

Original Article

Melanocortin-4 receptor rs17782313 polymorphisms are associated with serum triglycerides in older Chinese women

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Background and Objectives: MC4R (melanocortin-4 receptor) gene polymorphisms have been associated with serum triglycerides (TG) in Caucasians and Japanese, but no reports are available Chinese. The purpose of this study was to find whether there was an association of rs17782313 polymorphisms at the MC4R gene with serum TG in elderly Chinese. **Methods and Study Design:** 2,012 over 40 years participated in a cross-sectional study in which their body mass index (BMI), TG, high density lipoprotein-cholesterol (HDL-C), and MC4R rs17782313 polymorphisms were determined. **Results:** For women, carriers of the T/T genotype had significantly lower serum TG than those with C/C genotype ($p=0.006$). Carriers of the C/C genotype of this polymorphisms exhibited significantly lower fasting HDL-C levels compared with T/T and T/C genotypes ($p=0.025$), and increased glycosylated hemoglobin (HbA1c) ($p=0.043$), but no change in blood pressure. Higher serum TG in carriers of the C/C genotype of MC4R gene remained stable after adjustment for age, smoking, drinking, BMI, waist circumference (WC) and three or more components of the metabolic syndrome (MS) by multivariable linear regression ($p=0.01$) in women. The carriers of the C/C genotype of MC4R gene showed significantly greater odds ratio for TG than T/C and T/T genotypes, even when adjusted for age, smoking, drinking, BMI and WC in women. **Conclusions:** The rs17782313 C/C genotype is associated with higher TG levels in older Chinese women.

Key Words: melanocortin-4 receptor, serum triglyceride, polymorphisms, Chinese women, cross-sectional study

INTRODUCTION

Increased levels of serum triglyceride (TG) and decreased levels of high density lipoprotein-cholesterol (HDL-C) have played major roles in coronary heart disease (CHD).¹⁻³ These changes appears to be modulated by environmental and genetic factors.⁴⁻⁶ Recent genome-wide association studies (GWAS) have identified both known and novel loci associated with serum TG concentrations.⁷

The melanocortin-4 receptor (MC4R) is a G-protein-coupled receptor expressed in the central nervous system, and plays the role in regulating energy balance and controlling TG synthesis, lipid deposition, and lipid mobilization in white adipose tissue.^{8,9} Variations in MC4R, which is located in chromosome 18q22,¹⁰ have been reported to be associated with common forms of obesity.¹¹⁻¹³ Several cross-sectional studies have shown effects of the MC4R gene polymorphisms on serum total cholesterol (TC) and TG levels in Caucasian and Japanese,^{14,15} but there are still no relevant reports about the relationship between MC4R gene polymorphisms, serum TG levels and HDL-C concentrations in other Asians populations. Therefore, it is necessary to understand the effects of MC4R geno-

types modulating serum TG and HDL-C levels for enabling development of markers for CHD risk prediction and therapeutic interventions in other Asians. Therefore, we hypothesised that MC4R genotypes would be associated with lipoprotein metabolism.

The aim of this study was to examine the associations of rs17782313 polymorphisms at the MC4R gene with HDL-C and TG levels in elderly Chinese.

METHODS

Study populations

A total of 2,121 subjects (784 men: 64.5±13.9 years, body mass index (BMI): 23.3±3.4 kg/m²; 1,337 women: 64.7±12.0 years, BMI: 23.2±3.4 kg/m²) were recruited

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subjects from four communities of Yinchuan, Guyuan, Zhongwei, Qingtongxia and Dawukou, Ningxia, China by the methods of the cluster sampling during health examination. Forty nine subjects were excluded because of the incomplete data collection and another sixty subjects were also excluded because of low metabolic disease risks and aged under 40 years.¹⁶ Finally, a sample of 2,012 subjects (age: 64.8±12.7 years, BMI: 23.2±3.3 kg/m²) were examined in the present study.

The ethics committee of Ningxia Medical University approved all the study protocols, and all subjects provided written informed consent (No. 2014-200).

Anthropometric and biochemical measurements

Weight, height were recorded and BMI was calculated and expressed as kg/m². Concentrations of HDL-C and TG in serum were measured using the chromatographic enzyme method (OLYMPUS Automatic Biochemical Analyzer, AU400). Metabolic syndrome (MS) was defined by the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATPIII) for Asian-Americans.¹⁷ MS can be confirmed, if any 3 or more of the following 5 components are present: (1) abdominal obesity: waist circumference (WC) ≥90 cm for men or ≥80 cm for women; (2) hypertriglyceridemia: (3) TG ≥150 mg/dL; (3) low HDL cholesterol: HDL-C <40 mg/dL for men or <50 mg/dL for women; (4) high blood pressure: ≥130 mmHg systolic blood pressure (SBP) or ≥85 mmHg diastolic blood pressure (DBP); (5) high fasting glucose: fasting glucose ≥110 mg/dL.

