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Original Article

Correlation between polymorphism of FTO gene and type 2 diabetes mellitus in Uygur people from northwest China

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Abstract: Background: To explore the correlation between FTO (fat mass and obesity associated) gene, which is associated with 3 single nucleotide polymorphisms (SNP) of fat mass and obesity, type 2 diabetes and body mass index (BMI) in the Uygur population in northwest China. Methods: A total of 849 Uygur patients with type 2 diabetes mellitus were selected from the hospitalized patients in the First Affiliated Hospital of Xinjiang Medical University, the First People's Hospital of Kashi and the hospitals in the Turpan areas. At the same time, 873 cases of healthy persons who conducted a medical checkup in the physical examination centre of the above hospitals were enrolled as controls. The present investigation used the case-control research method, and physical examination and biochemical index determination were carried out. The Sequenom MassARRAY technology was employed in the detection of 3 SNP loci of the FTO gene. The representative population of each SNP in the control group was analyzed by Hardy-Weinberg law. The differences of each clinical parameter in the two groups were analyzed by t-test analysis. The differences of genotype and allele of each SNP in the two groups were analyzed by χ^2 test. Results: BMI, waistline (WL), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), total cholesterol (TC), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the type 2 diabetes group were higher than those in the control group, while the high density lipoprotein (HDL) and low density lipoprotein (LDL) were lower than those of the control group; 2. The allele frequency of A of rs8050136 and rs9939609 in the type 2 diabetes mellitus group was higher than that of the control group. The BMI of the whole population and type 2 diabetes group with genotype C/A+A/A of rs8050136 was higher than that in C/C group, and the BMI with genotype T/A+A/A of rs9939609 was higher than that in group T/T. Stratification was conducted on BMI according to the normal, overweight and obesity criteria. There were significant differences in the distribution of genotype frequency of rs9939609 in the type 2 diabetes group and the control group of the normal BMI group. Conclusion: Single nucleotide mutation of rs7195539 in FTO gene may be a protective factor against the Uygur type 2 diabetes. Single nucleotide mutations of rs8050136 and rs9939609 may be associated with the Uygur type 2 diabetes and obesity, with A as a potential risk allele. The gene polymorphism of rs8050136 may correlate with type 2 diabetes mellitus through the function of BMI, while the correlation between rs9939609 gene polymorphism and type 2 diabetes is not depending from BMI.

Keywords: FTO, gene polymorphism, type 2 diabetes, Uygur

Introduction

Type 2 diabetes is considered as a complex disease caused by a combination of genetic and environmental factors, of which the genetic factors play a vital role in the pathogenesis of type 2 diabetes. There are a total of 92.4 million adult diabetic people in China [1]. Obesity is a major risk factor for type 2 diabetes mellitus, and the genetic variation influencing obesity may also affect the onset of type 2 diabetes. In 2007, Frayling et al. discovered in the genome-wide association study (GWAS) on the susceptibility genes of type 2 diabetes mellitus, that there was a strong correlation between the sequence variation of the FTO gene located on chromosome 16 on the one hand and BMI, obesity and type 2 diabetes in European Caucasians on the other [2]. Subsequently, several research groups demonstrated that the common varia-

tion of FTO gene was correlated with type 2 diabetes independently of BMI in various populations [3-7]. Many SNPs of FTO gene were correlated with type 2 diabetes mellitus, but the results were different in different populations studied [2-4, 7-13]. The daily lifestyle and food habits of the Uygur people are different from those of the Han population. Furthermore, the contents of protein and fat in the diet of Uygur people are high, and the population shows a large number of overweight and obese people. Since abdominal obesity is largely diffused in the Uygur type 2 diabetic patients, the objective of the present study was to investigate the distribution characteristics of 3 SNPs of the FTO gene in the Uygur people of Xinjiang to investigate the correlation between the FTO gene polymorphism, Uygur type 2 diabetes and obesity, providing scientific basis for a future prevention and treatment of Uygur patients with type 2 diabetes mellitus.

