Molecular and Cellular Biomedical Sciences, Vol.9 No.3, November 2025, p.124-78
Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v9i3.655

RESEARCH ARTICLE

MCBS
Mol Cell Biomed Sci. 2025; 9(3): 149-56
DOI: 10.21705/mcbs.v9i3.655

TC Genotype of rs17782313 Near *MC4R* Gene Increases Obesity Risk

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Background: The genetic variant rs17782313 near the melanocortin-4-receptor gene (*MC4R*) is one of the robust risk factors for obesity and may be linked to its effect on dietary intake, which has different effect sizes between populations. The association between rs17782313 and obesity and dietary intake has not yet been published with the population from Jambi Malay. This study was conducted to analyze the association of genetic variation of *MC4R* rs17782313 and dietary intake among the Jambi Malay population.

Materials and methods: This study was an unmatched case-control study with 110 subjects, consisting of 55 obese and 55 non-obese individuals. All the subjects were Jambi Malay who reside in Jambi Province and are aged 19-60 years. The *MC4R* rs17782313 genotype was measured using the tetra amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) method. Dietary data were collected through food recall and analyzed using the NutriSurvey. Bivariate and multivariate analyses were performed.

Results: Bivariate analysis showed that subjects with TC genotype increased risk for obesity (*p*-value: 0.043; OR (95%CI): 3.044 (1.001-9.259). Multivariate analysis adjusted for age, gender and dietary intake, showed similar trends: the TC genotype increased the risk of obesity (*p*-value: 0.038; OR (95%CI): 3.376 (1.069-10.655). Dietary intake, including total calories, fat, carbohydrate, and protein intake, did not show a statistically significant association with the rs17782313 genotype in obese and non obese groups (*p*-value>0.05).

Conclusion: The TC genotype of rs17782313 near the *MC4R* gene significantly increases the obesity risk in the Jambi Malay population, independent of dietary intake.

Keywords: *obesity, MC4R, rs17782313, Malay, Jambi*

Submission: February 10, 2025
Last Revision: April 15, 2025
Accepted for Publication: April 17, 2025

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Introduction

Obesity is a global health issue that has been steadily increasing over the past few decades. This condition is characterized by excessive fat accumulation, which serves as a major risk factor for chronic diseases such as diabetes mellitus, hypertension, and cardiovascular diseases. Data from the World Health Organization (WHO) indicates that the prevalence of obesity among the adult population globally reached 16% in 2022, more than doubling since 1990.[1] In Indonesia, the prevalence of obesity rose from 21.8% in 2018 to 23.4% in 2023. In Jambi Province, the prevalence of obesity was reported to be 14.6% in 2023, according to the Indonesian Health Survey by the Ministry of Health.[2] Obesity is caused by excess fat accumulation, which is linked to low-grade chronic inflammation.[3] This contributes to disturbing cardiometabolic pathways that are linked to an increased risk of cardiovascular diseases.[4] Meta-analysis and systematic review reported that obesity increases the risk of type 2 diabetes mellitus and coronary artery diseases.[5]

Factors contributing to obesity include genetics, dietary patterns, physical activity, and lifestyle changes.[6,7] Heritability studies report that genetics account for 40-70% of obesity phenotypes, making it a critical component for understanding the physiological and molecular mechanisms underlying weight control.[6] The rs17782313 polymorphism near the melanocortin-4-receptor gene (*MC4R*) is strongly associated with obesity, but its effect size varies across populations.[8,9] This polymorphism is located downstream of the *MC4R* gene, which affects the MC4R protein expression or expression of adjacent genes through its role as regulator sequences. A previous study reported that this variant was associated with a disturbing melanocortin signaling pathway, increased ghrelin, leptin and decreased glucagon-like peptide-1 (GLP-1) which contributed to impaired satiety control and affected eating behavior.[10,11] In addition, this polymorphism increases cortisol which is linked to stress response.[10] Those pathways may explain the cross-talk between rs17782313 and obesity through its role in eating behavior which affects dietary intake. Previous phenotype-genotype associations have different results between populations regarding the association of rs17782313 and dietary intake or eating behaviour in interaction with obesity.[10,12-15]

To date, no studies have investigated the association between rs17782313, obesity, and dietary intake in the Jambi Malay population. Given the distinct genetic background and dietary patterns of this population, this study provides novel insights into the genetic predisposition to obesity in an understudied Indonesian cohort. The dietary intake of the Malay population is characterized by calorie-dense foods, with a greater emphasis on animal rather than vegetable sources, which may influence the association between genetics and obesity. This study was conducted to analyze the association between the rs17782313 polymorphism near the *MC4R* gene and obesity and dietary intake.

