The FTO Gene rs9939609 Polymorphism and its Association with BAI as Well as Other Adiposity Markers

Nilupher, Urvashi Gupta, Kshetrimayum Surmala Devi, Meenal Dhall, Renu Tyagi, Satwanti Kapoor

Department of Anthropology, University of Delhi, India

*Corresponding author: Meenal Dhall, Department of Anthropology, University of Delhi, India. Tel: +91-9650159434; Email: say2meenal@gmail.com

Citation: Nilupher, Gupta U, Devi KS, Dhall M, Tyagi R, et al.(2018) The FTO Gene rs9939609 Polymorphism and its Association with BAI as Well as Other Adiposity Markers. Arch Epidemiol: AEPD-126. DOI:10.29011/2577-2252.100026

Received Date: 22 November, 2018; Accepted Date: 18 December, 2018; Published Date: 24 December, 2018

Abstract

Introduction: The Fat mass and obesity associated (FTO) rs9939609 gene polymorphism has been studied in many parts of the world to find its implication on obesity and Type 2 diabetes mellitus.

Objective: The present study is conducted to find out the association of FTO gene polymorphism with adiposity markers among the adult population of North Delhi.

Materials and Method: Anthropometric measurements and intravenous blood sample were collected from 247 individuals who were residing in Delhi for more than 15 years. Informed written consent was also taken before conducting the study from each individual. DNA (Deoxyribose Nucleic Acid) isolation and genotyping were carried out using standard protocol. Statistical analysis was done using SPSS version 17.0.

Results: Maximum mean of waist circumference, body mass index and conicity index are found to be associated with the risk genotype of FTO marker.

Conclusion: This study revealed the difference in the prediction of FTO genotypes on different adiposity markers.

Keywords: Adiposity; Delhi; Genotype; Polymorphism

Introduction

In Indian context where diversity exists at every level, the prevalence of overweight and obesity varies in different populations [1]. Obesity has been reported to be as low as 1.50% to as high as 45.6% among Indian populations [2]. Uncoupling Protein 1 (UCP1) is mainly expressed in mitochondrial membrane of Brown Adipose Tissue (BAT) which plays an important role in thermogenesis [3]. UCP1 has been suggested as an obesity gene in humans and it has been reported to be associated with blood pressure as well [4]. The FTO protein is greatly articulated in hypothalamus, as well as in many other tissues such as mesenteric fat, adipose tissue, pancreas, and liver [5]. It helps in regulating the metabolic rate, expenditure of energy, homeostasis of energy, size of the body and accumulation of body fat [6]. First intron of FTO (Fat-mass and Obesity associated gene) rs9939609 (A/T variant) is especially attributed as one of the most known genetic factors predisposing humans to non-monomogenic obesity [7-9]. Numerous common genetic variants associated with obesity have identified by Genome-Wide Association Studies (GWAS) [10]. Obesity traits which could increase body mass index by 0.22-0.66 per risk allele were found to be consistently associated with Fat mass and the obesity-associated gene (FTO) locus in several populations [11-13].

It is well established that there is an association between FTO and obesity risk, however obesity risk related to FTO may be modulated by lifestyle [14]. Body fatness mediated by FTO may be attenuated in physically active individuals has been suggested by numerous studies [15-17]. Those individuals who carry the risk allele of FTO gene have been reported to have more weight, BMI, and Waist Circumference (WC), respectively [16]. The present study aims to determine the association of FTO gene polymorphism with adiposity markers among the adult population of North Delhi.
Materials and Methods

Study Subjects

The present study was a cross sectional study conducted among the heterogeneous population of Delhi, the capital city of India. The selected study population were the inhabitants of Delhi for more than 15-20 years. The study area covered North Delhi. A total of 247 participants of either sex (117 males and 130 females) in the age group of 20-55 years were randomly selected from the study population. Pre-informed written consent was taken prior to the study from each subject. Socio-demographic data such as name, age sex, place, education, income occupation etc. were recorded from each participants using standardized proforma after explaining the purpose of the study. The participants were in the lower-middle income group and mostly engaged in business. 2 ml of intravenous blood sample was also collected using single use syringe by a well-trained nurse. Ethical approval was taken from the departmental ethical committee.

