ISSN: 3032-3134 (ONLINE)
InaJBCS | Indonesian Journal of Biomedicine and Clinical Sciences

Genetic variation near the MC4R gene rs17782313 as a protective factor against high visceral fat: case control study in the Jambi Malay population

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https://doi.org/10.22146/inajbcs.v57i3.20568

Submitted: 2025-03-26
Accepted : 2025-06-30

ABSTRACT

Obesity is commonly assessed using the body mass index (BMI), which does not distinguish between fat and lean mass. Among fat distributions, visceral fat is more strongly associated with the risk of metabolic disease. Visceral or central obesity, characterized by excessive visceral fat accumulation, has become increasingly prevalent in recent years. Genetic factors, including rs17782313 polymorphism near the *melanocortin 4 receptor* (*MC4R*) gene, have been implicated in visceral fat accumulation. Previous studies reported varying effect sizes across different populations and inconsistent genotype-phenotype associations. However, no studies have investigated this association in the Jambi Malay Population. This case-control study aimed to evaluate the association between the *MC4R* rs17782313 polymorphism and visceral fat in the Jambi Malay population. A total of 110 Jambi Malay subjects participated in the study. Visceral fat was measured using bioelectrical impedance analysis (BIA), and genotyping was performed using the Tetra-ARMS PCR method. Bivariate and multivariate analyses were conducted to assess the association between genetic variation and visceral fat levels. Bivariate analysis showed that the TC genotype had a protective effect against high visceral fat compared to the TT genotype (p = 0.037; OR = 0.395). Similarly, the recessive model (CC+TC vs. TT) also indicated a protective effect (p = 0.022; OR = 0.375). In logistic regression model adjusted for calorie intake and physical activity, the protective effect persisted for both TC (p = 0.018; OR = 0.302) and the recessive model (p = 0.013; OR = 0.305). However, further adjustment for gender nullified the effect of the TC genotype, whereas the recessive model remained statistically significant, though the genetic effect was attenuated (p = 0.044; OR = 0.372). In conclusion, the TC genotype of MC4R rs17782313 is associated with a protective effect against visceral fat accumulation. This effect is influenced by calorie intake, physical activity, and gender.

Keywords:
Genetic association;
MC4R polymorphism;
Tetra ARMS-PCR;
Visceral fat;
Jambi Malay

ABSTRAK

Obesitas yang dinilai melalui indeks massa tubuh (IMT), memiliki keterbatasan karena tidak mampu membedakan massa lemak dan bukan lemak. Massa lemak viseral menunjukkan korelasi yang lebih kuat dengan risiko penyakit metabolik. Prevalensi obesitas viseral atau obesitas sentral, yang ditandai oleh akumulasi lemak viseral berlebihan terus meningkat di Indonesia. Penelitian asosiasi genotipe-fenotipe sebelumnya melaporkan bahwa polimorfisme rs17782313 didekat gen Melanocortin 4 Receptor (*MC4R*) berhubungan dengan akumulasi lemak visceral dengan nilai odds yang bervariasi. Namun demikian, belum ada penelitian yang melaporkan asosiasi ini pada Populasi Melayu Jambi. Penelitian kasus-kontrol ini bertujuan untuk menganalisis hubungan antara polimorfisme rs17782313 *MC4R* dan tingkat lemak viseral pada Populasi Melayu Jambi. Sebanyak 110 subjek Melayu Jambi ikut serta dalam studi ini. Pengukuran lemak viseral dilakukan menggunakan Bioelectrical Impedance Analysis (BIA), dan genotipe ditentukan dengan metode Tetra-ARMS-PCR. Analisis bivariat dan multivariat dilakukan untuk menilai asosiasi antara variasi genetik dan lemak viseral. Analisis bivariat menunjukkan bahwa genotipe TC memiliki efek protektif terhadap penigkatan presentase lemak viseral tinggi dibandingkan

