Int J Clin Exp Pathol 2015;8(10):13441-13449
www.ijcep.com /ISSN:1936-2625/IJCEP0014146

Original Article

Association of ATP-binding cassette transporter A1 gene polymorphisms with plasma lipid variability and coronary heart disease risk

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Received August 7, 2015; Accepted September 21, 2015; Epub October 1, 2015; Published October 15, 2015

Abstract: Objective: Our study aimed to investigate the association of *ABCA1* polymorphisms with plasma lipid variability and CHD risk in the Chinese Han population. Methods: 754 CHD patients and 760 controls were included in this case-control study. Three SNPs (rs363717, rs4149339, and rs4149338) in *ABCA1* 3'UTR and one nonsynonymous SNP (rs2230808) in *ABCA1* exon 35 were selected and genotyped. The analysis of genetic data was performed using the SNPstats program and the SPSS17.0 software. Results: Significant associations were observed between SNP rs363717 and CHD risk under different genetic models before or after Bonferroni corrections (codominant model: OR = 0.70, *P* = 0.003 for AG *vs*. AA; dominant model: OR = 0.71, *P* = 0.003 for GG + AG *vs*. AA). The nonsynonymous SNP rs2230808 was associated with higher total cholesterol levels (*P* = 0.047). The GCC haplotype (consisting of alleles of SNPs rs363717, rs4149339, and rs4149338) was associated with a decreased risk of CHD (OR = 0.8, *P* = 0.027). Three *ABCA1* SNPs interacted with high triglyceride levels to increase CHD risk (*P* values of interactions were 0.010 for rs363717, 0.010 for rs4149339, and 0.020 for rs4149338, respectively). Conclusions: Our results suggest that *ABCA1* polymorphisms influence plasma lipid variability and CHD risk. *ABCA1* polymorphisms could also modify the effects of plasma lipids on CHD risk.

Keywords: ATP-binding cassette transporter A1 gene, single nucleotide polymorphism, coronary heart disease, plasma lipids

Introduction

Coronary heart disease (CHD) is a leading cause of mortality and disability, and accounts for approximately 30% of all deaths worldwide [1, 2]. Epidemiological studies have shown that CHD is a multifactorial disease influenced by genetic variants, environmental factors, and alterations of plasma lipid levels as well as their interactions with each other [3, 4]. Coronary atherosclerosis, which is caused by the accumulation of cholesterol in arterial wall macrophages and the dysregulation of lipid metabolism, is generally considered to be the pathological foundation of CHD [5].

Adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) is a member of the superfamily of ATP-binding cassette transporters. It is highly expressed in a wide range of tissues such as liver, intestines, lung, leukocytes, and macrophages [6, 7]. ABCA1 hydrolyzes ATP, and the released energy is used to transport various molecules across cellular membranes [8]. ABCA1 has a major impact on lipid metabolism and atherosclerosis, and plays a critical role in the development of CHD [6, 9-11]. ABCA1 participates in the initial step of reverse cholesterol transportation by regulating the efflux of cholesterol and phospholipids from peripheral cells to lipid-poor apolipoprotein acceptors [12, 13]. In addition, it influences the initiation of high-density lipoprotein (HDL) particle formation in the liver and the intestine [14].

The ABCA1 gene (*ABCA1*) is located on chromosome 9q31.1. More than 100 mutations or single nucleotide polymorphisms (SNPs) have

Table 1. Baseline characteristics of CHD patients and control subjects

	CHD patients (n = 754)	Controls (n = 760)	*P**
Age (years)	63.12 ± 8.05	63.10 ± 8.37	0.960
Sex (M/F)	404/350	378/382	0.140
Smoking, n (%)	378 (50.1)	88 (11.6)	<0.001
Alcohol drinking, n (%)	107 (14.2)	55 (7.2)	<0.001
TG (mmol/L)	1.73 ± 1.12	1.25 ± 0.66	<0.001
TC (mmol/L)	4.35 ± 1.06	4.11 ± 0.80	<0.001
LDL-C (mmol/L)	2.78 ± 0.89	2.62 ± 0.71	<0.001
HDL-C (mmol/L)	1.15 ± 0.33	1.31 ± 0.25	<0.001

*Analyzed by Student's *t* test for continuous variables and by Pearson's Chi-square test for categorical variables.