Materials and methods

Study Design and Subject Recruitment

This study was an unmatched case-control design. The cases in this research were subjects with obesity, measured using body mass index (BMI), while the controls were non-obese individuals. The cases consisted of 55 subjects grouped as obese and 55 subjects grouped as cnon-obese. All the subjects had resided in Jambi Province for at least 5 years to reduce the effect of dietary intake differences. Ethnicity was determined from interviews, and the parents and grandparents were Malay. Subjects were selected based on inclusion criteria, including age between 19 and 60 years, willingness to participate in the study. The exclusion criteria included subjects undergoing routine medical treatments (*e.g.*, for cancer or autoimmune diseases), pregnant or breastfeeding women, individuals who had been on calorie restriction within the past three months. The research was carried out from July to November 2024.

All subjects provided written informed consent after receiving detailed information about the aims and procedure of this study. This study received ethical approval from the Ethics Committee of the Faculty of Medicine and Health Sciences, Universitas Jambi (No. 1887/UN21.8/PT.01.04/2024). Participant data confidentiality was ensured in accordance with the principles of research ethics.

Anthropometric and Food Intake Measurementl

Anthropometric data were collected by measuring body weight using a calibrated digital scale and height using a stadiometer, followed by calculating the body mass index (BMI) using the standard formula. Subjects with a BMI >27 kg/m² were categorized as obese, while those with a BMI between 18.5-26.9 kg/m² were categorized as non-obese.16

Dietary data were obtained using a 24-hour food recall method conducted three times (two weekdays and

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v9i3.655

one weekend day). The caloric intake results were analyzed using NutriSurvey software to estimate total daily caloric needs. Dietary patterns were categorized into two groups: above the recommendation (caloric intake exceeding total caloric needs) and at or below the recommendation (caloric intake meeting or below total caloric needs) based on the Indonesian Health Ministry.[17] All dietary data were collected and analyzed under the supervision of a well-trained and certified nutritionist.

Genotyping

Blood sampling was performed by trained medical personnel using sterile procedures. Venous blood samples were stored in EDTA tubes for Deoxyribonucleic acid (DNA) extraction. Blood samples, after being mixed with buffer and proteinase K, were incubated, centrifuged, and washed with ethanol solution to obtain pure DNA. The *MC4R* rs17782313 genetic variation was analyzed using the amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) method.

DNA was extracted from the venous blood buffy coat, a solid phase, using proteinase K DNA extraction kit (FavorPrep, Cat No: FABGK300, Favorgen BioTech Crop, Taiwan). DNA quality was measured using 2% agarose gel electrophoresis, which displayed a continuous 351 bp band. The mixing process involved combining several components into a 0.2 mL PCR tube in the following proportions: 15 µL of PCR master mix (GoTaq, Cat No: M&122, Promega, USA), 2 µL each of primers forward outer (FO) and reverse outer (RO), 3 µL each of primers forward inner (FI) and reverse inner (RI), 3 µL of nuclease-free water (NFW), and 2 µL of the DNA sample. The primer sequences were forward inner: GAAGTTTAAAGCAGGAGAGATTGTATACC; reverse inner: GCTTTTCTTGTCATTTCCAGCA; forward outer: TCCACATGCTATTGGTTTAAGACAA; reverse outer: TGCTGAGACAGGTTCATA AAAAGAG. The primer sequences are form a previous study.[18] The genotyping process employed a one-step tetra ARMS-PCR, which produced general and allele-specific products. The general product was 351 bp, allele T was indicated by an 184 bp and allele C was indicated by a 218 bp PCR product.

The mixture was then subjected to a thermocycler (Arktik TCA 0001, Cat No: N11467, Thermosientific, Finland) under the following PCR conditions: an initial denaturation at 94°C for 7 minutes, followed by 35 cycles of melting at 94°C for 1 minute, annealing at 56°C for 35 seconds, and elongation at 72°C for 1 minute.