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dengan genotipe TT (p = 0,037; OR = 0,395). Demikian pula, model resesif (CC+TC vs. TT) juga mengindikasikan efek protektif (p = 0,022; OR = 0,375). Dalam model regresi logistik yang menyertakan asupan kalori dan aktivitas fisik, efek protektif ini tetap signifikan untuk genotipe TC (p = 0,018; OR = 0,302) maupun model resesif (p = 0,013; OR = 0,305). Namun, setelah ditambahkan variabel gender, efek protektif genotipe TC menjadi tidak signifikan, sementara model resesif tetap signifikan meskipun efek genetiknya melemah (p = 0,044; OR = 0,372). Sebagai kesimpulan, genotipe TC dari polimorfisme rs17782313 *MC4R* diasosiasikan dengan efek protektif terhadap akumulasi lemak viseral, dengan efek ini dipengaruhi oleh asupan kalori, aktivitas fisik, dan gender.

INTRODUCTION

Central obesity plays a significant role in obesity-related health complications, primarily driven by the accumulation of visceral fat around abdominal organs, commonly referred to as visceral obesity. Unlike general obesity, which is commonly assessed using body mass index (BMI) without differentiating fat distribution, central obesity is characterized by excess visceral fat, posing greater metabolic risks.[1] Normally, excess fat is stored in the subcutaneous layer, but in cases of central obesity, fat accumulates more in the visceral layer due to disruptions in fat storage mechanisms.[2] Visceral fat exhibits stronger pro-inflammatory properties than subcutaneous fat, which ultimately leads to metabolic dysfunction, as evidenced by the frequent finding of high visceral fat in individuals with metabolic syndrome.[3,4] This metabolic disorder increases the risk of insulin resistance and significantly raises the likelihood of developing serious diseases such as diabetes, cardiovascular disease, and cancer.[5-7] Moreover, the proximity of visceral fat to the portal circulation increases the risk of liver steatosis, exacerbating metabolic complications.[8] Given its strong association with increased morbidity and mortality, central obesity represents a greater health risk than general obesity.[9] Furthermore, its prevalence continues to rise globally, reaching 41.5% worldwide.[10] In Indonesia, the prevalence increased from 26.6% in 2013 to 31% in 2018, while in Jambi, it has reached 24.6%, reflecting a growing health concern.[11]

Several factors contribute to obesity, especially central obesity, and significantly impact visceral fat levels. These factors include gender, age, race, ethnicity, dietary habits, lifestyle, hormone levels and medications.[1] Genetic predisposition also plays a crucial role in determining fat distribution and metabolism. Heritability studies have reported that genetics contribute to 40–70% of obesity.[12] Other genetic studies have consistently reported that genes are major contributors to obesity. In addition to controlling fat mass, genetic factors influence fat distribution throughout the body, determining whether fat accumulates in subcutaneous or visceral depots.[13]

Genome-wide association studies (GWAS) conducted in 2008, reported an association between the *MC4R* gene and obesity.[14] A meta-analysis study reported the rs17782313 *MC4R* gene has a strong association with obesity due to its essential role in regulating energy balance and appetite control.[15] Located downstream of the *MC4R*, this polymorphism affects *MC4R* protein expression through its role as a regulator sequence.[16,17] A previous study reported that the interaction between *MC4R* rs17782313 and diet was significantly associated with hip circumference, BMI, and visceral fat.[18] Similar findings in

Polish and Kuwaiti population also found a significant association between visceral fat and the MC4R gene.[19,20] However, not all populations have shown consistent results. Statistical analysis study in the German population found no association between the *MC4R* rs17782313 gene and visceral fat.[21]

Although numerous studies have reported a significant association between the *MC4R* gene and visceral fat, inconsistencies in findings across different populations persist. This variation highlights the need for further investigation into the association within diverse ethnic groups, including the Indonesian population. The importance of this study lies in its focus on the Jambi Malay population, a distinct ethnic group in Indonesia for which there is limited of genetic data related to obesity. Given the rising prevalence of central obesity in Jambi, understanding the specific genetic predispositions within this population is crucial for developing targeted public health interventions and personalized medicine strategies. To the best of our knowledge, research on the association between the *MC4R* rs17782313 gene polymorphism and visceral fat in the Jambi Malay population remains limited. Therefore, this study aims to investigate this association, contributing to a broader understanding of genetic influences on obesity across different ethnic backgrounds.

