

Association of rs9939609 FTO Gene Polymorphism as a Risk Factor of Obesity in Adults

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ABSTRACT

Background: The cause of obesity is an imbalance between the number of calories taken and the amount burned. Obesity is a complex disease. The FTO rs9939609 gene polymorphism is one of the genetic factors that contribute to obesity in addition to environmental factors. Numerous researches have suggested a connection between the prevalence of obesity and the FTO rs9939609 gene polymorphism

Aims: The purpose of this study is to ascertain how the FTO rs9939609 gene polymorphism relates to the prevalence of adult obesity.

Methods: At the Biomolecular and Genetics Laboratory of the UGJ Faculty of Medicine, an analytical observational study using a case-control design was carried out with 84 participants, 42 subjects in case group, and 42 subjects in control groups. Data were collected utilizing DNA from blood collection, PCR-RFLP for genotyping, and 2.5% electrophoretic gel for visualization. Chi-square was used for data analysis.

Results: Findings showed that there is no link between the FTO rs9939609 polymorphism and the prevalence of obesity ($p>0.05$, $OR=0.710$).

Conclusion: In the Indonesian population, the FTO rs9939609 gene polymorphism is not associated with an increased risk of obesity.

Keywords: *FTO polymorphism rs9939609, Obesity, Adult.*

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1. Introduction

In addition to being a health issue, obesity is linked to a rise in non-communicable diseases. Accumulation of fat or adipose tissue in the body can affect and contribute to several chronic illnesses, such as hypertension, cardiovascular disease, and hyperlipidemia (Panuganti et al., 2022). Both industrialized and developing nations are seeing an increase in the prevalence of obesity. According to 2018 Indonesian Basic Health Research data, roughly 21.8% of Indonesian adults over the age of 18 are obese. Since 2007, this data has tendency to increase, rising from 10.5% to 11.5% in 2013 and to 21.8% in 2018 (Ministry of Health, 2018). Based on the Central Bureau of Statistics on the prevalence of obesity in people aged >18 years according to sex in 2018 is 26.60% in males, and 44.40% in females (Central Bureau of Statistics, 2018). Obesity is a complex disease caused by an imbalance between calories consumed and calories expended, which is significantly impacted by nutrition (Janssen et al., 2005). The FTO gene rs9939609 is one of the genetic components that contribute to obesity. The primary purpose of the FTO gene is to play a part in the homeostatic control of food intake and energy expenditure in the hypothalamus, where it is highly expressed. Polymorphisms or mutations in the FTO gene can trigger adipogenesis through demethylation of m6A which plays a role in alternative splicing. Changes in the expression of the FTO gene can impact the dopamine signaling system and the feeling of reward or satiety, specifically the feeling of fullness after eating, which can impact the desire to seek out foods that are high in density or high in fat and increase the prevalence of obesity. Larder and Yeo's research explained that the FTO gene's abundant expression in the hypothalamus affects energy balance, the control of food intake, and the adipogenesis processes. Additionally, research by Zhao identifies rs9939609 as one of the risk factors for obesity. Silvia's study found a significant relationship between the FTO gene and an increase in BMI (Larder et al., 2011; Tung & Yeo, 2011; Zhao et al., 2019).

Genome-wide association studies (GWAS) have identified the FTO gene, which is located on chromosome 16q12.2, as a gene that affects the prevalence of obesity. FTO plays a role in adipogenesis, hunger regulation, and energy balance and is extensively expressed in the liver and brain. The single nucleotide polymorphism (SNP) in the FTO gene has been most associated with obesity. The risk allele (allele A) of rs9939609 is associated with higher dietary calorie consumption overall, higher protein and fat intake in both adults and children (Tung & Yeo, 2011).

The FTO gene is highly expressed in the hypothalamus, and when there is a lack of food intake, the FTO gene is upregulated, particularly in the arcuate nucleus. Peptide Y neurons (NPY) and melanocortin derived from proopiomelanocortin (POMC), a precursor protein that generates several hormone products, are two groups of neurons found in the arcuate nucleus that have opposite functions. One of the most potent appetite stimulants ever discovered is NPY, whereas melanocortin—particularly hypothalamic -melanocyte stimulating hormone (-MSH)—suppresses appetite (Yang et al., 2019). A study on murine samples found that FTO rs9939609 has a role in the regulation of food intake and energy consumption by modifying appetite and food intake affecting the expression of NPY in the hypothalamus (Cho et al., 2021). Several studies also showed that there is a positive relationship between the mRNA level of the FTO gene in subcutaneous adipose tissue and BMI (Abdelmajed et al., 2017; çöl et al., 2017). The results of a meta-analysis study conducted by Maryam showed that there was an indication of carrier allele A of the FTO rs9939609 polymorphism on increased body fat percentage (BF%) (çöl et al., 2017).

