Association of *MC4R* (rs17782313) with diabetes and cardiovascular disease in Korean men and women

Jae Woong Sull
Eulji University https://orcid.org/0000-0002-5178-0065
Jae Woong Sull
Eulji University
Gitae Kim
Eulji University
Sun Ha Jee (jsunha@yuhs.ac)
Yonsei University https://orcid.org/0000-0001-9519-3068

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Abstract

Background Diabetes is mostly assessed by the fasting glucose level. Several studies reported that serum fasting glucose levels are causally associated with MC4R.

Methods A total of 4,294 subjects participated in this study. We used multivariate linear regression models and multiple logistic regression analysis.

Results Individuals with the TC/CC genotype had a 1.29-fold higher risk of diabetes than did those with the TT genotype when adjusting for age, sex, and BMI (OR, 1.29; 95% CI, 1.04-1.60). For healthy subjects, the association was significant in females (OR, 1.99; 95% CI, 1.01-3.93). Male participants with the TC/CC genotype had a 1.21-fold higher risk of cardiovascular disease than did those with the TT genotype when adjusting for age, sex, and BMI (OR, 1.21; 95% CI, 1.04-1.41). The relationship between MC4R and cardiovascular disease was stronger in lean male individuals (OR, 1.40; 95% CI, 1.12–1.74, p = 0.0028) than in obese male subjects.

Conclusions This study suggests that the rs17782313 SNP in MC4R is related to diabetes and the SNP is also associated with cardiovascular disease in lean male individuals.

Background

Diabetes is mainly assessed by the fasting blood-glucose level [1]. Several previous studies reported that the melanocortin-4 receptor (MC4R) (MIM 155541) gene is a candidate as a causal gene for type 2 diabetes [2, 3]. MC4R deficiency is related to monogenic obesity [4]. The MC4R rs17782313 SNP has also been linked with obesity in Europeans and Koreans [5, 6]. The SNP rs17782313 was also associated with diabetes in several studies [3, 7, 8].

Recent studies have reported that the MC4R gene was related to cardiovascular disease [9, 10]. In this study, we investigated the relationship between diabetes, cardiovascular disease, and the rs17782313 MC4R SNP in Korean men and women. We also evaluated modification of the relationship of MC4R and cardiovascular disease by obesity.

Methods

Study population

There were 4,294 participants who had general health examinations in University hospitals from 1994 to 2012 [11, 12]. There were 1810 subjects with Cardiovascular Disease (CVD) among the 4294 subjects. The cases were obtained by the NHIC health-insurance reimbursement data. The codes of the International classification of Disease (ICD), 10th Revision (I00-I99), were used for the definition of CVD. Because of missing fasting blood-glucose level, body mass index, and SNP rs17782313 data, 35 subjects were excluded. Therefore, the final subjects included 4,259 people, and 1,782 subjects among them were

Cardiovascular Disease (CVD) patients. The other 2,477 subjects were the healthy subjects. This study's protocols were approved by the Institutional Review Board of Human Research of Yonsei University, and all subjects provided written, informed consent prior to enrollment.

Data collection

The subjects were interviewed using a structured questionnaire about smoking status and demographic characteristics (age, sex, etc.). The weight and height were measured with participants lightly clothed.

Peripheral venous-blood samples taken after a 12-hour fast and stored at −70°C were used for the measure of fasting blood sugar (FBS), total cholesterol, triglycerides, and HDL-C. We used a Hitachi-7600 analyzer (Hitachi, Ltd., Tokyo, Japan) for the clinical chemistry assays.

Genotyping assays

The TaqMan reaction was used for the genotyping of the rs17782313 MC4R gene SNP [13]. Only the SNPs with a concordance rate > 99% in duplicates and a genotype success rate > 98% were included.

Statistical analysis

Data are shown as means ± standard deviation. PLINK and SAS ver. 9.4 (SAS Institute, Cary, NC, USA) were used for most statistical analyses. Under an additive model, possible effects on fasting blood-glucose level were tested for each SNP. We used the multivariate linear regression models with covariates (age and sex) and multiple logistic regression analysis. Body mass index was divided by the median values. The association between the *MC4R* SNP, diabetes, and cardiovascular diseases were expressed by Odds ratios (ORs) with 95% confidence intervals (CIs). Diabetes was defined as fasting serum glucose ≥ 126 mg/dL or medication. All statistical tests were two-sided, and $p < 0.05$ was used for the statistical significance.