MATERIAL AND METHODS

Study design and subject recruitment

This study was approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Universitas Jambi, under approval number 1885/UN21.8/PT.01.04/2024. This case-control study involved 110 subjects, divided into two groups: the high visceral fat group (55 subjects) as cases and the normal visceral fat group (55 subjects) as controls. Both groups were matched based on age. The inclusion criteria were subjects between 19-59 y.o., and all included subjects successfully underwent the genotyping process using established methods. The exclusion criteria were subjects with incomplete demographic data or missing visceral fat measurements.

Anthropometric measurement and dietary

Visceral fat data were collected using a bioelectrical impedance analysis (BIA), Omron HBF-375. Measurements were conducted by first ensuring that the device was placed on a flat surface and that the subject's personal data (date of birth, gender, and height) were entered into the BIA system. The subject stood on the footing electrode and held the grip electrodes, keeping their hands and arms slightly away from the body. During measurement, the subject remained relaxed until the device completed the analysis. Visceral fat levels ranging from 0.5 to 9.5 were considered normal, while levels exceeding 10 were classified as high.[22]

Calorie intake was obtained using the 24-hr food recall method, in which participants were interviewed to recall all food consumed in the past 3x24 hr (two weekdays and one weekend day). NutriSurvey software was used to assess the caloric intake statistics and determine the total calories required daily.[23] Meanwhile, physical activity levels were assessed using the International Physical Activity Questionnaire – Short Form (IPAQ-SF). The inquiry concerns

the amount of time spent engaging in physical activity during the previous 7 d. Total value of physical activity is calculated in Metabolic Equivalent (MET)-min/wk. Low activity MET value less than 600 MET-min/wk, physical activity moderate 600 MET-min/wk or more, and high physical activity as more than 3000 MET min/wk.[24]

Genotyping

A 5 mL blood sample was collected from the cubital vein using a syringe with an angle of approximately 15° to 30°, and stored in EDTA tubes. To extract pure DNA, blood samples were combined with buffer and proteinase K, then incubated, centrifuged, and cleaned with ethanol solution. DNA extraction was performed using QIAamp DNA Blood Kits (Qiagen). Genotyping was conducted using the Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR), which generates both general and allele-specific products.[25] The primer design was adapted from a previous study.[26] Primer sequences and PCR product results are presented in TABLE 1.

The PCR mixture was prepared by combining several components into a 0.2 mL PCR tube with the following ratio: 15µL master mix (GoTaq, Cat No: M&122, Promega, USA); 2 µL each of outer primers, 3 µL each of inner primers, 3 µL nuclease-free water (NFW), and 2 µL sample DNA. The mixture was then vortexed and centrifuged at low speed for 30 sec to ensure homogeneity. The PCR reactions were performed in the thermocycler (Arktik TCA 0001, Cat No: N11467, Thermo Scientific, Finland) under the following conditions: initial denaturation at 94°C for 7 min; followed by 35 cycles of denaturation at 94°C for 1 min, annealing at 56°C for 35 sec, and elongation at 72°C for 1 min. A final elongation step was carried out at 72°C for 7 min. Following amplification, electrophoresis was conducted for 70 min at 50 V, and the PCR products were visualized under UV transillumination.

Data analysis

Data analysis was performed using both bivariate and multivariate approaches. Given the non-normal distribution of numerical data, the Mann-Whitney test was used for group comparisons. Bivariate analysis was performed using the Chi-square test or Fisher's Exact test, depending on the distribution and characteristics of nominal or ordinal variables.[27] For multivariate analysis, binary logistic regression was utilized to assess the association between *MC4R* gene polymorphism, dietary patterns, and obesity. All statistical analyses were performed using IBM SPSS Statistics 27.

RESULTS

Baseline subject characteristics

This study included 110 participants who met the inclusion criteria. TABLE 2 presents the univariate analysis of the baseline characteristics for the entire study participants. The mean age of the participants was 38.0 ± 10.01 yr. This study consisted of more women than men. The average calorie intake was 1438.94 ± 510.51 kcal. Regarding physical activity, the majority of participants were equally distributed between moderate and low activity levels, with a smaller portion engaging in high physical activity. The median visceral fat level for the study was 9.750 with a range from 1.00 to 20.00.

