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Research Article

ASSOCIATION OF THE FTO GENE (rs9940128) POLYMORPHISM WITH LIPID PROFILE IN PATIENTS OF TYPE 2 DIABETES MILLETUS IN NORTH INDIAN POPULATION

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ARTICLE INFO	ABSTRACT
Article History: Received 15 th December, 2017 Received in revised form 25 th January, 2018 Accepted 23 rd February, 2018 Published online 28 th March, 2018 <i>Key Words:</i> Genotype, gene variant, phenotype, allele frequency, obesity.	 Aim: In this study we have investigated the association of FTO gene variants rs9940128 (intron 1), in type 2 diabetes milletus patients and controls of Kanpur population across regulatory region of the fat mass and obesity associated (FTO) gene with obesity. Methods: This study related to with subjects (n= 150) and control (n=150) normal glucose-tolerant were controls and 150 cases (T2DM with obesity were randomly chosen from the Kanpur urban rural areas. The genomic DNA was isolated with Qaigen kit method. Genotyping was completed by the polymerase chain reaction polymorphism method, and 25% of samples were sequenced to authenticate the genotypes found. Results: The polymorphisms rs9940128 A/G of the FTO gene was associated with T2DM in our study population. The rs9940128 C/A variant was associated with obesity, and its association with obesity in the total study subjects, but when the NGT subjects alone were analyzed, the association with obesity was lost. The haplotype ACCTCT confers a lower risk of T2DM in this Kanpur population. Conclusions: The Kanpur population, the rs9940128 A/G, variants of the FTO gene were associated with T2DM, and similarly the rs9940128 C/A variant are also connected with obesity

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INTRODUCTION

The disease type 2 diabetes mellitus is painstaking and mainly governed by an amalgamation of genetic and environmental factors. Genetic factors are playing a crucial role in the pathogenesis of type 2 diabetes. There are around 50 million diabetic people are found in India (1). Obesity is a foremost risk factor for type 2 diabetes mellitus, and the genetic variation influencing obesity may also influence the beginning of type 2 diabetes. Frayling et al., 2007 has been observed the genome wide relationship study on the genes of type 2 diabetes mellitus and found that there was a strong association between the sequence variation of the FTO gene positioned on chromosome 16 on the one hand and BMI, obesity and type 2 diabetes mellitus in Indian population (2). Afterward, many researchers have confirmed that the common variation of FTO gene was interrelated with type 2 diabetes mellitus and BMI in the different populations (3). Several SNPs of FTO gene were associated with type 2 diabetes mellitus, but the results were

found different in different populations (4). The daily lifestyle and food habits of the Kanpur population are different from those of the USA population. Additionally, the contents of protein and fat in the diet of Kanpur persons are high, and the population has contained a large number of overweight persons. Because abdominal obesity is greatly found in the Kanpur type 2 diabetic patients.

During the last few years there are several studied have been conducted at genetic level to know the cause of FTO gene association with obesity and type 2 diabetes. It has been mentioned in the literature that at least 75 independent genetic loci of TCF7L2, PPARG, KCNJ11 and FTO genes are responsible for type 2 diabetes mellitus (5). Among above mentioned genes the *FTO* gene was found considerably coupled with the risk of type 2 diabetes mellitus (6). Fat mass and obesity linked protein, also famous as alpha-ketoglutarate-dependent dioxygenase, is an enzyme encoded by the *FTO* gene found on chromosome 16 of human being. Many

researchers have been also identified about 10 different FTO SNPs in the first intron of the gene, which connected to both BMI and type-2 diabetes mellitus.

The type 2 diabetes mellitus can found at any ages of peoples. In some patients the disease has been recorded at a young age, in some middle age, and in some after 60 years. It has already mentioned in literature that the polymorphisms in the gene FTO are perform an important role in the expansion of type-2 diabetes mellitus.

The objective of the present study was to explore out the diversity of the FTO gene SNP rs9940128 in the Kanpur people to inspect the correlation between the FTO gene polymorphism, Kanpur type 2 diabetes mellitus and obesity. The future aspect of this study is to give scientific method for the prevention and treatment of Kanpur patients with type 2 diabetes mellitus. This study was performing interestingly to find out the answer whether the polymorphism changes of the *FTO* gene is responsible for the development of type 2 diabetes mellitus in the patients of Kanpur.