Anthropometric Measurements and Classifications

Before starting the measurements of the body, all the participants were properly explained the protocols to be followed for active participation. Anthropometer rod, flexible steel tape and portable weighing machine were used to measure height and body weight respectively. Minimum waist circumference and maximum hip circumference were measured by using flexible steel tape. Waist circumference with >90 for males and >80 for females as risk [18]. Body Mass Index (BMI) is classified according to WHO[19]. Waist-Hip Ratio is classified according to Willett, et al. [20] as for male, the normal range is ≤ 0.95 and risk ≥ 0.95; for female, the normal range is ≤ 0.80 and risk ≥ 0.80. Body Adiposity Index (BAI) is classified by finding out the quartiles and Conicity Index (CI) is categorized as >1.25 for male and >1.18 for female as risk.

Genotyping

DNA isolation was done from 1ml of blood by using salting out method [21]. Genetic analysis was carried out from the isolated DNA. The FTO rs9939609 was amplified in 105 base pair by PCR using New England Biolabs PCR kit (forward primer: 5’-GGTTCCCTTGCGACTGCTGTGAAATT-3’ and reverse primer: 3’- GCTTTTATGCTCTCCCACTC- 5’. PCR reactions were carried out in a final volume of 20 μl which contained 3 μl of DNA, 1.0 μl of each of forward and reverse primer, 2 μl of 10X buffer (Mg free), 1.6μl of 2mM dNTPs, 1.6μl of 2mM MgCl₂, 0.5 μl of Taq DNA polymerase and the remaining volume by distilled water. PCR cycling conditions were set at 94C for 5 minutes,94C for 1 minute, 50C for 1 minute and 55C for 1 minute for complete 35 cycles and final extension at 72C for 10 minutes. The products of PCR were then digested with the ApoI restriction enzyme and set for overnight incubation at 37C. The digested products were then separated by using 2% agarose in 1X TAE buffer with ethidium bromide for fluorescence in gel electrophoresis at 120volt. The isolated genotypes were then visualized under the Gel Documentation system. The genotypes were AA, TAand TT.

Statistical Analysis

Data was analysed by using SPSS version 17.0. One way Anova test and multinomial logistic regression were found out to determine the association and risk of FTO polymorphism with adiposity markers.

Results

The polymorphism of FTO marker was found to be in Hardy-Weinberg Equilibrium. The genotype frequencies of TT, AA and TA were found to be 0.36, 0.16 and 0.48 respectively and the allele frequencies of T and A alleles were 0.6 and 0.4 respectively.

Mean and standard deviation of different anthropometric measurements and adiposity indices according to the three genotypes of FTO marker are displayed in (Table 1). Mean of stature and waist hip ratio are found to be maximum in the mild risk genotype (TA) as compared to the other genotypes. Maximum measures of body weight, waist circumference, hip circumference, body mass index, waist height ratio and conicity index are found among high risk variant of FTO marker.

The present study also explores the prediction of TA and AA genotypes on different adiposity markers by using multinomial logistic regression and it is provided in (Table 2). Waist circumference is found to have less than 1 times [OR= 0.96 (0.579-1.590)] probability of association with the risk alleles followed by waist height ratio [OR= 0.914 (0.529 - 1.580)]. Effect of risk alleles on body mass index, waist hip ratio, body adiposity index and conicity index are more than one times. Highest prediction is found to be associated with BAI [OR= 1.494 (0.798 - 2.799)] followed by CI [OR = 1.319 (0.690 - 2.523)], WHR [OR= 1.292 (0.782 - 2.135)] and BMI [OR = 1.071 (0.627 - 1.829)] respectively.

Citation: Nilupher, Gupta U, Devi KS, Dhall M, Tyagi R, et al.(2018) The FTO Gene rs9939609 Polymorphism and its Association with BAI as Well as Other Adiposity Markers. Arch Epidemiol: AEPD-126. DOI:10.29011/2577-2252.100026
**Table 1**: Mean and standard deviation of the basic characteristics.

| Characteristics                  | TT       | TA       | AA       | F-value |
|----------------------------------|----------|----------|----------|---------|
| Stature (cm)                     | 160.3 ± 9.34 | 161.7 ± 9.30 | 160.7 ± 8.26 | 0.415   |
| Body weight (kg)                 | 70.6 ± 16.23 | 70.4 ± 14.64 | 71.4 ± 15.56 | 0.070   |
| Waist circumference (cm)         | 85.9 ± 13.12 | 86.1 ± 16.31 | 87.3 ± 12.39 | 0.224   |
| Hip circumference (cm)           | 98.8 ± 10.67 | 96.7 ± 16.01 | 98.9 ± 8.57  | 0.700   |
| Body mass index                  | 27.3 ± 5.46 | 27.1 ± 5.80 | 27.6 ± 5.36 | 0.144   |
| Waist hip ratio                  | 0.86 ± 0.09 | 0.98 ± 0.80 | 0.88 ± 0.09 | 1.887   |
| Waist height ratio               | 0.53 ± 0.10 | 0.53 ± 0.07 | 0.54 ± 0.07 | 0.275   |
| Body adiposity index             | 30.9 ± 6.77 | 29.3 ± 9.67 | 30.7 ± 5.85 | 0.910   |
| Conicity index                   | 1.1 ± 0.08 | 1.2 ± 0.16 | 1.2 ± 0.08 | 0.330   |