TABLE 1. Primary rs17782313[26]

MC4R Gene Variation rs17782313	Sequence of primer (5'-3')	Product size (bp)
Forward Inner	GAAGTTTAAAGCAGGAGAGATTGTATACC	TT allele =184bp CC allele =218bp TC Outer =351bp
Reverse Inner	GCTTTTCTTGTCATTTCCAGCA	
Forward outer	TCCACATGCTATTGGTTTAAGACAA	
Reverse outer	TGCTGAGACAGGTTCATA AAAAGAG	

TABLE 2. Univariate analysis

Characteristic	Result
Age (mean ± SD yr)	38.0 ± 10.01[a]
Gender, [n (%)]	
• Man	45 (40.9)
• Woman	65 (59.1)
Calorie intake (mean ± SD kcal)	1438.94 ± 510.51[a]
Physical activity, n (%)	
• High	20 (18.2)
• Moderate	45 (40.9)
• Low	45 (40.9)
Visceral fat	9.75 (1.00-20.00)[b]

[a.] Normally distributed data; [b.]Not normally distributed data: median (min-max)

TABLE 3. Baseline subject characteristics

Characteristics	Visceral fat		p
	High (n=55)	Normal (n=55)	
Age (mean ± SD yr)	38.09 ±10.31	37.90 ± 9.79	0.925[a]
Gender [n (%)]			
• Man	32 (71.1)	13 (28.9)	<0.001[b]
• Woman	23 (35.4)	42 (64.6)	
Calorie intake (mean ± SD kcal)	1512.15 ± 498.20	1365.72 ± 516.66	0.133[b]
Physical activity [n (%)]			
• High	14(70)	6(30)	0.081[b]
• Moderate	18(40)	27(60)	
• Low	23(51.1)	22(48.9)	

[a.]Independent t-test; [b.]Chi-square;

This study consisted of 55 subjects with high visceral fat and 55 with normal visceral fat groups. Referring to TABLE 3, the mean age in the high visceral fat group was slightly higher than in the normal visceral fat group, but the difference was not statistically significant ($p = 0.925$). A significant gender difference was observed ($p < 0.001$), with men being more prevalent in the high visceral fat group, while women were more prevalent in the normal visceral fat group. Calorie intake was higher in the high visceral fat group compared to the normal visceral fat group, but this difference was also not statistically significant ($p = 0.133$). Regarding physical activity, high levels of physical activity were more common in the high visceral fat group, while moderate and low levels more prevalent in the normal visceral fat group. However, this difference was not statistically significant ($p = 0.081$).

Genotype distribution

Genotyping of *MC4R* rs17782313 genetic variation was performed using the Tetra-ARMS PCR method with specific primers. The success of the PCR reaction was confirmed by the appearance of the main band corresponding to a 351 bp DNA fragment, representing the general product. The allele-spesific PCR products included a 218 bp fragment for the C allele and 184 bp fragment for T allele.

The TT genotype was characterized by the presence of 184 bp and 351 bp fragments, while the CC genotype was identified by 218 bp and 351 bp fragments. The TC genotype exhibited all three bands: 184 bp, 218 bp, and 351 bp. The K marker served as a contamination control, where the absence of visible fragments indicates no contamination. The L marker represents a DNA ladder, used as references for determining fragment sizes. In this study, a 50 bp DNA ladder was utilized for size estimation.

