International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Analysis of FTO rs9939609 and MTHFR C677T Genotype among First Derivatives of DMT2 from Bengkulu's Lembak Ethnicity

Elvira Yunita[1], Risti Dwi Ocktaviani[2], Tiara Armilia Putri[2], Noor Diah Erlinawati[3], Besly Sinuhaji[4], Nikki Aldi Massardi[5], Annelin Kurniati[6], Sipriyadi[7], Diah Ayu Aguspa Dita[8]

[1]*Department of Biochemistry and Molecular Biology, Faculty of Medicine and Health Sciences, Bengkulu University, Indonesia.*
[2]*Medical Study Program, Faculty of Medicine and Health Sciences, Bengkulu University, Indonesia*
[3]*Department of Clinical Nutrition, Faculty of Medicine and Health Sciences, Bengkulu University, Indonesia.*
[4]*Department of Clinical Pathology, Suprapto Mental Hospital, Bengkulu, Indonesia.*
[5]*Department of Anatomical Pathology, Faculty of Medicine and Health Sciences Bengkulu University, Indonesia.*
[6]*Department of Internal Medicine, Faculty of Medicine and Health Sciences, University of Bengkulu, Bengkulu, Indonesia.*
[7]*Department of Microbiology, Faculty of Mathematics and Natural Sciences, Bengkulu University, Indonesia.*
[8]*Department of Medical Physiology, Faculty of Medicine and Health Sciences, Bengkulu University, Indonesia.*

Abstract

Obesity and hypertension are hereditary metabolic disorders caused by both genetic factors and unhealthy dietary practices. The FTO rs9939609 gene, characterized by Single Nucleotide Polymorphisms (SNP), impacts the control of appetite and fullness, as well as the propensity to choose energy-dense food choices. The MTHFR C677T gene polymorphism has been correlated to the progression of hypertension by beverages like coffee and tea. The Lembak Bengkulu tribe, specifically the "Neron" group, engages in the practice of consuming excessive amounts of sugar. This study was conducted on 58 samples obtained from the first derivation of the Lembak ethnic group in Bengkulu City. The samples were divided into two groups using consecutive sampling techniques. The presence of Single Nucleotide Polymorphisms (SNPs) was identified by the use of Polymerase Chain Reaction-Restriction Fragment Length Polymorphisms (PCR-RFLP). The analysis of gene polymorphisms was conducted using the chi-square test. The genotypic identification results of the FTO rs9939609 gene polymorphism indicate that the percentage of the risk allele was higher in the first-generation T2DM group. The FTO rs9939609 gene polymorphism was found to be linked to central obesity (p:0.004), and individuals with the AA/AT genotype had a significantly higher risk of central obesity, up to 18 times greater, compared to those with the TT genotype. No powerful associations were found between the MTHFR C677T gene polymorphism and the risk of hypertension in all genetic models examined in the logistic regression analysis. There was a significant correlation between the history of DM in parents with the likelihood of developing hypertension (p: 0.035). High blood pressure is more common among the Lembak Ethnic in Bengkulu City if there is a history of diabetes in the family.

Keywords: : central obesity, DMT2, FTO gene, lembak ethnic

Full length article **Corresponding Author*, e-mail: diahayuaguspadita@unib.ac.id

1. Introduction

The Lembak ethnic is one of the indigenous ethnics in Bengkulu Province. The Lembak people usually consume coffee or tea along with snacks such as pastries as a companion. This tradition or habit is known as "Neron". The frequency of neron by the Lembak people reaches 2-3 times a day or more. In doing Neron, the people of Lembak serve it with a ratio of coffee/tea and sugar, which is 1:2 tablespoons, and some people often add sugar if it is not sweet enough. This tradition or habit can be considered as a predisposing factor and a possible basis for the heritability of obesity and other metabolic diseases due to the high intake of simple carbohydrates in the Lembak people. Obesity is a global problem that is still a concern for the world of health. Obesity is the world's fifth largest cause of mortality [1]. Every year, at least 2.8 million individuals worldwide die as a result of obesity, with 44% of them suffering from diabetes [1]. Obese sufferers in Indonesia in 2018 reached 21.8%, this figure increased compared to 2013 which was 14.8% [2]. Previous research found that several gene loci contributed to the occurrence of obesity [3]. Numerous prominent obesity-related genes, such as the Fat-mass and Obesity Associated (FTO) gene polymorphism rs9939609, have been extensively investigated across diverse ethnic populations, with a special focus on European cohorts [4]. The study conducted before revealed a correlation between the FTO rs9939609 polymorphism and obesity among young women belonging to the Minangkabau ethnic group, which can be attributed to their dietary patterns [3]. The results align with the research conducted by Daya et al. (2019), whereby they observed a correlation between the FTO rs9939609 gene polymorphism and both the susceptibility to obesity and the inclination towards energy-dense meals among certain individuals in Indonesia [5]. The presence of SNPs in the FTO gene reduces the expression of these genes, affecting adiposity [6], insulin resistance, and body weight management, including energy intake [7].