**Table 2**: Multinomial logistic regression analysis of adiposity marker and genotypes.

| Adiposity Markers                  | TA- AA OR (95% CI) |
|------------------------------------|--------------------|
| Waist circumference Risk           | 0.960 (0.579 - 1.590) |
| Body mass index Overweight         | 1.071 (0.627 - 1.829) |
| Waist hip ratio Risk               | 1.292 (0.782 - 2.135) |
| Waist-height ratio Risk            | 0.914 (0.529 - 1.580) |
| Body adiposity index Lower quartile | 1.494 (0.798 - 2.799) |
| Body adiposity index Upper quartile | 0.933 (0.500 - 1.739) |
| Conicity index Risk                | 1.319 (0.690 - 2.523) |

**Discussion**

In the present study, various risk factors of obesity were evaluated among the adult population of Delhi. Hypertension and obesity are complex processes that involve environmental and genetic factors (eg, ethnic differences, age, sex, nutrition). It is not clear whether it is individual gene contributions to the obesity-hypertension syndrome, or the combination of different environmental variants [3]. In the present study, the FTO risk allele was found to have highest association with body adiposity index among the other adiposity indices. Approximately 1.5 times prediction of maximum BAI was determined to be associated with the risk FTO rs9939609 variants and that prediction more than the odds ratio of BMI. The reason for this might be due to influence of height in case of BMI. Attention to the gene’s functional effects had been turned up with the discovery of the consistent association of the FTO gene common variants with higher body weight [22]. Increment in BMI, waist circumference and waist height ratio was associated with the presence of FTO rs9939609 [23].

The present study also reported that more than 1 times prediction of overweight or obese body mass index was found in the risk alleles of the fat mass and obesity associated gene. Least association of waist height ratio and FTO gene polymorphism was found. This might be the result of genetic predisposition as well as the lack of awareness of the remedial measures to control the other factors contributing obesity. This finding was found to be consistent with the study conducted in Mexican and Chinese populations with 1.38 and 1.29 odds ratio respectively [24,25]. A study among the Chinese Han type 2 diabetes patients also depicted that presence of FTO risk gene was associated with risk for being obese [5]. The present study found 1.2 risk fold of high conicity index among the risk alleles of the FTO gene. The finding of the present study was consistent with the study that conicity index could be useful in identifying cardiovascular disease patients with abdominal obesity who were not necessarily overweight [26]. As evaluation of conicity index used waist circumference which had been considered as a good predictor of obesity, so conicity index might also contribute in obesity.
Conclusion

This study reveals the important genetic contribution on human obesity at different levels. Although there is a huge role of genetic factors, people must also be aware of the other factors such as environmental, lifestyle and psychological factors too have a higher impact on obesity. This can be controlled at individual level by transforming the earlier lifestyle habits because the inherited genes cannot be eradicated or replaced. Hence, mass level understanding of the primary and additive causes of obesity is very much important to reduce the rate of lifestyle diseases.

Acknowledgements

The authors are thankful to the participants of the study for their immense help and support. Financial assistance to RT from University Grants Commission, Delhi, India with reference no. UGC-PDFWM - No.F.15-1/2017/PDFWM-2017-18-DEC-44604 (SA-II) is greatly acknowledged. They are also grateful to the Department of Anthropology and R&D, University of Delhi for infrastructure, DST-SERB (Grant number: SB/YS/LS-60/2014) and DU DST Purse grant for financial assistance.

Conflict of interest:

The authors declared no conflict of interest.

