central obesity comprised of the waist circumference $\geq$ 90 cm in men and $\geq$ 80 cm in women (19). Subjects having blood pressure above 130/85 mmHg or already on anti-hypertensive medication or if they had a self-reported history of hypertension are included (20).

All subjects were evaluated for their diet by a registered dietitian (RD). The RD estimated the number of food intakes by various food groups and the details of carbohydrates, proteins, and lipids consumed daily. This information was entered in the institution's (tailor made) hospital management system (BIDE-HMS) software. HMS calculated and stored the data about intake of calories and macronutrients for each patient. The subjects were also grouped according to their dietary intake in high or low intake categories for energy and macronutrients. The energy requirement for each patient as per their physical activity was estimated using Mifflin's formula (21).

The subjects having different FTO variants were compared for their energy requirements and percentages of calories from various macronutrients. The proportion of subjects having high or low risk within high or low dietary intake groups were calculated separately for each genetic variant group and the differences were observed in the strength of diet-disease.

Statistical Analysis

Statistical Package for Social Science (SPSS ver.16.0) was used for data analysis. The continuous data were presented by mean ±SD and categorical data in number and percentage.

For examining the differences in diet-disease relationship, the differences in the linear association between (correlation Pearson's) diet and clinical variables were evaluated. Genetic variation in diet-disease associations was also estimated by non-parametric methods. The frequencies of alleles were analyzed by Hardy-Weinberg equilibrium. ANOVA and chi-square test were applied to determine the statistical significance of variations in means and percentages, respectively. The statistical significance level for results was $P<0.05$.

Results

A total of 198 type 2 diabetes (T2DM) subjects were recruited in this study. They were categorized according to their allele types (TT=53%, AA=88%& AT=57%), as described in a previous study. The mean age subjects in TT, AA and AT group was 49.7 ±9.7, 49.3 ±10.6 and 50.2 ±8.8 years, respectively. Table 1 shows a comparison of basic clinical characteristics and dietary components among different allele groups. The differences observed for

Table 1. Basic and clinical characteristics of subjects carrying different FTO alleles

	Allele Groups			
Characteristics	**TT (N=53)**	**AA (N=88)**	**AT (N=57)**	**P-value**
Age (years)	49.7 ±9.7	49.3 ±10.6	50.2 ±8.8	0.845
Male [n (%)]	33(62.3)	50(56.8)	27(47.4)	0.277
Female [n (%)]	20(37.7)	38(43.2)	30(52.6)	
Body Mass Index(kg/m²)	29.7 ±5.6	29 ±5.1	29.5 ±5.4	0.685
Systolic BP (mmHg)	125.09 ±14.19	129.68 ±18.55	133.77 ±19.05	0.038
Diastolic BP (mmHg)	77.26 ±8.18	80.85 ±9.44	81.75 ±11.12	0.036
Waist Circumference (cm)	40.94 ±10.94	39.01 ±10.1	38.6 ±4.51	0.370
HbA1c (%)	9.4 ±2.01	9.5 ±2.1	8.95 ±1.98	0.255
Total Cholesterol (mg/dL)	183.8 ±39.3	177.8 ±52	177.4 ±44.6	0.809
Triglycerides (mg/dL)	231.9 ±262.3	174.2 ±139.6	157.6 ±118.6	0.154
High Density Lipoprotein (mg/dL)	40.6 ±11.6	37.4 ±10.4	40.3 ±11.2	0.273
Low Density Lipoprotein (mg/dL)	110.7 ±33.4	100.4 ±37	101.4 ±40.9	0.37
Creatinine (mg/dL)	1.1 ±0.3	1.1 ±0.3	1.2 ±1.2	0.36
Dietary Component				
Fat% of Calories	35.28 ±10.69	33.97 ±8.11	34.45 ±8.27	0.702
Protein% of Calories	14.05 ±3.01	14.44 ±2.27	13.89 ±2.30	0.391
CHO% of Calories	50.67 ±8.77	51.58 ±7.38	51.65 ±7.51	0.755
Energy (Calories)	2022 ±659	1964 ±604	1739 ±412	0.021*
Energy (% of requirement)	103.52 ±27.4	103.3 ±29.94	113.31 ±30.01	0.101
Food Compliance				
Good compliance [n (%)]	2 (3.8)	10 (11.4)	8 (14)	0.282
Partial-compliance [n (%)]	42 (79.2)	70 (79.5)	43 (75.4)	
No or Poor compliance [n (%)]	9 (17)	8 (9.1)	6 (10.5)	