Major risk factors for cardiovascular disorders such as coronary heart disease, stroke, and heart failure include hypertension. The prevalence of hypertension is predicted to increase by 15–20% by 2025 [8]. Hypertension is associated with risk factors of genetics that can be determined through the manifestation of specific genes. The MTHFR C677T gene polymorphism is one of the genetic variables associated with hypertension. Researchers observed that increased levels of homocysteine (Hcy) in the blood were linked to the MTHFR C677T gene polymorphism. Plaque on the endothelial wall deposits and grows in response to raised blood Hcy levels [9,10]. Both obesity and hypertension are abnormalities that are strongly associated with type 2 diabetes mellitus.

Our previous publication showed that some genes are related as risk factors in degenerative diseases like heart coronary and type 2 diabetes mellitus [11–15]. Currently, there is insufficient data available to provide a report on the expression of these genes in the first-generation offspring of individuals with Type 2 Diabetes Mellitus (T2DM) in the Lembak Tribe of Bengkulu City. The present study was undertaken by researchers to investigate the potential association between the FTO rs9939609 gene polymorphism and the susceptibility to central obesity in individuals diagnosed with F1 type 2 diabetes mellitus (F1 DMT2) from the Lembak ethnic group residing in Bengkulu City. This study also analyses genotype polymorphism in MTHFR C677T. Performing a genotype polymorphism study of these genes can serve as a proactive measure for the initial offspring of individuals with type 2 diabetes mellitus (T2DM) who have a genetic predisposition to obesity and hypertension. So that preventive actions can be taken before obesity and hypertension develop.

2. Materials and methods

2.1. Participants and Sample Size

In this study, two groups were observed, namely the control/non-DM type 2 derivative group and the test/DM type 2 derivative group. Based on the categorical descriptive formula, a sample of 30 people was obtained in each group. the samples come from the Lembak ethnic who follow the Neron tradition (Fig. 1).

2.2. Anthropometric Measuring

The physical examinations carried out in this study were measurements of body weight, height, waist circumference, blood pressure, and BMI calculations. Body weight was measured to the nearest 0.1 kg while wearing exceptionally lightweight clothes. The light clothes lacked adaptability. Height measurements were obtained using a microtoise, with precision to the nearest 0.1 cm. The measurements were taken in a standing position, with the individual wearing socks and without any footwear. Germany, officially known as the Federal Republic of Germany (FRG), is a country located in Central Europe. It is bordered by the measurement of waist circumference was conducted in centimeters, with an accuracy of 0.1 cm. This measurement was taken when the participant was in a standing position, with their abdomen relaxed, feet together, and body weight evenly distributed over both legs. A flexible nonelastic tape, manufactured by Roche in Switzerland, was used for this purpose. All anthropometric measurements were obtained twice, with the average results used for data analysis.

2.3. DNA Isolation and PCR-RFLP

Blood samples were taken in the morning, followed by DNA isolation using the Promega Wizard® A1120 kit. Next, the concentration and purity of DNA were measured using the NanoDropTMOne Microvolume UV-Vis Spectrophotometer. The Polymerase Chain Reaction restriction fragment length polymorphism (PCR-RFLP) technique was been conducted to examine the expression of FTO rs9939609 and MTHFR C677T gene. Agilent Technologies SureCycler 8800 conventional PCR and GoTaq® Hot Start Green Master Mix M5122 Kit (Promega, Madison) were used for PCR-RFLP. This investigation used HinfI ER0801 and Apo1 (Thermo Scientific, Singapore) restriction enzymes. The Bioline HyperladderTM 100 bp BIO-33056 marker and BIO-RAD Mini-Sub Cell GT System electrophoresed were used in visualization. IBM SPSS 26 analyzed data.

A single PCR reaction consists of 50µl, comprising 5µl of reverse primer, 5µl of forward primer, 5µl of DNA template, 25µl of GoTaq® Green Master Mix, and the addition of

nuclease-free water (NFW) to achieve a final volume of 50µL. The PCR reaction conditions were as follows: an initial denaturation step at a temperature of 95°C for a duration of 5 minutes, performed once. Subsequently, denaturation was carried out at a temperature of 94°C for a duration of 30 seconds, followed by annealing at a temperature of 54°C for a duration of 30 seconds. Extension was then performed at a temperature of 71°C for a duration of 30 seconds, repeated for a total of 34 cycles. Finally, a final extension step was conducted at a temperature of 72°C for a duration of 5 minutes, performed once. The PCR-RFLP method was conducted with the addition of 5 µl of PCR amplification results and 0.5 µl of restriction enzyme Apo1 for FTO rs9939609 and HinfI for MTHFR C677T gene polymorphism. Amount 1 µl of tango and NFW were added to a total reaction volume of 10 µl, then incubated for 16 hours at 37oC. Then the PCR-RFLP results were electrophoresed and observed using gel documentation.

2.4. Statistical Analyses

SPSS version 26 was used to analyze the whole data. The Shapiro-Wilk test was employed to assess the normality of the data. The study presented continuous variables that followed a normal distribution using the format mean ± standard deviation (SD), while variables with non-normal distributions were presented as mean (minimum-maximum). Chi-square analyses were employed to compute the disparities among categorical variables.

