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Original Article

Relationship between single nucleotide polymorphism of ABCA1 gene and susceptibility of coronary heart disease in Mongolian/Han population

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Abstract: To investigate the distribution profiles of single nucleotide polymorphisms on the coding region (R219K, M233V) and non-coding region (-565C/T, 69C/T) of ATP-binding cassette transporter 1 (ABCA1) gene and their relationship with blood lipids and coronary heart disease (CHD) in Mongolian and Han population of the Inner Mongolia region. The target fragments of ABCA1 gene was amplified and analyzed by polymerase chain reaction (PCR) in 101 Mongolian, 111 Han patients with CHD and 102 Mongolian, 101 Han control subjects without CHD. The frequency of KK genotype and K allele of ABCA1 R219K gene in Mongolian and Han population was all significantly higher in controls than that in CHD patients (P<0.05). KK genotype significant higher in high-density lipoprotein cholesterol (HDL-C) level (P<0.05) and significant lower triglyceride (TG) level than RR genotype (P>0.05) in both Mongolian and Han population. The KK genotype odds ratio was -0.313 (95% CI = 0.233-0.419, *P*<0.05). Logistic analysis showed that KK genotype was protective factors for CHD. The frequency of TT genotype and T allele of ABCA1 69C/T gene in Mongolian and Han population was significantly higher in CHD patients than that of controls (*P*<0.05). The TT genotype odds ratio was 2.698 (95% CI 1.408-5.170, *P*<0.05). Logistic analysis showed that TT genotype was a risk factor for CHD. There was no significant difference in the frequency of -565C/T and M233V genotype between Mongolian and Han population (*P*>0.05). No significant difference was found in the levels of HDL-C, low-density lipoprotein cholesterol (LDL-C), cholesterol (TC) or TG among genotype of 69C/T, -565C/T and M233V gene (*P*>0.05). There was no difference in the distribution of R219K, 69C/T, -565C/T or M233V between Mongolian population and Han population. ABCA1 gene R219K and 69C/T polymorphisms were associated with CHD susceptibility in Mongolian and Han population. The KK genotype benefits blood lipids, which may be a novel genetic marker for CHD. The C69T TT genotype polymorphism of the ABCA1 gene is associated with increased CHD risk.

Keywords: ATP binding cassette transporter 1, polymorphism, coronary heart disease

Introduction

ATP-binding cassette transporter A1 (ABCA1) belongs to the super-family of ATP-binding cassette transporter. Up to now more than 90 ABCA1 gene locus mutations, including coding and non-coding regions (promoter region included), have been found associated with various diseases. Although there is less single nucleotide polymorphism in the coding region, in the study of hereditary diseases the single nucleotide polymorphism is of great significance. The single nucleotide polymorphism located in the promoter sequences affects gene expression and impacts the human health. Coronary heart disease (CHD) might be a polygenic disease, but there is few studies regarding the single nucleotide polymorphisms in coding and non-coding regions in patients with CHD. Therefore, in the present study, we focused on the distribution of single nucleotide polymorphism of R219K, M233V genes of the coding regions and -565C/T, 69C/T gene of the non-coding regions in the Mongolian and Han population, as well as their relationship with CHD susceptibility and blood lipids, which may explain the genetic predisposition of Mongolian and Han individuals to CHD. The possible genetic diversity of Mongolian and Han population was explored due to the previous discovery on variation of gene expression in different races and population.

Table 1. PCR primers for R219K, -565C/T, M233V, 69C/T genes

Gene	Upstream	Downstream
R219K	5'-GTATTTTTGCTACCAGTTACATTTGACA-3'	5'-GATTGGCTTCAGGATTGTTGGAA-3'
M233V	5'GCAAGGCTACCAGTTACATT3'	5'GTCCAAGGAAAAGCCTCAC3'
-565C/T	5'-CTCGGGTCCTCTGAGGGACCT-3'	5'-CCGCAGACTCTCTAGTCCAC-3'
69C/T	5'GGCTTTGACCGATAGTAACCT3'	5'CTCTTTCTCCTACCCCTTGAC3'

