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Association between *APOE* polymorphism and metabolic syndrome in Uyghur ethnic men

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ABSTRACT

Objectives: This study aimed to examine the association between apolipoprotein E (*APOE*) polymorphism and metabolic syndrome (MetS) among Uyghur ethnic men in Xinjiang, China.

Participants: A total of 482 patients with MetS and 510 healthy sex-matched and age-matched controls were recruited from the Xinjiang Uyghur Autonomous Region of China. The participants were subjected to routine physical and blood biochemical tests, and *APOE* genotyping was performed.

Results: The *APOE ε3/3* was the predominant type, with a frequency of 71.8%, while *ε2/2* was less common than *ε4/4* in Uyghur males. The frequencies of the *APOE2, E3* and *E4* alleles in Uyghur males were 8.5%, 80.0% and 11.5%, respectively. However, the distribution of *APOE* genotypes was significantly different between the MetS and control groups (p<0.001). In the MetS group, the frequencies of the ε2 and ε4 alleles and the frequencies of the *ε2/2*, *ε2/3 and ε2/4* genotypes were significantly lower than those of the control group. Those individuals without the ε2 and ε4 alleles had higher MetS prevalence than the other gene carriers, and the ORs of these individuals developing MetS were 1.5 and 1.27 compared to the gene carriers. Triglyceride, serum total cholesterol and low-density lipoprotein cholesterol levels were lower and serum high-density lipoprotein was higher in the ε2 carriers than the ε3 carriers, and the prevalence of MetS, central obesity, high blood pressure, hypercholesterolaemia and hypertriglyceridaemia was lower in the *APOE*2 group than in the *APOE*4 group. The risks of these individuals with ε4 allele carriers getting these changes were 1.327, 1.780, 1.888, 1.428 and 2.571 times greater than those of ε2 allele carriers.

Conclusions: *APOE*4 is associated with many individual components of MetS, whereas *APOE*2 was associated with a reduced risk of MetS at the univariate level in Uyghur ethnic men.

Strengths and limitations of this study

- This is the first study of Uyghur ethnic men to explore the association between apolipoprotein E (*APOE*) polymorphism and metabolic syndrome (MetS).
- The study was limited by lack of independent replication.
- The study lacks more detailed in-depth studies to confirm the link between *APOE* polymorphisms and MetS risk.

INTRODUCTION

Metabolic syndrome (MetS) is characterised by a cluster of disorders that promotes atherosclerosis and increases the risk of cardiovascular diseases and diabetes mellitus,[1] for example: atherogenic dyslipidemia, insulin resistance and diabetes, hypertension, or abdominal obesity[2–6] and other diseases.[7–10]

The apolipoprotein E (*APOE*) gene, containing four exons and three introns, is mapped on the long arm of chromosome 19 (19q13.2).[11] There are three common alleles (ε2, ε3 and ε4); the ε3 allele is the most common and can be found in more than 80% of the general population, followed by ε4 and ε2.[12 13]

APOE is a multifunctional protein found in all lipoproteins except for low-density lipoprotein cholesterol (LDL-C); it plays a critical role in lipoprotein metabolism.[14–16] Therefore, it is biologically possible for *APOE* to influence an individual's susceptibility to MetS, especially in terms of both triglyceride and cholesterol levels, which are major complications of MetS.[17] The altered expression or genetic polymorphism of *APOE* is considered as a risk factor for MetS.[18 19] Although the possible association of *APOE* with the risk of MetS has been widely investigated in different populations,[20–22] MetS still remains underrepresented in the Xinjiang population, especially in the Uyghur ethnic group. Our previous study found that in the Uyghur ethnic population, there is a tendency of higher frequency of the clustering of MetS.[23–25] Thus, this is the first study in terms of the

Table 1 Comparison of the quantitative variables between the MetS and non-MetS groups