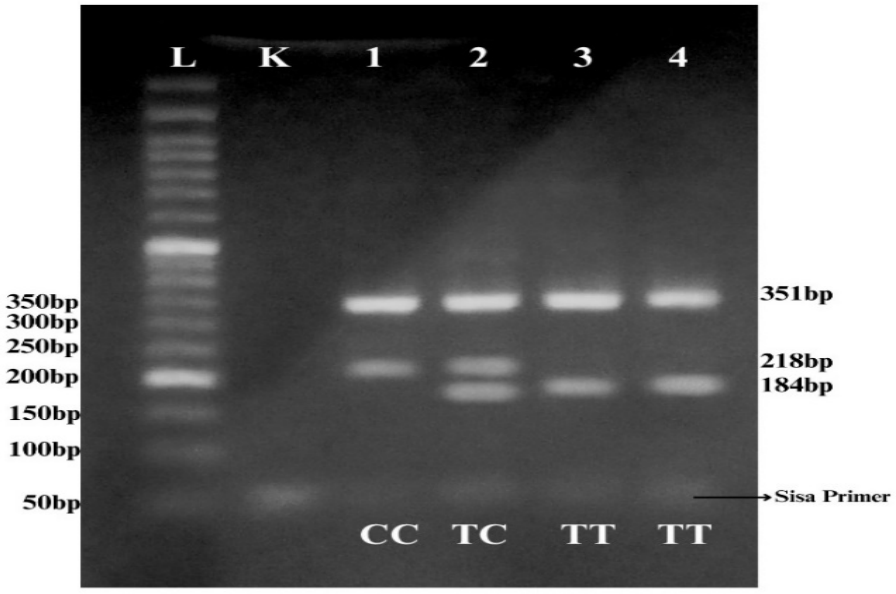

FIGURE 1. ARMS-PCR electrophoresis of rs17782313. An 184 bp PCR product shows the T allele, a 218 bp PCR product shows the C allele and a 351 bp PCR product shows the general product. Lane 2 shows a heterozygous TC. Lane 1 shows a homozygous CC. Lanes 3 and 4 show TT homozygous

TABLE 4. Genotype distribution and Hardy Weinberg equilibrium of *MC4R* rs 17782312 gene polymorphism

Genotype	Observation frequency [n (%)]	Expected frequency	$\chi 2$	p	MAF
TT	77 (70.0)	76			
CC	4 (3.6)	3	0.367	0.832	0.16
TC	29 (26.4)	31			
Total	110 (100)	110			

MAF: minor allele frequency

Referring to TABLE 4, the genotype frequency distribution indicates that the TT genotype was the most prevalent in the study population, followed by the TC genotype, while the CC genotype was the least frequent. The Hardy-Weinberg equilibrium (HWE) test is a fundamental principle in population genetics used to assess whether the observed genotype frequencies in a population differ from the frequencies expected under a set of assumptions, including random mating and the absence of evolutionary influences like mutation, selection, and genetic drift. In genetic association studies, the HWE test might also serves as a quality control measure to check for potential genotyping errors or population stratification. The HWE test yielded p-value of 0.832 ($p>0.05$), suggesting that the genotype distribution conforms to HWE expectations. Furthermore, the MAF for the C allele suggests a relatively low prevalence of this allele within the study population.

Association of genotype with increase in visceral fat

TABLE 5 shows the association between genetic variation of the *MC4R* gene and visceral fat distribution categorized into high and normal in the TC genotype and CC+TC recessive model. The TT genotype was used as a reference in this analysis. Individuals with the TT genotype were more likely to be in the high visceral fat group. The OR showed that individuals with TC and CC+TC genotypes were less likely to have significantly high visceral fat ($p<0.05$).

TABLE 6 presents the results of the multivariate logistic regression analysis, which assessed the independent association of *MC4R* rs17782313 genotypes with visceral fat after adjusting for potential confounders. In Model 1, which adjusted for calorie intake and physical activity, the protective effect remained statistically significant. Specifically, the TC genotype showed a significant protective association against high visceral fat ($p = 0.018$; adjusted OR = 0.302), as did the recessive model (CC+TC) ($p = 0.013$; adjusted OR = 0.305). However, in Model 2, after further adjustment for gender, the significant association for the TC genotype was nullified ($p = 0.061$). In contrast, the protective effect of the recessive model (CC+TC) persisted, although it was attenuated ($p = 0.044$; adjusted OR = 0.372). This suggests that gender is a significant moderator in the association between the *MC4R* rs17782313 polymorphism and visceral fat levels.