3. Results and Discussions

3.1. Subject Characteristics

A total of 60 people participated in this study, consisting of 30 people with F1 diabetes mellitus type 2 and 30 people with F1 non diabetes mellitus type 2. Table 1 shows that in the F1 group DM was dominated by women (58, 6%), and the F1 non-DM group was dominated by men (51.7%). Based on the age range, it was found that both groups were dominated by the age range of 15-25 years (51.7%) in the F1 DM group and 79.3% in the F1 non-DM group. Due to the implementation of a random sampling technique in this study, all individuals who met the requirements for exclusion and inclusion were included. Based on a family history of obesity, it was found that 41.4% of subjects in the F1 DMT2 group had a history of obesity in their core family and 6.9% of F1 non-DMT2 subjects had a history of obesity in their core family. Both research groups had normal BMIs ranging from 18.5-25.0 kg/m2. Based on the results of waist circumference measurements, 65.5% of subjects were classified as central obese in the F1 DMT2 group. Meanwhile, in the F1 non-DMT2 group, there were 20.7% classified as central obesity. In the F1 DMT2 group, 65.5% were determined to be centrally obese. Meanwhile, in the F1 non-DMT2 group, there were 79.3% of subjects had waist circumference in the normal category. From these results, it can be seen that the F1 DMT2 group tends to central obesity, this is suspected to be related to a family history of obesity and its interaction with genetics. According to Morales et al, the FTO rs 9939609 polymorphism is linked to higher body weight and waist circumference [3]. Figure 2 shows that the first derivatives of DM sufferers tend to have higher mean systolic blood pressure (122.83 ± 9.348 vs 117.17 ± 11.498) and diastolic (79.33 ± 5.040 vs 76.17 ± 7.032) than the first derivatives of non-DM. The comparison showed no statistically significant difference. Analysis of blood pressure was also performed in the history of DMT2 parents. There was a significant correlation between histories of DM in parents with the likelihood of developing hypertension (p:0.035).

3.2. FTO rs9939609 and MTHFR C677T Genotypes

The PCR amplification of the research samples on electrophoresis produced a band at 105 bp. The results of cutting using restriction enzymes in the study sample obtained bands at 105 bp (AA), 105 bp, 85 bp, and 20 bp (AT), and 85 bp and 20 bp (TT) as shown in Figure 3. Figure 4 displayed MTHFR C677T gene restriction findings in lanes 1, 2, 3, 4, 5, 6, and 7 and a 100 bp ladder marker in lane M. Lane 1 has the TT (homozygous polymorphic) genotype restriction at 175 bp. The CT genotype (heterozygous polymorphism) cut at 198 and 175 bp in lanes 2, 3, and 6. CC (wild type) genotypes are clipped at 198 bp in lanes 4, 5, and 7. Table 2 revealed that the frequency of the genotypes FTO rs9939609 of the F1 non-DMT2 and F1 DMT2 from the Lembak ethnicity of Bengkulu City. Based on the genotype identification of the FTO rs9939609 gene polymorphism results presented in Table 2, it can be observed that the frequency of the AA genotype (Homozygous Mutant) was higher in the F1 DMT2 population. However, it should be noted that the observed difference was not statistically significant (p: 0.189; $p > 0.05$). The AT (Heterozygous Mutant) genotype was found in 37.9% of the F1 non-DMT2 group compared to the F1 DMT2 group (27.6%). The TT genotype (Wildtype) was found to be less in the F1 DMT2 (13.8%) than in the F2 non-DMT2 group (20.7%). The allele A frequency was found more frequently in the F1 DMT2 group (36.2%) than in the F1 non-DMT2 group (30.2%). The T allele was found to be more common in the F1 non-DMT2 group (19.8%) than in the F1 DMT2 group (13.8%). The minor allele frequency (MAF) of SNP rs9939609 (allele A) was found to be 66.4% in the general population. The observed frequencies of alleles in the two groups did not exhibit a statistically significant difference (p: 0.169). Therefore, it can be said that the FTO rs9939609 gene shows no influence and association with the first generation of type 2 DM in the Lembak ethnic population of Bengkulu City. In their study, Xi et al. (2010) identified a significant association between the FTO rs 9939609 polymorphism and many anthropometric measures, including body weight, waist circumference, waist-to-hip circumference ratio, BMI, and percentage of body fat, in a population of children and adolescents [16]. In the F1 DMT2 group, 19 people (65.5%) were found to be centrally obese category. Meanwhile, in the F1 non-DMT2 group, 6 people (20.7%) had waist circumference in the central obesity category. From these results, it can be seen that the F1 DMT2 group tends to central obesity, this is suspected to be related to a family history of obesity and its interaction with genetics. Genetic interactions such as the FTO rs 9939609 gene polymorphism are associated with an increase in waist circumference [3]. The findings align with previous research conducted on the adult population in Pakistan, which revealed a significant association between the FTO rs9939609 gene and waist circumference [17].