Variable(s)	Non-MetS group (510)	MetS group (482)	p Value
Age (years)	46.77±13.27	47.54±11.83	0.0680
BMI (kg/m^2)	26.52±4.11	28.16±3.15	<0.0001
Waistline (cm)	92.79±10.65	98.43±9.08	<0.0001
SBP (mm Hg)	120.61±12.26	126.92±14.64	<0.0001
DBP (mm Hg)	85.33±13.78	96.62±12.10	<0.0001
FPG (mmol/L)	5.01±1.13	5.59±1.77	<0.0001
Triglyceride (mmol/L)	1.97±1.45	3.26±1.65	<0.0001
TC (mmol/L)	4.37±1.27	4.06±1.60	0.0010
HDL-C (mmol/L)	1.23±0.53	1.10±0.51	<0.0001
LDL-C (mmol/L)	2.67±0.86	2.74±0.78	0.1920

Data are shown as mean±SD.
The Mann-Whitney U test was used to analyse the differences in the quantitative variables between the MetS and non-MetS groups.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol.

distribution of *APOE* genetic polymorphisms and their association with metabolic profiles in patients with MetS, aimed at identifying possible genetic markers for this disease in this special population.

METHODS AND MATERIALS

Participants and study design

This case control study recruited 992 participants who were selected from the Affiliated Hospitals of Xinjiang Medical University Urumqi China. These participants were all Uyghur men who resided in the Xinjiang area, 482 with MetS, whereas the age-matched healthy control subjects had no history of MetS. All of the participants were fully informed of the purpose of this study, and every participant provided written informed consent before enrolment in the study.

Data collection and blood tests

A questionnaire was used to collect data on the demographic, lifestyle and disease histories from all of the participants. A physical examination was also performed on every participant, including taking measurements of height (measured in centimetres with an error of <0.5 cm), body weight (measured in kilograms with an error of <0.1 kg), body mass index (BMI), waist circumference (WC) and hip circumference (calibrated weekly to within 1 mm using a plastic tape). The WC was measured at the end of a gentle expiration midway between the lowest rib and the iliac crest with the study participant standing, while the hip circumference was measured at the greater trochanter. The waist-to-hip ratio was determined as the WC (cm) divided by the hip circumference (cm). Blood pressure was measured using an automatic clinical blood pressure monitor three times in the sitting position following a standard protocol. All of the participants were at rest for at least 10 min before the physical examination.

All of the participants were also asked to fast for at least 12 h and to not consume any alcohol or high-fat foods the night before blood withdrawal. Two millilitres of venous blood was collected from each participant to assess the serum triglyceride and cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C and fasting plasma glucose levels as measured using the 7060 Automatic Biochemical Analyzer (Hitachi, Ltd, Tokyo, Japan). All of the laboratory analyses were performed in the same certified laboratory. Quality control measures were followed for the estimation of all the variables.

Standard of diagnosis

The participants were divided into two groups based on affliction with MetS. The diagnostic criteria for MetS were according to the 2005 National Cholesterol Education Program Adult Treatment Panel III,[26] the 2005 International Diabetes Federation,[27] the 2004 Chinese Diabetes Society[28] and the 2007 Joint Committee for Developing Chinese Guidelines for the

Table 2 Genotype and allele distributions of the *APOE* in the MetS and non-MetS groups

	Total (992)	Non-MetS group (510)	MetS group (482)
Genotype			
ε2/2	25 (2.5%)	20 (3.9%)	5 (1.0%)
ε2/3	105 (10.6%)	66 (12.9%)	39 (8.1%)
ε2/4	14 (1.4%)	11 (2.2%)	3 (0.6%)
ε3/3	712 (71.8%)	332 (65.1%)	380 (78.8%)
ε3/4	59 (5.9%)	32 (6.3%)	27 (5.6%)
ε4/4	77 (7.8%)	49 (9.6%)	28 (5.8%)
χ^2 Value	–	29.1	
p Value	–	<0.0001	
Allele			
ε2	169 (8.5%)	117 (11.5%)	52 (5.4%)
ε3	1588 (80.0%)	762 (74.9%)	826 (85.5%)
ε4	227 (11.5%)	139 (13.7%)	88 (9.1%)
χ^2 Value	–	37.7	
p Value	–	<0.0001	

Data are shown as n (%). Pearson's χ^2 test was used to analyse the differences of *APOE* (genotype or allele) between the MetS and non-MetS groups.
MetS, metabolic syndrome.