Genotyping

Genomic deoxyribonucleic acid (DNA) was prepared from leukocytes in blood by a DNA Extractor WB Kit (Wako Pure Chemical, Japan). The rs17782313 polymorphisms of the MC4R was determined by an allelic discrimination assay-by-design TaqMan Real Time PCR method on Applied Biosystems 7900HT Fast Real-Time PCR System as described previously.^{18,19}

Statistical analysis

Data analysis was done with SPSS statistical analysis software (Version 13.0, SPSS Inc., Chicago, USA). Results were expressed as mean±SD, the genotypes distribution, allele frequency and Hardy-Weinberg equilibrium were tested by chi-square (χ^2) analysis. Differences in continuous variables among the genotype-based groups were analyzed by ANOVA followed a bonferroni post-hoc test. Multiple linear regression analysis was conducted to investigate whether MC4R rs17782313 was correlated with TG and HDL-C concentration independently or not. The significance assessment was conducted by a nominal two-sided *p*-value of less than 0.05.

RESULTS

Demographics

Descriptive results for age, height, weight, and BMI for the 2,012 participants are provided in Table 1. The average age of subjects were 64.8±12.7 years. The average height, weight and BMI were 155±9.2 cm, 56.1±11.2 kg and 23.2±3.3 kg/m², respectively. Compared with women, men had significantly higher height, body weight, WC,

DBP, TG, TG/HDL-C ratio, fasting serum glucose, and lower TC, Low-density lipoprotein cholesterol (LDL-C) and free fatty acid, and a significantly higher rate of alcohol consumption. The prevalence of the MS was 10.9% in men and 8.6% for women.

Association of MC4R rs17782313 and TG and HDL-C concentrations

The rs17782313 polymorphisms of the MC4R of the subjects showed that 1,235 were homozygous for the wild-type genotype (T/T), 664 were heterozygous for the variant genotype (T/C) and 113 were homozygous for the variant genotype (C/C). Frequency of the variant allele was as high as 0.22 for all the subjects. The genotypes distributions of the MC4R rs17782313 were in accordance with the Hardy Weinberg equilibrium ($\chi^2=3.56$, *p*>0.05).

For women, TG levels increased in the order of C/C, T/C, and T/T genotypes. Participants with C/C genotypes had significantly higher TG level (126±100 mg/dL) than those with T/C (107±50.0 mg/dL) or T/T (106±55.8 mg/dL) genotype (*p*=0.006). On the other hand, these individuals (C/C) tended to have lower HDL-C levels (*p*=0.025), and higher glycosylated hemoglobin (HbA1c) (*p*=0.043) than the carriers (C/T and T/T) of T allele. There were no significant differences among three genotypes in age, BMI, TC, LDL-C, free fatty acid, C-reactive protein, fasting serum glucose and blood pressure. Participants with C/C genotype had significantly higher TG/HDL-C ratio than those with T/C and T/T genotypes (*p*=0.006) (Table 2). For men, there were no significant differences between genotypes in parameters related to MS (Table 2).

Multiple linear regression analysis revealed that MC4R gene polymorphisms were independently related to TG (*p*=0.01), smoking (*p*=0.001), BMI (*p*=0.006), TC and three or more components of the MS were significantly associated with TG in women participants (Table 3). There were significant differences in age (*p*=0.048), smoking (*p*=0.001), TC (*p*=0.003) and three or more components of the MS (*p*<0.001) in men participants (Table 3).

The binomial logistic regression analysis with MS by gender were significantly associated with drinking (*p*=0.015), WC (*p*=0.001), TG (*p*<0.001), HbA1c (*p*<0.001), SBP (*p*<0.001), and DBP (*p*=0.02) in women participants. We found a strong independently related to WC (*p*<0.001), TG (*p*<0.001), HbA1c (*p*<0.001), SBP (*p*=0.017), and DBP (*p*=0.028) in men participants.

