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Association of *APOA1* gene polymorphisms (rs670, rs5069, and rs2070665) with dyslipidemia in the Kazakhs of Xinjiang

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ABSTRACT. The aim of this study was to investigate the potential association between apolipoprotein A1 (*APOA1*) gene rs670, rs5069, and rs2070665 polymorphisms and dyslipidemia in the Kazakh population of Xinjiang, China. Matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS) was used to identify *APOA1* (rs670, rs5069, and rs2070665) genotypes in 736 subjects (341 dyslipidemia patients and 395 control subjects). The frequencies of the CC genotype for rs1421085 were found to be 7.2% (obese group), 4.4% (overweight group), and 5.6% (control group). Polymorphisms of the three loci of the *APOA1* gene in Kazakh subjects met Hardy-Weinberg equilibrium. The frequencies of the A allele for rs670 were found to be 14.3% (dyslipidemia group) and 12.7% (control group). The frequencies of the T allele for rs5069 and rs2070665 were: dyslipidmia group (7.2 and 30.1%, respectively) and control group (7.7 and 32.5%, respectively). Frequency distributions

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of the 3 types of genotypes and alleles of the three loci showed no statistically significant difference ($P > 0.05$). Significant differences were observed in lipoprotein (α) [Lp(α)] between patients with the rs2070665 CT + TT and CC genotypes ($P < 0.05$); however, none of the other relevant indicators differed significantly between the two genotypes. No significant association was identified between rs670 or rs5069 and the lipid-related metabolic indices assessed in the study. These findings indicate that the polymorphisms in the *APOA1* gene (rs670, rs5069, and rs2070665) are not associated with dyslipidemia in the Kazakh population assessed in this study.

Key words: APOA1 gene; Gene polymorphism; Kazak; Dyslipidemia

INTRODUCTION

Dyslipidemia is defined by an abnormality in or abnormal amounts of lipids and lipoproteins in the blood. It is characterized by increased plasma total cholesterol (TC), increased low-density lipoprotein (LDL) cholesterol and triglyceride (TG) concentrations, and decreased plasma high-density lipoprotein (HDL) cholesterol concentration in the blood (Duval et al., 2007). Due to the result of the Westernization of diet and other lifestyle changes, the prevalence of dyslipidemia is high and increasing in most developed countries as well as in many developing countries (Wietlisbach et al., 1997). Dyslipidemia is associated with serious medical conditions such as coronary artery disease (CAD), hypertension, and stroke (Yin et al., 2011). Pilot data showed that dyslipidemia prevalence was 31.8% in the Kazak nationality, which was higher than that in the Uygur nationality (42.4%) (Guo et al., 2014). The prevalence of disease in Kazaks was significantly higher than in adults (> 18 years old) in eleven cities and provinces in China (18.6%) (Zhao et al., 2005).

Although it is well known that the reason for dyslipidemia is the interactions of multiple environmental and genetic factors (Choy et al., 2004; Yamada et al., 2007), the underlying mechanisms remain poorly understood. Pagani et al. (1990) reported a common MspI enzyme site 75 bp upstream from the initiating transcription site of the human apolipoprotein A1 (*APOA1*) gene. The relevance between serum lipid patterns and *APOA1* gene polymorphisms had been a focus ever since. Extensive studies conducted on different races in different nations have shown conflicting results (Sigurdsson et al., 1992; Xu et al., 1993; Barre et al., 1994). Since the conclusions have not been consistent, this has prompted the notion that differences in such associations may exist between ethnicities and regions.

A case-control study was adopted in this research to explore the association between gene mutations and dyslipidemia in Kazak nationalities in Xinjiang, China. The findings of this investigation may provide a theoretical basis for further in-depth study of the role of genetic factors in the occurrence of dyslipidemia and therefore in dyslipidemia prevention and control.

MATERIAL AND METHODS

Subjects

This study was conducted from 2010 to 2011 in the Nalati Township in Xinyuan

County of the Xinjiang Yili Region of Northern Xinjiang Province, which is a predominantly Kazakh area. The subjects were selected using an area-stratified cluster random sampling method. Six villages and 5692 Kazakh residents (≥ 18 years) were randomly selected from the Nalati Township, after which a cross-sectional study was conducted. All participants provided informed consent.

The sample size was calculated according to the case-control study sample size computational formula, and based on China's Adult Dyslipidemia Prevention Guide, which was proposed by the China Adult Dyslipidemia Prevention Guide Formulate Joint Committee (2007). In our study, 341 dyslipidemia patients were randomly selected as the case group and 391 non-dyslipidemia subjects were randomly selected from the same population as the control group using the group-matching method.