Table 2. Information on *ABCA1* SNPs

SNP	Gene position	Alleles (major/minor)	MAF (case/control)	%Geno	*P* value of HWE in controls
rs363717	3'UTR	A/G	0.19/0.23	98.9	0.68
rs4149339	3'UTR	T/C	0.29/0.29	99.1	0.06
rs4149338	3'UTR	T/C	0.29/0.30	98.9	0.10
rs2230808	Exon 35	G/A	0.36/0.36	98.9	0.69

%Geno, the percentage of non-missing genotypes for each marker; UTR, untranslated region; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

been identified in *ABCA1* [15-17]. Mutations in *ABCA1* cause Tangier disease and familial HDL deficiency, which are characterized by reduced plasma HDL-C levels and increased susceptibility to CHD due to the impairment of cholesterol clearance from vascular endothelial cells back to the liver [15, 17-20]. Genetic association studies have demonstrated that common polymorphisms in the coding and untranslated regions (UTRs) of *ABCA1* were associated with CHD susceptibility, and the results suggest a relationship between *ABCA1* polymorphisms and plasma lipid levels [6, 9, 11, 17, 21-24].

Previous studies have investigated the association of *ABCA1* polymorphisms with plasma lipid levels and CHD risk, but the published results are inconsistent in different ethnic populations. Furthermore, the interaction of genetic variation and plasma lipids on the risk of CHD has not been thoroughly explored. This study aimed to investigate whether four *ABCA1* SNPs (three in the 3'UTR and one in the coding region) are associated with the risk of CHD and the variability in lipid levels, and evaluate the interaction of these SNPs and plasma lipids on the risk of CHD in the Chinese Han population.

Materials and methods

Study subjects

1,514 participants, including 754 CHD patients and 760 control subjects, were enrolled in this case-control study. Patients with CHD were recruited from the PetroChina Jilin General Hospital and the First Bethune Hospital of Jilin University in Changchun, Jilin Province, China. Age and sex matched controls were randomly recruited from the Health Examination Center of these two hospitals at the same time. CHD was diagnosed by two or more experienced cardiologists and confirmed by coronary angiography (> 50% diameter stenosis in at least one of the major coronary arteries) according to the criteria of the World Health Organization. Control subjects were free of CHD by clinical evaluation and electrocardiographic profiling. None of the control subjects had a history of diabetes and hypertension. Both patients and control subjects were unrelated Chinese Hans from Northeast China.

The protocol of this study was approved by the Ethics Committee of Jilin University School of Public Health, and complied with the Helsinki declaration of ethical principles for medical research involving human subjects. Informed consents were obtained from all participants of the study.

Epidemiological survey and biochemical examination

Demographic information and clinical characteristics were collected with standardized questionnaire. Fasting blood samples were obtained from all participants. Plasma lipid concentrations were measured by the MODULE P800 automated biochemistry analyzer (ROCHE, USA). Plasma lipids examined in both case and control subjects included triglycerides (TG),

Table 3. Lipid profiles in control subjects carrying different *ABCA1* genotypes or alleles

		TG (mmol/L)	TC (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)
rs363717	n				
AA	448	1.26 ± 0.73	4.10 ± 0.81	2.62 ± 0.72	1.31 ± 0.25
AG	274	1.25 ± 0.57	4.13 ± 0.78	2.63 ± 0.70	1.31 ± 0.25
GG	38	1.15 ± 0.40	4.18 ± 0.90	2.66 ± 0.72	1.38 ± 0.23
P^a		0.584	0.783	0.931	0.161
AA+AG	722	1.25 ± 0.67	4.11 ± 0.80	2.62 ± 0.71	1.31 ± 0.25
P^b		0.316	0.647	0.719	**0.066**
rs4149339	n				
TT	372	1.28 ± 0.74	4.12 ± 0.78	2.61 ± 0.71	1.31 ± 0.25
CT	335	1.22 ± 0.60	4.10 ± 0.82	2.63 ± 0.72	1.31 ± 0.25
CC	53	1.19 ± 0.43	4.14 ± 0.90	2.64 ± 0.78	1.36 ± 0.22
P^a		0.325	0.770	0.925	0.310
TT+CT	707	1.25 ± 0.68	4.11 ± 0.79	2.62 ± 0.71	1.31 ± 0.25
P^b		0.453	0.714	0.752	**0.090**
rs4149338	n				
TT	363	1.27 ± 0.71	4.12±0.76	2.61 ± 0.69	1.31 ± 0.25
CT	339	1.24 ± 0.65	4.10 ± 0.83	2.63 ± 0.73	1.31 ± 0.26
CC	58	1.18 ± 0.42	4.13 ± 0.89	2.64 ± 0.77	1.35 ± 0.22
P^a		0.560	0.926	0.915	0.431
TT+CT	702	1.25 ± 0.68	4.11 ± 0.80	2.62 ± 0.71	1.31 ± 0.25
P^b		0.359	0.798	0.779	0.181
rs2230808	n				
GG	310	1.28 ± 0.76	4.03 ± 0.81	2.57 ± 0.69	1.30 ± 0.26
AG	355	1.21 ± 0.52	4.17 ± 0.81	2.66 ± 0.75	1.33 ± 0.25
AA	95	1.30 ± 0.80	4.16 ± 0.73	2.63 ± 0.67	1.31 ± 0.25
P^a		0.248	0.138	0.364	0.416
AG+AA	450	1.23 ± 0.59	4.17 ± 0.79	2.66 ± 0.73	1.32 ± 0.25
P^c		0.250	**0.047**	0.184	0.291