The DM's first derivatives group in this study showed that wildtype homozygous genotypes (CC), heterozygous (CT), and polymorphism (TT) with percentages of 66.66%, 30.00%, and 3.33%, respectively (p: 1.000). Hardy-Weinberg Equilibrium (HWE) calculations showed that the DM's first derivatives sample population was in HWE (p> 0.05). The first derivatives group of non-DM showed that CC genotypes (76.66%), CT genotypes (16.66%), and TT genotypes (6.66%) (p: 0,165) (Table 2). In this population, mutation is present if the HWE p-value is greater than 0.05. The data of this study showed that the prevalence of the MTHFR C677T gene variant was greater in the first-generation parents with diabetes mellitus than in the other group. First-generation people with DM are 1.64 times more likely to have the MTHFR C677T gene polymorphism than first-generation people without DM.

The results showed that Bengkulu City's Lembak Ethnic had parents with DM and non-DM. Parental DM increased hypertension risk (p: 0.035). Diabetes-related insulin resistance and hyperinsulinemia raise blood pressure. Insulin increases salt resistance, sympathetic nervous system activity, and endothelial cell function due to decreased NO availability [18]. Case-control investigation on hypertension exposure variables, the OR between parents' diabetes and their offspring's hypertension was 16.537 (95%CI 10.070–21.157) [19]. This statistical test shows that people with DM parents are 16.537 times more likely to have hypertension than those without. Having a parent or sibling with diabetes is a strong predictor of developing hypertension in one's offspring [19].

3.3. FTO rs9939609 Genotype is Linked to Central Obesity

The findings presented in Table 3 demonstrate the correlation between the FTO rs9939609 gene polymorphism and central obesity among the F1 non-DMT2 and F1 DMT2 groups. AA/AT genotype was higher in the CO group on F1 DMT2 than in the other group. Results analysis demonstrating the determinants of central obesity are available in Table 4. According to Table 4, persons with the AA/AT genotype had an 18 times greater risk of central obesity than those with the TT genotype. Females, in addition to possessing a familial predisposition towards fat, exhibit an elevated susceptibility to the development of central obesity. Gender, age, family history of obesity, DMT2 paternal history, and genotype were statistically associated (p: 0.05).

3.4. Hypertension and MTHFR C677T Gene Polymorphism

According to the data presented in Table 5, the majority of samples in both groups exhibited the CC genotype of the MTHFR C677T gene. Individuals in the pre-hypertension group exhibit a higher likelihood of possessing a CC genotype, which is 1.643 times more prevalent compared to the group with normal blood pressure. Pre-hypertension has 2.071 times more recessive genotypes than normal blood pressure. Pre-hypertension patients are 1.455 times more likely to have the co-dominant genotype. Pre-hypertension had 1.625 times more allele C than normal blood pressure.

The data of this study showed that the Lembak Ethnic group of Bengkulu City did not correlate with hypertension and the MTHFR C677T gene polymorphism. The development of hypertension in individuals under the age of 40 can be influenced by factors beyond genetics. However, numerous more risk factors exist that exert a more substantial influence on the development of hypertension within a shorter timeframe. Genes play a role in determining the susceptibility to hypertension, but additional risk factors are required for the hypertensive phenotype to emerge. Khasanah's (2022) research shows that the case number of hypertension in Indonesians aged 18 is affected by several factors. Gender (p: 0.000), age (p: 0.000), activity level (p: 0.015), and weight status (p: 0.000) all fall into this category [20]. Previous studies have linked the MTHFR C677T polymorphism to a rising risk of developing hypertension.

The MTHFR C677T polymorphism causes a change in the amino acid sequence, from alanine to valine, which leads to the development of a thermally unstable enzyme. Individuals possessing the TT genotype exhibit a reduced enzyme activity of around 30% than the individuals with the MTHFR C677C (wildtype) genotype. Similarly, individuals with the CT genotype have a diminished enzyme activity of only 65% when compared to the standard level of enzyme activity [21]. Consequently, cellular synthesis of 5-methylTHF and S-adenosylmethionine (SAM) is diminished [22]. The findings from in vitro investigations conducted on Escherichia coli indicate that MTHFR mutations result in a greater loss of FAD cofactors compared to enzymes with the wild-type genotype. Consequently, this reduction in FAD cofactors leads to a decrease in the overall functionality of the MTHFR enzymes [23]. Within the one-carbon metabolic cycle, the FAD-dependent methylenetetrahydrofolate reductase (MTHFR) enzyme plays a major step in the synthesis of 5-methyltetrahydrofolate (5-methylTHF).

A person with the TT genotype had more decreasing levels of 5-methylTHF and higher levels of 10-formylTHF in their red blood cells. Reduced MTHFR enzyme activity has been linked to a change in folate distribution in RBCs, as observed here [24]. The mutant enzyme also had a mutation in its active site, which impaired its ability to bind FAD [25]. Modulating endothelial nitric oxide synthase (eNOS) activity is another potential mechanism through which MTHFR contributes to the onset of hypertension [26]. Independent of the MTHFR C677T genotype, previous research has shown a link between 5-methylTHF levels in vascular tissue and endothelial function. This relationship is mediated by the nitric oxide (NO) generation pathway, wherein prostacyclin serves as a vasodilator [27,28]. Nitric Oxide (NO) protects the endothelium from Hcy by producing S-nitroso homocysteine which can inhibit the formation of oxidative compounds Hydrogen Peroxide (H2O2) [28]. The availability of nitric oxide (NO) and the action of endothelial nitric oxide synthase (eNOS) are both tightly regulated by vascular 5-methylTHF [29].