Materials and methods

Patients

A total number of 849 Uygur patients with type 2 diabetes mellitus, 530 male and 319 female with mean age of 51.30 ± 9.84, were selected from the First Affiliated Hospital of Xinjiang Medical University, the First People's Hospital of Kashi and the hospitals in the Turpan areas, during the period between March 2012 and September 2013. In addition, a total number of 873 healthy Uygur people, 557 male and 316 female with mean age of 50.44 ± 9.94, without any kinship and diabetes, who conducted medical checkup in the above mentioned hospitals during the same period of time, were employed as controls. There was no significant difference of age and gender in the diabetic group and in the control group. All the recruited subjects filled informed consents before participating in this study, and the research program has been approved by the ethics committee of the First Affiliated Hospital of Xinjiang Medical University.

The diagnosis criteria of diabetes used in the present investigation were consistent with the criteria applied by the World Health Organization (WHO) in 1999 and in previous years, to diagnose type 2 diabetes [14]. The recruited subjects were divided into 3 groups according to the Guidelines for the prevention and control of the Chinese adult overweight and obesity: normal group: BMI < 24 kg/m^2; overweight group: 24 kg/m^2 ≤ BMI < 28 kg/m^2; obesity group: BMI ≥ 28 kg/m^2 [15].

Research methods

Physical examinations such as height, weight, waist circumference, systolic and diastolic blood pressure, were carried out on all the subjects. Family and current disease history were asked and reported in details. All the research subjects were fasted for 8 hours. Four mL fasting venous blood was collected for anticoagulation and non-anticoagulation analysis. Blood serum was separated in 2 hours at 3500 rpm, and biochemical indexes such as Scr, UA, FPG, TG, TC, HDL, LDL, AST and ALT were measured. The above indexes were examined and analyzed by the Hitachi 7600 automatic biochemical analyzer in the First Affiliated Hospital of Xinjiang Medical University laboratory, and quality control was qualified. Anticoagulant venous blood was divided into EP tubes and stored in the -80°C refrigerator for further DNA extraction, avoiding a frequent freeze-thaw procedure.

The DNA of the peripheral blood was extracted by the automatic extraction instrument of the Beijing hundred Taike Biotechnology Co. Ltd., and the specific operation steps were consistent with the nucleic acid automatic extraction instrument method. The extracted DNA of the whole blood genome was analyzed by 1% agarose gel electrophoresis, and the concentration and DNA degradation degree were subsequently estimated. The DNA A260/A280 ratio (OD) obtained by Quality inspection was in the range of 1.8-2.0, with a DNA concentration of more than 50 ng/uL and good quality gel electrophoresis bands. This DNA was thus perfect to be subsequently used. The samples were then transferred to 96-well plates and stored at -20°C for further analysis.

All the 3 SNPs of the FTO gene were investigated by the analysis of the hotspot in SNP, function candidate SNP and labeled SNP including rs7195539, rs7203521, rs8050136, rs9939609. The detection of SNPs was carried out by the Beijing CapitalBio Corporation by using Sequenom MassARRAY RSNP technology. The success rate and accuracy rate of genotyping in this study was more than 98%.

Table 1. Comparison of various clinical indexes in the type 2 diabetes group and in the control group

Variable	Control	Case	*P*
Sex (M/F)	557/316	530/319	0.554
Age	50.44 ± 9.94	51.30 ± 9.84	0.072
BMI (kg/m^2)	27.04 ± 3.93	28.34 ± 4.70	< 0.001
WL (cm)	95.70 ± 10.15	99.46 ± 11.11	< 0.001
SBP (mmHg)	123.10 ± 18.31	126.69 ± 18.97	0.001
DBP (mmHg)	77.38 ± 12.58	78.81 ± 11.72	0.037
Scr (umol/L)	70.82 ± 18.55	68.79 ± 49.71	0.269
UA (umol/L)	282.12 ± 69.17	273.34 ± 134.87	0.093
FPG (mmol/L)	4.95 ± 0.82	9.25 ± 3.67	< 0.001
TG (mmol/L)	2.46 ± 1.98	2.40 ± 2.07	0.596
TC (mmol/L)	4.31 ± 1.70	4.63 ± 1.36	< 0.001
HDL (mmol/L)	1.25 ± 0.33	0.94 ± 0.32	< 0.001
LDL (mmol/L)	2.99 ± 0.81	2.81 ± 0.90	< 0.001
AST (U/L)	21.94 ± 18.18	24.82 ± 29.87	0.019
ALT (U/L)	29.30 ± 34.33	35.20 ± 52.66	0.011