Data Analysis

Data were analyzed using both bivariate and multivariate approaches. Numerical data were analyzed with the Mann-Whitney test due to the non-normal distribution of the data. Bivariate analysis was performed using the chi-square test for nominal or ordinal data. Multivariate analysis was conducted using binary logistic regression, with the TT genotype as the reference for the additive and dominant models and the TC+TT genotype (T allele) as the reference for the recessive model, to analyze the association between *MC4R*, dietary patterns, and obesity. SPSS 25 from IBM was used for statistical analysis. The TT genotype was used as the reference because it is considered the wild-type genotype, and the T allele is recessive for the obesity phenotype in this study. The C allele, being the minor allele, was considered dominant in increasing the risk of obesity.

Results

Higher Proportion of Females Observed in Obese Group

The proportion of females in the obese group was higher than that of males, and this difference was statistically significant (Table 1). The obese group also had a slightly older mean age and a higher proportion of subjects whose dietary intake exceeded the recommended caloric needs, although these differences were not statistically significant.

Genotype Distribution and Minor Allele Frequency

The TT genotype of *MC4R* rs17782313 was the most common in both groups, followed by the TC genotype, while the CC genotype was the least frequent (Table 2). Hardy-Weinberg equilibrium (HWE) analysis showed no deviation in the obese group (p=0.999), whereas the non-obese group deviated from HWE (p=0.013), suggesting a loss of heterozygosity. The minor allele (C) frequency was 0.14 in the obese group and 0.08 in the non-obese group..

TC Genotype Increased the Risk of Obesity

Individuals with the TC genotype had a significantly increased risk of obesity compared to those with the TT genotype (OR=3.044; 95% CI=1.001–9.259; p=0.043). After adjusting for age, gender, and dietary intake, the association remained significant (adjusted OR=3.376; 95% CI=1.069–10.655; p=0.038). Although the CC genotype in the additive model and the dominant/recessive models showed trends toward increased risk, these did not reach statistical significance (Table 3).

Table 1. Macroscopic and microscopic characteristics of bacterial isolates.

Characteristic	Obese (n=55)	Non-obese (n=55)	*p*-value
Gender			
Male, n (%)	14 (36.8)	24 (63.2)	0.045 [a]
Female, n (%)	41 (56.9)	31 (43.1)	
Age (years old)	34.67±39.11	31.68±38.36	0.176 [b]
Dietary Intake			
Higher than recommended calories, n (%)	20 (58.8)	14 (41.2)	0.302 [a]
Proper to recommended calories, n (%)	35 (46.1)	41 (53.9)	
Total calories (kcal)/day	1,395.9±521.4	1,427.2±419.7	0.455 [a]

a: Chi-square, b: Mann-Whitney Test.

No Association Found Between Genotype and Dietary Intake

No statistically significant differences were observed in total calorie or macronutrient intake based on genotype in either the obese or non-obese group (Table 4). In the obese group, TC carriers had higher total calorie and carbohydrate intake, while TT carriers had higher protein and fat intake. In the non-obese group, TC carriers had the highest total calorie intake, and CC carriers had the highest carbohydrate percentage. However, none of these differences reached statistical significance.

MC4R rs17782313 Genotyping Confirmed Using Tetra Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR) Method

The *MC4R* rs17782313 genotyping was successfully confirmed using the tetra ARMS-PCR method. The presence of the C allele was indicated by a 218 bp band, the T allele by a 184 bp band, and the common PCR product by a 351 bp band. A negative control was included to confirm the absence of contamination in PCR components (Figure 1).

Discussion

This study shows that the *MC4R* rs17782313 genetic variation is a risk for obesity. Subjects with the TC genotype have higher odds of developing obesity compared to those with the TT genotype, even after adjusting for dietary intake. Previous meta-analysis studies reported the polymorphism of rs17782313 increases the risk of obesity in the additive model or dominant model, the CC and TC genotype poses a risk for obesity.[8,19,20] The effect size varies across populations, and the effect is more pronounced in East Asia and Caucasians.[9] This difference may be linked to the multifactorial causes of obesity, which involves interaction between genetic and obesogenic environment. The high-calorie intake, low fibre intake, low physical activities and higher stress were obesogenic environments which increased the risk of obesity.[6]

Table 2. Genotype distribution, minor allele frequency, and Hardy-Weinberg equilibrium of *MC4R* rs17782313.