MATERIALS AND METHODS

Sample size

A total number of 300 Kanpur patients with type 2 diabetes mellitus, 150 male and 150 female with mean age of 50.00±0.00, were collected from the Rama Medical College, Hospital & Research Centre, Kanpur (India), during the period between May 2016 and July 2017. The samples were collected randomly under the supervision of specialist team of doctors who performed medical checkup in the above mentioned hospitals during the same period of time. The collected samples were not having any significant difference of age and sex in both diabetic as well as in the control groups. All the participants were proper informed and written consents forms were filled before participating in this study. The study program was approved and affiliated by the ethics committee of the Rama Medical College, Hospital & Research Centre.

The pathogenesis of type 2 diabetes patients was followed in the present study as the procedure functional by the World Health Organization in 1999, to diagnose type 2 diabetes mellitus (7). The selected subjects (cases) were grouped into 3 categories as the rule and guidelines for the deterrence and control of the Indian obese and obesity; normal group have the BMI< 24 kg/m²; overweight group had BMI in between 24 kg/m²-28 kg/m²; and the obese group had BMI> 28 kg/m² (8).

Methods

All the parameters such as height, weight, waist circumference, systolic and diastolic blood pressure, were recorded from all the cases. Family and current disease history were aknowledged and recorded. Two ml fasting (8 hours) venous blood were taken in EDTA sterile vial for the molecular and biochemical analysis. Serum from the blood were isolated by centrifuge at 4000 rpm and conducted biochemical analysis such as estimation of uric acid, fasting plasma glucose, triacylglycerol, total cholesterol, high density lipoprotein, low density lipoprotein, low density lipoprotein, glutamic-pyruvic transaminase and glutamic oxalacetic transaminase were conducted. All the parameters mentioned above were estimated

by the Hitachi 7600 automatic biochemical analyzer Rama Medical College, Hospital & Research Centre.

The DNA were isolated from fresh blood (2ml) by using Qaigen kit following with standard protocol of user manual. Purity of DNA was checked on 1% agarose gel. The quantification of DNA was done with Nano drop (Thermo fisher). The absorbance of DNA ($A_{260/A280}$) ratio was estimated and found its value of the range of 1.8-2.0. The DNA concentration was found approximately 40ng/µl. This DNA was stored at -20°C for further analysis. Primers were got synthesized from Chromous Biotech Pvt. Ltd, Bangaluru. DNA were amplified with PCR (Bio-RAD) and the amplified DNA were separated with 1.2% agarose gel containing ethidium bromide. Gel photographs were documented in gel documentation system (Bio-RAD).

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 (SPSS, USA) in this study. Hardy-Weinberg equilibrium for genotypes was checked by χ^2 analysis for both cases and controls. Obesity and type 2 diabetes mellitus were estimated by logistic regression analysis assuming log-additive model. A P-value of <0.01 ($\alpha=0.05/5$) was measured significant after Bonferroni correction. All quantitative trait values were inverse normally transformed to achieve normal distribution and then analyzed using linear regression. Means and standard deviations are offered in inverse normal units of the parameters in the tables. For quantitative traits association, a P-value of <0.00053 ($\alpha=0.05/(5x19)$) was estimated up to significant level. Association with obesity and quantitative traits was performed only in control subjects. Meta-analysis of stage 1 and 2 results were performed by combining summary data of two study population both under fixed and random models. Similarly, the summary data of previous studies on Indians for association with type 2 diabetes mellitus (9) and this study were combined for meta-analysis. Association of variants with type 2 diabetes mellitus, obesity and quantitative traits were also conducted by mixing the data for two study population and adjusting for study population. Allele frequencies of cases and controls of two study population were compared by equality of proportions Z-test. All the data analyses were accustomed for age, sex and BMI as necessary. The odds ratio (OR) and 95% confidence interval (CI) were considered for the study.