References

1. Pradeepa R, Anjana RM, Joshi SR, Bhansali A, Deepa M, et al. (2015) Prevalence of generalized & abdominal obesity in urban & rural India: the ICMR-INDIAB Study (Phase-II)[ICMR-INDIAB-3]. The Indian journal of medical research142: 139-150.
2. Kshatriya GK, Acharya SK (2016) Triple burden of obesity, undernutrition, and cardiovascular disease risk among Indian tribes25:11.
3. DhallM, Chaturvedi MM, Rai U, Kapoor S (2012) Sex-dependent effects of the UCP1-3826 A/G polymorphism on obesity and blood pressure.Ethn Dis 22:181-184.
4. Kotani K, Sakane N, Saiga K (2007) The uncoupling protein-1 gene23826A/G polymorphism and hypertension in Japanese subjects. ClinChem Lab Med 45:1186-1189.
5. Kang Y, Liu F, Liu Y (2017) Is FTO gene variant related to cancer risk independently of adiposity? An updated meta-analysis of 129,467 cases and 290,633 controls. Oncotarget 8:50987-50996.
6. Hernández-Caballero M E, Sierra-Ramirez, J A (2015) Single nucleotide polymorphisms of the FTO gene and cancer risk: an overview. Molecular biology reports 42:699-704.
7. Frayling TM, TimpsonNJ, WeedonMN (2007)"A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity". 316: 889-894.
8. Livingstone KM, Celis-Morales C, Navas-Carretero S, San-Cristobal R, Forster H, et al. (2016) Fat mass-and obesity-associated genotype, dietary intake and anthropometric measures in European adults: the Food4Me study. British Journal of Nutrition115: 440-448.
9. Klimentidis YC, Arora A, Chougule A, Zhou J, Raichlen DA (2016) FTO association and interaction with time spent sitting. International Journal of Obesity 40: 411-416.
10. Hosseini-Esfahani F, Koochakpoor G, Daneshpour MS, Sedaghat- khayat B, Mirmiran P, et al. (2017) Mediterranean Dietary Pattern Adherence Modify the Association between FTO Genetic Variations and Obesity Phenotypes. Nutrients 9: 1064.
11. Peng S, Zhu Y, Xu F, Ren X, Li X, et al. (2011) FTO gene polymorphisms and obesity risk: a meta-analysis. BMC medicine 9:71.
12. Vimalaswaran KS, Ångquist L, Hansen RD, Van Der ADL, Bouatia-Naji N, et al. (2012) Association between FTO variant and change in body weight and its interaction with dietary factors: the Diogenes study. Obesity 20: 1669-1674.
13. Vimalaswaran KS, Bodhini D, Lakshmiyini N, Ramya K, Anjana RM, et al. (2016) Interaction between FTO gene variants and lifestyle factors on metabolic traits in an Asian Indian population. NutrMetab 13: 39.
14. West NR, Dorling J, Thackray AE, Hanson NC, Deombel SE (2018) Effect of obesity-linked FTO rs9939609 variant on physical activity and dietary patterns in physically active men and women. Journal of obesity 2018.
15. Andreason CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, et al. (2008) Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes 57: 95-101.
16. Celis - Morales C, Marsas CF, Livingstone KM, Navas - Carretero S, San - Cristobal R, et al. (2016) Physical activity attenuates the effect of the FTO genotype on obesity traits in European adults: the Food4Me study. Obesity24: 962-969.
17. Kim JY, DeMenna JT, Puppala S, Chittoor G, Schneider J, et al. (2016) Physical activity and FTO genotype by physical activity interactive influences on obesity. BMC Genet17:47.
18. Cordeiro AC, Qureshi AR, Stenvekink M, Heimburger O, Axelsson J, et al. (2009) Abdominal fat deposition is associated with increased inflammation, protein-energy wasting and worse outcome in patients undergoing hemodialysis. Nephrology Dialysis Transplantation25: 562-568.
19. Who EC (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet363: 157-163.
20. Willett WC, Dietz WH, Colditz GA (1999) Guidelines for healthy weight. N Engl J Med341:427-434.
21. Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16: 1215.
22. Dina C, Meyre D, Gallina S, Durand E, Körner A, et al. (2007) Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 39: 724-726.
23. Muñoz-Yañez C, Pérez-Morales R, Moreno-Macias H, Calleros-Rincon E, Ballesteros G, et al. (2016) Polymorphisms FTO rs9939609, PPARG rs1801282 and ADIPOQ rs4632532 and rs182052 but not lifestyle are associated with obesity related-trait in Mexican children. Genet MolBiol39: 547-553.
24. Villalobos-Comparán M, Flores-Dorantes MT, Villarreal-Molina MT, Rodríguez-Cruz M, García-Ulloa, et al. (2008) The FTO gene is associated with adulthood obesity in the Mexican population. Obesity 16:2296-2301.

25. Xi B, Shen Y, Zhang M, Liu X, Zhao X, et al. (2010) The common rs9939609 variant of the fat mass and obesity-associated gene is associated with obesity risk in children and adolescents of Beijing, China. BMC Med Genet 11:107.

26. Stenvinkel P, Zoccali C, Ikizler TA (2013). Obesity in CKD—what should nephrologists know?. J Am SocNephrol24:1727-1736.