Data presented as mean ±SD or n (%)
ANOVA and chi-square test were performed for group comparison.
* P<0.05, ** P<0.01, considered statistically significant.

the majority of the clinical characteristics were statistically insignificant. The BMI was not statistically significant for all groups except the protective allele TT, which was observed to have higher central obesity among the groups. As compared to risk genotype AA and heterozygous genotype AT groups, the allele TT was observed to have a significantly lower frequency of hypertension. Biochemical parameters like HbA1c, cholesterol, triglyceride, HDL, LDL, and creatinine were not observed to have statistically significant differences among the groups. The total calorie intake of allele AT group was found to be significantly lower in contrast to other groups ($p<0.021$). However, in terms of energy intake percentage of requirements was found to be statistically insignificant among groups.

Table 2 shows a correlation (Pearson's) of the dietary component with hypertension and lipid profile variables in different FTO alleles. The link of BMI and waist circumference with dietary factors was found to be more pronounced and statistically significant for risk alleles AA. Blood pressure was observed to be similar in risk alleles AA and protective alleles TT. The percentage of calories obtained from fat has a positive and significant correlation while that of from carbohydrates was observed to have a significant negative correlation with SBP in both risk alleles AA and protective alleles TT. DBP was found to have a positive and significant correlation only in protective alleles TT. No consistent pattern in the correlation between lipid profile and dietary factors were observed, however, it varied according to risk alleles. There were significant differences in protective alleles TT and heterozygous alleles AT for LDL-cholesterol and serum triglycerides, respectively.

Table 3 and 4 describes the association between categories of metabolic syndrome risk indicators with that of energy intake, protein, and carbohydrate. Higher energy intake and metabolic syndrome markers were found to be significantly associated with risk alleles AA. Higher energy intake and protein intake were also related to a higher frequency of hypertension and their link was prominent and statistically significant in risk alleles AA, while results were found statistically insignificant for intake of carbohydrate.

Discussion

FTO gene SNP has been linked to polygenic obesity. In earlier studies, BMI-increasing alleles of FTO variants were reported to have an association with increased food intake, total energy intake, fat or protein intake, implying the link of diet with BMI (22–24). It has also been reported that physical activity may decrease the effect of

Table 2. Correlation between dietary components (Fat, CHO, Protein, and Energy) with BMI, hypertension and lipid profile.

	Body mass index (kg/m²)			Waist circumference (cm)			Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)			LDL-cholesterol (mg/dL)			Serum Triglyceride (mg/dL)		
	AA	AT	TT	AA	AT	TT	AA	AT	TT	AA	AT	TT	AA	AT	TT	AA	AT	TT
Percent calories from Fat	0.32*	0.09	0.05	0.38**	0.12	0.04	0.35**	0.08	0.22*	0.17	0.08	0.12	0.26	0.27	0.27*	0.00	0.01	0.06
Fat in grams	0.15	0.23	0.13	0.56**	0.23	0.02	0.10	0.06	0.08	0.03	0.04	0.02	0.05	0.25	0.21	0.00	0.10	0.12
Percent calories from Carbohydrates (CHO)	0.36*	0.11	0.03	0.37**	0.16	0.00	–0.32*	0.02	–0.22*	0.13	0.14	0.10	0.38	0.22	0.42	0.58	0.45**	0.09
Percent calories from Proteins	0.01	0.05	0.10	0.16	0.09	0.17	0.22	0.22	0.11	0.22	0.15	0.12	0.31	0.22	0.25*	0.00	0.01	0.03
Protein in grams	0.00	0.11	0.00	0.32*	0.13	0.20	0.28*	0.15	0.15	0.16	0.03	0.08	0.14	0.24	0.21	0.12	0.11	0.23
Energy balance	0.33*	0.32*	0.19	0.11	0.38**	0.02	0.17	0.17	0.03	0.14	0.12	0.05	0.53	0.52	0.21	0.01	0.18	0.02
Energy (Kcal)	0.00	0.14	0.11	0.17	0.14	0.16	0.06	0.21	0.07	0.12	0.04	0.44**	0.54	0.59	0.10	0.14	0.13	0.02

Pearson's correlation was applied.
* P<0.05, ** P<0.01, considered statistically significant.