2. Methods

Study design

An analytic observational study with a case-control design was conducted at the Biomolecular and Genetics Laboratory of the UGJ Faculty of Medicine.

Population and samples

In this research, involved 84 people with 42 cases in each case group and 42 control groups. The sampling technique in this study is consecutive sampling.

Measurement

Data were obtained by blood sampling and genotyping using PCR-RFLP, and visualization using 2.5% electrophoretic gel. Respondents who met the criteria were contacted for informed consent, interviewed, and 3cc blood sampled and stored in the EDTA tube. Blood samples were then used for DNA extraction and subjected to Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP).

Data collection

The primary data collection method used in this research is questionnaires: Statistical analysis used univariate and bivariate analysis with spearman test. Research data collection was carried out after obtaining a letter of ethical approval from the research ethics commission of the faculty of medicine Swadaya Gunung Jati University issued on June 6th, 2022 (No.151/EC/FKUGJ/VI/2022)

Instruments

The amplification of the FTO rs99039609 gene polymorphism was done using the following primers, forward 5'-AAC TGG CTC TTG AAT GAA A-TAG GAT TCA GA-30 and reverse primer: 5'-AGA G-TAA CAG AGA CTA TCC AAG TGC AGT AC-3'. PCR was carried out with a volume of 25µL using thermal cycler program with initial denaturation of 95°C for 5 minutes followed by 35 cycles with denaturation of 95°C for 30 seconds, annealing of 65°C for 30 seconds, and extension of 72°C for 30 seconds. The final extension is done at 72°C for 5 minutes. The 182-bp amplicons were digested using the restriction enzyme Sca1 (New England Biolabs) which cut into 154bp and 28bp at 37°C for 15 minutes. The results of the restriction were visualized on a 2.5% agarose gel.

Analysis data

The research results are presented in the form of a textual table. Statistical analysis used univariate and bivariate analysis with chi-square.

3. Results

A total of 84 people were enrolled in the study. The distribution of genotypes, polymorphisms, and allele frequencies was examined using univariate statistical analysis, and the results were as follows:

Table 1. Allele Frequency Distribution

Allele	Cases		Control	
	n	%	n	%
T	50	59.5%	53	63.1%
A	34	40.5%	31	36.9%
TOTAL	84	100%	84	100%

There were 50 T alleles (59.5% of the total) and 34 A alleles (40.5%) in the case group's distribution of allele frequencies for the FTO rs9939609 gene polymorphism. A total of 31 A alleles (36.9%) and 53 T alleles (63.1%) were present in the control group.

Table 2. Genotypic Frequency Distribution

Genotype	Cases		Control	
	n	%	n	%
TT	14	33.3%	11	26.2%
TA	22	52.4%	31	73.8%
AA	6	14.3%	0	0%
TOTAL	42	100%	42	100%

By using PCR-RFLP analysis, the genotype frequency distribution of the FTO rs9939609 gene polymorphism was discovered. The outcomes were homozygous TT (182 bp) for the wild type, heterozygous TA (182,154, and 28 bp), and homozygous AA (154 bp and 28 bp) for the mutant.

The relationship between adult-age group obesity and the FTO rs9939609 gene polymorphism was investigated using bivariate analysis. The statistical analysis used the chi-square test with a significance level of (0.05). The results of the bivariate analysis are shown in Table 3.

Table 3. Relationship of Polymorphism with Obesity

Polymorphism	Cases		Control		p	OR	χ^2	CI
	n	%	n	%				
Polymorphism +	28	66.7%	31	73.8%	0.474	0.710	0.513	95%
Polymorphism -	14	33.3%	11	26.2%				

According to the findings of the bivariate analysis, 14 participants (33.3%) and 28 subjects (66.7%) in the case group, respectively, did not have polymorphism. There were 11 participants (26.2%) who did not have polymorphism and 31 subjects (73.8%) who did so in the control group. This demonstrates that the polymorphism in the control group is higher than in the case group.

