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## Original Article

# AT Genotype of FTO rs9939609 Enhances Risk for Central Obesity Under Obesogenic Lifestyle

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**ABSTRACT**

**Background:** Central obesity is a major risk factor for cardiovascular diseases, influenced by both genetic and lifestyle factors. The rs9939609 variant of Fat Mass and Obesity-Associated (FTO) gene has been associated with increased risk of central obesity, potentially modulated by dietary intake and physical activity. This study aimed to investigate the association between the FTO rs9939609 variant and central obesity, and its interaction with dietary intake and physical activity among adults in Jambi, Indonesia.

**Method:** A cross-sectional study was conducted on 175 adults. Central obesity was defined using NCEP ATP III criteria. Dietary intake and physical activity were assessed using 24-hour food recall and the IPAQ, respectively. Genotyping was performed using the Tetra ARMS-PCR. Bivariate analysis was used to assess associations.

**Results:** Individuals with the AT genotype had a significantly increased risk of central obesity (OR= 3.29; 95% CI: 1.30–8.35; p= 0.01). Under the dominant model (AAAT), the association remained significant (OR= 2.90; 95% CI: 1.17-7.16; p= 0.02). The risk was higher among individuals with high caloric intake (OR= 4.64) and low to moderate physical activity (OR= 4.77).

**Conclusion:** The FTO rs9939609 variant is associated with increased central obesity risk, and in the presence of obesogenic lifestyle factors.

**Keywords:** FTO; rs9939609; central obesity; dietary intake; physical activity.

## INTRODUCTION

Central obesity, defined as the accumulation of visceral fat in the abdominal region, is a major contributor to metabolic syndrome and cardiovascular diseases. The global prevalence of central obesity has been rising steadily, with a systematic review reporting that approximately 41.5% of adults worldwide were centrally obese as of 2020.[1] In Indonesia, central obesity is also a growing concern. The 2018 Basic Health Research (RISKESDAS) reported a prevalence of 28.3% among adults. This trend is also evident in Jambi Province, where central obesity contributes significantly to the regional burden of non-communicable diseases.[2]

Central obesity is a multifactorial condition influenced by both environmental and genetic factors. While lifestyle behaviors such as unhealthy diets, high intake of saturated fat, and sedentary lifestyles are well-established risk factors, genetic predisposition also plays a critical role in determining an individual's susceptibility to fat accumulation, particularly in the abdominal area. Among the genetic contributors, the Fat Mass and Obesity-Associated (FTO) gene has emerged as one of the most consistently implicated genes in the development of obesity. A single nucleotide polymorphism (SNP) in this gene, rs9939609, located in intron 1, has shown a strong association with obesity risk across diverse populations.[3,4]

The A allele of rs9939609 has been associated with higher body mass index (BMI), increased waist circumference, and central adiposity. Mechanistically, this allele is thought to increase FTO gene expression in the hypothalamus, affecting neural circuits involved in hunger and satiety. Furthermore, it influences the expression of downstream genes such as IRX3 and IRX5, which promote the development of white adipocytes and reduce the thermogenic capacity of adipose tissue.[4] Carriers of the A allele also tend to consume more calories, particularly from fat-rich and energy-dense foods, which further contributes to obesity risk.[5,6]

However, the association between FTO gene variants and obesity is not universally consistent. Several studies have suggested that the phenotypic expression of FTO-related risk is highly dependent on environmental exposures, especially dietary patterns and physical activity levels. Individuals carrying the A allele who maintain healthy lifestyles may not exhibit increased obesity risk, while those with poor lifestyle habits are more likely to be affected.[7] These findings highlight the significance of gene–environment interaction in modulating obesity susceptibility.

To the best of our knowledge, research on the FTO rs9939609 variant and its association with central obesity remains limited in Jambi population. This study aims to investigate the association between the FTO rs9939609 variant and central obesity, as well as its interaction with dietary intake and physical activity among adults in Jambi population.

## METHOD

### Participants

This cross-sectional study involved 165 participants residing in Jambi, Indonesia. The participants were divided into two groups: 64 individuals with central obesity and 101 individuals without central obesity (control group). Eligible participants were aged between 19 and 59 years. Exclusion criteria included pregnancy, breastfeeding, and currently undergoing a weight-loss or dietary program. Ethical approval for this study was obtained from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Universitas Jambi with number 1893/UN21.8/PT.01.04/2024.

