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Research Article

EFFECT OF FTO rs9939609 POLIMORPHISM ON OBESITY IN TURKISH POPULATION

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ABSTRACT

Obesity is a disease that is affected by environmental conditions as well as genetic predisposition. This is a case-control study that aimed to investigate the relationship between FTO rs9939609 polymorphism and obesity. The relation between the rs9939609 polymorphism and obesity in 80 ower-weight (BMI≥30) and 131 under/normal weight (BMI<30) subjects was examined. The allele and genotype frequencies of each group were determined by the allele counting method. The relationship between single nucleotide exchange and obesity risk was calculated using the odds ratio. Statistical analyzes were performed with SPSS 18.0.

Results: The frequency of T allele was 0.58 and 0.45 respectively in the healthy and overweight group when allele frequencies of both groups were compared. The change in allele frequency increased the obesity rate by 1.8 fold. The rs99399609 polymorphism increases obesity risk by2.7 fold in the homozygotes model.

Conclusions: In this research, we found statistically significant results in allele frequency difference and allele positivity. The relationship between rs9939609 polymorphism and obesity will be highlighted by larger population studies.

Keywords: *Adiposity, FTO, rs9939609, BMI; Body composition.*

1. INTRODUCTION

Obesity is a major problem in the 21st century affecting the public health andis directly related to increased risk of premature death, coronary heart diseases, diabetes mellitus, cancer, hypertension, dyslipidemia and shock (Finkelstein et la. 2009). Obesity case havebeen increasing in the last three decades, the reason for this rise pointed as malnutrition, unhealthy lifestyles, immobility, and overeating (Hu, 2003; Rizzi et al., 2016).

Usually, lifestyle changes enhance treatment success and decrease obesity. However, with nutritional genomics, the importance of lifestyle changes gradually decreased. The discovery of obesity-related genes inspirits in an enhanced personalized treatment regime(Doaei et al., 2017).It's predicted that genetic factors are responsible for 40-90% of patients who hasbody mass index (BMI) variation. (Fawcett and Barroso, 2010).

One of these genes is the FTO gene, which exists onlyvertebrates and marine algae. The expression of the FTO gene is associated with food intake and energy balance. (Doaei et al., 2017, Guifang et al., 2008). FTO proteins were seen to have similar sequences with E. Coli enzyme AlkB (enzyme which hydroxylating DNA methyl groups and repairing DNA methylation damages) family proteins and its eukaryotic homologs. FTO gene proteins, oxidatively demethylates dsDNA3-meT in the presence of iron(II), dioxygen and 2-oxoglutarate. Therefore the nucleic acid demethylase activity on DNA and RNA was noted (Fawcett and Barroso2010; Speakman, 2015). Its affinity is primarily on RNA and thiamine /uracil due to its crystal structure (Speakman, 2015). Its thought that reversing the methylation by FTO can be a signal for gene regulation (Fawcett and Barroso, 2010; Guifang et al., 2008) and nucleic acid demethylase activity of FTO can regulate expression of metabolism enzyme genes and this dysregulation process can result in obesity (Fawcett and Barroso, 2010). FTO levels were less in starved animals while high lipid intake animals had increased FTO levels. An increase in FTO levels negatively affect food intake while a decrease in FTO levels induce food intake(Yeo, 2011).In rodents, FTO expression was bidirectional sensible to nutritional state and physical activity. Starvation state decrease FTO mRNA levels and FTO immunopositive cell numbersin the hypothalamus. This effect was recovered by intraperitoneal glucose. Functional coupling analysis has revealed that this issue may be in relationship with Brain-derived Neurotrophic Factor(BDNF) taking the role of food intake regulation (Speakman, 2015)

FTO gene has 9 exons and is located in the 16thChromosome (16.q12.2). The most strong signal of obesity is 1st and 2ndintrons of FTO gene. This region consists of 89 variants and approximately 47000 (Clausnitzer et al, 2015). In GWAS studies, in 2007, it was declared that a common variant of FTO gene (rs9939609) plays a predisposing role for Type 2 diabetes mellitus patients in the European population and that this relationship is seen to be mediated with BMI (Fawcett and Barroso 2010; Yang 2010).