Survey methods

A self-developed questionnaire was used to collect detailed information from all respondents during face-to-face interviews. The information acquired included demographic information, history of personal illness, family history of cardiovascular disease, smoking and drinking history, as well as details on diet and exercise habits.

Standard methods were used to measure sitting blood pressure, height, weight, waist circumference (WC), and hip circumference (HC) of each subject.

Laboratory testing of a number of factors was also conducted, including testing for fasting total serum cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (APOA1), apolipoprotein B (APOB), and lipoprotein (α) [Lp(α)]. These analyses were carried out using an automatic biochemical analyzer (Germany Olympus Corporation, Germany).

DNA extraction

Fasting blood (200 μL) was taken from each subject, after which genomic DNA was extracted from each sample using a blood genomic DNA extraction kit (centrifugal columnar) purchased from Tektronix Biotechnology Co, Ltd. (Beijing, China). Extracted DNA was verified by 0.7% gel electrophoresis and a NanoDrop spectrophotometer (NanoDrop Technologies, Inc, Wilmington, DE, USA) was used to quantify DNA concentration and purity. Suitable DNA samples were diluted in autoclaved, double-distilled water to adjust DNA concentrations to 10-30 ng/μL. DNA samples were stored at -80°C until use.

Matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF-MS)

Primers were designed using the Mysequenom tool (www.mysequenom.com/Home) and Assay Designer 3.0 software. Final polymerase chain reaction (PCR) reaction volumes of 5 μL included 0.7 μL DNA, 1.35 μL water, 0.5 μL 10 PCR buffer, 0.4 μL $MgCl_2$, 0.1 μL dNTPs, 0.15 μL Taq enzyme, and 1.8 μL PCR amplification primer mixture. Reactions were prepared in an ice bath and negative control reactions were prepared in the same way as the test reaction, except that the DNA was replaced with water.

To ensure accurate single-base extension in the PCR reactions, excess dNTPs were

removed from the reaction mixtures after PCR using shrimp alkaline phosphatase (SAP). The final SAP reaction volumes used were 2.0 mL, which included 1.53 μL double-distilled water, 0.17 μL 10X SAP buffer, and 0.3 μL SAP enzyme. A single-base extension reaction (EXTEND) was conducted in a final reaction volume of 2.0 μL consisting of 0.2 μL 5X iPlex buffer, 0.619 μL water, 0.2 μL iPlex terminator, 0.94 μL primer mix, and 0.041 μL iPlex enzyme. Samples were purified using resin. A mass ARRAY Nanodispenser (Sequenom, San Diego, CA, USA) was used to transfer the purified product to a SpectroCHIP (Sequenom), after which MALDI-TOF-MS analysis was conducted. Results were encoded using TYPER 4.0 software (Sequenom).

Statistical analysis

Epidata 3.02 software was used to establish a database, and the double entry method was used for data input and logic error detection. The SPSS 17.0 (SPSS, Inc. Chicago, IL, USA) statistical package was used to carry out chi-square tests. SHEsis software (http://analysis.bio-x.cn/myAnalysis.php) was used for haplotype analysis and the Phase software (http://stephenslab.uchicago.edu/software.html) was used for linkage disequilibrium analysis. Allele frequencies were determined by direct counting. Differences with $P < 0.05$ were considered statistically significant.

RESULTS

Comparisons of general data and clinical biochemical indices of the subjects

General clinical data of the dyslipidemia group and control group of Kazaks are shown in Table 1. No significant difference in sex and age was noted between groups ($P > 0.05$). No significant SBP difference was measured between the two groups ($P > 0.05$). In the dyslipidemia group, height, weight, WC, HC, TG, TC, LDL-C, DBP, APOB and BMI were greater and APOA1 and HDL-C were lower compared with the control group ($P < 0.05$).

Hardy-Weinberg equilibrium test

The results of a comparison of observed values with expected values for the three SNP loci genotypes of *APOA1* gene show that differences in the three sites were not statistically significant ($P > 0.05$), indicating that the three loci exhibited genetic equilibrium and were thus representative of the Kazakh population.

Comparison of genotype and allele frequencies of rs670, rs5069, and rs2070665 polymorphisms

Logistic regression analysis was used to eliminate the influence of age and sex, after which the genotypes and the allele frequencies of the rs670, rs5069, and rs2070665 loci were compared between the dyslipidemia groups and the control groups (Table 2). No statistically significant differences were observed ($P > 0.05$).

Table 1. Comparison of clinical and biochemical indices between dyslipidemia group and control group in Kazaks.