Prevention and Treatment of Dyslipidemia in Adults definitions,[29] meeting at least three of the following criteria: (1) abdominal obesity (WC>90 cm for men; (2) triglyceride level ≥1.7 mmol/L; (3) reduced HDL-C levels <0.9 mmol/L in men; (4) raised systolic or diastolic blood pressure (DBP) of 140/90 mm Hg or higher or previously diagnosed hypertension; (5) raised fasting plasma glucose level of 6.1 mmol/L or higher or previously diagnosed type 2 diabetes mellitus.

Genomic DNA extraction and *APOE* genotyping

The detailed method of genomic DNA extraction and *APOE* genotyping was performed as described previously.[30–33]

Statistical analysis

The data were summarised as numbers, percentages or means±SDs; organised in EpiData 3.0 software (The EpiData Association, Odense, Denmark); and analysed using the SPSS V.16.0 for Windows software package (SPSS, Chicago, Illinois, USA). Simple descriptive statistics were used to describe the variables among the participants. The differences in the measurements from different groups were compared with Student t test and a one-way analysis of variance. The *APOE* genotypes and frequencies were analysed with Pearson's χ^2 test if the genotypes met the Hardy-Weinberg equilibrium. A p value of <0.05 was considered statistically significant.

RESULTS

Characterisation of the study population

The summary statistics of the study population are shown in table 1. The data indicate that, except for age and LDL-C, other quantitative variables were statistically significant (p<0.05), and except for the HDL-C level, the other quantitative variables in the MetS group were higher than those in the non-MetS group (table 1).

Comparison of the *APOE* allele frequencies and genotype distribution in the MetS group with those of the control group

The allele and genotype distributions of the *APOE* polymorphisms are presented in table 2. There was no evidence of significant deviation from the Hardy-Weinberg equilibrium in any distribution. The frequencies of the *APOE* alleles ε2, ε3 and ε4 in Uyghur men were 8.5%, 80.0% and 11.5%, respectively, and the frequencies of different *APOE* alleles and genotypes between the MetS and non-MetS groups were different (p<0.05). In the MetS group, the frequencies of the *APOE* ε2 and ε4 alleles were lower, and the frequencies of the *ε2/2, ε2/3 and ε2/4* genotypes were significantly lower (p<0.05) than those in the non-MetS group (table 2).

Table 3 Comparison of the anthropometric, biochemical and clinical parameters among different *APOE* genotypes in the two groups (mean±SD)

	Non-MetS group						MetS group					
	Total	*APOE2*	*APOE3*	*APOE4*	p^a	p^b	Total	*APOE2*	*APOE3*	*APOE4*	p^a	p^b
n	499	86	332	81	–	–	479	44	380	55	–	–
BMI (kg/m^2)	26.48±4.09	25.52±3.36	26.76±4.44	26.37±3.02	0.012*	0.439	28.15±3.14	28.11±3.36	28.13±3.16	28.33±2.87	0.973	0.666
Waistline (cm)	92.71±10.55	90.59±10.90	93.12±10.79	93.28±8.92	0.048*	0.898	98.31±8.93	100.88±14.90	98.22±8.22	96.93±6.88	0.061	0.318
SBP (mm Hg)	120.81±12.27	118.66±14.02	120.65±11.46	123.70±13.05	0.178	0.044*	126.55±14.59	129.50±25.14	126.16±12.19	129.51±17.17	0.147	0.108
DBP (mm Hg)	85.52±13.82	82.44±13.51	85.81±13.78	87.56±13.40	0.043*	0.308	96.74±12.04	95.59±18.34	96.75±11.10	97.55±12.18	0.545	0.649
FPG (mmol/L)	5.00±1.14	5.16±1.79	4.96±0.81	5.00±1.38	0.145	0.787	5.58±1.75	5.67±1.21	5.58±1.80	5.46±1.77	0.761	0.623
Triglyceride (mmol/L)	1.94±1.39	1.71±1.00	2.02±1.49	1.85±1.32	0.065	0.329	3.26±1.65	3.27±1.50	3.25±1.71	3.37±1.34	0.928	0.579
TC (mmol/L)	4.34±1.25	4.19±1.18	4.31±1.26	4.61±1.25	0.404	0.063	4.05±1.60	4.25±1.84	4.05±1.58	3.90±1.54	0.449	0.504
HDL-C (mmol/L)	1.23±0.52	1.17±0.43	1.23±0.53	1.25±0.57	0.284	0.733	1.10±0.51	1.18±0.89	1.10±0.47	1.05±0.33	0.333	0.483
LDL-C (mmol/L)	2.68±0.86	2.29±0.82	2.74±0.85	2.86±0.81	0.000*	0.230	2.74±0.79	2.64±0.62	2.78±0.80	2.58±0.83	0.263	0.691

