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Association of Apolipoprotein A-V Gene Polymorphisms and Lipid Metabolism in Mongolian Patients with Metabolic Syndrome

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Objectives: Our study determined the genetic effect of Apolipoprotein A-V *(APOA5)* gene polymorphisms on lipid parameters in patients with metabolic syndrome (MetS). **Methods:** 160 patients with MetS and 144 healthy individuals were selected for the case and control groups, respectively. *APOA5* gene polymorphisms (-1131T>C, IVS3+476G>A, c.1177C>T, c.1259T>C) were genotyped using PCR-RFLP. **Results:** Serum levels of total cholesterol and triglyceride were higher in the MetS group than the control group (p=0.028, p<0.001), while high density lipoprotein levels was lower in the MetS group than the control group (p=0.048). The -1131C allele frequency was higher in the MetS group than the control group (p=0.048). Results of regression analysis showed that *APOA5*–1131C carriers had increased incidences of MetS (OR=1.87, p=0.010). The frequency of the haplotype C-A-T-C was higher in the MetS group than the control group (p=0.027). In the MetS group, the triglyceride level was significantly higher in the minor allele carriers of -1131T>C, IVS3+476G>A, c.1177C>T. **Conclusion:** Our results suggest that, among the *APOA5* SNPs, the C allele of -1131T>C polymorphism is a risk factor for MetS.

Keywords: Metabolic Syndrome X, Lipid Metabolism, Triglycerides, Apolipoprotein A-V, Single Nucleotide Polymorphism

Introduction

Metabolic syndrome (MetS) is corresponds similarly to multiple risk factors clustering syndrome [1]. A large number of longitudinal studies indicate significantly increased risk of developing cardiovascular diseases and type 2 diabetes among patients with the MetS [2]. Among the general Mongolian population, the prevalence of MetS has been reported at 32.7% [3]. Environmental and genetic factors play an important role in the development of MetS [4, 5]. Genetics could effect the

development of MetS in multiple ways, but the mechanisms involved are not yet been fully understood. Each of the key components of MetS—obesity, dyslipidemia, dysglycemia, and high blood pressure—have a genetic basis and candidate genes have been identified [6].

Transgenic mice over-expressing human *Apolipoprotein A-V (APOA5)* have decreased serum triglyceride (TG) concentrations, about one-third of that in the control mice; conversely, knockout mice lacking *APOA5* have four times as much plasma TG than the controls [7]. Since the discovery of *APOA5*, it has been considered to be an important modulator of serum TG levels. The human *APOA5* gene consists of 4 exons and codes a 369 amino acid protein expressed almost exclusively in the liver [7, 8]. Interestingly, the concentration of *APOA5* in human plasma is very low compared with other major high density lipoprotein (HDL) apolipoproteins such as *APOA1* (157μg/L *APOA5*≈1g/L *APOA1*) [9]. *APOA5* is associated with chylomicrons, very low density lipoprotein (VLDL), HDL, and it enhances the catabolism of TG-rich lipoproteins by lipoprotein lipase (LPL) [10]. Some variants of *APOA5* have been described to be associated with not only elevated TG levels, but also to independently affect the risk of MetS, cardiovascular diseases, and type 2 diabetes among various ethnicities [11-16].

In this study, we intended to determine the genetic effect of *APOA5* polymorphisms on lipids parameters among Mongolian patients with MetS.

Materials and Methods

1. Study subjects

160 MetS patients (86 males, 74 females, aged 18 to 60 years) were selected from Ulaanbaatar, Mongolia for the case group. MetS was diagnosed at the Coronary Care Unit of The Shastin Central Hospital according to the International Diabetes Federation (IDF) criteria. MetS was defined as the presence of 3 or more of the following criteria: abdominal obesity with waist circumference (WC)≥90cm for men and ≥80cm for women, systolic blood pressure (SBP)≥130 mmHg, diastolic blood pressure (DBP)≥85 mmHg, serum TG level≥150mg/dl, serum HDL<40/50mg/dl for men/women, fasting blood glucose (FBG)≥100mg/dl. The control group consisted of 144 healthy individuals (71 males, 73 females, aged 18 to 60 years), all of whom received a health check at the same hospital. All participants gave their informed consent, and the study approved by the Ethics Committee of Mongolian National University of Medical Science and Ministry of Health in Mongolia.

2. Biochemical parameters

Total cholesterol (TC), TG, HDL and FBG were analyzed using commercially available kits (AGAPPE DIAGNOSTICS SWITZERLAND GmbH, Switzerland). LDL levels was measured using a standard calculation method [17].