Results

The mean age in male subjects and in female subjects was 51.9 and 52.7 (Table 1). Diabetes patients were about 8.9% of the subjects; 37.3% of males and 3.9% of females were current smokers of the sample dataset. Cardiovascular disease patients were 44.7% of men and 35.9% of women. Table 2 shows the *p* values from a linear regression model for FBS levels when age and sex were included as covariates. The rs17782313 SNP in the *MC4R* gene was related to mean FBS level and BMI (effect per allele, 1.542 mg/dL, $p = 0.0057$, and 0.227 mg/dL, $p = 0.0018$). For healthy individuals, the rs17782313 SNP in the *MC4R* gene was related to mean FBS level and BMI (effect per allele, 1.477 mg/dL, $p = 0.0205$, and 0.237 mg/dL, $p = 0.0096$).

The relationship between diabetes and the *MC4R* gene SNP rs17782313 was examined (Table 3). Individuals with the TC/CC genotype had a 1.29-fold higher risk of diabetes than did those with the TT genotype when adjusting for age, sex, and BMI (OR, 1.29; 95% CI, 1.04-1.60). When analyzed by sex, the

relationship between *MC4R* and diabetes was significant only for men (OR, 1.33; 95% CI, 1.04-1.70), not women (OR, 1.10; 95% CI, 0.70-1.75). For healthy subjects, individuals with the TC/CC genotype had a 1.40-fold higher risk of diabetes than did those with the TT genotype when for adjusting age, sex, and BMI (OR, 1.40; 95% CI, 1.01-1.95). However, the association was stronger in females (OR, 1.99; 95% CI, 1.01-3.93), and the association of MC4R with diabetes was not found in males (OR, 1.24; 95% CI, 0.85-1.81).

The relationship of the *MC4R* gene SNP rs17782313 to cardiovascular disease was also examined (Table 4). Male subjects with the TC/CC genotype had a 1.21-fold (range, 1.04–1.41-fold) higher risk of cardiovascular disease than did those with the TT genotype when for adjusting age, sex, BMI (OR, 1.21; 95% CI, 1.04-1.41). In contrast, the relationship of MC4R with cardiovascular disease was not found in females.

Table 5 shows the analysis by BMI for male subjects. The relationship between *MC4R* and cardiovascular disease was stronger in males with BMI < 24.75 (OR, 1.40; 95% CI, 1.12–1.74, $p = 0.0028$) than in subjects with BMI >= 24.75 ($p = 0.6461$). However, the interaction between BMI and *MC4R* (rs17782313) genotype for cardiovascular disease was not significant (p for interaction = 0.0753).

Discussion

In a cohort of 4,259 people, the rs17782313 SNP in the MC4R gene was related to serum glucose level, as in previous studies. A meta-analysis of 123,373 individuals reported that the rs17782313 polymorphism in MC4R gene has the BMI independent significant association with risk of type 2 diabetes [7]. A recent study reported a strong association with MC4R loci for type 2 diabetes (OR = 1.70) [2]. Another study reported that the rs17782313 SNP was significantly associated with increased risk of diabetes [3]. A recent study reported that a Mediterranean dietary pattern could influence the relationship between MC4R gene rs17782313 polymorphisms and the risk of type 2 diabetes [8]. In our study for healthy subjects, the association of MC4R gene rs17782313 with diabetes was stronger in females than in males. A study also reported that the allele C of MC4R (rs17782313) was associated with a higher risk of type 2 diabetes mellitus in women [14].

The MC4R gene was associated with BMI and is involved in the regulation of insulin secretion [5, 15]. Loos et al. [5] in a meta-analysis from European subjects reported a significant association between rs17782313 in the MC4R gene and BMI in adults and children. A study also demonstrated that genetic variants in MC4R affect the obesity phenotype in Koreans [6]. In another meta-analysis, the association of the MC4R gene with insulin resistance and type 2 diabetes was reported even after adjustment for BMI [7]. The MC4R gene (rs17782313 and rs17700633) were related to obesity risk and insulin resistance in two genome-wide association studies [5, 16]. In this study, we found a linear relationship to BMI and weight with MC4R SNP rs17782313.