Table 2. The PCR reaction systems

R219K reaction system	M233V reaction system	-565C/T reaction system	69C/T reaction system
10 × Buffer 2 μl	10 × Buffer 2.0 μl	10 × Buffer 2 μl	10 × Buffer 2 μl
PCR product 10 μl	PCR product 10 μl	PCR product 4 μl	PCR product 10 μl
Xag-I 1.0 μl	CviA II 0.6 μl	AciI 1 μl	*BsmA* I 0.4 μl
Pure water 18 μl	Pure water 7.4 μl	Pure water 14 μl	Pure water 7.6 μl
37°C Digestio 12 h	25°C Digestio 18 h	37°C Digestio 16 h	37°C Digestio 16 h

Patients and methods

Patients

203 cases of Inner Mongolia individuals (101 cases of CHD patients and 102 cases of control) and 212 cases of Han individuals (111 cases of CHD patients and 101 cases of control) were recruited into this study. Inner Mongolia individuals are from local residents. CHD patients were positive in cardiology coronary angiography examined in the department of cardiology, Mongolia Medical College First Affiliated Hospital (Huhhot. China) during January 2009 to June 2015 (at least one coronary artery stenosis ≥50%); the control group was confirmed by coronary angiography to exclude coronary artery disease. Other exclusion criteria includes: severe liver or kidney dysfunction, blood diseases, tuberculosis, cancer, and artery disease. Questionnaire interviews were used to collect basic data, medical history, family history, and smoking history. Standard of smoking history was set as "smoking more than 10 cigarettes daily in the past one or more than one year, without taking any lipid-control medicine".

Measurement of lipid levels

3 ml of morning fasting blood was used in all laboratory tests. The lipid levels were measured after serum was separated. Triglyceride (TG) and cholesterol (TC) were measured using oxidase method; high-density lipoprotein (HDL-C) and low density lipoprotein (LDL-C) were detected with PEG allosteric enzymatic assay. Detection reagents were purchased from Leadman Company (Beijing, China). OLYMPUS AU 600 automatic biochemical analyzer (Japan) was used in the study.

DNA extraction

3 ml of peripheral venous blood was collected with EDTA anticoagulated vacutainer, and then stored in -80°C before use. Blood DNA was extracted according to the manual in the blood/cell/tissue extract genomic DNA Extraction kit.

PCR primers

The sequences of upstream and downstream primer of R219K, -565C/T, M233V, 69C/T gene are shown in **Table 1**, which were provided by the Shanghai Biological Engineering Co., Ltd.

PCR procedure of ABCA1 polymorphic gene

PCR reaction was carried out in a type PTC-200 cycler. The 50 μL of PCR reaction system includes 25 μL 2 × Taq PCR Master Mix, 2.0 μL DNA, 1.0 μL upstream and downstream primers respectively, and 21 μL sterilized ultrapure water. PCR reaction procedure was as follows: 94°C denaturation for 5 min; 94°C denaturation for 30 s, 53-58°C annealing for 30 s, 72°C extension for 40 s, a total of 35 cycles; 72°C terminal extension for 5 min.

PCR product digestion

The procedure was shown in **Table 2**. Endonuclease XagI (EcoNI), CviA II, AciI, BsmA I, and 10 × buffer were provided by BioLabs Company (USA). Digestion products were measured in 2% agarose gel by electrophoresis. The sample genotype was determined. The DNA Marker is BioMarker I.

Table 3. General information

Groups	Han Control	Han CHD	Mongolian Control	Mongolian CHD
N	101	111	102	101
Male/Female	42/59	60/51	51/51	73/28*
Age	60.87±10.73	61.28±10.01	57.47±12.80	59.37±11.62
High blood pressure +/-	48/53	58/53	53/49	60/41
Diabetes +/-	13/88	29/82	12/90	19/82
Smoking history +/-	25/76	46/65	18/84	48/53
HDL-C (mmol/L)	1.12±0.33	1.04±0.26*	1.25±0.36	1.05±0.34*
LDL-C (mmol/L)	2.71±0.86	2.84±0.87	2.99±0.90	2.91±0.83
TG (mmol/L)	1.64±0.95	1.75±0.92	1.51±0.82	1.89±1.11*
TC (mmol/L)	4.18±1.27	4.29±0.98	4.60±1.21	4.40±1.18

*P<0.05 compared with control group.