Table 1. Basic characteristic subjects

Variabel	F1 Non DMT2 (%)	F1 DMT2 (%)
Gender		
Men	51.7	41.4
Woman	48.3	58.6
Age (years)		
15-25	79.3	51.7
26-35	20.7	48.3
Family history of obesity		
	93.1	58.6
	6.9	41.4
Antropometri		
	56.03 (45.50-69.35)	58.65 (48.45-72.90)
	162.55 (147-176)	162.51 (150-180)
BMI (Kg/m^2)		
< 18,5	0	0
18,5 – 22,9	100	100
23,0 – 24,9	0	0
≥25,0	0	0
< 18,5		
Waist circumference		
Non central obesity	79.3	34.5
Central obesity	20.7	65.5

different test: Chi-squared test ($p<0.05$)
mean (min-max)

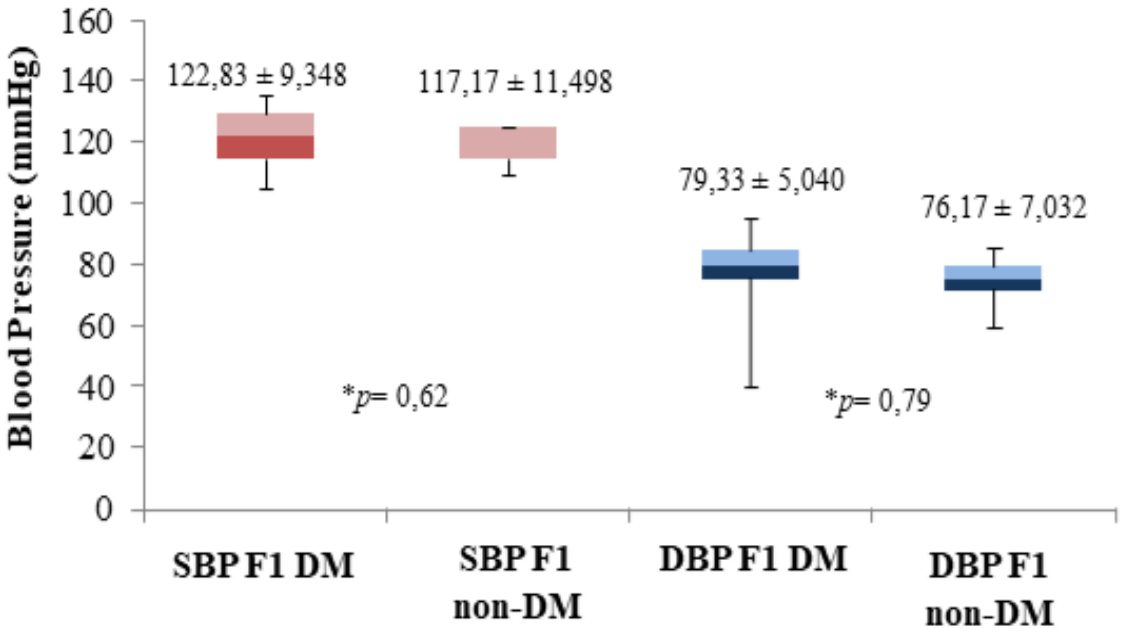

Figure 2. Plot Graph of Blood Pressure Measurement Results; Note: SBP F1 DM (Systolic Blood Pressure of DM's first-derivatives group); SBP F1 non-DM (Systolic Blood Pressure of non-DM's first-derivatives group); DBP F1 DM (Diastolic Blood Pressure of DM's first-derivatives group); DBP F1 non-DM (Diastolic Blood Pressure of non-DM's first-derivatives group). Mann Whitney Statistical Analysis