TABLE 5. Bivariate analysis of the association between *MC4R* gene polymorphism and visceral fat

Genetic variation	Visceral fat [n (%)]		p	OR (95% CI)
	High	Normal		
Additive models				
• TT	44 (57.1)	33 (42.9)	Reff.	Reff.
• CC	1 (25.0)	3 (75.0)	0.229[a]	0.250(0.025-2.513)
• TC	10 (34.5)	19 (65.5)	0.037[b]	0.395(0.162-0.960)
Recessive/dominant model				
• CC+TC	11(33.3)	22 (66.7)	0.022[b]	0.375(0.160-0.880)
• TT+TC	54 (50.9)	52 (49.1)	0.309[a]	0.321(0.032-3.186)

[b.] Fisher's exact test; [b..] Chi-square

TABLE 6. Multivariate analysis

Genetic variation	Visceral fat [n (%)]		Model 1		Model 2	
	High	Normal	Adjust p	Adjust OR (95% CI)	Adjust p	Adjust OR (95% CI)
TT	44 (57.1)	33 (42.9)	Ref.	Ref.		
CC	1 (25.0)	3 (75.0)	0.241	0.234 (0.021-2.652)	0.307	0.274 (0.023-3.295)
TC	10 (34.5)	19 (65.5)	0.018	0.302 (0.112-0.814)	0.061	0.379 (0.137-1.047)
CC+TC	11 (33.3)	22 (66.7)	0.013	0.305 (0.120-0.780)	0.044	0.373 (0.143-0.975)
TT+TC	54 (50.9)	52 (49.1)	0.365	0.339 (0.033-3.523)	0.406	0.353 (0.030-4.112)

Model 1: Multivariate analysis of genotype, calories, and physical activity; Model 2: Multivariate analysis of genotype, calories, physical activity, and gender

To further investigate the modifying effect of gender, a stratified analysis was conducted (TABLE 7). Among men, the combined CC+TC genotype showed a statistically significant protective effect against high visceral fat after adjustment for calorie intake and physical activity (adjusted p = 0.048; adjusted OR = 0.187), suggesting that carrying the C-allele is associated with a lower risk of high visceral fat specifically in males within this population. In contrast, no signification associations were observed among women for any of the genetic models. Both the TC genotype (adjusted p = 0.220) and the CC+TC recessive mode (adjusted p = 0.282) showed no significant protective effect in women. These findings highlight a clear gender-specific interaction, where the protective influences of the rs17782323 C-allele against visceral fat accumulation is evident in men but not in women.

TABLE 7. Gender-stratified analyses

Genetic Variation	Men visceral fat [n (%)]		p	OR	Adjusted value	Adjusted OR	Woman visceral fat [n (%)]		p	OR	Adjusted value	Adjusted OR
	High	Normal					High	Normal				
TT	28 (77.8)	8 (10.4)	Ref.	Ref.	Ref.	Ref.	16 (39.0)	25 (61.0)	Ref.	Ref.	Ref.	Ref.
CC	0 (0.0)	1 (100.0)	0.243	-	1.00	0.00	1 (33.3)	2 (66.7)	0.671	0.781	0.723	0.614
TC	4 (50.0)	4 (50.0)	0.125	0.286	0.097	0.230	6 (28.6)	15 (71.4)	0.416	0.625	0.220	0.442
CC+TC	4 (44.4)	5 (55.6)	0.063	0.229	0.048	0.187	7 (29.2)	17 (70.8)	0.422	0.643	0.282	0.514
TT+TC	32 (72.7)	12 (27.3)	0.289	-	1.00	0.00	22 (35.5)	40 (64.5)	0.716	0.909	0.925	0.885

*Ref. = reference category. OR = odds ratio; Adj. OR = adjusted odds ratio, adjusted for calorie intake and physical activity.