Table 4. Distribution frequencies of R219K genotype and allele in CHD and control among Mongolian population

Groups	N	Genotype frequency			Allele frequency	
		RR	RK	KK	R	K
Mongolian Control	102	16 (15.7)	54 (52.9)	32 (31.4)	86 (42.2)	118 (57.8)
Mongolian CHD	101	34 (33.7)	53 (52.5)	14 (13.7)	121 (59.9)	81 (40.1)
χ^2			13.5		12.8	
P			0.001		0.000	

Table 5. Distribution frequencies of R219K genotype and allele in CHD and control among Han population

Groups	N	Genotype frequency			Allele frequency	
		RR	RK	KK	R	K
Han Control	101	18 (17.82)	49 (48.51)	34 (33.66)	85 (42.08)	117 (57.92)
Han CHD	111	43 (38.74)	53 (47.75)	15 (13.51)	139 (62.61)	83 (37.39)
χ^2			17.34		17.89	
P			0.0002		0.000	

Statistical analysis

Data were expressed as the mean and standard deviation and statistically analyzed with one-way Analysis of Variance (ANOVA) using SPSS13.0. Comparison between groups of count data was done with the chi-square test. OR and 95% CI were calculated by logistic regression analysis. P<0.05 was considered significant.

Results

General information

The general information on Mongolian CHD and control group, the Han CHD and control groups is shown in **Table 3**. A balancing test was performed to the genotypes distribution of CHD and control groups. The χ^2 test showed that the distribution of ABCA1 gene R219K, M233V, -565C/T and 69C/T of Mongolian and Han genotypes was in coincidence with the Hardy-Weinberg equilibrium laws of inheritance and had group representation.

Distribution frequencies of R219K genotype and allele and comparison of lipids in genotype groups among Mongolian and Han population

Distribution frequencies of R219K genotype and allele in CHD and control among Mongolian and Han population are shown in **Tables 4** and **5**. RR and R-type allele in CHD group of both Mongolian and Han population were significantly higher than control (P<0.05); KK and K allele were significantly lower than control (P<0.05). The HDL levels in KK genotype of Mongolian and Han population were significantly higher than that in RR type and RK type (P<0.05),

Table 6. Comparison of lipids in R219K genotype groups among Mongolian population

Groups	HDL-C	LDL-C	TG	TC
RR	1.08±0.30	3.11±0.87	2.03±1.30	4.67±1.18
RK	1.12±0.28	2.97±0.90	1.68±0.85	4.50±1.20
KK	1.28±0.52*	2.74±0.75	1.37±0.81*	4.32±1.19
F	4.08	2.23	5.52	1.04
P	0.0184	0.1107	0.0046	0.3542

*P<0.05 compared with RR group.

Table 7. Comparison of lipids in R219K genotype groups among Han population

Groups	HDL-C	LDL-C	TG	TC
RR	1.02±0.29	2.92±1.01	2.03±1.30	4.61±1.45
RK	1.07±0.27	2.69±0.73	1.68±0.85	4.08±0.89
KK	1.25±0.37*	2.73±0.85	1.37±0.81*	4.11±1.01
F	4.64	2.17	4.86	4.74
P	0.0107	0.1171	0.0087	0.0097

*P<0.05 compared with RR group.

Table 8. Logistic regression analysis of the major risk factors of CHD

		Estimate	Standard error	Wald χ^2	P
Intercept		1.6573	0.4471	13.7418	0.0002
Diabetes	-	-0.4095	0.1548	7.0010	0.0081
Smoking history	-	-0.5103	0.1238	16.9882	<.0001
HDL		-0.9229	0.3856	5.7272	0.0167
Genotype R219	KK	-0.7223	0.1895	14.5234	0.0001
	RK	0.000220	0.1525	0.0000	0.9988
Genotype 69	CC	-0.9425	0.1669	31.8785	<.0001
	TC	-0.1215	0.1551	0.6133	0.4335

while TG levels were significantly lower than that in RK and RR type (P<0.05), as shown in **Tables 6** and **7**.

