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Identification of the FTO gene variant rs9939609 in young Sundanese women with excess body fat

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ABSTRACT

Background: The FTO gene has been widely studied, and numerous research findings have demonstrated that variants like rs9939609 are strongly related to increased body mass index (BMI), adiposity, and a heightened obesity risk. However, no study was conducted on the FTO rs9939609 gene variant among Sundanese obese young women. This study to identify the prevalence and distribution of the Fat Mass and Obesity-Related (FTO) rs9939609 polymorphism among Sundanese obese young women.

Methods: In this cross-sectional study, 38 Sundanese women aged between 18 and 25 y.o. were included. These women had been classified as obese, with a total body fat higher than 35%. FTO rs9939609 genotyping was performed using PCR and sequencing method.

Results: Our findings revealed that 50% of the subjects had the heterozygous variant TA, 42.1% had the homozygous variant TT, and only 7.9% had the variant AA homozygote. Chi-square test showed that the FTO rs9939609 variant among subjects was in Hardy-Weinberg equilibrium ($p > 0.05$), and the minor allele frequency was 0.329. These results provide the first insights into the prevalence of FTO rs9939609 variation among Sundanese obese women, making a contribution to obesity research and clinical practice.

Conclusions: The minor allele frequency obtained aligns with global patterns of FTO variants, suggesting a genetic predisposition to obesity. The results of this study can be a basis for further research such as obesity interventions among Sundanese obese women.

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KEYWORDS

FTO rs9939609, obese women, Sundanese ethnicity.

INTRODUCTION

The rising prevalence of overweight and obesity across all age groups in Indonesia reflects a significant public health concern, aligning with global trends[1,2]. Obesity is a major risk factor for numerous chronic diseases, including type 2 diabetes, cardiovascular disorders, hypertension, and certain cancers. Advances in next-generation sequencing (NGS) also genome-wide association studies (GWAS) have enhanced our understanding of genetic factors associated with obesity[3,4]. This underscores the importance of our study, which focuses on a specific gene linked to the prevalence of obesity in the broader context of global health and research.

Several research reviews have documented the consistent association of a common variant within the first intron of the FTO gene (fat mass and obesity-associated) with obesity in adults and children[3,4]. The most studied variant in the intronic region of the FTO gene is the SNP rs9939609. Variants at this site are associated with an increased risk of obesity[5]. The FTO rs9939609 gene exhibits three genotypes: TT, AA, and AT. The A allele, encompassing the TA and AA genotypes, is identified as the 'risk allele' due to its association with increased obesity susceptibility, whereas the TT genotype is considered the 'non-risk allele' or wild type[6-8].

Research on FTO rs9939609 polymorphism within Indonesia has predominantly focused on diverse populations, including children and adults, across various health statuses and ethnic groups. For instance, studies have explored its relation with obesity and traits among the Balinese population, revealing a significant correlation between the A allele and increased body mass index (BMI)[7,8]. Similarly, investigations among Indonesian obese female adolescents have examined the relationship be-

tween this polymorphism and insulin resistance, although findings have been inconclusive[9].

Despite these efforts, there remains a notable gap in research concerning the prevalence and impact of the FTO rs9939609 gene variant among obese young women of Sundanese ethnicity. Given the unique genetic and cultural background of the Sundanese population, understanding the role of this polymorphism in obesity within this group is essential[7,9-15]. This research aims to study the FTO rs9939609 gene polymorphism in obese young Sundanese women residing in Bandung City, Indonesia.

METHODS

Subjects

The research employed a cross-sectional design and was conducted in November 2023 at the Universitas Pendidikan Indonesia, Bandung, Indonesia. The recruitment of obese participants was carried out purposively from Bandung City, Indonesia. The research protocol was subjected to a comprehensive and stringent review process to ensure adherence to ethical principles and scientific rigor. Following a thorough assessment, formal ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Padjadjaran University (FK UNPAD). The approval was granted under the reference number 1068/UN6.KEP/EC/2023, signifying compliance with established ethical guidelines for human research and reinforcing the integrity of the study.

The study population was women aged 18-25 years with a fat percentage of >35%, lived in Bandung City with Sundanese ethnicity, engaged in light to moderate physical activity based on the Physical Activity Level (PAL) classification or reported infrequent exercise. The study included a total of 38 female participants, selected through a purposive sampling method to ensure the inclusion of individuals meeting specific criteria relevant to the research objectives. The minimum required sample size was determined to be 30, based on established statistical guidelines ensuring sufficient power for data analysis and the validity of the study's findings[16].

The inclusion criteria included women with a high percentage of body fat >35%[17] who had a sedentary lifestyle or never exercised, were of Sundanese origin, fell within the 18–25 age range, had normal fasting blood glucose levels, and voluntarily participated after providing a signed consent form. Besides, exclusion criteria were women who were either pregnant or breastfed, women with a history of suffering from any form of chronic disease, women who have been habitually consuming antioxidant dietary supplements and phytopharmaceuticals within six months prior to the research, and women participating in other research. The number of participants is calculated using the hypothesis test formula for two independent samples based on Sastroasmoro & Ismael[18].