Genetic Variants	Observed frequency (n)	Expected frequency (n)	X^2 (df)	*p*-value	MAF
Obese					
TT	41	41			
TC	13	13	0.0007	0.999	0.14
CC	1	1			
Non-Obese					
TT	48	46			
TC	5	8	8.579	0.013	0.08
CC	2	1			

MAF: minor allele frequency; X^2 (df): Chi-square.

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v9i3.655

Table 3. Association between *MC4R* rs17782313 genotype and obesity risk.

Genetic Variation	Obese (n= 55)	Non Obese (n= 55)	*p*-value	OR (95%CI)	Adjusted p-value	Adjusted OR (95%CI)
Additive model						
TT	41(46.1%)	48(53.9%)	-	-	-	-
TC	13(72.2%)	5(27.8%)	0.043 [a]	3.044 (1.001-9.259)	0.038 [c]	3.376 (1.069-10.655)
CC	1(33.3%)	2(66.7%)	1.00 [b]	0.585 (0.051-6.692)	0.643 [c]	1.803 (0.149-21.815)
Recessive model						
TT+TC vs. CC	54(50.5%)	53(49.5%)	1.00 [b]	0.491 (0.043-5.575)	0.535 [b]	2.178 (0.186-25.478)
Dominant model						
CC+TC vs. TT	14(66.7%)	7(33.3%)	0.089 [a]	2.341 (0.863-6.355)	0.079 [b]	2.511 (0.898-7.024)

a: Chi-square, b: fisher exact test, c: binary logistic. For additive and dominant models, the TT genotype was used as the reference. For recessive model the TT+TC genotype (T allele) was used as the refference.

The rs17782313 polymorphism is located downstream of the *MC4R* gene. Although this polymorphism is located in the non-coding area of the *MC4R* gene, its effect on obesity is greater than that of polymorphism located within the *MC4R* gene. The *MC4R* receptor consists of three G proteins, one of them is G protein stimuli (Gs) which is activated by cAMP. *In vitro* study in cell line have reported the polymorphic allele (C allele) of rs17782313 is associated with decreased cAMP may lead to the inability of *MC4R* activation. The loss of *MC4R* activation is linked to loss of satiety. The decrease of cAMP in this context is mediated by increased expression of DNAJC27, a protein which is increased in obesity.[11] In addition, an observational study reported this polymorphism genotype CC and TC are associated with higher plasma levels of ghrelin, leptin and GLP-1 than TT. These increases may affect eating behavior and increase cortisol, which is linked to stress.[10] In this study, the TC genotype was identified as risk factor of obesity, but not CC, possibly due to the low MAF of CC (low frequency of CC genotype).

Linked to the pathway previously explained above, previous studies in Iranian and China reported the association of rs17782313 and eating behavior, amounts of calories or macronutrient intake.[10,14] However, this recent study found otherwise, this polymorphism is not associated with total calorie intake and macronutrient intake both in obese and non obese group. The TC genotype both in obese and non obese groups consumed higher total calories, but the differences were not statistically significant. Previous studies in Denmark, Korea and Philipina also found no significant association between food intake and *MC4R* rs17782313 genetic variation. This report is consistent with meta-analysis studies that found no association with diet intake but did find an association with eating behaviour.[13,15,21] The *MC4R* receptor in the hypothalamus functions to regulate appetite, energy expenditure, and metabolism. Activation of this receptor suppresses hunger and increases energy expenditure.[10] This difference in results may be linked to calorie and macronutrient intake or eating behavior among individuals is often influenced by age, sex, lifestyle factors and dietary habits rather than genetic factors alone.[22,23]

Baseline characteristic of the subjects in this recent study indicated that being female increased the risk of obesity. Meanwhile, age and dietary intake did not reach statistically significant levels of risk of obesity. This gender disparity may be associated with differences in fat distribution, and hormonal differences, women tend to have more obesogenic lifestyles like uncontrolled eating, emotional eating and lower physical activities.[24-26] In addition, to minimize effect of calories restriction this study exclude the subjects who had been calories restriction in recent 3 months. Previous meta-analysis based on random control trial reported in various caloric restriction regimen the modest weight lost after 1-3 month.[27]

Table 4. Calories and macronutrients intake by *MC4R* rs17782313 genotype.