Comparison of R219K genotype and allele distribution frequency between Mongolian and Han population

There was no difference in R219K genotype distribution between Mongolian and Han population (P>0.05).

Logistic regression analysis of the major risk factors of CHD

As shown in **Table 8**, the possible risk factors of the CHD were selected out of gender, nationality, diabetes, hypertension, smoking history, family history, age, HDL, LDL, TG, TC, cholesterol, genotype R219K and genotype 69C/T by the method of the Logistic regression analysis. **Table 9** shows OR values of major risk factors of CHD. **Figure 1** shows the ROC curve of the established model. The AUC (Area under the curve) = 0.7779. As shown in **Table 10**, the major risk factors, KK and TT genotypes of 69C/T gene were introduced into the regression model, stepwise regression and Logistic regression were used to analyze the KK genotype: OR = -0.313; 95% CI is 0.233-0.419, P<0.05. The results imply that the KK genotype in Mongolian and Han population significantly reduced the risk of CHD. The main independent risk factors in Logistic regression analysis include diabetes, smoking history, family history, age, low HDL-C, TT genotype of 69C/T gene.

Distribution frequencies of 69C/T genotype and allele and comparison of lipids in genotype groups among Mongolian and Han population

The distribution frequencies of 69C/T genotype and allele were shown in **Tables 10** and **11**. The TT genotype and T allele of CHD in Mongolian and Han were significantly higher than control (P<0.05), while the CC and C allele were significantly lower than control (P<0.05). There is no significant difference in HDL-C, LDL-C, TG, and TC between three genotypes in Mongolian and Han population (P>0.05). Logistic regression analysis of TT genotype revealed that OR = 3.125, 95% CI was 1.408-5.170, P<0.05, which implies that the TT genotype in Mongolian and Han population increased prevalence of CHD risk.

Comparison of 69C/T genotype and allele distribution frequency between Mongolian and Han population

There was no difference in 69C/T genotype distribution between Mongolian and Han population (P>0.05).

Distribution frequencies of -565C/T genotype and allele and comparison of lipids in genotype groups between Mongolian and Han population

There was no difference in distribution frequencies of -565C/T genotype and allele of CHD between Mongolian and Han population compared with control (P>0.05). The HDL-C, LDL-C, TG, TC levels among genotypes -565C/T CC,

Table 9. OR values of major risk factors of CHD

	Point estimation	95% Wald confidence limit	
Diabetes Yes-No	0.441	0.240	0.809
Smoking history Yes-No	0.360	0.222	0.586
HDL	0.397	0.187	0.846
R219 genotype RR-KK	0.236	0.122	0.457
R219 genotype RR-RK	0.486	0.283	0.833
69 genotype TT-CC	0.134	0.070	0.257
69 genotype TT-TC	0.306	0.165	0.565