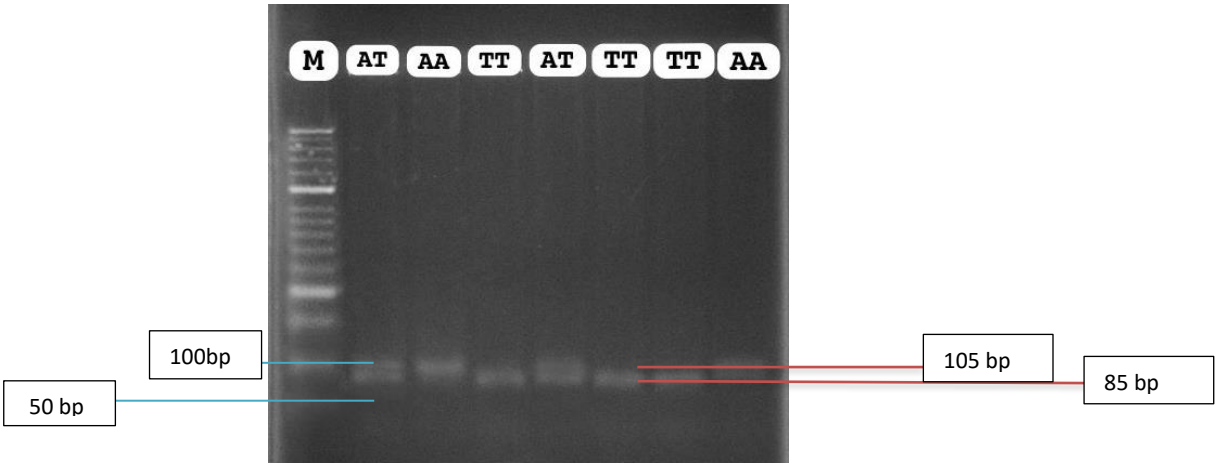

Figure 3. The results of genotyping polymorphism rs9939609 FTO gene, AA genotype was not cut off with 1 band: 105bp, TT genotype had 2 bands: 85 bp and 20 bp, AT genotype had 3 bands: 105 bp, 85 bp, and 20 bp (not shown in figure 20 bp).), M= marker: 50 bp

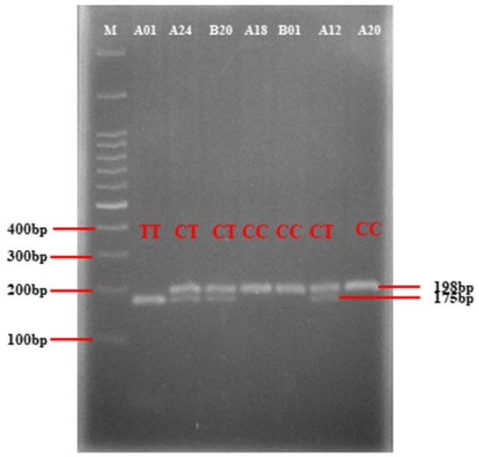

Figure 4. Photo results of the MTHFR C677T RLFP; M (Marker, which uses DNA Ladder 100 bp); A01 (first derivative of DM with sample code A01); A24 (first derivative of DM with sample code A24); B20 (first derivative of DM with sample code B20); A18 (first derivative of DM with sample code A18); B01 (non-DM first derivative with sample code B01); B12 (first non-DM derivative with sample code B12); A20 (first derivative of DM with sample code A20)

Table 1. FTO rs9939609 genotype and allele frequency in F1 non-DMT2 and F1 DMT2 groups

Genotype	Total (%)	F1 Non DMT2 (%)	F1 DMT2 (%)
FTO rs9939609 genotype			
TT	17.2	20.7	13.8
AT	32.8	37.9	27.6
AA	50	41.4	58.6
Alel T	33.6	19.8	13.8
Alel A	66,4	30.2	36.2
MTHFR C677T genotype			
CT & TT (polymorphic)	28.33	23.33	33.33
CC (wildtype)	71.67	76.67	66.67

statistical test: Chi-squared test (p>0.05)

Table 2. FTO rs9939609 and central obesity in F1 non DMT2 and F1 DMT2 populations

Genotype	F1 Non DMT2 (%)		F1 DMT2 (%)	
	Non-CO	CO	Non-CO	CO
TT	72.4	6.9	31	0
AA+AT	3.5	17.2	3.5	65.5

statistical test: Chi-squared test ($p<0.05$); CO: Central Obesity

Table 3. Determinants of central obesity variable

Variable	Non-CO (%)	CO (%)	OR (95% CI)
Gender			
Men	39.65	8.63	18 (4.92-68.70)
Woman	10.34	41.38	
Age (years)			
15-25	48.27	18.96	5.51 (1.67-18.17)
26-35	10.35	22.42	
Family history of obesity			
Absent	34.48	24.14	3.46 (1.13-10.57)
Present	12.07	29.31	
Parental history of DMT2			
Absent	39.66	17.24	0.137 (0.04-0.44)
Present	10.34	32.76	
FTO rs9939609 Genotype			
TT	51.72	3.45	18 (23.59-137.34)
AA/AT	3.45	41.38	

statistical test: Chi-squared test ($p<0.05$); CO: Central Obesity

Table 5. Association of the MTHFR (rs1801133) polymorphism with risk of developing hypertension

SNP	Pre-Hipertension (n (%))	Normal (n (%))	OR 95%CI	P
Genotypic				
TT	1	2	0,435 (0,037 – 5,161)	0,938
CT	6	8	0,652 (0,193 – 2,201)	0,701
CC	23	20		
Dominant				
CC	23	20	1,643 (0,527–5,120)	0,284
CT + TT	7	10		
Recessive				
CC + CT	29	28	2,071 (0,178-24,148)	0,500
TT	1	2		
Co-dominant				
CC + TT	24	22	1,455 (0,435 – 4,860)	0,381
CT	6	8		
Allelic				
C	52 (86,7%)	48 (80,0%)	1,625 (0,612 – 4,316)	0,462
T	8 (13,3%)	12 (20,0%)		

Recommendations for future research include the mitigation of additional confounding variables that serve as risk factors for hypertension. The impact of the MTHFR C677T polymorphism on the onset of hypertension can then be more closely assessed. Ghufron reported that increasing age is associated with the incidence of central obesity [30]. The increasing risk of obesity with age is caused by the body's metabolic processes, which tend to slow down, resulting in diminished muscular function and higher amounts of body fat [11]. Previous research explained that the susceptibility to obesity with age is mediated by genetics, one of which is the FTO gene. Women have a high risk of obesity due to body composition based on gender differences.