DISCUSSION

This present study identified an association between the *MC4R* rs17782313 and a reduced risk of high visceral fat accumulation in the Jambi Malay population. The TC and CC+TC genotypes were identified as protective genotypes. After adjustment for calorie intake and physical activity, the association remained statistically significant, although slightly attenuated. Further adjustment for gender nullified the association for the TC genotype, while the protective effect of the CC+TC genotype persisted, albeit with a weaker effect size. This suggests a possible interaction between gender and the TC genotype, where the protective effect may be more pronounced in specific subgroups. Previous studies have frequently reported *MC4R* rs17782313 as a risk factor for visceral fat accumulation, particularly in Polish and Kuwaiti populations.[19,20] Conversely, results from the German population have suggested an opposing trend.[21] These differences may be attributed to the multifactorial nature of visceral fat accumulation, which is influenced by both genetic and environmental determinants. Furthermore, gene-environment interactions may play a crucial role in modulating *MC4R* expression and function, thereby contributing to population-specific effects.

A previous study conducted in the Polish population examined the association between the *MC4R* gene and visceral fat accumulation, reporting that men carrying the C allele at rs17782313 exhibited higher levels visceral fat, with the highest accumulation observed in homozygous CC subjects.[19] Similar results were also reported in a study of the Kuwaiti population, which reported a significant interaction between *MC4R* rs17782313 and visceral fat.[20]

The *MC4R*, a member of the G protein-coupled receptor family primarily located in the ventromedial hypothalamus, plays a critical role in regulating food intake and energy homeostasis. Its primary ligand is alpha-melanocyte-stimulating hormone (a-MSH). The *MC4R* gene is located on chromosome 18q21. The rs17782313 polymorphism, located approximately 190 kilobases downstream of the *MC4R* gene, represents a single nucleotide variation involving a thymine (T) to cytosine (C) substitution. Despite being located outside the *MC4R* gene, rs17782313 has been reported to exert

a greater influence on obesity than certain polymorphic loci within *MC4R*.[17] An *in vitro* study conducted on cell lines suggests that the polymorphic allele of rs17782313 is associated with reduced cyclic adenosine monophosphate (cAMP) levels, potentially impairing *MC4R* activation. This reduction in receptor activity has been linked to decreased satiety, and is hypothesized to be mediated by upregulation of DNAAJC27, a protein found to be elevated in obesity.[16]

The *MC4R* acts as a key regulator of energy balance through a functionally distinct central melanocortin neural pathway that modulates both food intake and energy expenditure. Single nucleotide polymorphisms (SNPs) located near the *MC4R* gene have been associated with body fat distribution, with some also linked to total body fat content. The *MC4R* rs17782313 polymorphism has been implicated in visceral fat accumulation through its role in regulating energy balance. This gene encodes the melanocortin-4 receptor, which plays a crucial role in controlling energy homeostasis, hunger, and body fat distribution. *MC4R* is predominantly expressed in the hypothalamus, the central appetite-regulating region responsible for modulating food intake and energy expenditure.[19]

A study conducted in German population reported contrasting findings, as no association was observed between *MC4R* rs17782313 and visceral fat accumulation. Instead, body composition analysis indicated a tendency toward subcutaneous fat storage, which is associated with a lower metabolic risk. This suggests that SNP rs17782313 near the *MC4R* gene may contribute to metabolically harmless obesity.[21] Similarly, a study in the United States found no significant association between SNP rs17782313 and visceral fat in the overall white population. However, gender-stratified analysis revealed a significant association in men, but not in women.[26] This finding is consistent with our study. In contrast, a study conducted in China reported the opposite trend, with a significant association observed in women, but not in men.[28]

In our study, after further adjustment for gender, the association remained significant only for the recessive models (CC+TC). This finding underscores the potential for sex-specific genetic effects, as observed in previous studies where *MC4R* polymorphisms were associated with obesity risk in men but not in women, or vice versa.[26,28] This sex-specific effect was further elucidated in our gender-stratified analysis (TABLE 7), which revealed that the protective association of the C-allele carrier genotypes (CC+TC) was significant only in men, while no such association was found in women. The interaction between *MC4R* rs17782313 and gender may be attributed to differences in hormonal and metabolic environments. In premenopausal women, estrogen promotes fat storage in subcutaneous adipose tissue (SAT) rather than visceral fat (VAT) by inhibiting lipid storage and lipolysis in VAT. Additionally, estrogen upregulates the expression of anti-lipolytic α2A-adrenergic receptors in SAT, further favoring subcutaneous fat accumulation.[29] In contrast, men exhibit greater abdominal visceral fat accumulation, which is linked to higher dietary fat absorption. The presence of larger and more abundant chylomicrons in men may obstruct the lamina propria and lymphatic system, leading to increased fatty acid deposition in visceral adipocytes and subsequent fat storage.[30]