DISCUSSION

Epidemiological evidence indicates that serum TG concentration is a strong independent risk factor for cardiovascular disease.²⁰ A patient's serum TG concentration may be determined by common and rare variants in multiple genes and environmental influences as well. Identifying genes and genetic variants associated with serum TG concentration will enrich our understanding of biochemical pathways involved in TG-rich lipoprotein metabolism, enabling identification of subjects with increased susceptibility to MS, and development of therapeutic interventions to improve serum TG concentration

Table 1. Subject demographic characteristics

Characteristics	Men (n=737)	Women (n=1,275)	p-value*
Age, years	64.8±13.8	64.9±12.0	N [†]
Alcohol status, %			
Non-drinker	46.1	63.4	N
1-3 cup/day	37.7	28.3	<0.001
>3 cup/day	16.2	8.3	<0.001
Smoking status, %			
Non-smoker	36.7	75.6	<0.001
<20 cigarettes/day	60.4	24.0	0.031
≥20 cigarettes/day	2.9	0.4	N
Parameters related to MS			
Height, cm	163±7.0	150±6.6	<0.001
Body weight, kg	62.4±11.5	52.4±9.1	<0.001
BMI, kg/m ²	23.3±3.3	23.1±3.4	N
TC, mg/dL	199±32.2	213±32.6	<0.001
LDL-C, mg/dL	115±27.9	130±28.7	0.001
TG/HDL-C, mg/dL	1.80±2.51	1.60±1.56	0.049
Free fatty acid, mg/dL	695±309	747±311	<0.001
HbA1c, %	5.33±0.81	5.38±0.58	<0.001
Features of the MS			
WC, cm	83.3±9.4	80.8±10.0	<0.001
TG, mg/dL	121±96.8	107±57.8	0.001
HDL-C, mg/dL	98.5±51.4	96.5±53.9	N
Fasting serum glucose, mg/dL	100±22.6	97.1±16.9	N
SBP, mmHg	131±17.1	131±18.3	N
DBP, mmHg	78.8±10.8	76.0±10.9	<0.001
Number of components of the MS			
0	30.5	26.7	
1	35.1	39.8	
2	23.5	25.0	
3	9.1	6.6	0.076
4	1.8	1.9	
Three or more components of the MS	10.9	8.6	

Data are presented as means±SD or %. One cup=10 mL alcohol.

BMI: body mass index; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; MS: metabolic syndrome. All *p* values were two-sided.

**p*<0.05 was significant. [†]N: non-significant.

Bonferroni post-hoc test was used to assess the differences in variants by gender.

χ^2 test was used to compare the frequency of alcohol status, smoking status and components of the MS between men and women.

and reduce cardiovascular disease risk. MC4R gene polymorphisms has been reported to be associated with common forms of obesity.¹¹⁻¹³ Up to now, only a few studies on MC4R gene polymorphisms and serum TG levels have been conducted in Caucasian or special Japanese populations,^{14,15} but there are still no relevant reports between MC4R gene polymorphisms, serum TG levels and HDL-C from other Asian population. From present study, we found that carriers of the C/C genotype at rs17782313 in the MC4R gene may independently have a significant risk effect on higher TG, lower HDL-C levels, and higher TG/HDL-C ratio in our study population. The minor allele frequencies were 0.22 in the all subjects. The genotype distribution in our results were similar to those reported previously and did not deviate significantly from Hardy-Weinberg equilibrium.

In recent studies, the minor allele of MC4R rs17782313 frequencies were 0.14 in controls and 0.185 in the obese group in Hong Kong²¹ and 0.20 in controls and 0.22 in the obese group in a Chinese Han population,²² respectively. There were considerable differences in dietary, lifestyle and population demographics among these populations, which may explain the inconsistency

with the results of the three studies.

It is interesting that we found an association between rs17782313 and the serum levels of TG, HDL-C and high TG/HDL-C ratio in elderly Chinese women. This is the first demonstration of the relationship between rs17782313 at MC4R, TG, HDL-C and high TG/HDL-C ratio. Katsuura-Kamano also reported that MC4R rs17782313 polymorphisms were associated with serum TG levels in an Asian population, independent of food intake and obesity.¹⁵ It can therefore be assumed that rs17782313 does not influence serum lipid levels through BMI. Recently, significant associations between near MC4R rs17782313 and MS were reported by several studies.^{23,24} However, above-mentioned reports did not show the result for each component of MS, including serum TG levels. Clearly, more data need to be collected to assess the phenotypic consequences of the rs17782313 polymorphisms of the MC4R in elderly Chinese women. It is important to enable identification of subjects with increased susceptibility to disorders of metabolism, and develop of therapeutic interventions to improve serum TG concentrations and ameliorate cardiovascular disease risk in elderly women.