Statistical analyses

SPSS 21.0 statistical software was used in the current research. The Hardy-Weinberg equilibrium in the control group was used to evaluate whether statistical sampling are representative of the population. Data were expressed as mean ± standard deviation. After normalizing the values, *t*-test was used for two groups' comparison and one-way ANOVA was used for multiple groups' comparison. χ^2 test was used for the comparison of the enumerated data, the genotype and allele frequency of each SNP in two groups and genotype and allele frequencies between groups. $P < 0.05$ was considered statistically significant.

Results

Various clinical indexes in the type 2 diabetes group and in the control group

There was no significant difference in gender and age between the type 2 diabetes group and the control group (P = 0.554, 0.072). There was no significant difference in Scr and UA between the two groups (P = 0.269, 0.093). BMI, WL, SBP, DBP, FPG, TC, AST and ALT in type 2 diabetes group were higher than those of the control group, although HDL and LDL were lower than those of the control group ($P < 0.05$) (**Table 1**).

Genotype and allele frequency distribution of each SNP in the type 2 diabetes mellitus group and in the control group

The genotype distribution of each SNP in the control group was in accordance with Hardy-Weinberg balance ($P > 0.05$). The genotype and allele frequency distributions of each SNP in the two groups are illustrated in **Figure 1** and **Table 2**. Significant differences in genotype distribution of rs7195539 and rs9939609 in the two groups (P = 0.015, 0.025) were found. The A allele frequency of rs8050136 and rs9939609 in the type 2 diabetes mellitus group was higher than that in the control group (P = 0.027, 0.006).

Genotype distribution of each SNP in two groups with different BMI levels, and comparison of BMI (kg/m^2) of each SNP with different genotypes

After stratification of BMI according to normal, overweight and obesity, significant differences were found in the distribution frequency of rs9939609 genotype in the type 2 diabetes subgroup and in the control subgroup both belonging to the normal BMI group (P = 0.044) (**Table 3**). The BMI of the group with C/A+A/A genotype of rs8050136 in the whole population and type 2 diabetes group was bigger than that of C/C group ($P < 0.05$), and the BMI of the group with T/A+A/A genotype of rs9939609 was higher than that of T/T group ($P < 0.05$) (**Table 4**).

Discussion

FTO gene is a gene related to fat mass and obesity discovered in white race by Frayling et al. [2] in 2007. This gene is located on chromosome 16q12.2, possesses a total length of about 430 kb and contains 9 exons and 8 introns. The encoded product of the FTO gene is a member of the non-heme dioxygenase superfamily [16], which is highly similar to *Escherichia coli* ALKB enzyme and human ABH family. Mouse FTO protein also possesses similar double stranded β-folding structure, which contains 4 conserved residues that can interact with Fe^{2+} and 2-oxoglutarate [17], both important for the function of the FTO protein. 2-ketoglutaric acid oxygenase is involved in