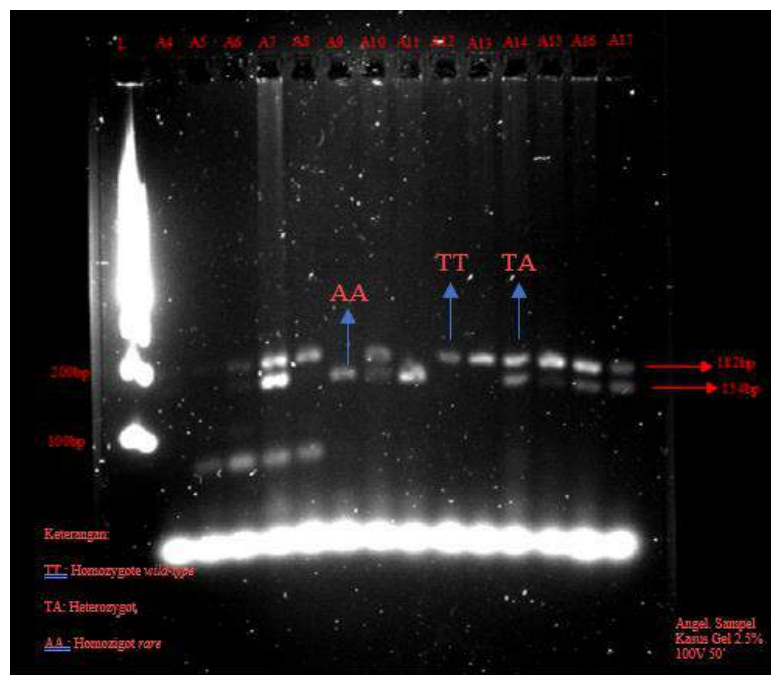


Figure 1. Agarose gel of rs9939609 FTO gene polymorphism PCR-RFLP product, digestion result (TT: 182 bp; TA: 182 bp, 154 bp, 28 bp; AA: 154 bp, 28 bp), B: Blank, M: Marker

4. Discussion

Obesity is a complex disease that has many potential causes, and it is linked to insulin resistance, dyslipidemia, and cardiovascular disease. The FTO gene, which is linked to adiposity, has been the subject of numerous studies in the field of genetic molecular biology. One such study was carried out by Yang et al. (2019), which demonstrated a significant impact of the SNP gene FTO rs9939609 on obesity. According to a study by Cho, persons with the SNP FTO rs9939609 genotype (AT+AA) had a greater BMI than those with the homozygous wild type (TT) genotype in a population in northwest China¹⁰ (Abdelmajed et al., 2017; çöl et al., 2017).

The findings of this study were based on the frequency distribution of the T allele in the case group of 50 research participants (59%), the A allele in the case group of 34 participants (40.5%), and the T allele in the case group of 53 participants (63.1%), with 31 participants (36, 9%) carrying the allele A. The AA genotype was uncommon (genotype mutant) with 154bp and 28bp and was more prevalent in the case group of 6 cases (14.3%) than in the control group. One chunk of 154 bp is visible when viewed from the gel electrophoresis visualization, while the 28 bp section is not. There were 14 members of the case group (33.3%) and 11 members of the control group (26.2%) had the TT genotype, indicating that the case group had a higher percentage of TT genotypes than the control group. The FTO rs9939609 gene polymorphism has an odds ratio of 0.710, which means that those who have it have a 0.7 times higher chance of being obese than those who do not. However, statistically, the p value is 0.474 ($p > 0.05$), which indicates that there is no significant association between polymorphisms and the incidence of obesity, along with a 95% confidence interval (CI= 0.277-1.818) between polymorphism and obesity.

According to the study's results, the rs9939609 polymorphism of the FTO gene was not substantially associated with the prevalence of obesity in adults ($p > 0.05$), although it is still feasible that this polymorphism may play a role in obesity due to population differences and other factors. The distribution of migration, chance marriage, and ethnicity is significantly influenced by the topic's genetic component and the prevalence of obesity. The T nucleotide base will change to A because the rs9939609 polymorphism of the FTO gene is a variant intron. The produced protein's amino acid makeup is unaffected by this nucleotide alteration, though. Studies show that although the FTO rs9939609 gene did not affect protein levels, it has a significant impact on fat metabolism and risk, and that the effect is related to increased high-calorie intake. Allele A bearers had lower levels of fat cell lipolysis than the rest.

Several previous studies regarding the rs9939609 polymorphism of the FTO gene on the incidence of obesity which had insignificant results includes a study by (çöl et al., 2017), which linked the rs9939609 polymorphism of the FTO gene to the incidence of obesity in adults with a total sample of 200 divided into 2 groups of cases and 100 control samples each with a p -value > 0.05 (çöl et al., 2017). Another research conducted by Abdelmajed et al. (2017), examining the relationship between FTO gene polymorphism as a factor the risk of obesity in children and adults in the Egyptian population, showed insignificant results with ($p > 0.05$) with a sample size of 100 case groups and 100 control groups (Abdelmajed et al., 2017). These two studies are in line with research by do Nascimento et al. (2019), with no results that there is a relationship between rs9939609 with obesity in children and adults ($p = 0.67$).

5. Conclusion

There is no significant relationship between the FTO rs9939609 gene polymorphism and the incidence of obesity with a $p = 0.474$ OR = 0.710 in Indonesian population. It will be interesting to conduct a full FTO gene sequence on Indonesian obese population to identify common polymorphisms and mutations that may be contributing to obesity or a genome-wide association studies to identify genes that are associated with obesity in Indonesian population.

Conflict of Interest

The authors declare no conflicts of interest for the results.

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