A t test was used to analyse the differences in parameters among different *APOE* genotypes.
P^a: p values that were obtained when comparing *APOE2* participants with *APOE3* participant.
P^b: p values that were obtained when comparing *APOE3* participants with *APOE4* participants. (1) *APOE3* group: participants carrying the ε3/ε3 genotype; (2) *APOE2* group: participants carrying the ε2/ε2 or ε2/ε3 genotype; (3) *APOE4* group: participants carrying the ε4/ε4 or ε3/ε4 genotype. Participants with the ε2/ε4 genotype (n=14) were excluded from the extra analyses because of the opposite effects of the ε2 and ε4 alleles on the lipid levels.
*The mean difference was significant at the 0.05 level.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS: metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol.

Comparison of the means of anthropometric, biochemical and clinical parameters between different *APOE* genotypes in the two groups

To evaluate the effect of the *APOE* genotype and the anthropometric, biochemical and clinical parameters, the participants in our study were subdivided into three groups: (1) ε3/ε3 participants (*APOE*3 group), (2) participants carrying ε2/ε2 or ε2/ε3 genotypes (ε2 carriers, *APOE*2 group) and (3) participants carrying ε4/ε4 or ε3/ε4 (ε4 carriers, *APOE*4 group). The participants with the ε2/ε4 genotype (n=14) were excluded from this analysis because of the opposite effects of the ε2 and ε4 alleles on the lipid levels.

In the MetS groups, none of the parameters had significant associations when comparing ε3 allele carriers with ε4 allele carriers, in contrast to the comparison of ε2 allele carriers with ε3 allele carriers. In the non-MetS group, the BMI, waistline, DBP and LDL-C in the ε2 allele carriers were lower (p<0.05) than those in the ε3 allele carriers). In contrast, the ε4 allele carriers had significantly higher means of these parameters than the ε2 allele carriers (table 3).

The prevalence of MetS and the individual components of dyslipidemia between the *APOE2* and *APOE4* groups

By evaluating the effects of MetS and the individual components of dyslipidemia between the *APOE2* and *APOE4* groups, we found that the prevalence of MetS, abdominal obesity, high blood pressure, hypertriglyceridaemia and hypercholesterolaemia were lower in the *APOE2* group (p<0.05); the prevalence of hyperglycaemia and low HDL-C was higher in the *APOE2* group but had no significant association (p>0.05) (table 4).

DISCUSSION

The *APOE* genotypes and allele distributions vary among different races and geographic areas.[34] In this study, we found that the general distribution of *APOE* allele E3 in Uyghur men was 80.0%, which is between the distributions reported in the Han Chinese and Caucasian populations. Our data indicated that the Uyghurs had a different allele distribution from the Han Chinese and Caucasians, prompting a different genetic background of the Uyghur. Indeed, an earlier study which was aimed at identifying the origin of human species applying DNA sequencing technology to have analysed a Uyghur mummy that was unearthed 3000 years ago from a dry desert in the Tarim basin of Xinjiang, China, has demonstrated that the Uyghur ethnic group currently living in Xinjiang, China originated from Europe.[35] Our current data of the *APOE* polymorphism may provide additional evidence for this finding. However, after approximately 3000 years of evolution, one may expect that the *APOE*3 allele may have changed. We previously demonstrated that the MetS prevalence was higher in the Uyghur ethnic group.[36 37] This ethnic group has a different genetic background, diet and lifestyle; furthermore, these people live in a special area in China, with a unique environment and natural conditions, and their population is relatively stable.