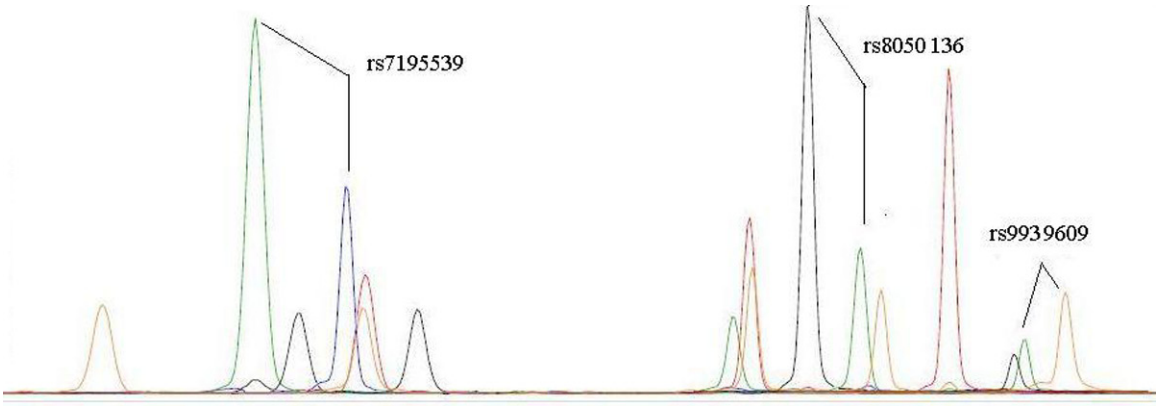

Figure 1. rs9939609, rs8050136, rs7195539 genotype in the type 2 diabetes mellitus group. Note: (ddGTP = blue peak; ddATP = green peak; ddTTP = red peak; ddCTP = black peak).

Table 2. Genotype and allele frequency distribution of each SNP in the type 2 diabetes mellitus group and in the control group

SNP	Group	Genotype n (%)			HWE *P*	*P value*	Allele n (%)		*P value*	OR (95% CI)
rs7195539		A/A	A/G	G/G			A	G		
	Control	787 (90.1)	85 (9.7)	1 (0.1)	0.404	0.015	1659 (95.0)	87 (5.0)	0.226	1.220 (0.884-1.683)
	Case	785 (92.5)	58 (6.8)	6 (0.7)			1628 (95.9)	70 (4.1)		
rs8050136		C/C	C/A	A/A			C	A		
	Control	460 (52.7)	348 (39.9)	65 (7.4)	0.942	0.084	1268 (72.6)	478 (27.4)	0.027	1.181 (1.019-1.368)
	Case	409 (48.2)	357 (42.0)	83 (9.8)			1175 (69.2)	523 (30.8)		
rs9939609		T/T	T/A	A/A			T	A		
	Control	443 (50.7)	350 (40.2)	80 (9.2)	0.367	0.025	1236 (70.8)	510 (29.2)	0.006	1.225 (1.060-1.415)
	Case	382 (45.0)	364 (42.9)	103 (12.1)			1128 (66.4)	570 (33.6)		

HWE: Hardy-Weinberg equilibrium; OR: odd ratio; CI: confidence interval; HWE: Hardy-Weinberg equilibrium; OR: odd ratio; CI: confidence interval.

Table 3. Genotype distribution of each SNP in the type 2 diabetes mellitus group and in the control group with different BMI levels

SNP	Group	Control n (%)			Case n (%)			*P value*
		A/A	A/a	a/a	A/A	A/a	a/a	
rs7195539	Normal	136 (92.5)	11 (7.5)	0	112 (92.6)	9 (7.4)	0	0.989
	Overweight	280 (90.9)	27 (8.8)	1 (0.3)	239 (91.2)	22 (8.4)	1 (0.4)	0.982
	Obesity	252 (92.3)	21 (7.7)	0	390 (94.0)	21 (5.1)	4 (1.0)	0.052
rs8050136	Normal	80 (54.4)	58 (39.5)	9 (6.1)	70 (57.9)	36 (29.8)	15 (12.4)	0.089
	Overweight	167 (54.2)	118 (38.3)	23 (7.5)	121 (46.2)	116 (44.3)	25 (9.5)	0.153
	Obesity	142 (52.0)	103 (37.7)	28 (10.3)	195 (47.0)	180 (43.4)	40 (9.6)	0.335
rs9939609	Normal	75 (51.0)	60 (40.8)	12 (8.2)	65 (53.7)	36 (29.8)	20 (16.5)	0.044
	Overweight	159 (51.6)	119 (38.6)	30 (9.7)	113 (43.1)	118 (45.0)	31 (11.8)	0.128
	Obesity	140 (51.3)	105 (38.5)	28 (10.3)	185 (44.6)	186 (44.8)	44 (10.6)	0.206

Normal: BMI < 24 kg/m^2, Overweight: 24 kg/m^2 ≤ BMI < 28 kg/m^2. Obesity: BMI ≥ 28 kg/m^2. AA: wild type homozygote; Aa: heterozygote; aa: homozygous mutant.