The findings of this study have several potential implications for clinical practice and public health strategies, particularly within the Jambi Malay population. Identifying individuals with the high-risk TT genotype could allow for early and targeted preventive interventions. Clinicians could use this genetic information to counsel at-risk patients more effectively, emphasizing

the importance of lifestyle modifications such as dietary management and increased physical activity to mitigate their inherent predisposition to visceral fat accumulation. From a public health perspective, these results could inform the development of population-specific screening programs aimed at identifying individuals at higher genetic risk for central obesity and its associated metabolic complications, thereby enabling a more personalized approach to disease prevention.

These inconsistent findings suggest that the association between rs17782313 and *MC4R* expression remains unclear and is influenced by multifactorial and polygenic mechanisms. Variations in ethnicity, age, gender, genetic background, study design, sample size, measurement methods, environmental factors, and gene-gene interactions may contribute to these discrepancies.[31]

This study found that the MAF of the C allele was 0.16. In comparison, the reported MAF values for the Chinese, European and African populations were 0.185, 0.265, and 0.315, respectively.[32] Based on HWE analysis, the observed value was 0.367 with a p-value of 0.832 ($p>0.05$). This indicates conformity with Hardy-Weinberg equilibrium, suggesting that allele and genotype frequencies in the population remain stable across generations unless influenced by external factors.[33]

In this study, age was matched between groups to ensure no significant differences. Aging is known to influence body composition, leading to increased visceral fat, metabolic alterations, and a proinflammatory shift.[34] The analysis revealed a significantly higher proportion of men than women. Greater abdominal visceral fat accumulation in men has been associated with increased dietary fat absorption.[30] Furthermore, calorie intake was higher in the high visceral fat group, supporting its role in fat accumulation. Previous studies have shown a significant association between dietary intake and visceral fat, particularly with the consumption of high-energy-density foods such as fast food.[2] Moreover, high visceral fat was more prevalent among individuals with low physical activity levels, highlighting the role of physical inactivity in fat accumulation and metabolic disorders. Existing evidence indicates that sedentary behavior is a significant contributor to increased visceral fat deposition.[35]

To the best of our knowledge, this is the first study conducted in the Jambi Malay population, providing novel insights into the association between *MC4R* and visceral fat. The study utilized a multivariate approach to ensure comprehensive analysis of contributing factors. Although the sample size was limited, it fulfilled the minimum statistical requirements for validity. However, a key limitation is that obesity phenotypes are influenced by multifactorial and polygenic factors, which may affect the generalizability of the findings. Therefore, further research with larger sample sizes, more ethnically diverse populations, and expanded analysis of additional genetic and environmental factors is necessary to enhance understanding of the role of *MC4R* in obesity and visceral fat distribution.

CONCLUSION

The TC genotype of *MC4R* rs17782313 polymorphism appears to be a protective factor against high visceral fat levels in the Jambi Malay population. While the effect of the TC genotype was attenuated after adjusting for calorie intake, physical activity, and gender, the protective association of the the recessive model (CC+TC) remained significant. These findings suggest that the role of *MC4R* in visceral fat accumulation is modified by lifestyle and gender. This

strengthening the evidence that central obesity is multifactorial condition, interaction of genetic and non-genetic factor simultaneously influence the phenotype appearance. These insights could be pivotal for developing targeted, personalized preventive strategies against central obesity in this specific ethnic group.

ACKNOWLEDGEMENT

We would like to express our sincere gratitude to the Universitas Jambi for providing the necessary facilities and support for this research. We also appreciate the research team, laboratory staff, and all participants who contributed their time and effort to this study. Special thanks to the Faculty of Medicine and Health Sciences, Universitas Jambi, for their ethical approval and guidance throughout the research process. Lastly, we acknowledge the invaluable support from our colleagues and mentors, whose insights and encouragement have greatly contributed.

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