The percentage of body fat in women is higher due to differences in hormones and also the physiology of women who are prepared to become future mothers [12]. The hormones estrogen and leptin influence each other. Women with higher concentrations of estrogen also have high concentrations of the hormone leptin [12]. The hormone estrogen can also affect the process of lipolysis-lipogenesis in adipocytes which affects the growth of adipose tissue and affects the development of obesity [13]. Metabolism in women is also slower than in men [14]. Based on the sociocultural environment, it is explained that women have a greater tendency to consume foods high in sugar [11]. The Ministry of Health stated that one of the risk factors for obesity is a family history of diabetes so the offspring of diabetics are advised to keep their bodies from obesity. Furthermore, the Ministry of Health has shown that children who have a familial predisposition to obesity are more likely to develop obesity. Several prior researchers have found that genetic variables impact obesity risk in adults with a family history of obesity [31]. The mechanism of obesity occurs through genetic factors, namely in terms of controlling adipogenesis [3].

4. Conclusions

The study's findings suggest a significant association between the FTO rs9939609 gene polymorphism and the susceptibility to central obesity. Furthermore, female gender, age, and a family history of obesity all point to a greater incidence of central obesity in the Lembak community. The presence of the MTHFR C677T gene variation was not significantly correlated with hypertension. Individuals of the Lembak Ethnic Group living in Bengkulu City who have a family history of diabetes mellitus (DM) are at an increased risk factor for developing hypertension.

Acknowledgments

The present study is a component of a larger research endeavor conducted by Bengkulu University, focusing on the Lembak Ethnicity. The present study was entirely financed through a grant from Bengkulu University, which was derived from non-tax revenue sources. This research has been conducted in the Research Laboratory of the Faculty of Medicine and Health Sciences, Bengkulu University, and the Basic Science Laboratory, Biology Department in the Faculty of Mathematics and Sciences.

Ethical Approvals

The ethical clearance of this study was permitted by the Bengkulu University Health Research Ethics Committee number 97/UN30.14.9/LT/2022.

Declaration of Interest Statement

Based on the available information, it is currently understood that there are no conflicts of interest, whether financial or otherwise, as explicitly mentioned in the manuscript after the debate.

References

[1] World Health Organization (WHO). World health statistics (2022) (Monitoring health of the SDGs). 2022.

[2] O. Nainggolan, D. Hapsari, C. R. Titaley, L. Indrawati, I. Dharmayanti, & A. Y. Kristanto. (2022). The relationship of body mass index and mid-upper arm circumference with anemia in non-pregnant women aged 19–49 years in Indonesia: Analysis of 2018 Basic Health Research data. PloS one, 17(3), e0264685.

[3] Susmiati. (2017). Associations between Fat-mass Obesity Associated (FTO) gene variants 9939609 polymorphism, dietary intake, physical activity, and gut microbiota with adolescent obesity. Advanced Drug Delivery Reviews. [Indonesian].

[4] K. Shinozaki, M. Okuda, Y. Hinoda, N. Okayama, T. Fukuda, and I. Kunitsugu. (2014). Fat-mass and obesity-associated gene variant and changes of body mass index from ages 3 to 13 years. Obes Res Clin Pract, 8, 5–10.

[5] M. Daya, D. A. Pujianto, F. Witjaksono, L. Priliani, J. Susanto, W. Lukito. (2019). Obesity risk and preference for high dietary fat intake are determined by FTO rs9939609 gene polymorphism in selected Indonesian adults. Asia Pac J Clin Nutr, 28, 183–191.

[6] C. H. Andreasen, K. L. Stender-Petersen, M. S. Mogensen, S. S. Torekov, L. Wegner, G. Andersen, et al. (2008). Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes, 57, 95–101.

[7] J. R. Speakman, K. A. Rance, and A. M. Johnstone. (2008). Polymorphisms of the FTO gene are associated with variation in energy intake, but not energy expenditure. Obesity, 16, 1961–1965.

[8] P. G. Hunter, F. A. Chapman, and N. Dhaun. (2021). Hypertension: Current trends and future perspectives. Br J Clin Pharmacol, 87, 3721–3736.

[9] M. Ward, C. F. Hughes, J. J. Strain, R. Reilly, C. Cunningham, A. M. Molloy, et al. (2020). Impact of the common MTHFR 677C→T polymorphism on blood pressure in adulthood and role of riboflavin in modifying the genetic risk of hypertension: evidence from the JINGO project. BMC Med, 18, 1–11.

[10] L. K. Sarna, N. Wu, S. Y. Hwang, Y. L. Siow, and O. Karmin. (2010). Berberine inhibits NADPH oxidase mediated superoxide anion production in macrophages. Can J Physiol Pharmacol, 88, 369–378.

[11] C. Mauli, A. Pane, R. Yolanda, A. AF, N. Lestari, I. Fahri, et al. (2023). Analysis of Sex and ABO Blood Group on Vascular Endothelial Growth Factor-A and Apolipoprotein-E Gene Polymorphisms in the First Descendant of Coronary Heart Disease Patients, 24, 442–448.