Numerous evidences showed FTO SNPs are in relationship with apetite ratings, satiety, loss of eating control, obesity, diabetes and metabolic syndrome. In this study, we examined FTO rs9939609 polymorphism and obesity in Çanakale population.

2. MATERIAL AND METHOD

2.1. Ethics Committee Approval

This research has beenapproved by Canakkale Onsekiz Mart University Faculty of Medicine, Canakkale, Turkey ethics committee (Approval number 2011-KAEK-27/2016-E.26510) Written and verbal consent was btained from all the participants. This research was conducted with consideration of Declaration of Helsinki(revised-2000) principles.

2.2. Study design and implementation

Case-control study is conducted for genotyping and allelic profiles of polymorphic FTO gene in general population.

2.3. Patient profile

This study includes 131 control and 80 obese patient. Including criterias were BMI <30 kg/m^2 for control groups and BMI ≥30 kg/m^2 for case group.Excluding criterias were having any medical problem such as hypertansion, diabetes, metabolic syndrome, psoriasis etc. For both groups. A questionnaire was conducted for getting personal and familial medical history. Obesity diagnosis was made according to Body Mass Index (BMI).

2.4. Genotyping

All the blood samples were collected in EDTA tubes for genotyping. Genotype analyses were conducted with peripheral blood with Real-time PCR reaction after genomic DNA analysis made with commercial isolation kit according to supplier's instructions.FTO rs9939609 polimorphism was genotyped in case and control groups by real time PCR. Real time PCR reaction was conducted with 50 ng of genomic DNA,7.4 µl PCR-grade fluid, 1.6 µl Mg^{+2} solution, 4 µl probes/primers mix and 2 µl Master mix real-time PCR in a total volume of 20 µlreaction mixture. Thermal cycling was performed under the following conditions; 10 min at 95°C(hold step), denatauration step as 45 cycles at 92°C for 15 second followed by annealing/extension60°C for 1 min. FTO rs9939609 T>A polymorphism was geneotyped by TaqMan allelic discrimination assay.

2.5. Statistical Analysis

Allele and genotype frequences were determined according to allele counting method.Chi-square, pearson-chi-square, fisher exact test were used for comparing subgroups. All statistical analyses were conducted via SPSS statistical software. Lower than 0.5 of p value was expressed as statistically significant. Genotype relations and relative risk was evaluated with Odds ratio using Armitage test.

3.RESULTS

In this research, we evaluated the association between FTO rs99399609 polymorphism and obesity in Turkish population.Obese patients recruited in this study (n=80) had an avarage of 35.93±3.54 years, and the control group consisted of 131 normal-weight volunteers with an avarage of 35.08±15.17 years.The BMI distribution of obese and control groups were 35.01 ±2.49 and 25.40±4.49 respectively.We observed the distribution of the genotypes in obese group were as follows: out of 80 cases, 18 were determined to have the wild (TT) genotype, 36 the heterozygotous genotype (AT) and 26 the mutant genotype (AA). The wild allele frequency (T allele) for FTO rs9939609 polymorphism was calculated as 0.45±0.041 among obese individuals. Genotype distribution in the control groupas follow: out of 131 cases, 45 had the wild genotype (TT), 62 had heterozygous genotype (AT) and 24 had mutant genotype (AA). The frequency of the T allele was determined as 0.45 ± 0.04(Table 1).

Table 1. Genotypes and allele frequencies of the FTO gene rs99399609 polymorphism in obese individuals and healthy controls.

Genotype	**Obese (*n*: 80) (%)**	**Controls (*n*: 131) (%)**	***Odds Ratio* *P-value***
TT	18 (16.20)	45 (44.09)	
AT	36 (39.60)	62 (63.82)	AT vs AA OR: 1.058 95%CI: [0.35-3.198] P:0.92
AA	26 (24.20)	24 (23.09)	AA vs TT OR: 1.714 95%CI: [0.498-5.899] P:0.392
Allele frequency			**Allele freq. difference**
T allele	0.45 ± 0.041	0.58 ±0.031	Odds_ratio=1.689
	p=0.42 (Pearson)	p=0.74 (Pearson)	C.I.=[1.136-2.511] chi^2=6.76 p=0.009 (P)