3. Genotyping of SNPs

APOA5 gene (ID:116519)-1131T>C, IVS3+476G>A, c.1177C>T, c.1259T>C single nucleotide polymorphisms (SNPs) were selected as our study targets. DNA from patients and control subjects was extracted using the "G-spin™ Total DNA Extraction Kit" (iNtRON Biotechnology, Inc, South Korea). According to previous published protocols (Table 1), SNPs in *APOA5* were genotyped by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) using the "Maxine PCR PreMixKit" (iNtRON Biotechnology, Inc, South Korea) [18, 19].

4. Statistical analysis

This case-control study was analyzed using SPSS 21.0 (IBM corporation, USA). Allele frequency was estimated by direct counting, and data was represented as means±SD. Statistical significance was evaluated using the t-test to compare the differences between the two groups, and the Mann-Whitney test was used for not normally distributed variables. Qualitative data were shown as percentages and were further analyzed using the Chi-square test. Multiple logistic regression analysis was used to assess the effect of the SNP genotype on the development of MetS. SNPalyse version 7.0 Pro (Dynocom, Chiba, Japan) was used for haplotype analysis.

Results

1. Clinical data and biochemical parameters

Clinical parameters of the MetS patients and the controls are summarized in Table 2. The mean age of the MetS patients was 41.7±11.3, and the mean age of the control group was

Table 1. Primers and restriction enzymes used for the identification of APOA5 polymorphisms

SNPs[a]	Forward (F) and reverse (R) primers	Restriction enzymes	Products
-1131T>C *(rs662799)*	F;GATTGATTCAAGATGCATTTAGGAC R;CCCCAGGAACTGGAGCGAAATT	*MseI*	TT;165,23 TC;188,165,23 CC;188
IVS+476G>A *(rs2072560)*	F;TGGTTCCCCCAGAGGATCAG R;ATCCAGGCCGTCAGACTGCTATGC	*Eco0109I*	GG;54,24 GA;78,54,24 GG;78
c.1177C>T	F;CTCTGAGCCTCTATCATGGTTGAGT R;GAGCATTCCCAAATGAGCAC	*HinfI*	CC;101,73 CT;124,101,73 TT;124,73
c.1259T>C *(rs2266788)*	F;ACCAAAGGGGCTGCTGTCTCGTGCA R;GAGCATTCCCAAATGAGCAC	*ApaLI*	TT;92,23 TC;115,92,23 CC;115

[a]SNPs, single nucleotide polymorphisms

41.2±10.2. No significant gender differences were found between the case and control groups (p=0.924). Serum levels of TC and TG were higher in the MetS group than the control group (p=0.028, p<0.001), while the HDL levels in MetS group was lower than the control group (p=0.048). There was no difference in LDL levels between the two groups.

2. Allele frequency of *APOA5*-SNPs

Genotypes and allele frequencies of the four SNPs were calculated for the MetS group and the control group. As shown in Table 3, results of the multiple logistic regression model was used to determine the significance of the minor alleles of the four SNPs as probable independent risk factors for MetS. Significant association was not observed under the genotype model (TT vs TC and TT vs CC) for -1131T>C, but the allele model showed that -1131TC and CC minor allele carriers had increased risk for MetS (OR=1.87, p=0.010) compared with -1131TT carriers. The data analysis of IVS3+476G>A, c.1177C>T, c.1259T>C

Table 2. Main characteristics of the MetS and control groups

Parameters	MetS (n=160)	Control (n=144)	p-value
Age (years)	41.7±11.3	41.2±10.2	0.924
Gender (M/F)	86/74	71/73	0.527
BMI (kg/m2)	31.27±4.23	26.64±3.75	<0.001
WC (cm)	100.97±1.10	89.01±12.75	<0.001
SBP (mmHg)	128.75±13.97	114.02±14.44	<0.001
DBP (mmHg)	88.42±9.92	77.95±9.52	<0.001
FBG (mg/dl)	92.07±66.57	71.69±12.69	0.012
TC (mg/dl)	157.72±36.42	148.47±36.73	0.123
TG (mg/dl)	147.82±97.21	77.39±42.93	<0.001
HDL (mg/dl)	32.04±11.49	36.44±15.63	0.048
LDL (mg/dl)	96.85±40.38	95.75±39.53	0.867

The values are indicated as mean±standard deviation; M, male, F, female; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

SNPs showed no significant association between those SNPs and MetS. As shown in Table 4, we observed five haplotypes among all the possible haplotypes that accounted for more than 5% of the frequency. The frequency of the *APOA5**5 haplotype C-A-T-C was higher in the MetS group compared with the control group (p=0.027).