### Anthropometric Measurement

Waist circumference was measured at the midpoint between the superior iliac spine and the lower margin of the last palpable rib using a non-elastic anthropometric tape following the World Health Organization (WHO) protocol.[8] Central obesity was defined according to the criteria by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), which classifies central obesity as a waist circumference of ≥102 cm for men and ≥88 cm for women.[9]

### Dietary Intake Assessment

Dietary intake was evaluated using a 24-hour food recall method conducted on two weekdays and one weekend day to represent habitual dietary patterns. This method is widely used in epidemiological studies for its practicality and ability to capture short-term dietary intake with reasonable accuracy.[10] The collected data were analyzed using the Nutrisurvey software. Based on total caloric

intake, participants were categorized into two groups: low-to-normal intake and high intake.

**Physical Activity Assessment**

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), which records physical activity across various domains. The IPAQ is validated and commonly used in international physical activity surveillance due to its ease of administration and comparability across studies.[11] The results were expressed in metabolic equivalent task (MET)-minutes per week and categorized into two groups: low-to-moderate activity (<3000 MET-min/week) and high activity (≥3000 MET-min/week).

**Genotyping**

Peripheral venous blood samples were collected for DNA extraction using the Favorgen DNA extraction kit. Genotyping of the FTO rs9939609 variant was performed using the Tetra-primer Amplification Refractory Mutation System Polymerase Chain Reaction (ARMS-PCR) method.[12] The PCR mixture (25 µl total volume) contained 15 µl master mix, 1 µl of each primer, 1 µl DNA sample, and 5 µl nuclease-free water. PCR conditions were as follows: initial denaturation at 94°C for 4 minutes, followed by 35 cycles of denaturation at 94°C for 35 seconds, annealing at 59°C for 45 seconds, and extension at 72°C for 45 seconds, with a final extension at 72°C for 10 minutes. A negative control was included in each PCR run to ensure amplification specificity and rule out contamination. PCR products were visualized using 2% agarose gel electrophoresis under UV illumination.

**Table 1**. FTO gene rs9939609 primer[13]

| FTO gene rs9939609 | Forward primer | Reverse primer | Product size |
|---|---|---|---|
| Outer | 5'-GTT CTA CAG TTC CAG TCA TTT TTG ACA GC-3' | 5'-AGC CTC TCT ACC ATC TTA TGT CCA AAC A-3' | 436 bp |
| Inner | 5'-TAG GTT CCT TGC GAC TGC TGT GAA TAT A-3' | 5'-GAG TAA CAG AGA CTA TCC AAG TGC ATC TCA-3' | Alel T: 293bp<br>Alel A: 201bp |

**Statistical analysis**

Genotype distributions and associations with central obesity were analyzed using bivariate analysis with Pearson's Chi-square test and Fisher's Exact test. Stratified analyses were conducted to examine interactions between FTO rs9939609 genotype and dietary caloric intake or physical activity levels. A p-value of <0.05 was considered statistically significant. All analyses were conducted using IBM SPSS statistic software.

## RESULTS

**Basic subject characteristics**

The baseline characteristics of study subjects in the central obesity and control groups are presented in Table 2. The median age of participants in the central obesity group was significantly higher compared to the control group. There was a significant difference in gender distribution between two groups, with a lower proportion of males in the central obesity group than in the control group. Daily caloric intake, categorized as low to normal, and high, did not differ significantly between the groups. Similarly, total physical activity (measured in MET-minutes/week) did not show a significant difference between the central obesity and control groups.