Table 3. Associations between Energy Intake and metabolic syndrome markers (BMI, central obesity, and hypertension) in different FTO alleles.

		Genotype Information					
		TT		AA		AT	
		Adequate energy ≤100%	Excess Energy ≥100%	Adequate energy ≤100%	Excess energy ≥100%	Adequate energy ≤100%	Excess energy ≥100%
BMI categories	Overweight	95.8%	93.1%	86%	97.8%	83.3%	94.9%
	Non-overweight	4.2%	6.9%	14%	2.2%	16.7%	5.1%
	P-value	0.66		0.04*		0.15	
Central obesity	Normal	17.4%	10.7%	34.2%	13.3%	22.2%	11.4%
	Central obesity	82.6%	89.3%	65.8%	86.7%	77.8%	88.6%
	P-value	0.49	0.02*	0.29			
Hypertension	Hypertensive	12.5%	34.5%	37.2%	57.8%	61.1%	51.3%
	Non-hypertensive	87.5%	65.5%	62.8%	42.2%	38.9%	48.7%
	P-value	0.06		0.05		0.48	

Overweight; BMI>23
Non-overweight; BMI<23
Hypertension; 130/85 mmHg
Chi-square was performed for group comparisons.
* P<0.05, ** P<0.01, considered statistically significant.

FTO on BMI, especially in old age. Many other studies have reported similar results about the relation of dietary factors with obesity (25). In a previous study, a strong association between FTO variant and Type 2 diabetes in South Asians was reported. The clinical results of the current study are based on a diet-disease relationship with risk alleles AA, protective alleles TT and heterozygous alleles AT. The FTO genotype effect through adiposity was not reported to have an impact on insulin resistance and diabetes (26). In another randomized long-term dietary intervention case study, the influence of FTO genetic variance along with dietary macronutrients was observed on alteration in insulin resistance. An association of energy and macronutrient intake along with other clinical factors was observed among subgroups type-2 diabetes with various FTO gene alleles. Minor yet statistically significant differences were found to be associated with FTO genotype in the sources of dietary energy intake. It was observed that the individuals carrying the FTO risk allele consumed significantly higher proportions of dietary energy from fats and proteins. It was also found that FTO linked with BMI and waist circumference are the key indicators of metabolic syndrome mainly CVD. The impact of increased BMI on public health has been reported as an increment of one unit is associated with an 8% increase in the risk of coronary heart disease, which is more prominent in younger age as it increases the overall risk of death (27). The physical inactivity in South East Asians (17%) was reported to be about half to that of the Europeans (34.8%) (28). This results in developing obesity in physically inactive individuals as compared to physically active ones. The positive correlation between FTO gene and a high fiber intake on lowering BMI and waist circumference was reported in this study. The subjects who generally consume low dietary fibers have increased BMI. In another study, it was reported that FTO expression is decreased by glucose and amino acid deprivation, implying the role of FTO in sensing of

Table 4. Associations between carbohydrate and protein intake with metabolic syndrome markers (BMI, central obesity, and hypertension) in different FTO alleles.