In this study, the rs17782313 SNP in the MC4R gene was related to cardiovascular disease in males. The association was stronger in lean male subjects than in obese subjects. In a recent study, the MC4R gene

polymorphisms were associated with BMI and coronary artery disease [9]. They reported that the MC4R gene SNPs were associated with coronary artery disease ($p < 5 \times 10^{-8}$). They also explained that the mechanisms whereby MC4R SNPs contribute to obesity can increase the liability to coronary artery disease. Another study reported that the MC4R variants contribute to the risk of large artery atherosclerotic stroke in the Chinese Han population [10].

MC4R is localized to chromosome 18q21.3 [17], is highly expressed in the hypothalamus, and is related to appetite and energy control [18]. In mice research, the MC4R gene is associated with hyperinsulinemia before the onset of extreme obesity [19]. Lipocalin-2 crosses the blood brain barrier and binds to MC4R in the paraventricular and ventromedial neurons of the hypothalamus. A recent loss- and gain-of-junction experiment in mice reported that osteoblast-derived lipocalin-2 maintains glucose homeostasis [20]. Another recent study reported that the MC4R gene SNPs influence the body fat content and distribution, as well as relative increase in postprandial carbohydrate utilization [21].

Conclusion

Asian people may have genetic backgrounds different from those of Western individuals [22]. However, this Korean cohort showed that the rs17782313 SNP in the MC4R gene is related to diabetes and obesity. The SNP was also associated with cardiovascular disease in lean males.

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

Study design: JWS, SHJ. Subjects recruitment and acquisition of data: SHJ. Analysis and interpretation of data: JWS, GK, SHJ. Revision of manuscript content: all authors. Approving final version of manuscript: all authors.

Ethics approval and consent to participate

The Severance Medical Ethics Committee approved the study, and all participants provided written, informed consent prior to participation.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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Tables

Table 1. General characteristics of the study population

Subjects		All	Men	Women
N		4259	2896	1363
		Mean ± SD	Mean ± SD	Mean ± SD
Age, year		52.2±10.2	51.9±10.3	52.7±10.1
Weight, kg		67.4±11.1	71.8±9.6	58.1±7.7
Body mass index, kg/m^2		24.4±3.0	24.8±2.7	23.5±3.2
Fasting blood sugar, mg/Dl		97.0±22.6	98.8±24.0	93.1±18.7
Systolic blood pressure, mmHg		121.9±14.5	123.3±13.9	118.9±15.3
Diastolic blood pressure, mmHg		78.2±10.8	79.7±10.6	75.0±10.5
		%	%	%
Smoking status	Ex	28.4	40.1	2.4
	Current	26.9	37.3	3.9
Cardiovascular disease		41.8	44.7	35.9
Diabetes*		8.9	10.2	6.2
Family history of diabetes		14.5	14.1	15.4

SD, standard deviation

* Diabetes was defined as fasting serum glucose ≥ 126 mg/dL or medication.

Table 2. Association between the rs17782313 single nucleotide polymorphism in the MC4R gene and fasting blood-sugar levels based on a linear regression model

Phenotypes	Genotypes				
	TT	TC	CC	Effect (mg/dL)	*P*-value
	Mean±SD	Mean±SD	Mean±SD		
All subjects	(N=2428)	(N=1578)	(N=253)		
Fasting blood sugar, mg/dL	96.0±21.3	98.6±24.9	96.5±18.4	1.542	0.0057
Body mass index, kg/m^2	24.3±2.9	24.5±3.0	24.8±3.2	0.227	0.0018
Weight, kg	67.2±11.0	67.6±11.1	68.6±11.1	0.739	0.0010
Systolic blood pressure, mmHg	121.7±14.6	122.0±14.3	122.7±15.0	0.452	0.2032
Diastolic blood pressure, mmHg	78.2±11.0	78.2±10.4	78.4±11.2	0.061	0.8184
Healthy subjects	(N=1439)	(N=882)	(N=156)		
Fasting blood sugar, mg/dL	93.6±18.5	96.3±22.5	93.7±13.3	1.477	0.0205
Body mass index, kg/m^2	24.0±2.9	24.2±3.0	24.3±2.6	0.237	0.0096
Weight, kg	66.5±11.2	66.9±11.5	67.8±10.6	0.839	0.0035
Systolic blood pressure, mmHg	119.4±13.5	119.3±13.3	119.8±12.1	0.156	0.7119
Diastolic blood pressure, mmHg	78.8±10.9	78.5±10.5	78.8±10.1	-0.039	0.9068

Estimated effect size (β) and *p* values in the multiple linear regression model considered age and sex in the additive model.