**Table 2**. Basic Subject Characteristics

| Characteristic | Central Obesity (n=73) | Control (n=102) | p-value |
|---|---|---|---|
| Age (years) | 40.5 (19.0-64.0) | 34.0 (16.0-68.0) | **0.020**[b] |
| Gender | | | |
| - Male | 7 | 50 | **<0.001**[a] |
| - Female | 66 | 52 | |
| Total calories (Kcal/day) | | | |
| - Low to normal | 29 | 42 | 0.847[a] |
| High | 44 | 60 | |
| Physical activity (MET-minutes/week) | | | |
| - Low to moderate | | | |
| - High | 59 | 84 | 0.796[a] |
| | 14 | 18 | |

[a]*chi-square;* [b]*non-parametric test*

## Genotyping

Following PCR amplification, the resulting products were analyzed by electrophoresis on a 2% agarose gel. The PCR products were visualized under ultraviolet (UV) light to detect DNA fragments. The results of the PCR amplification are shown in Figure 1.

Genotyping of the FTO rs9939609 variants was performed using the Tetra-AMRS PCR method. The genotyping results showed that homozygous TT (wildtype) produced DNA fragment of 293 and 436 bp; homozygous AA (variant) yielded fragment of 201 and 436 bp; and heterozygous AT was identified by presence of DNA fragments at 201, 293, and 436 bp.

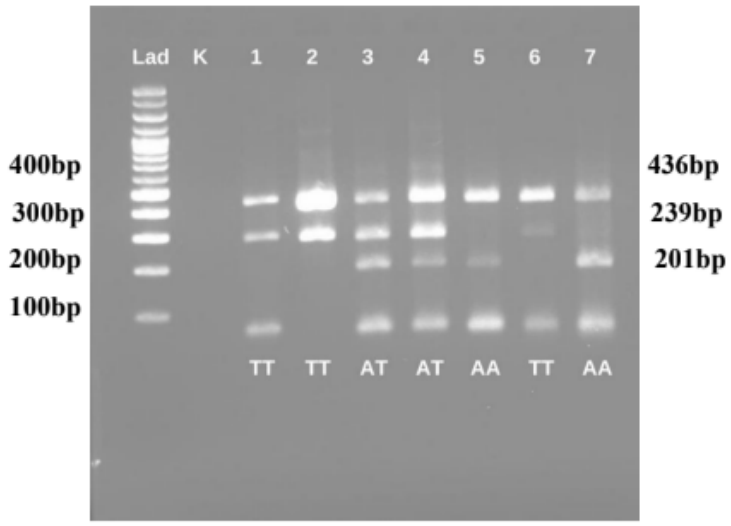


**Figure 1**. Identification of FTO rs9939609 variant using the ARMS-PCR method. TT = homozygous wildtype; AT = heterozygous; AA = homozygous variant; Lad = marker; and K = negative control.

**Table 3.** Genotype distribution and Hardy Weinberg Equilibrium

| Genotype | Observation Frequency | Expected Frequency | χ2 | p-value | MAF |
|---|---|---|---|---|---|
| TT | 31 | 36.6 | 2.88 | 0.08 | 0.45 |
| AT | 98 | 86.8 | | | |
| AA | 46 | 51.6 | | | |

MAF: Minor Allele Frequency

**Genotype distribution and Hardy-Weinberg Equilibrium**

Table 3 shows the genotype distribution and Hardy-Weinberg equilibrium analysis. A total of 175 individuals were genotyped for FTO gene variant. The genotype distribution did not deviate significantly from Hardy-Weinberg equilibrium (p = 0.08).

**Association between FTO rs9939609 and central obesity in relation to dietary caloric intake and physical activity levels**

Association of FTO rs9939609 and central obesity shown in Table 4. Subjects with the heterozygous AT genotype had a significantly higher risk of central obesity compared to those with the wild-type TT genotype, with an Odds ratio (OR) of 3.29 (95% CI: 1.30–8.35; p = 0.01). Subjects with the homozygous risk genotype AA also showed an increase risk of central obesity compared to the TT genotype, although the association was not statistically significant (OR = 2.20; 95% CI: 0.79–6.17; p = 0.13). Under the dominant model (AAAT vs TT), a significant association with central obesity was observed with an OR of 2.90 (95% CI: 1.17–7.16; p = 0.02).