		Genotype information								
		TT			AA			AT		
		Carbohydrate adequacy (%)			Carbohydrate adequacy (%)			Carbohydrate adequacy (%)		
		Low	Med	High	Low	Med	High	Low	Med	High
		>50% E	50–60%E	>60%E	>50% E	50–60%E	>60%E	>50% E	50–60%E	>60%E
BMI categories	Over weight	94.1%	94.1%	100%	91.7%	95%	83.3%	89.5%	91.4%	100%
	Non-overweight	5.9%	5.9%		8.3%	5.0%	16.7%	10.5%	8.6%	
	P-value		0.94			0.42			0.83	
Central obesity	Normal	18.8%	12.1%	0%	12.1%	28.2%	36.4%	17.6%	15.2%	
	Central obesity	81.3%	87.9%	100.0%	87.9%	71.8%	63.6%	82.4%	84.8%	100.0%
	P-value		0.694			0.14			0.77	
Hypertension	Hypertensive	23.5%	26.5%	0	50.0%	52.5%	25.0%	63.2%	51.4%	33.3%
	Non-hypertensive	76.5%	73.5%	100.0%	50.0%	47.5%	75.0%	36.8%	48.6%	66.7%
			0.69			0.23			0.53	
		Protein adequacy (%)			Protein adequacy (%)			Protein adequacy (%)		
		<.8 g/k	.8–1 g/K	>1 g/K	<.8 g/k	.8–1 g/K	>1 g/K	<.8 g/k	.8–1 g/K	>1 g/K
BMI categories	Over weight	0%	0%	15.8%	0%	0%	21.2%	3.6%	0%	33.3%
Central obesity	Non-overweight	100%	100%	84.2%	100%	100%	78.8%	96.4%	100%	66.7%
	P-value		0.05			0.00**			0.00**	
	Normal	4.8%	8.3%	27.8%	12.9%	9.5%	41.9%	11.1%	7.7%	33.3%
	Central obesity	95.2%	91.7%	72.2%	87.1%	90.5%	58.1%	88.9%	92.3%	66.7%
	P-value		0.09			0.00*			0.13	
Hypertension	Yes	57.1%	76.9%	94.7%*	40.6%	40.9%	69.7%	32.1%	56.3%	58.3%
	No	42.9%	23.1%	5.3%	59.4%	59.1%	30.3%	67.9%	43.8%	41.7%
	P-value		0.02*			0.03*			0.16	

Overweight; BMI>23
Non-overweight; BMI<23
Hypertension; 130/85 mmHg
E; energy.
Chi-square was performed for group comparisons.
* P<0.05, ** P<0.01, considered statistically significant.

cellular nutrients (29). In this study, the observed rates of obesity or overweight were similar in FTO variants while diet-disease relationships were found to be different. In this study, FTO risk alleles (AA) were observed to be more responsive to dietary changes than other variants (30). The reduction in food-craving response to a high-protein diet intake is also associated with the FTO A allele. This suggests a greater promise for dietary interventions for controlling certain complication in type-2 diabetics with AA genotype. Further research is needed to understand the sensitivity of AA genotype toward dietary requirements and its influence on metabolic response to energy and macronutrient intakes. The current study has shown that the effect of the *FTO* gene can be modulated by the intake of carbohydrate and dietary fibers. It also suggests a more pronounced influence of SNP in subjects who also consume high carbohydrate and dietary fibers. in a large amount.

Conclusion

Genetic profiles are likely to affect both the dietary pattern and the relationship between diet and metabolic syndrome markers. This study concluded that the association between diet and disease is more pronounced in the high-risk genotype AA compared to protective genotype TT and heterozygous genotype AT.

Limitations

Inadequate sample size and simple sampling with a single dietary data input are the major limitations of this study. The limited number of subjects from a single tertiary care unit without a control population further added to the disadvantages. This could put limits on real implications and the effect the generalizability of this study. However, with limited reported data from this part of the world on genetic influence and data from the current research will be incremental for future studies accounting all these shortfalls.

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gineering (KIBGE), the University of Karachi for facilitating the DNA analysis at their institute.

Ethics

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was also obtained from the Institutional Review Board (IRB) of Baqai Institute of Diabetology and Endocrinology, Baqai Medical University.

Author Contributions

Idea/Concept: Asher Fawwad, Iftikhar Ahmed Siddiqui, Abdul Basit; Design: Asher Fawwad, Iftikhar Ahmed Siddiqui, Abdul Basit; Control/Supervision: Asher Fawwad; Data Collection and/or Processing: Asher Fawwad, Fariha Shaheen, Rubina Hakeem, Syeda Nuzhat Nawab; Analysis and/or Interpretation: Fariha Shaheen, Rubina Hakeem, Syeda Nuzhat Nawab, Asher Fawwad; Literature Review: Asher Fawwad, Nazish Waris, Fariha Shaheen; Writing the Article: Asher Fawwad, Nazish Waris, Fariha Shaheen, Rubina Hakeem; Critical Review: Syed Muhammad Shahid, Asher Fawwad, Abdul Basit, Iftikhar Ahmed Siddiqui; References and Fundings: Nazish Waris; Materials: Asher Fawwad, Syeda Nuzhat Nawab.
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References

1. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, Najjar S, Nagaraja R, Orrú M, Usala G, Dei M, Lai S, Maschio A, Busonero F, Mulas A, Ehret GB, Fink AA, Weder AB, Cooper RS, Galan P, Chakravarti A, Schlessinger D, Cao A, Lakatta E, Abecasis GR. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet. 2007;3:e115.
2. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007;316:889-894.
3. Hinney A, Nguyen TT, Scherag A, Friedel S, Brönner G, Müller TD, Grallert H, Illig T, Wichmann HE, Rief W, Schäfer H, Hebebrand J. Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. PLoS One. 2007;2:e1361.
4. Moore SC, Gunter MJ, Daniel CR, Reddy KS, George PS, Yurgalevitch S, Devasenapathy N, Ramakrishnan L, Chatterjee N, Chanock SJ, Berndt SI, Mathew A, Prabhakaran D, Sinha R. Common genetic variants and central adiposity among Asian-Indians. Obesity (Silver Spring). 2012;20:1902-1908.
5. Okada Y, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N, Maeda S, Wen W, Dorajoo R, Go MJ, Zheng W, Kato N, Wu JY, Lu Q, Tsunoda T, Yamamoto K, Nakamura Y, Kamatani N, Tanaka T. Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. Nat Genet. 2012;44:302-306.
6. Vasan SK, Fall T, Neville MJ, Antonisamy B, Fall CH, Geethanjali FS, Gu HF, Raghupathy P, Samuel P, Thomas N, Brismar K, Ingelsson E, Karpe F. Associations of variants in FTO and near MC4R with obesity traits in South Asian Indians. Obesity (Silver Spring). 2012;20:2268-2277.
7. Fawwad A, Siddiqui IA, Basit A, Zeeshan NF, Shahid SM, Nawab SN, Siddiqui S. Common variant within the FTO gene, rs9939609, obesity and type 2 diabetes in population of Karachi, Pakistan. Diabetes Metab Syndr. 2016;10:43-47.
8. Karns R, Viali S, Tuitele J, Sun G, Cheng H, Weeks DE, McGarvey ST, Deka R. Common variants in FTO are not significantly associated with obesity-related phenotypes among Samoans of Polynesia. Ann Hum Genet. 2012;76:17-24.
9. Li H, Kilpeläinen TO, Liu C, Zhu J, Liu Y, Hu C, Yang Z, Zhang W, Bao W, Cha S, Wu Y, Yang T, Sekine A, Choi BY, Yajnik CS, Zhou D, Takeuchi F, Yamamoto K, Chan JC, Mani KR, Been LF, Imamura M, Nakashima E, Lee N, Fujisawa T, Karasawa S, Wen W, Joglekar CV, Lu W, Chang Y, Xiang Y, Gao Y, Liu S, Song Y, Kwak SH, Shin HD, Park KS, Fall CH, Kim JY, Sham PC, Lam KS, Zheng W, Shu X, Deng H, Ikegami H, Krishnaveni GV, Sanghera DK, Chuang L, Liu L, Hu R, Kim Y, Daimon M, Hotta K, Jia W, Kooner JS, Chambers JC, Chandak GR, Ma RC, Maeda S, Dorajoo R, Yokota M, Takayanagi R, Kato N, Lin X, Loos RJ. Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. Diabetologia. 2012;55:981-995.
10. Kong X, Xing X, Hong J, Zhang X, Yang W. Genetic variants associated with lean and obese type 2 diabetes in a Han Chinese population: a case-control study. Medicine (Baltimore). 2016;95:e3841.
11. Sanghera DK, Ortega L, Han S, Singh J, Ralhan SK, Wander GS, Mehra NK, Mulvihill JJ, Ferrell RE, Nath SK, Kamboh MI. Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: PPARG2 (Pro12Ala), IGF2BP2, TCF7L2 and FTO variants confer a significant risk. BMC Med Genet 2008;9:59.
12. Rees SD, Islam M, Hydrie MZ, Chaudhary B, Bellary S, Hashmi S, O'Hare JP, Kumar S, Sanghera DK, Chaturvedi N, Barnett AH, Shera AS, Weedon MN, Basit A, Frayling TM, Kelly MA, Jafar TH. An FTO variant is associated with Type 2 diabetes in South Asian populations after accounting for body mass index and waist circumference. Diabet Med. 2011;28:673-680.
13. El-Sohemy A. Nutrigenetics. Forum Nutr. 2007;60:25-30.
14. Qi Q, Downer MK, Kilpelainen TO, Taal HR, Barton SJ, Ntalla I, Standl M, Boraska V, Huikari V, Kiefte-de Jong JC, Körner A, Lakka TA, Liu G, Magnusson J, Okuda M, Raitakari O, Richmond R, Scott RA, Bailey ME, Scheuermann K, Holloway JW, Inskip H, Isasi CR, Mossavar-Rahmani Y, Jaddoe VW, Laitinen J, Lindi V, Melén E, Pitsiladis Y, Pitkänen N, Snieder H, Heinrich J, Timpson NJ, Wang T, Yuji H, Zeggini E, Dedoussis GV, Kaplan RC, Wylie-Rosett J, Loos RJ, Hu FB, Qi L. Dietary intake, FTO genetic variants, and adiposity: a combined analysis of over 16,000 children and adolescents. Diabetes. 2015;64:2467-2476.
15. Loria-Kohen V, Espinosa-Salinas I, Marcos-Pasero H, Lourenço-Nogueira T, Herranz J, Molina S, Reglero G, Ramirez de Molina A. Polymorphism in the CLOCK gene may influence the effect of fat intake reduction on weight loss. Nutrition. 2016;32:453-460.
16. Fawwad A, Siddiqui IA, Basit A, Zeeshan NF, Shahid SM, Nawab SN, Siddiqui S. Common variant within the FTO gene, rs9939609, obesity and type 2 diabetes in population of Karachi, Pakistan. Diabetes Metab Syndr. 2016;10:43-47.
17. Shim JS, Oh K, Kim HC. Dietary assessment methods in epidemiologic studies. Epidemiol Health. 2014;36:e2014009.
18. World Health Organization. The Asia-Pacific perspective, redefining obesity and its treatment. International Diabetes Institute, Health Communications Australia Pvt. Ltd; 2000:50 (Last reviewed December 06, 2016).
19. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. Belgium: International Diabetes Federation; 2006:24 (Last reviewed December 06, 2016).