RESULTS

In this study different clinical parameters of the type 2 diabetes mellitus were estimated. There was no significant difference observed in sex and age between the type 2 diabetes mellitus cases and the controls. There was no any significant difference observed in the uric acid between the cases and the controls. BMI, waist length, systole blood pressure, diasystol blood pressure, glutamic-pyruvic transaminase and glutamic oxalacetic transaminase 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). Clinical and biochemical parameters: The clinical and biochemical data was obtained and represented on the (Table 1). The clinical parameters such as BMI, waist circumference, fasting plasma glucose, and systolic and diastolic blood pressures were having significant P value <0.0001, which was found significantly greater in cases as compared to controls. Involvement of FTO gene polymorphisms with type 2 diabetes was demonstrated the genotype and allele frequencies of the selected FTO SNP (rs9940128) in the study population. The genotype frequencies of the FTO gene in cases with type 2 diabetes were found in Hardy-Weinberg equilibrium. The rs9940128 A/G gene polymorphism of the FTO gene was recorded significant involvement with type 2 diabetes mellitus, and the AG genotype was noted significantly higher in type 2 diabetes mellitus and obesity. The frequency of the GG alleles was initiated higher significantly in type 2 diabetes mellitus cases (P<0.0001). Logistic regression analysis was applied for AG and GG genotypes with respect to AA, which was assume as a reference genotype. Association of FTO gene polymorphisms with obesity was demonstrated the genotype and allele frequencies of the FTO SNP (rs9940128) with obesity. The frequencies of the alleles was also found significantly for obesity cases (P<0.0001).

To estimate the effect of the genotypes on the disease, logistic regression analysis was performed. The comparison between the AG and GG genotypes gained an unadjusted OR of 1.69, which was statistically significant (0.021), furthermore significance was retained after adjusting for age, sex, and diabetes. When we compared the AA genotype with the GG genotype, the OR remained significant, conferring 1.50 times higher risk towards obesity, even after adjusting for age, sex, and diabetes.

Thus genotype and allele frequencies of the rs9940128 A/G polymorphisms were found significantly higher difference between the obese and non-obese patients.

Table 1 General characteristics of the populations

S.N.	Characteristics	Type 2 diabetes mellitus	Control	P -value
1.	No.	150	150	< 0.0001
2.	Sex (M/F)	75/75	75/75	< 0.0001
3.	Age (years)	≥30	≥ 30	< 0.0001
4.	Diabetic record time (years)	11.4±7.4	-	-
5.	BMI (kg/m2) (M/F)	21.75±2.2/24.46±1.5	22.27±1.6/26.71±1.5	0.722
6.	Waist circumference (cm) (M/F)	80.16±2.4/89.11±2.6	87.56±4.3/89.91±6.8	0.05
7.	Fasting Plasma Glucose (mmol/l)	7.90±5.4	5.49±0.27	< 0.0001
8.	2-h Post Plasma Glucose (mmol/l)	14.6±2.4	5.84±0.4	< 0.0001
9.	Fasting Plasma Insulin (pmol/l)	12.21±4.8	32.90±7.6	< 0.0001
10.	HbA1c (%)	8.28±2.7	4.90±0.9	< 0.0001
11.	Total cholesterol (nmol/l)	4.47±1.7	4.58±1.5	< 0.0001
12.	Urea (mmol/l)	9.65±3.7	8.70 ± 2.8	< 0.0001
13.	Uric acid (mmol/l)	290.66±2.7	291.23±1.9	< 0.0001
14.	Creatinine (mmol/l)	76.88±6.1	67.80±1.6	< 0.0001
15.	Systolic BP (mmHg)	133±3.7	121±2.12	< 0.0001
16.	Diastolic BP (mmHg)	80±3.4	79±1.99	< 0.0001
17.	Triglycerides (mmol/l)	1.59±3.8	1.31±8.8	< 0.0001
18.	hsCRP (mg/l)	2.30±1.1	1.26 ± 2.9	< 0.0001
19.	C-peptide (nmol/l)	0.95±1.6	50.99±3.6	< 0.0001

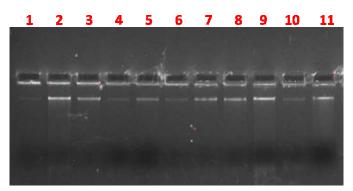


Fig 1 Isolated DNA from whole blood by Qaigen kit method.