Data Collection

Participants' demographic information, including age, education level, and occupation, was obtained through direct interviews. Anthropometric and body composition measurements were conducted using standardized instruments to ensure accuracy. Body weight, body mass index (BMI), and total body fat percentage were measured using the Karada Body Composition Monitor HBF-375 (OMRON Corporation, Tokyo, Japan), a bioelectrical impedance analysis (BIA) device known for its accuracy in evaluating body composition. Height was recorded in centimeters to the nearest 0.1 cm using a calibrated stadiometer (SAGA, Bekasi, Indonesia) to ensure precise and consistent stature measurements. Before the collection of blood samples, participants underwent a thorough health assessment to evaluate their overall health status and confirm their eligibility for the study. This included measuring resting pulse rate, systolic and diastolic blood pressure using a digital sphygmomanometer and assessing fasting blood glucose levels with a glucometer.

Gene Screening

A blood sample of about 3 cc was withdrawn after an overnight 12-hour fast, then entered to a sterile tube that contains EDTA, and then kept on ice. The buffy coat was isolated through centrifugation at 1600 rpm at a temperature of 4°C for 10 minutes and subsequently preserved at -80°C for further analysis of the FTO rs9939609 gene. Genomic DNA was extracted utilizing the Genomic DNA Mini Kit, adhering strictly to the manufacturer's standardized protocol to ensure optimal yield and purity. This method was employed to obtain high-quality DNA suitable for subsequent genetic analysis, minimizing potential contaminants and preserving sample integrity for accurate downstream applications (Geneaid, Taiwan).

Primer pairs for PCR reverse and forward, obtained from IDT, Indonesia, were prepared for genotyping on gDNA. Electrophoresis was carried out to see the presence of the FTO gene as a result of PCR. Sequencing was then performed to see each participant's FTO gene sequence. Finally, the FTO variant examination was conducted using the Chromas application (Australia). Blood sampling was analysed at the Genetic Molecular Laboratory, Padjadjaran University, Bandung, Indonesia.

Data Analysis

The collected data were analyzed using the SPSS statistical software, version 26.0 for Windows (IBM Corp., Armonk, NY, USA), ensuring efficient and accurate data processing. Descriptive statistical methods were employed to summarize the demographic and clinical characteristics of the study population, providing an overview of key variables. Frequency distributions were assessed to determine the prevalence of genotypes and alleles within the sample. To evaluate whether

genotype frequencies conformed to expected Mendelian inheritance patterns, the Hardy-Weinberg equilibrium (HWE) model was applied. Furthermore, statistical comparisons of genotype and allele distributions were conducted using the chi-square (χ^2) test with a contingency table to identify potential associations. All quantitative data were presented as mean ± standard deviation (SD) to maintain clarity and consistency in reporting. A p-value of less than 0.05 was considered the threshold for statistical significance, ensuring rigorous interpretation of the results.

RESULTS

Baseline Data

The baseline characteristics of the study participants are presented in Table 1. All individuals included in the study were female, with a mean age of 21 ± 2.0 years (mean ± SD). The majority had completed high school or an equivalent level of education and were currently enrolled as university students in Bandung City. All participants are of Sundanese ethnicity, seen from the subject's father and/or mother being of Sundanese descent. In this respect, the nutritional status of all the study subjects was evaluated after the screening. The average body weight of the participants was 84.3 ± 12.0 kg, while their mean height was recorded at 156.6 ± 5.7 cm. Based on the World Health Organization (WHO) classification, the majority of participants (89.5%) were categorized as obese (BMI ≥30 kg/m²), whereas the remaining 10.5% were classified as non-obese. These findings provide an overview of the anthropometric profile of the study population, highlighting the high prevalence of obesity within the sample.

FTO distribution

The Hardy-Weinberg equilibrium (HWE) for the FTO rs9939609 gene was assessed using chi-square (χ^2) analysis. The findings demonstrated that the genotype distribution was consistent with HWE, as indicated by a p-value greater than 0.05. Additionally, the minor allele frequency (MAF) was calculated to be 0.329, aligning with previously reported data[19-21]. The results of the subject's FTO variant are presented in Table 2. The results show that 19 subjects (50%) had the heterozygous variant TA, 16 subjects (42.1%) had the homozygous variant TT, and the remaining 3 subjects (7.9%) had the variant AA homozygote. If a comparative ratio is made from these results, it is known that the TA:TT: AA ratio is 6.3: 5.3: 1.

These results are similar to Yajnik et al., who found that around 45-50% of subjects had the TT allele, around 40% had the TA allele, and the remaining 10% had the AA allele in type 2 DM subjects of Indo-European ethnicity. The heterozygous variant (TA) is usually the most common, while the homozygous variant A (AA) is the rarest compared to other variants[3,9].