Table 2. Characteristics of 2,012 subjects grouped by MC4R genotypes

Characteristics	Men			<i>p</i> values*	Women			<i>p</i> values*
	TT (n=426)	TC (n=268)	CC (n=43)		TT (n=809)	TC (n=396)	CC (n=70)	
The C allele frequency			0.24				0.21	N [†]
Age, years	65.0±13.6	64.0±14.6	66.4±11.7	N	65.2±12.2	64.9±11.1	62.3±14.0	N
Alcohol status, %								
Non-drinker	26.8	16.2	3.1	N	36.8	20.4	4.4	N
1-3 cup/day	23.2	11.7	2.8	N	19.2	7.5	1.6	N
>3 cup/day	9.0	6.2	1.0	N	5.3	2.7	0.3	N
Smoking status, %								
Non-smoker	22.1	12.1	2.5	N	49.7	21.8	4.1	N
<20 cigarettes/day	34.8	21.7	3.9	N	14.4	7.9	1.7	N
≥20 cigarettes/day	1.9	1.0	0.0	N	0.24	0.12	0.04	N
Parameters related to MS								
Height, cm	163±7.1	163±6.8	163±6.7	N	150±6.6	150±6.6	152±7.2	N
Body weight, kg	62.1±11.2	62.8±12.1	62.9±10.5	N	52.2±8.9	52.5±9.6	54.2±9.1	N
BMI, kg/m ²	23.2±3.3	23.4±3.5	23.5±3.0	N	23.0±3.3	23.2±3.4	23.5±3.3	N
TC, mg/dL	198±33.2	198±30.6	206±31.1	N	207±32.4	213±33.0	214±31.7	N
LDL-C, mg/dL	113±28.2	116±27.2	116±28.7	N	126±28.1	129±29.3	132±27.3	N
TG/HDL-CI, mg/dL	1.96±2.87	1.60±2.00	1.38±1.10	N	1.55±1.52	1.59±1.27	2.15±2.76 [#]	0.006
Free fatty acid, mg/dL	694±311	692±310	725±292	N	723±299	725±295	756±320	N
HbA1c, %	5.32±0.79	5.32±0.81	5.46±1.01	N	5.35±0.57	5.38±0.55	5.46±0.62	0.043
Features of the MS								
WC, cm	83.3±9.5	83.4±9.2	83.5±10.4	N	81.0±10.0	80.1±10.0	82.6±9.9	N
TG, mg/dL	124±105	117±88.6	112±52.7	N	106±55.8	107±49.9	126±99.8 [#]	0.006
HDL-C, mg/dL	97.1±52.2	99.3±49.9	107±51.9	N	99.4±54.7	92.2±52.6	87.5±50.1	0.025
Fasting serum glucose, mg/dL	100±23.5	101±21.7	101±19.3	N	96.6±12.4	97.1±18.1	97.1±16.7	N
SBP, mmHg	130±17.3	132±17.5	132±14.1	N	129±20.0	130±19.6	131±17.6	N
DBP, mmHg	78.7±10.8	78.7±10.9	81.0±10.4	N	74.3±9.76	75.4±10.7	76.5±11.0	N
Number of components of the MS								
0	17.5	10.0	3.0	N	18.2	7.2	1.2	N
1	20.5	13.4	1.2	N	24.8	13.0	2.0	N
2	14.1	7.4	2.0	N	15.8	7.4	1.8	N
3	6.1	2.6	0.5	N	4.0	2.0	0.6	N
4	1.4	0.3	0.2	N	1.6	0.4	0.0	N
≥3 of components of the MS	7.4	2.9	0.6	N	5.6	2.4	0.6	N

Data are presented as means±SD. BMI: body mass index; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; MS: metabolic syndrome. MC4R: melanocortin-4 receptor.

All *p* values were two-sided. **p* value less than 0.05 is regarded as statistically significant. [#]was significant between TT genotype and CC genotype. [§]was significant between TC genotype and CC genotype.

[†]N: non-significant. Bonferroni post-hoc test was used to assess the differences in variants by genotype subgroups.

χ^2 test was used to compare the frequency of alcohol status, smoking status and components of the MS among genotype subgroups.