Fig 2 DNA amplification with PCR and 100 bp ladder.

ACTGAGATAAGAAAACTGAGGACGAAGCAGGTCTGG GGTGAATCAGGTGCTATCCCTTTGGACAGTCACATGA CTGGTGTCTGTTCAGCACCCAAGGGACCATCAAAGAG GCTGTTGTGGAGAGGGAATCCGAAGGTCAGGGCCAG AGATAGAAATCTGGGGAGTCATCCACTATATAGGTGA TGGGTTAAAGCCTTAGAACTCTTCTTTTCATGAATCAT TGTTGTTCTTTAGGTTGTAATGAAGTTTTAGGCCTCAG CTTCCCTGAACTGGAGTGTTTTTCCTTCACCTTTTCCG GTCTCTGGGTTGCATCGCCAGACTGTCTCTAAGCCCA ACAAACGCGTTCCTTCCAGGCAAAAGCAGGAGATGA CACACACCATGAGCCAGATTTTCCATGGCA

Fig 3 Partial FTO gene sequences of *Homo sapiens, FTO* gene variant after PCR and gene sequencing, the fragment size was originated 400 bp.

 Table 2 List of primers and their Tm used for DNA amplification

S.N.	Primers sequences	Tm (°C)
1.	5'-ACTGAGATAAGAAAACTGAGGACGA-3'	55.5
2.	5'-TGCCATGGAAAATCTGGCTCATGGT- 3'	60.0

Table 3 Genotypes of *FTO* gene and their frequencies of alleles in the study populations for type 2 diabetes and obesity

SN	Genotype	Frequency of alleles (Diabetic & obese patients)	P-Value	Adjusted OR value	CI (95%) Value
1.	AA	40.28%	< 0.0001	Reference	Reference
2.	AG	50.25%	0.021	1.70	1.40-2.21
3.	GG	9.47%	< 0.0001	2.00	1.65-3.11

DISCUSSION

There are numerous genome-wide studies have revealed a association of the *FTO* gene variants with obesity and type 2 diabetes mellitus in Caucasian (10) and Asian (11) populations. In this study it was recorded that an association of the *FTO* gene variants was found with type 2 diabetes mellitus and obesity in population of north Indians. The chosen SNP (rs9940128 A/G) was known to establish in intron 1 of *FTO* gene. This SNP was selected because of their positive connection with obesity and type 2 diabetes mellitus has been recorded in diverse populations (12). The rs9940128 A/G SNP has been mentioned by Scuteri *et al.*, (13) which confirmed a

significant relationship with type 2 diabetes mellitus and obesity. In this study the existed GG genotype directed two fold elevated risk of type 2 diabetes mellitus. With the adjustment of age, sex, and BMI the GG genotype frequency was established high. These results were parallel and connected with the outcome of Chinese and Malay populations (14). Whereas, there were no significant relationship found with obesity and *FTO* gene polymorphism was originated in this study however, a significant association of obesity with *FTO* gene polymorphism has been reported in Japanese population (15).

Additionally, numerous reports have been accredited about the significant involvement of the *FTO* variants with obesity within intron 1. The first intron of the *FTO* gene was distinguished to be decidedly preserved across species. The bordering region of intron 1 is consist of *FTO* gene variants primarily rs9940128 which was measured in our studied population (16).

With this study, it has found that this is the first study to report on *FTO* gene variants (rs9940128 A/G) in Kanpur population. In the composite genetic correlation of the *FTO* gene has been demonstrated a probable role in energy homeostasis, which is a foremost regulating factor that regulates complex disorders such as type 2 diabetes mellitus and obesity. In future, such type of studies are required to recognize the strength and exact nature of the genetic used to know about which of the variant inside a haplotype cluster would be functionally associated to obesity or type 2 diabetes mellitus (17).

At last, the FTO gene polymorphisms rs9940128 A/G was found worried with type 2 diabetes mellitus in our study for the Kanpur populations. This study also showed the significant correlation with obesity in the Kanpur population.

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