Clinical and biochemical indices	Dyslipidemia group (N = 341)	Control group (N = 395)	χ2/t	P value
Gender (male/female)	177/164	192/203	0.797	0.372
Age (years)	43.84 ± 14.11	42.05 ± 13.53	-1.747	0.081
Height (cm)	164.68 ± 8.76	162.90 ± 9.60	-2.587	0.010
Weight (kg)	70.8 ± 14.57	62.05 ± 11.35	-8.887	0.000
WC (cm)	89.95 ± 13.00	82.14 ± 10.93	-8.638	0.000
HC (cm)	98.69 ± 8.49	94.96 ± 8.11	-5.992	0.000
TG (mM)	1.80 ± 1.34	0.84 ± 0.40	-12.863	0.000
TC (mM)	4.67 ± 1.59	3.99 ± 0.66	-7.355	0.000
LDL-C (mM)	2.57 ± 1.06	1.91 ± 0.52	-10.405	0.000
HDL-C (mM)	1.22 ± 0.50	1.54 ± 0.33	10.207	0.000
SBP (mmHg)	136.51 ± 25.98	133.10 ± 25.10	-1.798	0.073
DBP (mmHg)	86.87 ± 15.42	83.98 ± 13.60	-2.654	0.008
APOA1 (g/L)	1.20 ± 0.43	1.36 ± 0.26	6.219	0.000
APOB (g/L)	0.91 ± 0.45	0.64 ± 0.21	-9.959	0.000
BMI (kg/m^2)	26.04 ± 4.52	23.56 ± 6.82	-5.634	0.000

Data are expressed as mean ± standard deviation. WC, waist circumference; HC, hip circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; APOA1/B, apolipoprotein A1/B. *P < 0.05, dyslipidemia group *vs* control group in the same nationality; #P < 0.05; comparison of biochemical indicators between Uygurs and Kazakhs.

Table 2. Comparison of frequencies of rs670, rs5069 and rs2070665 genotypes and alleles between dyslipidemia group and control group n (%).

		Genotype frequencies			χ^2	P value	Allele frequencies		χ^2	P value
		GG	GA	AA			G	A		
rs670	Dyslipidemia group	248 (73.0)	87 (25.5)	5 (1.5)	1.491	0.474	583 (85.7)	97 (14.3)	0.779	0.378
	Control group	301 (76.4)	86 (21.8)	7 (1.8)			688 (87.3)	100 (12.7)		
		CC	CT	TT			C	T		
rs5069	Dyslipidemia group	293 (86.2)	46 (13.5)	1 (0.3)	0.773	0.679	632 (92.8)	48 (7.2)	0.247	0.619
	Control group	336 (85.3)	55 (13.9)	3 (0.8)			727 (92.3)	61 (7.7)		
		CC	CT	TT			C	T		
rs2070665	Dyslipidemia group	162 (47.8)	152 (44.6)	26 (7.6)	1.727	0.422	476 (69.9)	224 (30.1)	0.040	0.841
	Control group	179 (45.5)	174 (44.1)	41 (10.4)			532 (67.5)	256 (32.5)		

Association between the rs670, rs5069, and rs2070665 polymorphisms of the *APOA1* gene and lipid-related metabolic indices

For the rs2070665 locus, individuals with the TT genotype had lower Lp(α) levels than those with the CC + TC genotype (P = 0.049), while no significant differences were noted between the TG, TC, LDL-C, HDL-C, APOA1 and APOB values between these groups (P > 0.05). In the case of the rs670 locus, no significant differences were noted in lipid-related traits between the CC and the CT + TT genotypes (P > 0.05). Significant differences were also not observed in the lipid-related traits between the CC and CT + TT genotypes at the rs5069 locus (P > 0.05) (Table 3).

Table 3. Comparison of clinical biochemical indices among different genotypes of rs2070665 in a Kazak population.