3. Association of *APOA5*-SNPs with lipid parameters

We evaluated the alleles of the carriers and non-carriers for all SNPs (Table 5). In the MetS group, TC levels were significantly higher in -1131TC and CC carriers than -1131TT non-carriers (p=0.018), and TG levels were higher in carriers of -1131T>C, IVS+476G>A, and c1177C>T, compared with non-carriers (p<0.001, p=0.045, p=0.038 respectively).

Discussion

Our study revealed that, compared with Koreans and Japanese, TC and LDL levels were lower among Mongolians, even though Koreans and Japanese are reported to intake large amounts

Table 3. Association between ApoA5 genotypes and MetS

SNPs	Genotype	MetS group	Control group	OR (95% CI)	p-value
-1131T>C *(rs662799)*	TT	28.8% (46)	43.1% (62)	1.00	
	TC	58.8% (94)	47.2% (68)	1.86 (0.928-3.740)	0.080
	CC	12.5% (20)	9.7% (14)	1.925 (0.367-5.82)	0.246
	TC+CC	71.2% (114)	56.9% (82)	1.874 (1.165–3.014)	0.010*
IVS+476G>A *(rs2072560)*	GG	6.3% (10)	4.2% (6)	1.00	
	GA	63.3%(100)	67.3% (97)	0.612 (0.139-2.702)	0.517
	AA	30.4% (48)	28.4% (41)	0.720 (0.153-3.391)	0.678
	GA+AA	92.5% (148)	95.8% (138)	0.643 (0.148-2.794)	0.556
c.1177C>T	CC	72.2% (114)	70.1% (101)	1.00	
	CT	22.8% (36)	27.0% (39)	0.789 (0.376-1.657)	0.532
	TT	5.1% (8)	2.8% (4)	1.754 (0.308-9.989)	0.526
	CT+TT	27.9% (44)	29.8% (43)	0.877 (0.435-1.771)	0.715
c.1259T>C *(rs2266788)*	TT	55.6% (89)	62.5% (90)	1.00	
	TC	35.6% (57)	30.6% (44)	1.302 (0.649-2.611)	0.458
	CC	8.9% (14)	6.9% (10)	1.432 (0.422-4.853)	0.564
	TC+CC	44.5% (71)	37.5% (54)	1.326 (0.691-2.544)	0.396

OR, odds ratio; 95% CI, confidence interval; multiple logistic regression analysis was performed with adjustment for age, gender, and BMI.

*p-value < 0.05 significant

Table 4. Haplotype frequency of APOA5 SNPs

Haplotypes	-1131T>C	IVS3+476G>A	C1177C>T	c.1259T>C	Frequency		p-value
					MetS group	Control group	
*ApoA5**1	C	A	C	C	0.266	0.222	0.574
*ApoA5**2	C	A	C	T	0.215	0.222	0.917
*ApoA5**3	T	A	C	T	0.127	0.167	0.049
*ApoA5**4	T	A	T	T	0.089	0.153	0.001*
*ApoA5**5	C	A	T	C	0.089	0.056	0.027*

*p-value < 0.05 significant

Table 5. Lipid parameters in MetS and control groups according to the SNPs

SNPs	Lipid parameters	MetS group			Control group		
		Non-carriers	Carriers	p-value	Non-carriers	Carriers	p-value
-1131T>C	TC (mg/dl)	155.06±37.12	176.05±25.62	0.018*	148.94±35.82	148.11±37.17	0.893
	TG (mg/dl)	133.10±82.22	250.83±132.87	0.001*	72.63±32.4	121.57±89.94	0.103
	HDL (mg/dl)	32.69±11.63	27.48±9.79	0.627	36.39±15.87	36.82±14.50	0.928
	LDL (mg/dl)	94.84±35.85	96.10±40.84	0.857	92.80±41.66	99.97±39.09	0.301
IVS+476G>A	TC (mg/dl)	161.41±36.07	149.6±37.41	0.708	147.36±34.83	151.35±42.11	0.973
	TG (mg/dl)	111.79±51.85	150.20±99.49	0.045*	78.81±42.44	73.70±45.09	0.104
	HDL (mg/dl)	31.64±12.04	32.69±10.53	0.955	36.69±16.25	35.65±14.0	0.371
	LDL (mg/dl)	99.03±25.69	95.67±40.47	0.796	108.87±10.16	96.31±41.01	0.457
c.1177C>T	TC (mg/dl)	158.49±37.24	144.48±22.22	0.579	148.02±37.16	164.15±3.88	0.085
	TG (mg/dl)	136.33±75.01	177.43±136.72	0.038*	76.72±43.04	100.86±43.75	0.099
	HDL (mg/dl)	32.22±11.7	27.07±7.53	0.174	36.44±15.78	36.34±13.88	0.251
	LDL (mg/dl)	97.84±39.03	90.91±41.20	0.328	95.10±41.26	100.86±37.96	0.441
c.1259T>C	TC (mg/dl)	161.07±34.97	155.23±38.11	0.324	148.67±37.31	148.35±36.8	0.959
	TG (mg/dl)	154.92±93.67	142.09±101.73	0.413	81.58±48.38	74.87±39.67	0.365
	HDL (mg/dl)	31.24±10.37	32.53±12.49	0.486	36.02±12.4	36.67±17.33	0.814
	LDL (mg/dl)	94.27±43.57	97.97±34.10	0.564	96.78±44.0	96.98±33.0	0.978

TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

*p-value < 0.05 significant

of dietary carbohydrate, while Mongolians consume large quantities of protein and fat from meat and dairy products [20-23]. The cause of this difference has not been identified precisely, but the difference in TC and LDL levels may be an example of ethnic differences due to genetics.

The role of *APOA5* variants and their involvement in various diseases, such as cardiovascular diseases and type 2 diabetes, has been studied widely in different populations. -1131T>C, IVS3+476G>A, and c.1259T>C SNPs have been the most frequently studied variants in the *APOA5* locus. The aim of our case-control study was to investigate the effect of -1131T>C, IVS3+476G>A, c.1177C>T and c.1259T>C SNPs on lipid metabolism and to present our observations on the relationship between these SNPs and the development of MetS. We found that the -1131T>C polymorphism was significantly associated with MetS. This association has been previously reported among some European, Asian, and African populations [12, 24-30]. The -1131C allele has also been shown as a risk factor for MetS among obese adolescents [30]. Additionally, some studies have shown that the frequency of the C allele in -1131T>C is much higher in Asians than Europeans [7, 31-33]. Matsunaga et al. have reported on the effect of lipid modulators on SNPs, such as the interactions between gene expression and SNPs in the *APOA5* gene [34]. Interestingly, their findings have shown that the -1131T>C polymorphism alone has no effect. Another study has suggested that the IVS3+476G>A

variant confers a risk for the development of MetS (OR=3.52, p=0.009) in Hungarians [35]. However, our results showed that there was no association between IVS3+476G>A, c.1177C>T, c.1259T>C and MetS.

Our haplotype frequency analysis showed that the frequency of the C-A-T-C (*APOA5**5) haplotype, which carries the minor alleles of all the polymorphic sites, was significantly higher in the MetS group than the control group (p=0.027). A haplotype consisting of the −1131C, c.56C, c553G, and c.1259T alleles has been shown to be associated with the MetS in Morracan patients [29]. Additionally, a haplotype which contains the minor alleles of -1131T>C, IVS3+476G>A, and c.1259T>C was shown to be higher in patients with hypertriglyceridemia than the control subjects [34]. Our results support the previous observations that the C-A-T-C haplotype is related to MetS.

Many studies have found that *APOA5* variants are related to the level of TG [11, 18, 25, 26, 36]. Several studies have provided evidence that *APOA5* variants have been related not only to the level of TG, but also to the levels of TC, HDL, and LDL in various populations [25, 30, 35, 36]. Additionally, accumulating evidence has established an association between *APOA5* SNPs and the risk of obesity [37-39]. Our study demonstrated that, in the MetS group, there were higher TG levels among carriers of the -1131C, IVS3+476A, c.1177C>T compared to non-carriers, but carriers of c.1259T>C was not associated with TG levels.

Limitations to our study included the small sample size and the differences within the sample of ethnicity, environmental factors, dietary patterns, and other genetic factors. Moreover, only four SNPs of *APOA5* were investigated in this study. There are many other SNPs of *APOA5*, gene-gene interaction factors, and gene-environment interaction factors that must be investigated. Finally, the molecular mechanism for the effect of -1131T>C on the gene transcription is still unclear. Despite these limitations, our study confirms that the -1131T>C polymorphism is a risk factor for the development of MetS because it increases TG and TC levels.

Conflict of Interest

The authors declare that they have no competing interests.

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