**Table 4.** Association Of FTO Rs9939609 Gene Variation With Central Obesity

| Genotype | Central obesity (n) | Control (n) | *p-value* | OR (95% CI) |
|---|---|---|---|---|
| TT | 4 | 13 | ref | |
| AT | 34 | 23 | **0.009**[a] | **4.80 (1.39-16.59)** |
| AA | 4 | 3 | 0.167[b] | 4.33 (0.67-28.11) |
| AAAT | 38 | 26 | **0.009** | **4.75 (1.39-16.20)** |

*[a]Chi-square; [b]Fisher exact test*

**Tabel 5.** The Association Between FTO Rs9939609 Variant And Central Obesity Stratified By Dietary Caloric Intake

| Genotype | Low to normal dietary intake | | p-value | OR (95% CI) | High dietary intake | | p-value | OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | Central Obesity (n = 29) | Control (n = 42) | | | Central Obesity (n = 44) | Control (n = 60) | | Central Obesity (n = 29) |
| TT | 3 | 8 | ref | | 4 | 16 | TT | 3 |
| AT | 19 | 25 | 0.49[b] | 2.03 (0.47-8.68) | 29 | 25 | AT | 19 |
| AA | 7 | 9 | 0.45[b] | 2.07 (0.39-10.84) | 11 | 19 | AA | 7 |
| AAAT | 26 | 34 | 0.51[b] | 2.04 (0.49-8.45) | 40 | 44 | AAAT | 26 |

*[a]Chi-square; [b]Fisher exact test*

The bivariate analysis of the FTO rs9939609 variant and central obesity, stratified by dietary caloric intake shown in Table 5. In the group with low to normal caloric intake, there was no statically significant association between the risk genotypes (AT and AA) and central obesity. The dominant model (AAAT vs TT) also did not show a significant association. However, in the high-calorie intake group, a significant association was found between the AT genotype and central obesity. Subjects with the AT genotype had a significantly higher risk of central obesity compared to those with TT genotype (OR = 4.64; 95% CI: 1.37–15.70; p = 0.01). A similar result was observed under the dominant model (AAAT vs TT) with an OR of 3.64 (95% CI: 1.12–11.79; p = 0.02).

**Table 6.** The association between FTO rs9939609 variant and central obesity stratified by physical activity

| Genotype | Low to moderate physical activity | | *p-value* | OR (95% CI) | High physical activity | | *p-value* | OR (95% CI) Central Obesity (n = 59) |
|---|---|---|---|---|---|---|---|---|
| | Central Obesity (n = 59) | Control (n = 84) | | | Central Obesity (n = 14) | Control (n = 18) | | |
| TT | 4 | 20 | ref | | 3 | 4 | TT | 4 |
| AT | 41 | 43 | **0.01[a]** | **4.77 (1.05-15.14)** | 7 | 7 | AT | 41 |
| AA | 14 | 21 | 0.06[a] | 3.33 (0.94-11.85) | 4 | 7 | AA | 14 |
| AAAT | 55 | 64 | **0.01[a]** | **4.30 (1.38-13.33)** | 11 | 14 | AAAT | 55 |

*[a]Chi-square; [b]Fisher exact test*

The analysis of the association between FTO variant and central obesity based on physical activity level is shown in Table 6. Among individuals with low to moderate physical activity the heterozygous AT genotype was significantly associated with an increased risk of central obesity (OR = 4.77; 95% CI: 1.05–15.14; p = 0.01). The homozygous risk genotype AA also showed an increase risk, although the association was not statistically significant (OR = 3.33; 95% CI: 0.94–11.85; p = 0.06). The dominant model (AAAT vs TT) showed a significant association with central obesity (OR = 4.30; 95% CI: 1.38–13.33; p = 0.01). In contrast, no significant association was found between risk genotypes and central obesity among individuals with high physical activity.

## DISCUSSION

This study demonstrated a significant association between the FTO rs9939609 gene variant and central obesity in the Jambi population. Specifically, individuals carrying the heterozygous AT genotype showed a markedly increased risk of central obesity, and this association was even more pronounced in those with high caloric intake and low-to-moderate physical activity.