Indices	CC (N = 343)	CT/TT (N = 393)	t/Z	P value
Height (cm)	163.39 ± 10.05	163.97 ± 8.58	-0.830	0.407
Weight (kg)	66.21 ± 13.89	65.87 ± 13.45	0.329	0.742
WC (cm)	86.16 ± 13.00	85.33 ± 12.14	0.887	0.375
HC (cm)	96.62 ± 8.02	96.68 ± 8.87	-0.092	0.927
TG (mM)	4.32 ± 1.28	4.30 ± 1.20	0.276	0.783
TC (mM)	1.27 ± 1.17	1.30 ± 0.98	-0.296	0.767
LDL-C (mM)	2.24 ± 0.90	2.20 ± 0.87	0.656	0.512
HDL-C (mM)	1.38 ± 0.45	1.40 ± 0.46	-0.740	0.460
APOA1 (g/L)	1.27 ± 0.34	1.30 ± 0.37	-1.039	0.299
APOB (g/L)	0.77 ± 0.37	0.77 ± 0.37	0.182	0.856
Lp(α) (mg/L)	88.6 (46.4, 154.7)	98.6 (54.4, 222.7)	-1.970	0.049

Data are expressed as mean ± SD or M (Q_L, Q_U). WC, waist circumference; HC, hip circumference; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; APOA1/B, apolipoprotein A1/B; Lp(α), lipoprotein (α).

DISCUSSION

The *APOA1* gene is part of the *APOA1-C3-A4* gene cluster located on chromosome 11q23-q24 which has three exons and encodes the APOA1 precursor with 243 amino acids and a molecular weight of 28 KDa (Groenendijk et al., 2001; Davidson and Thompson, 2007). It is well known that low levels of HDL-C is an independent traditional risk factor of CAD (Castelli, 1988). APOA1 is required for normal HDL-C synthesis as the primary core component and its gene variations can lead to extremely low HDL-C levels (Rader, 2006). Additionally, APOA1 can take part in the regulation of reverse-cholesterol transport from peripheral tissues to the liver as a cofactor of lecithin-cholesterol acyltransferase (LCAT) (Jones et al., 2009). As a result, APOA1 plays a key role in lipid metabolism and is a protective factor against coronary heart disease (Ordovas et al., 2002).

Rs670 (G-75A) is located at -75 bp upstream from the *APOA1* transcription start site, while rs5069 (C83T) and rs2070665 are located in the first and third introns, respectively, of the *APOA1* gene (Pagani et al., 1990; Wang et al., 1995; Henkhaus et al., 2011). The variations of *APOA1* gene polymorphisms will change the expression of APOA1, thereby affecting serum lipid concentrations. The *APOA1* gene polymorphisms in European populations have been shown to be associated with lipid levels in Turkish and Dutch populations (Souverein et al., 2005; Coban et al., 2014); however, findings on the relationship between the *APOA1* gene and serum lipid levels in Asian populations have proven inconsistent.

In this study, there were no significant differences in the distributions of the rs670, rs5069, and rs2070665 genotype frequencies between the dyslipidemia and control groups in Kazakhs. For rs670, the GG genotype and G allele frequency in the Kazakh control group in this study was 76.4 and 87.3%, respectively, which were lower than reported in a Brazilian population by Chen et al. (2009) but notably higher than the frequencies in the Hei Yi Zhuang population (48.1 and 70.3%, respectively) (Li et al., 2008). In this study, the frequency of the A allele in the patient group was higher than that in the control group; however, this difference was not statistically significant. Coban et al. (2014) found the rs670 locus polymorphism was associated with dyslipidemia in Turkish male adults, suggesting that the correlation of the polymorphism at this locus and dyslipidemia may be sex-related. For rs5069, the T allele

frequency in the Kazakh control group was 7.7%, which is notably higher than the 3% in Caucasians but clearly lower than the 56% in Japanese reported by Buzza et al. (2001). Huang et al. (2011) studied the Kazakh population and found the T allele frequency of rs5069 was 12.5%, which was inconsistent with our result. The difference may be due to different sample size, as our study had a larger sample size. For rs2070665, the T allele frequency in the Kazakh control group was 32.5%. The allele mutation rate was higher than the foreign report (Henkhaus et al., 2011), but lower than the 42.0% of Chinese nationals reported by Hao and He (2014). The findings indicate that ethnic differences exist in the genotype and allele frequencies of this locus of the *APOA1* gene.

Our study findings showed that the rs670, rs5069, and rs2070665 polymorphisms are not associated with lipid-related metabolic indices in the Kazakh population assessed in the study. These findings are not consistent with those reported by Meng et al. (1997), Needham et al. (1994), and Ma et al. (2005), possibly due to differences in the sample groups between the studies (ethnicity, sex, etc.). We report here that the rs2070665 polymorphism is associated with Lp(α) levels ($P < 0.05$), which has not been found in other studies.

Domestic and international research on *APOA1* gene polymorphisms and dyslipidemia have had varying conclusions. In order to resolve this issue, large sample, multi-ethnic, and multi-area research must be carried out to explore the real relationship between *APOA1* polymorphisms, environmental and behavioral factors, and dyslipidemia.

Conflicts of interest

The authors declare no conflict of interest.

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