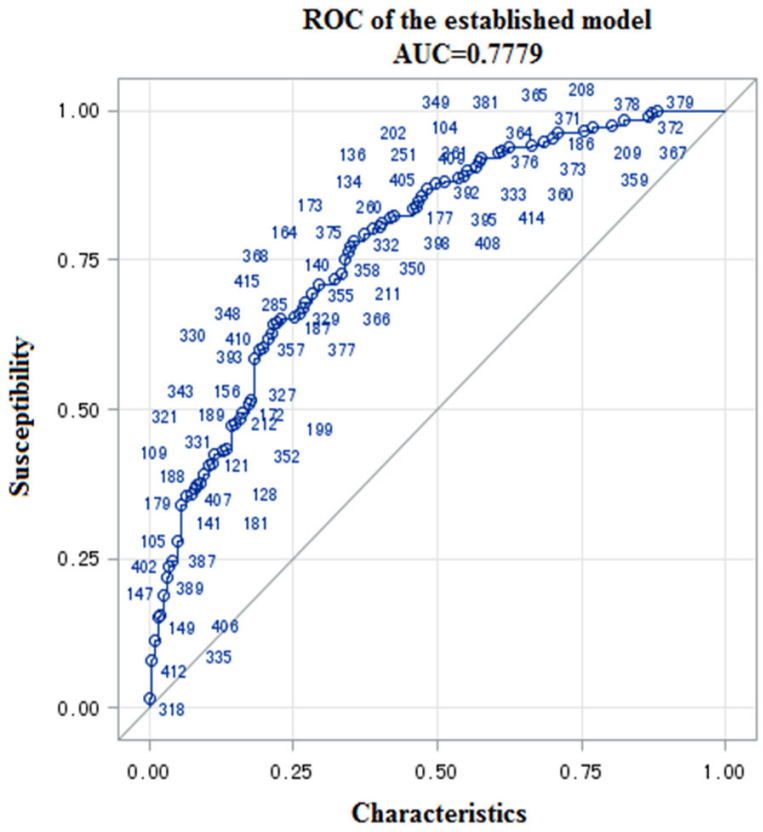

Figure 1. The ROC curve of the established model. Susceptibility of CHD = 1.6573-0.4095* Diabetes-0.5103* Smoking history -0.9229* HDL-0.7223* R219 genotype KK/RR+0.00022* R219 genotype RK/RR-0.942569* genotype CC/TT-0.121569* genotype TC/TT). The AUC (Area under the curve) = 0.7779.

TC, TT in Mongolian and Han population showed no difference (P>0.05).

Comparison of -565C/T genotype and allele distribution frequency between Mongolian and Han population

There was no difference in -565C/T genotype distribution between Mongolian and Han population (P>0.05).

Distribution frequencies of M233V genotype and allele and comparison of lipids in genotypes

The M233V polymorphisms of ABCA1 gene in Mongolian and Han population were presented in genotypes MM, MV and VV. There was no difference in distribution frequencies of M233V genotype and allele in Mongolian and Han population between CHD and control (P>0.05). The HDL-C, LDL-C, TG, TC levels among genotypes MM, MV, VV in Mongolian and Han population showed no difference (P>0.05).

Comparison of M233V genotype and allele distribution frequency between Mongolian and Han population

There was no difference in M233V genotype distribution between Mongolian and Han population (P>0.05).

Discussion

The function of ABCA1 is to mediate the efflux of excess cholesterol within cell to apolipoprotein, then package it into HDL. As an important carrier in the regulation of plasma HDL-C and intracellular cholesterol levels, it plays an important role in the formation of atherosclerosis. The ABCA1 gene mutations may impair the cholesterol efflux from macrophages and reduce cholesterol and phospholipid efflux; thereby the apolipoprotein A1 could not combine with it effectively. It could be quickly cleared by kidneys and causes HDL-C synthesis disorders, which leads to massive ester accumulation of cholesterol and cholesterol in macrophages and foam cells formation, followed by infiltration into the vessel wall and development of atherosclerosis and CHD. ABCA1 gene mutation is closely related to the

Table 10. Distribution frequencies of 69C/T genotype and allele in CHD and control among Mongolian population

Groups	N	Genotype frequency			Allele frequency	
		TT	TC	CC	T	C
Mongolian Control	102	10 (9.80)	46 (45.10)	46 (45.10)	66 (32.35)	138 (67.65)
Mongolian CHD	101	32 (31.68)	46 (45.54)	23 (22.77)	110 (54.46)	92 (45.54)
χ^2			19.1860		20.1906	
P			0.000		0.000	

Table 11. Distribution frequencies of 69C/T genotype and allele in CHD and control among Han population

Groups	N	Genotype frequency			Allele frequency	
		TT	TC	CC	T	C
Han Control	101	12 (11.88)	38 (37.62)	51 (50.50)	62 (30.69)	140 (69.31)
Han CHD	111	37 (33.33)	48 (43.24)	26 (23.42)	122 (55.96)	96 (44.04)
χ^2			21.6112		27.1986	
P			0.000		0.000	

occurrence and development of atherosclerosis as well as lipids. Some mutations, such as R219K, may increase the levels of HDL-C [1], develop anti-atherosclerosis ability and reduce the risk of CHD. Some mutations, such as R230C, R1587K, and V825I [2, 3], may decrease HDL-C levels. The single nucleotide polymorphisms in the promoter region, such as 69C/T [4], may increase the risk of CHD. Some mutations, such as If -14 bp and ZNF [5], may have little or no impact on the function of ABCA1 or no significant correlation with plasma HDL-C levels.