Table 3. Odds ratios (OR) of the polymorphic rs17782313 MC4R genotypes for diabetes in the population

		Normal	Diabetes *				
				Model 1		Model 2	
Subjects	Genotype	*N* (%)	*N* (%)	OR (95% CI[a])	*P*-value	OR (95% CI[b])	*P*-value
All	TT	2233 (57.6)	195(51.5)	1.00 (reference)		1.00 (reference)	
(n = 4,259)	TC /CC	1647 (42.4)	184(48.6)	1.32(1.07-1.64)	0.0113	1.29(1.04-1.60)	0.0218
Men	TT	1513 (58.2)	151(51.4)	1.00 (reference)		1.00 (reference)	
	TC/ CC	1089 (41.8)	143(48.6)	1.34(1.05-1.72)	0.0182	1.33(1.04-1.70)	0.0219
Women	TT	720 (56.3)	44(51.8)	1.00 (reference)		1.00 (reference)	
	TC/ CC	558 (43.7)	41(48.2)	1.25(0.80-1.96)	0.3337	1.10(0.70-1.75)	0.6878
All Healthy	TT	1357 (58.6)	82(50.9)	1.00 (reference)		1.00 (reference)	
(n = 2,477)	TC /CC	959 (41.4)	79(49.1)	1.46(1.05-2.02)	0.0234	1.40(1.01-1.95)	0.0424
Men	TT	887 (59.9)	67(54.9)	1.00 (reference)		1.00 (reference)	
	TC/ CC	594 (40.1)	55(45.1)	1.27(0.88-1.85)	0.2082	1.24(0.85-1.81)	0.2580
Women	TT	470 (56.3)	15(38.5)	1.00 (reference)		1.00 (reference)	
	TC/ CC	365 (43.7)	24(61.5)	2.13(1.09-4.19)	0.0277	1.99(1.01-3.93)	0.0490

Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, and body mass index

[a] CI, confidence interval. * Diabetes was defined as fasting serum glucose ≥126 mg/dL or medication.

Table 4. Odds ratios (OR) of the polymorphic rs17782313 MC4R genotypes for cardiovascular disease in the population (n = 4,259)

Subjects		Normal	Cardiovascular Disease				
				Model 1		Model 2	
	Genotype	*N* (%)	*N* (%)	OR (95% CI[a])	*P*-value	OR (95% CI)	*P*-value
All	TT	1439 (58.1)	989 (55.5)	1.00 (reference)		1.00 (reference)	
	TC /CC	1038 (41.9)	793 (44.5)	1.13 (1.00-1.28)	0.0599	1.11 (0.98-1.26)	0.1174
Men	TT	954 (59.5)	710 (54.9)	1.00 (reference)		1.00 (reference)	
	TC/ CC	649 (40.5)	583 (45.1)	1.22 (1.05-1.42)	0.0096	1.21 (1.04-1.41)	0.0144
Women	TT	485 (55.5)	279 (57.1)	1.00 (reference)		1.00 (reference)	
	TC/ CC	389 (44.5)	210 (42.9)	0.94 (0.75-1.19)	0.5990	0.89 (0.71-1.13)	0.3474

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, and body mass index

[a] CI, confidence interval

Table 5. Odds ratios (OR) of polymorphic rs17782313 MC4R genotypes for cardiovascular disease in Korean men (n = 2,896)

		Normal	Cardiovascular Disease		
Subjects	Genotype	*N* (%)	*N* (%)	OR[a] (95% CI[b])	*P*-value
BMI<24.75	TT	516(61.4)	325(53.4)	1.00 (reference)	
	TC/ CC	325(38.6)	284(46.6)	1.40(1.12-1.74)	0.0028
BMI>=24.75	TT	438(57.5)	385(56.3)	1.00 (reference)	
	TC/ CC	324(42.5)	299(43.7)	1.05(0.85-1.30)	0.6461

[a] Adjusted for age and BMI [b] CI, confidence interval

* *p* for the interaction between obesity (BMI >= 24.75) and MC4R (rs17782313) =0.0753.