Table 3. Multivariable linear regression with triglyceride grouped by gender

Variables	Men				Women			
	Adjusted R ²	F	β	P values*	Adjusted R ²	F	β	P values
	0.236	14.0		<0.001	0.165	14.1		<0.001
Age, years			-0.082	0.048			-0.017	0.599
Drinking			-0.111	0.092			-0.068	0.496
Smoking			0.132	0.001			0.111	0.001
BMI, kg/m ²			0.083	0.114			0.122	0.006
WC, cm			0.064	0.224			-0.010	0.826
TC, mg/dL			0.192	0.001			0.152	0.003
HDL-C, mg/dL			0.186	0.012			-0.003	0.981
LDL-C, mg/dL			-0.058	0.296			0.028	0.550
Free fatty acid, mg/dL			0.068	0.093			0.012	0.721
HbA1c, %			0.045	0.263			-0.016	0.660
Three or more components of the MS			0.282	0.000			0.321	0.000
MC4R (1: T/T, 2: C/T, 3: C/C)			-0.026	0.519			0.085	0.010

p values of variants associated with triglyceride were expressed by gender. MC4R: melanocortin-4 receptor. BMI: body mass index; WC: waist circumference; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin; MS: metabolic syndrome.

The MC4R, a G-protein-coupled receptor expressed in the central nervous system, plays a role in regulating energy balance and controlling TG synthesis, lipid deposition and lipid mobilization in white adipose tissue.⁸ Variations in MC4R gene have been reported association with common forms of obesity.^{11,12} Several cross-sectional studies have shown effects of the MC4R gene polymorphisms on serum TC and TG levels in Caucasian and Japanese.^{14,15,22} Moreover, pharmacological inhibition of MC4R in rats and genetic disruption of MC4R in mice potentially promote lipid uptake, TG synthesis, and fat accumulation in white adipose tissue.²⁵ To some extent, this evidence may explain the significant association with the elderly Chinese women between the variant at MC4R and serum lipid concentrations.

In conclusion, we failed to replicate the association between rs17782313 and BMI in the elderly Chinese women, but we did pinpoint associations between rs17782313 and serum levels of TG, HDL-C and TG/HDL-C ratio. The findings of our study may only be relevant for subjects with CHD or a high risk of CHD in elderly Chinese women. However, our study represents a substantial subset of the population due to the high prevalence of CHD in elderly Chinese women. Furthermore, participants with the C/C allele of rs17782313 were recognized at being of an elevated risk for higher TG and participants with MS have a strong independent relationship with TG. Although confirmation and additional research are required, we believe that our findings may provide new insights into the complex regulation of serum TG levels in elderly Chinese women.

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AUTHOR DISCLOSURES

The authors declare that they have conflicts of interest to disclose.

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Original Article

Melanocortin-4 receptor rs17782313 polymorphisms are associated with serum triglycerides in older Chinese women

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黑色素皮质激素-4 受体基因 rs17782313 多态性与中国老年女性血清甘油三酯的相关性研究

背景与目的：研究显示高加索人和日本人的黑色素皮质激素-4受体（MC4R）基因多态性与血清甘油三酯（TG）相关，但没有关于中国人的报道。本研究的目的是研究黑色素皮质激素-4受体基因rs17782313多态性是否与中国老年人血清甘油三酯有关。**方法与研究设计：**本研究采用横断面的研究方法调查了2012位年龄在40岁以上的成年人，测定其体质指数、甘油三酯、高密度脂蛋白胆固醇以及黑色素皮质激素-4受体基因rs17782313多态性等指标。**结果：**携带T/T基因型的女性血清甘油三酯明显低于携带C/C基因型的女性（ $p=0.006$ ）。携带C/C基因型的女性的高密度脂蛋白胆固醇则明显低于携带T/T和T/C基因型的女性（ $p=0.025$ ），但其糖化血红蛋白显著高于携带T/T和T/C基因型的女性（ $p=0.043$ ），血压无统计学意义。在校正了年龄、吸烟、饮酒、体质指数、腰围和代谢综合征等因素后，多元线性回归分析发现携带C/C基因型的女性有较高的血清甘油三酯（ $p=0.01$ ）。在女性中，即使校正了年龄、吸烟、饮酒、体质指数和腰围，携带C/C基因型的女性甘油三酯的比值比（OR值）仍然显著高于携带T/C和T/T基因型的女性。**结论：**中国老年女性的黑色素皮质激素-4受体基因rs17782313的C/C基因型与较高的血清甘油三酯有关。

关键词：黑色素皮质激素-4 受体、血清甘油三酯、多态性、中国女性、横断面研究