In addition to genetic findings, participant characteristics showed that both age and gender differed significantly between the central obesity and control groups. Individuals in the central obesity group were older, suggesting that aging contributed to visceral fat accumulation through physiological mechanisms including hormonal changes, decreased basal metabolic rate and reduced physical activity.[1,14] Moreover, the higher prevalence of central obesity among females may be attributed to hormonal differences that influence fat distribution, particularly postmenopausal shifts in estrogen levels.[15]

These findings are consistent with previous studies across diverse populations, which report that the A allele of the FTO gene is associated with increased body mass index (BMI) and central adiposity, particularly under obesogenic environmental exposures.[2,16,17] In this study, the Minor Allele Frequency (MAF) of the A allele in this study was 0.45, aligning with previous reports from Asian populations, where MAFs typically range from 0.40 to 0.48.[18,19] The A allele is more prevalent in European populations (0.45–0.50), less common in African populations (0.12–0.18), and shows intermediate frequency in East and Southeast Asian populations (0.40–0.48), consistent with our findings.[20-22] This suggests that the genetic predisposition conferred by FTO rs9939609 may vary across ethnic groups, emphasizing the importance of population-specific research in understanding its impact on obesity phenotypes.

The association between FTO rs9939609 and central obesity has also been reported in various populations. In European cohorts, the A allele has been strongly associated with waist circumference and visceral fat accumulations, independent of BMI.[22-23] Studies in Middle Eastern populations have similarly observed a higher risk of central obesity among AA or AT genotype carriers, particularly in high-calorie diets and sedentary lifestyles.[24,25] In Asian populations, including Chinese and Malaysian cohorts, carriers of the A allele showed significantly higher central adiposity markers and body fat distribution indices.[26,27] These findings support the cross-ethnic relevance of FTO in modulating central fat accumulation, although effect sizes may vary depending on genetic background, cultural dietary habits, and environmental exposures.

This study highlights the role of gene-environment interaction. Participants with high caloric intake and the AT genotype had up to a 4.64-fold increased risk of central obesity. Previous studies showed that carriers of the A allele tend to consume fat, carbohydrates and total energy.[5,6,28] Functional MRI studies show that individuals carrying the A allele of rs9939609 exhibit increased activation of reward-related brain regions in response to high-calorie food cues, which may lead to greater susceptibility to overeating.[29]

This increased consumption may be driven by the polymorphism's impact on appetite regulation and preference for energy-dense foods.[30,31] Conversely, physical activity appeared to attenuate the genetic risk. Among participants with high levels of physical activity, the association between FTO genotype and central obesity was not statistically significant. This suggests that physical activity may counterbalance the obesogenic effects of the A allele by improving energy expenditure, increasing insulin sensitivity, and modifying adipokine profiles.[7,32,33] This gene–environment interaction has been reported in other populations, and it reinforces the value of lifestyle interventions, particularly increasing physical activity and moderating caloric intake in mitigating genetic susceptibility to obesity.[34,35] A previous study showed that poor dietary patterns and physical inactivity significantly contributed to the increased prevalence of obesity among urban adults in Jambi.[36] These findings reinforce the importance of addressing modifiable lifestyle factors in populations with a genetic predisposition to obesity.

At the molecular level, the A allele of rs9939609 increases expression of the FTO gene in the hypothalamus, affecting neural pathways that regulate hunger and satiety.[29] Additionally, this allele alters the expression of IRX3 and IRX5 genes, promoting the differentiation of white adipocytes over beige adipocytes, which have energy-burning properties, thereby contributing to fat accumulation.[4] These biological pathways provides a plausible basis for explaining the association between FTO gene variant, dietary intake, and physical activity in central obesity. Findings from other populations also indicate that the A allele of FTO affects food preferences and nutrient consumption patterns, supporting the interpretation that genetic risk may be mediated by behavior.[30,37,38] A prior study proposed that FTO polymorphisms not only regulate hypothalamic pathways, but also modulate peripheral lipid metabolism and adipogenesis, supporting their role as potential biomarkers in precision nutrition approaches.[39] Based on these findings, lifestyle interventions, such as individualized dietary modifications and increased physical activity remain critical approaches, especially in individuals with higher genetic susceptibility.

## CONCLUSION

This study highlights the significant association of FTO rs9939609 gene variant, particularly AT genotype, and central obesity in the Jambi population. The genetic risk was more pronounced among individuals with high caloric intake and low to moderate physical activity. These findings suggest the need for further investigation into gene-environment interactions and support the potential utility of personalized lifestyle interventions based on genetic risk profiles to reduce the burden of central obesity within the community.

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