many reactions such as DNA repair, fatty acid metabolism and post translational modification. Fe^{2+} uses oxygen as a cofactor. Rat recombinant FTO protein can catalyze demethylation of 3-methylthymidine in the single stranded DNA under conditions of Fe^{2+} and 2-oxoglutarate [18]. Fawcett et al. reported that the demethylation of FTO might regulate the

Table 4. Comparison of BMI (kg/m^2) of each SNP with different genotypes in the whole population, in the type 2 diabetes group and in the control group

SNP	Whole		Control		Case	
	A/A	A/a + a/a	A/A	A/a + a/a	A/A	A/a + a/a
rs7195539	27.77 ± 4.39	27.16 ± 4.52	27.08 ± 3.97	26.54 ± 3.46	28.38 ± 4.65	27.82 ± 5.37
rs8050136	27.31 ± 4.21	28.15 ± 4.55*	26.86 ± 3.86	27.24 ± 4.00	27.76 ± 4.49	28.89 ± 4.84*
rs9939609	27.38 ± 4.20	28.04 ± 4.55*	26.94 ± 3.86	27.14 ± 4.01	27.82 ± 4.49	28.78 ± 4.84*

AA: wild type homozygote; Aa: heterozygote; aa: homozygous mutant. *P < 0.05.

expression of genes related to some metabolic processes, and their dysregulation may be related to type 2 diabetes, although the specific molecular mechanism is still not clear [19]. Moreover, the mutation of FTO gene leads to a lack of control of the appetite and consequent morbid hunger, increased ingestion reflex, inhibition of metabolism and reduced energy consumption efficiency, all symptoms that may lead to obesity. Gerken et al. found a high expression of FTO mRNA in the brain tissues of wild mice, especially in the hypothalamic area where it reaches the highest concentration [18]. The hypothalamic area plays critical roles in the control of energy balance, thus indicating that the FTO gene may regulate the pathogenesis and development of obesity mainly through its effect on hypothalamic energy centre.

The present study shows that the levels of BMI, WL, SBP, DBP, FPG, TC, AST and ALT in the type 2 diabetes group were higher than those in the control group (P < 0.05), suggesting that type 2 diabetes was associated with abdominal obesity, hypertension, dyslipidemia, non-alcoholic fatty liver and other abnormal metabolism dysfunctions, which may be considered to be related to insulin resistance (IR). The HDL and LDL levels in Type 2 diabetes mellitus group were lower than those in the control group (P < 0.05), with no significant difference of TG between the two groups. These effects may be both associated with lipid regulating agents' treatment because of the combined dyslipidemia and atherosclerosis.

In the current research, the BMI of the genotype C/A+A/A of rs8050136 group in the whole population and the type 2 diabetes group was bigger than that of C/C group, and the level of BMI of the genotype T/A+A/A of rs9939609 group was higher than that of the T/T group (P < 0.05), indicating that the rs8050136 and rs9939609 gene polymorphism was correlated with the obesity of Uygur people, as it was confirmed in many studies [8, 3, 10, 20-22].

In the present study, the frequency of the A allele of rs8050136 was 29.1%, and the frequencies of the A allele of the Chinese and the Europeans in the HapMap database were 13.9% and 46% respectively. The frequency of the allele A of rs9939609 was 31.4%, and the frequencies of the Chinese and the Europeans in the HapMap database were 15% and 46%, suggesting that the rs8050136 and rs9939609 allele frequency risk in the Uygur people was between that of the Han population of China and the European population. Moreover, the genotype frequency distribution of rs8050136 and rs9939609 of FTO displayed racial and regional differences. The differences of gene frequency between the races may partly explain the different results obtained in the study of different races Furthermore, the interaction of gene-environment may be one of the causes of the distribution difference.

In summary, the single nucleotide mutation of rs7195539 in FTO gene may be a protective factor of Uygur type 2 diabetes. The single nucleotide mutations of rs8050136 and rs9939609 may be associated with the Uygur type 2 diabetes and obesity, with A as the risk allele. The correlation of the rs8050136gene polymorphism with type 2 diabetes mellitus may be mediated by BMI, while the association between rs9939609 gene polymorphism and type 2 diabetes is not depending from BMI.

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Disclosure of conflict of interest

None.

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