Previous studies have shown that the single nucleotide polymorphisms of the same ABCA1 gene among different ethnic and regions had different impacts on lipid levels and CHD. The results obtained by Li et al [6] revealed that the R219K polymorphism of ABCA1 gene is a protective factor for CHD in Asian populations, but in Caucasian population it has no correlation with the incidence of CHD. Andrikovic [7] reported that in the Hungarian population, the KK genotype is a protective factor for CHD. Doosti et al [8] found a significant correlation between R219K with CHD in Iran population. Compared to KK (AA) type, RR (GG) genotype increases the risk of CHD, making it an independent risk predictor for CHD. A meta-analysis found out that the R219K in KK genotype was a protective gene for CHD in Asians and Caucasians, while KK genotypes was associated with increased HDL-C [9]. Jing et al [1] suggested that the K allele in R219K genotype might reduce CHD susceptibility, K allele frequency in Asians (40%) was higher than that in the West (25%). Coban's findings, however, contradicted the above conclusions. They revealed that the K allele in R219K increased the risk of CHD in women in Turkey, accompanied by increased TG levels [10]. There are fewer studies regarding the comparison of R219K between different ethnic groups in China. Sun et al reported a difference in R219K polymorphism in ABCA1 gene between Han and Xinjiang Uygur population, which is closely related to the serum high-density lipoprotein and triglyceride glycerol levels. However, no comparative study was done about the distribution of R219K genotypes of ABCA1 gene between the Inner Mongolian and Han population and CHD susceptibility. Results in the present study showed that there was no difference in the distribution of R219K genotypes of ABCA1 gene between Inner Mongolian and Han population. However, the KK genotypes in both Mongolian and Han population are protective factors for CHD. KK gene can produce beneficial clinical lipids spectrum, suggesting that the polymorphism may alter plasma HDL-C levels by changing the activity of encoding products [6], thereby affecting individual susceptibility to CHD.

The results obtained by Versmissen indicated that the risk of patients suffering from CHD

with TT genotype in promoter 69C/T gene is 1.7 times of that of CC genotype promoter 69C/T gene [4], which is consistent with the results of the present study. Our study showed that the TT genotype in 69C/T gene of both Mongolian and Han population had increased prevalence of CHD risk, but there was no difference in blood lipids in patients with various genotypes. Moreover, there was no difference in the distribution of 69C/T genotypes and alleles in ABCA1 gene between Mongolian and Han population. Studies regarding the correlation between CHD and -565C/T polymorphism are controversial. Ruiz et al reported that the T allelic mutations of -565C/T increased the risk of subclinical cardiovascular disease and coronary atherosclerosis severity [11]. Inconsistent with Ruiz's study, Rejeb [12] reported that -565C/T mutation had no correlation with CHD in Tunisians, which is consistent with our study. In the present study we revealed that there was no difference in distribution frequency in -565C/T allelic mutations of ABCA1 gene in Mongolia and Han population. The -565C/T allelic mutations of ABCA1 gene had no significant correlation with the incidence of CHD, indicating that the -565C/T is not a CHD susceptibility gene in either the Inner Mongolian or Han population, which suggests that ABCA1 polymorphism genetic changes vary between different races.

M233V, a newly discovered single nucleotide polymorphism of ABCA1 gene, was barely reported in previous studies. The present study revealed a new mutation site of M233V in Mongolian and Han population, namely VV genotype. The impact of VV genotype on blood lipids and CHD is uncertain yet, which might be associated with genetic factors (it may be affected by other genotype mutation or genes), ethnic and regional differences. Further study with larger sample is needed to explore the specific mechanisms.

Conclusions

In the present study, we revealed that certain mutation on the ABCA1 gene was associated with blood lipid and CHD. The studies upon the relationship between the ABCA1 gene (R219K, M233V, -565C/T, 69C/T gene) in Inner Mongolian and Han population and blood lipid and CHD provide clues for further exploration on the association between atherosclerosis, CHD rate and these four genes. It is possible that we can further develop or search for medicines affecting ABCA1 gene expression, which is valuable for the prevention and treatment of hyperlipidemia, atherosclerosis and CHD.

Disclosure of conflict of interest

None.

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