Variable	TT	TC	CC	*p*-value
Obese	n=41	n=13	n =1	
Total calories (kcal)	1,258.00 (405.00-3,095.00)	1,205.00 (974.00-2,503.00)	-	0.612 [a]
Protein (%)	16.66 ± 6.51	14.15 ± 5.86	-	0.222 [b]
Carbohydrate (%)	43.39 ± 15.48	48.31 ± 19.57	-	0.354 [b]
Fat (%)	31.83 ± 12.65	27.15 ± 14.11	-	0.264 [b]
Non Obese	n=48	n=5	n=2	
Total calories (kcal)	1,407.05 (821.00-2410.00)	1,654.30 (897.00-1812.00)	1,166 (678.00-1,654.00)	0.693 [a]
Protein (%)	16.00 (4.00-32.00)	18.00 (14.00-33.00)	16.50 (14.00-19.00)	0.512 [a]
Carbohydrate (%)	51.50 (16.00-76.00)	47.00 (31.00-67.00)	52.00 (43.00-61.00)	0.987 [a]
Fat (%)	29.00 (7.00-47.00)	36.00 (15.00-40.00)	31.50 (25.0-38.00)	0.526 [a]

[a]non parametric test; [b]independent t-test. The mean or median of CC genotype not available in obese group due to the frequency of CC genotype in obese group found in one subject.

The Hardy-Weinberg equilibrium test showed a chi-square value of 2.7517 with a p-value of 0.2526. This study found a MAF of C with a frequency of 10.91%. The global MAF is 24%, with the allele C frequency. These results are similar to the MAF found in the Asian population, with 18.5% in China and 25% in Korea.[14,21] Iran has a population frequency of 44%, and Kuwait has 28%.[11,18] If a population does not deviate from Hardy-Weinberg equilibrium, it means that the allele and genotype frequencies observed in the genetic data are consistent with what is expected according to Hardy-Weinberg principle.

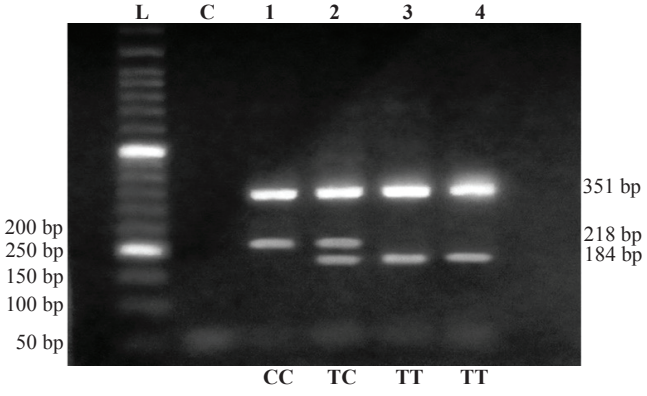

Figure 1. Tetra ARMS-PCR amplification products for *MC4R* rs17782313 genotyping. Electrophoresis image showed: 184 bp (T allele), 218 bp (C allele), and 351 bp (common product). C: Negative control.

To the best of our knowledge, this study was the first study in the Jambi Malay population to investigate the association between obesity, dietary intake and rs17782313. Further research involving a larger sample, multiple ethnicities with a more prominent obese population, stricter inclusion criteria for cofounding variable, a more comprehensive obesogenic environment and multiple genetics risk should be performed to reinforce this recent study findings.

Conclusion

TC genotype of rs17782313 near MC4R gene significantly increases the risk of obesity in Jambi Malay population.

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v9i3.655

While no association was found between this polymorphism and the intake of calories or macronutrients, the presence of the TC genotype remains a notable risk factor for obesity in this population, regardless of dietary intake. These findings highlight the potential role of genetic factors in obesity susceptibility within the Jambi Malay population.

Authors' Contributions

AM and AP were involved in the conception and planning of the research. CM, AM, RH, and AP performed data acquisition and collection. RNE, CM, RH, and WIDA analyzed the experimental data. AM and AP drafted the manuscript and designed the figures. WIDA assisted in interpreting the results. AM, AP, CM, RH, RNE, WIDA and RH contributed to the critical revision of the manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest or competing interests related to the content of this manuscript.

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