20. American Diabetes Association. Standards of medical care in diabetes--2008. Diab Care. 2008;31:S12-54.
21. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51:241-247.
22. Lee HJ, Kim IK, Kang JH, Ahn Y, Han BG, Lee JY, Song J. Effects of common FTO gene variants associated with BMI on dietary intake and physical activity in Koreans. Clin Chim Acta. 2010;411:1716-1722.
23. McCaffery JM, Papandonatos GD, Peter I, Huggins GS, Raynor HA, Delahanty LM, Cheskin LJ, Balasubramanyam A, Wagenknecht LE, Wing RR. Obesity susceptibility loci and dietary intake in the Look AHEAD Trial. Am J Clin Nutr. 2012;95:1477-1486.
24. Brunkwall L, Ericson U, Hellstrand S, Gullberg B, Orho-Melander M, Sonestedt E. Genetic variation in the fat mass and obesity-associated gene (FTO) in association with food preferences in healthy adults. Food Nutr Res. 2013;57:20028.
25. Moleres A, Ochoa MC, Rendo-Urteaga T, Martínez-González MA, Azcona San Julián MC, Martínez JA, Marti A; GENOI. Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case-control study of children. Br J Nutr. 2012;107:533-538.
26. Bressler J, Kao WH, Pankow JS, Boerwinkle E. Risk of type 2 diabetes and obesity is differentially associated with variation in FTO in whites and African-Americans in the ARIC study. PLoS One. 2010;5:e10521.
27. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006;355:763-778.
28. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012;380:247-257.
29. Gulati P, Cheung MK, Antrobus R, Church CD, Harding HP, Tung YC, Rimmington D, Ma M, Ron D, Lehner PJ, Ashcroft FM, Cox RD, Coll AP, O'Rahilly S, Yeo GS. Role for the obesity-related FTO gene in the cellular sensing of amino acids. Proc Natl Acad Sci U S A. 2013;110:2557-2562.
30. de Luis DA, Aller R, Izaola O, Primo D, Urdiales S, Romero E. Effects of a high-protein/low-carbohydrate diet versus a standard hypocaloric diet on weight and cardiovascular risk factors: role of a genetic variation in the rs9939609 FTO gene variant. J Nutrigenet Nutrigenomics. 2015;8:128-136.