Our study found that the frequencies of the *APOE* alleles ε2, ε3 and ε4 in Uyghur men were 8.5%, 80.0% and 11.5%, respectively; that the frequencies of the *APOE* ε2 and ε4 alleles were lower in the MetS group than in the non-MetS group; and that the *ε2/2*, *ε2/3* and *ε2/4* genotype frequencies were clearly lower in the MetS group than in the non-MetS group (p<0.05). The frequency of the ε2/2 genotype was higher in the MetS group than the frequency of the ε4/4 genotype in the control subjects, but in patients with MetS, the ε2/2 carrier frequency was lower than that of ε4/4. Variations in the genetic structures in different populations are possible, but differences in testing methods should also be considered. The frequency of *APOE*2 was lower in the MetS group than in the non-MetS group. The *APOE*2 genotype carriers had the lowest HDL-C and LDL-C levels. The mechanism of this effect is most likely due to decreased conversion of the very low-density lipoprotein (VLDL) into LDL-C as observed in *ε2* carriers.[38] Thus, a high frequency of the *ε2* allele would appear to predict a favourable lipid profile, indicating that *APOE*2 may be a protective factor against MetS.

Many studies have suggested that variation in the *APOE* gene is associated with the lipid levels.[16 39 40] We

Table 4 The prevalence of MetS and the individual components of dyslipidemia between the *APOE*2 and *APOE*4 groups

	APOE2	*APOE4*	OR (95% CI)	p Value
n	130	136	–	–
MetS (no/yes)	86/44 (33.8%)	81/55 (40.4%)	1.327 (0.806 to 2.186)	0.266
Abdominal obesity (no/yes)*	46/84 (64.6%)	32/104 (76.5%)	1.78 (1.042 to 3.039)	0.034
Hypertension (no/yes)*	67/63 (48.5%)	49/87 (64.0%)	1.888 (1.156 to 3.085)	0.011
Hypertriglyceridaemia (no/yes)	61/69 (53.1%)	52/84 (61.8%)	1.428 (0.877 to 2.327)	0.152
Hypercholesterolaemia (no/yes)*	120/10 (7.7%)	112/24 (17.6%)	2.571 (1.177 to 5.617)	0.015
Hyperglycaemia (no/yes)	114/16 (12.3%)	125/11 (8.1%)	0.627 (0.299 to 1.407)	0.255
Low HDL-C (no/yes)	103/27 (13.6%)	115/21 (10.6%)	0.697 (0.371 to 1.307)	0.259

Pearson's χ^2 test was used to analyse the differences.
Power by YOZOSOFT.
*The mean difference was significant at the 0.05 level.
HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome.

found that the triglyceride and LDL-C levels were lower in the ε2 allele carriers than in the ε3 allele carriers. In contrast, the ε4 allele carriers had significantly higher means of these plasma lipid levels than did the ε2 and ε3 allele carriers. The prevalence of abdominal obesity, high blood pressure, hypertriglyceridaemia and hypercholesterolaemia was lower in the *APOE*2 group than in the *APOE*4 group. The risks of these individuals with ε4 allele gene carriers for getting these changes were 1.327, 1.780, 1.888, 1.428 and 2.571 times greater than the risks of those with ε2 allele gene carriers.

Some limitations of this study should be considered. Since we only genotyped the *APOE* gene of the participants, and could not do population stratification analyses, we could not ensure whether there were biases due to confounding by ancestry or not. However, since all the participants were recruited from the same geographic region and reported to be Uyghur, the issue of population stratification should be limited in the current study. Besides, although we found that *APOE* alleles were associated with MetS risk for Uyghur men residing in the Xinjiang area, studies in a larger sample or other population to replicate this result are urged.

In conclusion, the distribution of the *APOE* alleles and genotype frequencies in Uyghur men is unique and is associated with MetS risk. *APOE*4 is associated with hypertriglyceridaemia, with a slightly increased risk for MetS, but *APOE*2 is associated with protection against MetS in Uyghur males in China. However, this study is an initial step in understanding the relationship between *APOE* gene polymorphisms and MetS in Uyghur men, and more detailed in-depth studies in the future are needed to confirm the link between *APOE* polymorphisms and MetS risk.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University and was conducted according to the standards of the Declaration of Helsinki.

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