We observed that mutant genotype was significantly higher in obese individuals then normal-weight ones and increased obesity risk was 2.7 times higher in in homozygotous model [OR: 2.71, C.I.=[1.24-5.90] and p-value:0.01]. In addition, allele possitivity increased the obesity risk 1.8 fold more [OR:1.80, C.I.=[0.953-3.407], chi^2=3.33 and p-value: 0.067]. In overal evaluation, the FTO rs9939609 increase the obesity risk 1.64 times in Turkish population. [OR:1.64, chi^2=6.33, p=0.012]. In contrast, there was no significant difference found in heterozygotous comparations. [OR: 1.45, C.I.=[0.733-2.876], chi^2=1.15, p=0.28](Table 2) .

Table 2. Comparison of FTO rs99399609polymorphism in different models among obese patient and control subjects.

Genotype	**Obese (*n*: 80)**	**Controls (*n*: 131)**	***P***
Dominant Model TT : AA + AT	**18 : 62**	**45 : 86**	OR: 1.802 95%CI [0.95-3.41] p=0.068
Recessive Model AA : AT + TT	**26 : 44**	**24 : 107**	OR: 2.14 95% CI [1.12-4.08] z-statistics:2.32 p: 0.020
Over-dominant Model AA + TT : AT	**44: 36**	**69 : 62**	OR:0.911 95%CI [0.52-1.59] z-statistics:0.329 p: 0.74

4. DISCUSSION and CONCLUSION

Numerous evidences showed FTO rs9939609 in relationship with apetite ratings, satiety, loss of eating control together with higher BMI across different populations (Frayling et al. 2007, Al-Serri et al 2018, Wardle et al. 2008, Hunt et al. 2008). Wardle et al. (2008) has conducted Satiety Responsiveness and Enjoyment of Food questionnaire to children and genotyped them for FTO rs9939609. The results showed that AA homozygote childen have a decreased satiety response score and increased adiposity. Tanofsky-Kraff et al (2009) investigated rs9939609 polymorphism and the eating behavior of the children. Their study showed that rs9939609 polymorphism didnot affect resting/basal metabolism rates but the loss of control during eating was declared frequently by adolescents. Children with AA/AT genotype preferred energy-dense, palatable foods more than those who have the TT genotype. Aside, 34,7% of AA/AT subjects has loss of control response while 18,2% of TT subjects shown loss of control response in 190 children (Tanofsky-Kraff et al., 2009) A meta analysis collecting data from 37 research revealedFTO rs9939609 genotype significantly effect total energy and carbonhydrate intake over large scale cohort including 177,330 subject (Qi et al., 2014). The relationship between energy intake, physical activity, and rs9939609 variant is researched in 1978 Afroamerican and Euroamerican subjects and significance were not noted and its seen that rs9939609 variant doesn't affect gender, energy intake, and physical activity in adiposity related phenotypes (Liu et al., 2010). In several studies FTO rs9939609 polymorphism is linked with different obesity related causes and rs9939609. Song et al (2008) have hown the cumulative effects rs9939609 risk-allele "A" with BMI and speculated that each copy of "A" increased 0.45 kg/m(2) in BMI and waist circumference.

FTO genetic variations are associated with obesity in several populations (Yang et al 2012, Wood et al, 2016). González-Sánchez et al have evaluated FTO rs9939609 gene and obesity and shown that the "FTO AA genotype" was more frequent and related to increased waist circumference in the obese individuals among the Spanish population. Merra et al (2020) have shown the association ofrs9939609 polymorphism with incerased BMI and android fat mass-FM% in Italian population. In another study, FTO rs9939609 is associated only with increased Body mass index but not obesity-related metabolic traits in Tawain population (Hsiao and Lin, 2016).

This research reveals interactions between FTO rs9939609 polymorphismwith BMI in Turkish population and our results were similiar to previous studies (Ağagündüz and Gezmen-Karadag, 2019; Solak et al., 2014). It could be speculated that genetic predispositionassociated with obesity. The relationship between rs9939609 polimorphism and obesitywas highlighted by larger population studies previously and we confirmed that FTO rs9939609 polimorphism increased the obseity risk in Turkish population.

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