DISCUSSION

The distribution of FTO rs9939609 genotypes among research subjects is a critical aspect of understanding the genetic basis of obesity. For instance, Li et al[23]. proved that AA genotype is more frequently related to higher body mass index and adiposity, while TT genotype exhibited a protective effect against obesity. In a comparative analysis of Asian populations, the AA genotype was found to be in lower proportions than Caucasians, reflecting the allele frequency dispar-

Table 1. Participant's characteristics

Variable	Category	TT (n=16)	AT (n=19)	AA (n=3)	P
Age (years)	18-25	20.8±2.0	21.3±2.1	20.0±0.0	0.547
Education	High School	12 (31.6%)	15 (39.5%)	3 (7.9%)	
	College	4 (10.5%)	4 (10.5%)	0 (0%)	
Work	Student	10 (26.3%)	15 (39.5%)	3 (7.9%)	
	Employee	6 (15.8%)	4 (10.5%)	0 (0%)	
Weight (kg)	-	85.5±10.4	81.2±10.9	97.3±20.3	0.079
Height (cm)	-	156.9±4.4	156.3±6.7	157.3±7.0	0.939
Body mass index (kg/m^2)	-	34.7±4.1	33.2±3.7	39.3±7.9	0.070
Total body fat (%)	-	39.7±2.5	38.4±2.7	41.6±4.4	0.118

All values are mean ± SD (standard deviation).

Table 2. FTO rs9939609 distribution

BMI	Genotypes	*n* (frequency)	% (percentage)	Alleles	*n* (frequency)	% (percentage)	*p*-value
Non-	TT	1	2.6	A	25	32.9	> 0.05
Obese	TA	3	7.9	T	51	67.1	
	AA	0	0.0	Total	76	100.0	
	Subtotal	4	10.5				
Obese	TT	15	39.5				
	TA	16	42.1				
	AA	3	7.9				
	Subtotal	34	89.5				
	Total	38	100.0				

ity previously noted. However, even within Asian populations, variability in genotype distribution exists due to genetic diversity across subpopulations[24]. The findings showed a specific distribution pattern, where the AT genotype was the most common, followed by TT and AA, matching with previous studies in other Asian subgroups. This aligns with the lower prevalence of the A allele in Asian populations compared to Caucasians, as reported in broader genetic studies[25]. Making a comparison of the FTO polymorphism between Asians and Caucasians showed that 41% of Caucasians had the A allele of FTO rs9939609, compared to only 24.8% of Asians; hence, it suggests that Caucasians could be more predisposed to obesity-related to this factor. However, no significant variation could be evidenced in FTO rs9939609 risk allele between Asian and Caucasian populations[5].

Extensive research has demonstrated that individuals harboring the A allele of the FTO rs9939609 polymorphism tend to exhibit significantly higher body weight, body mass index (BMI), waist circumference, hip circumference, and waist-to-hip ratio compared to those with the TT genotype[24,26,27]. A comprehensive meta-analysis further substantiates these findings, indicating that carriers of the A allele have an increased body fat percentage, reinforcing the role of this genetic variant in adiposity regulation[26,28]. Additionally, emerging evidence suggests that waist-to-hip ratio may serve as a more accurate predictor of cardiovascular disease risk than BMI, as it better reflects central adiposity and metabolic health[29,30]. Given these insights, the present study provides valuable foundational data that can inform the development of targeted intervention programs for obesity management at both the individual and population levels.

This study has several notable strengths and limitations. One of its key strengths lies in its focus on a specific population, namely Sundanese obese young women, which addresses a research gap in the genetic study of FTO rs9939609 in this demographic. This study further reinforces the expanding body of literature that establishes a connection between FTO gene polymorphisms and obesity-related phenotypes, including body weight and fat distribution variations. These findings underscore the critical role of genetic predisposition in the etiology of obesity, contributing to a broader understanding of the complex interplay between genetic and environmental factors in metabolic health. Nevertheless, certain limitations must be acknowledged. One notable constraint is the relatively small sample size compared to other studies investigating similar associations. A limited sample may decrease the statistical power of the analysis, potentially affecting the robustness of the findings and limiting their generalizability to broader populations. Future research with larger and more diverse cohorts is necessary to validate these results and enhance their applicability across different demographic groups. A larger sample size would improve the reliability of genotype distribution analysis and strengthen the conclusions. Moreover, the study did not account for potential confounding factors such as lifestyle, diet, and physical activity, which could influence the observed associations.

CONCLUSION

This research is consistent with previous studies, in which the heterozygous variant TA FTO rs9939609 is the most common variant among participants, followed by the homozygous variant TT, called wild-type, and the homozygous variant AA is the least. Even though this research was conducted on Sundanese ethnic women aged 18-25 years who had obese nutritional status based on fat percentage, the ratio between the FTO rs9939609 gene variants was not much different

from other studies that used different types of participants (such as gender, age, comorbidities, ethnicity). This research can be used as primary literature for any further intervention program. Further research may needed using other physiological types of obesity, a greater sample size, or using normal subjects as the control group.

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