[12] R. S. Prayogo, E. Yunita, R. Yolanda, I. Fahri, N. Lestari, M. Asteria, et al. (2022). Carotid intima-media thickness in the first descendant of coronary artery disease patients with Apolipoprotein-E4 genotype. Bali Med J, 11, 1774–1779.

[13] D. A. A. Dita, E. Yunita, R. D. Ocktaviani, and P. Melati. (2023). Literature Review: Genetic Polymorphisms as Risk Factors for Obesity. J Ilmu Kedokt dan Kesehat, 10, 2267–2280.

[14] E. Yunita, C. E. Putri, A. Indrian, L. A. Umar, D. Ayu, and A. Dita. (2022). Literature Review: Association of Genetic Polymorphism Effect on Risk Events of Diabetes Mellitus. J Med Malahayati, 6, 403–410.

[15] F. Anwari, N. Lestari, M. Asteria, S. Sipriyadi, I. Fahri, and E. Yunita. (2021). VEGF-A Gene Polymorphism (rs2010963) in First Descendants of Patients with Coronary Heart Disease (CHD). Bioedusains: Jurnal Pendidik Biol dan Sains, 4, 325–335.

[16] X. Guo, L. Zheng, Y. Li, S. Yu, G. Sun, H. Yang, et al. (2012). Differences in lifestyle behaviors, dietary habits, and familial factors among normal-weight, overweight, and obese Chinese children and adolescents. Int J Behav Nutr Phys Act, 9, 1–9.

[17] T. M. Frayling, N. J. Timpson, M. N. Weedon, R. M. Freathy, C. M. Lindgren, J. R. B. Perry, et al. (2007). Index and Predisposes to Childhood and Adult Obesity. Science (80-), 316, 889–894.

[18] M. S. Zhou, A. Wang, and H. Yu. (2014). Link between insulin resistance and hypertension: What is the evidence from evolutionary biology? Diabetol Metab Syndr, 6, 1–8.

[19] L. Li, Q. Peng, Y. qin Shao, X. Fang, Y. ying Zhang. The interaction on hypertension between family history and diabetes and other risk factors. Sci Rep, 11, 1–7.

[20] D. N. Khasanah. (2022). the Risk Factors of Hypertension in Indonesia (Data Study of Indonesian Family Life Survey 5). J Public Heal Res Community Heal Dev, 5, 80.

[21] R. Nair, A. Khanna, and K. Singh. (2012). MTHFR C677T polymorphism and recurrent early pregnancy loss risk in North Indian population. Reprod Sci, 19, 210–215.

[22] P. Frosst, H. J. Blom, R. Milos, P. Goyette, C. A. Sheppard, R. G. Matthews, et al. (1995). A candidate genetic risk factor for vascular disease: A common mutation in methylenetetrahydrofolate reductase. Nat Genet, 10, 111–113.

[23] B. Guenther, C. Sheppard, P. Tran, R. Rozen, R. Matthews, L. Martha. (1999). The structure and properties of methylenetetrahydrofolate reductase from Escherichia coli suggest how folate ameliorates human hyperhomocysteinemia. Nat Struct Biol, 6, 359–365.

[24] P. J. Bagley and J. Selhub. (1998). A common mutation in the methylenetetrahydrofolate reductase gene is associated with an accumulation of formylated tetrahydrofolates in red blood cells. Proc Natl Acad Sci U S A, 95, 13217–13220.

[25] K. Shahzad, A. Hai, A. Ahmed, N. Kizilbash, and J. Alruwaili. (2013). A Structured-based Model for the Decreased Activity of Ala222Val and Glu429Ala Methylenetetrahydrofolate Reductase (MTHFR) Mutants. Bioinformation, 9, 929–936.

[26] R. M. Candrasatria, S. Adiarto, and R. Sukmawan. (2020). Polymorphism as a Risk Factor for Hypertension in a Rural Population.

[27] C. Antoniades, C. Shirodaria, P. Leeson, O. A. Baarholm, T. Van-Assche, C. Cunnington. (2006). 5-Methyltetrahydrofolate rapidly improves endothelial function and decreases superoxide production in human vessels: Effects on vascular tetrahydrobiopterin availability and endothelial nitric oxide synthase coupling. Circulation, 114, 1193–1201.

[28] B. Bandini. (2014). Homocysteine Level with Preeclampsia Severity in H.Adam Malik Hospital and USU FK Network Hospital Medan. Department of Obstetrics and Gynecology. Faculty of Medicine, University of North Sumatra. HOSPITAL. H. Adam Malik. Medan.

[29] C. Antoniades, C. Shirodaria, P. Leeson, A. Baarholm, T. Van-Assche, C. Cunnington. (2009). MTHFR 677 C→T polymorphism reveals functional importance for 5-methyltetrahydrofolate, not homocysteine, in regulation of vascular redox state and endothelial function in human atherosclerosis. Circulation, 119, 2507–2515.

[30] G. Fuadi Ghufron Aziz. (2020). The Relationship between Carbohydrate Intake and the Incidence of Obesity in School-Age Children. [Indonesian].

[31] R. I. Kemenkes (2018). Obesity classification after BMI measurement. In: Ministry of Health of the Republic of Indonesia. [Indonesian].