P^a, comparisons among all genotypes; P^b, minor allele homozygote serves as the reference; P^c, major allele homozygote serves as the reference; *P* values were calculated with ANCOVA adjusted for age, sex, smoking, and alcohol drinking; Bold *P* values are statistically significant.

total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

DNA extraction

The peripheral blood of each participant was collected in non-anticoagulant plexiglass tubes and stored at -20°C until DNA extraction. Genomic DNA was extracted using a blood DNA extraction kit (ClotBlood DNA kit, Cwbio, Beijing, China) according to the manufacturer's instructions. DNA samples were checked for purity and concentration by ultraviolet spectrophotometer (Beckman, USA) with ultraviolet readings at 260 nm and 280 nm, respectively.

SNP genotyping

Four SNPs in *ABCA1* were selected using the HapMap website and the Haploview 4.2 software (Daly Lab. at the Broad Institute, USA). SNPs rs363717, rs4149339, and rs4149338 reside in the 3'UTR of *ABCA1*, and the nonsynonymous SNP rs2230808 (or Arg-1587Lys) resides in exon 35 of *ABCA1*. The minor allele frequency (MAF) of these four SNPs was greater than 5%. SNP genotypes were determined by Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS) of the MassARRAY system (Sequenom, San, Diego, CA, USA) [25]. Polymerase chain reactions (PCRs) were performed in 384-well plate format using a MassARRAY Nanodispenser (Sequenom). PCR primers were designed using the Assay Design 3.1 software (Sequenom Inc., San Diego, CA, USA).

Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as absolute and percentage. Student's *t* test was applied for comparison of the mean of continuous variables between cases and controls. The distribution of categorical variables between cases and controls were compared by the Chi-square (c^2) test. Hardy-Weinberg equilibrium (HWE) test [26] and genotype distributions of SNPs were also performed by Chi-square test. Analysis of covariance (ANCOVA) was used to assessing the effect of different genotypes on plasma lipid levels. Unconditional logistic regression analysis was used to evaluate the association be-

Table 4. Genotype distribution and allele frequency of four *ABCA1* SNPs

SNP	CHD (%)	Controls (%)	x^2	*P*
rs363717 (n = 1497)				
AA	488 (66.2)	448 (58.9)	8.43	**0.015**
AG	219 (29.7)	274 (36.1)		
GG	30 (4.1)	38 (5.0)		
G allele	279 (18.9)	350 (23.0)	7.57	**0.006**
rs4149339 (n = 1500)				
TT	362 (48.9)	372 (48.9)	0.38	0.828
CT	332 (44.9)	335 (44.1)		
CC	46 (6.2)	53 (7.0)		
C allele	424 (28.6)	441 (29.0)	0.05	0.826
rs4149338 (n = 1497)				
TT	356 (48.3)	363 (47.8)	1.12	0.570
CT	335 (45.5)	339 (44.6)		
CC	46 (6.2)	58 (7.6)		
C allele	427 (29.0)	455 (29.9)	0.34	0.562
rs2230808 (n = 1497)				
GG	281 (38.1)	310 (40.8)	3.46	0.177
AG	378 (51.3)	355 (46.7)		
AA	78 (10.6)	95 (12.5)		
A allele	534 (36.2)	545 (35.8)	0.05	0.832

Data were analyzed by Pearson's Chi-square test. Bold *P* values are statistically significant.

tween *ABCA1* polymorphisms and CHD risk. The Akaike information criterion (AIC) was used to determine the best genetic model for each SNP. Bonferroni correction was applied for multiple testing to reduce Type I error in association analyses. LD blocks were constructed by the Haploview software for evaluating the association between different haplotypes and CHD risk [27]. Interactive effects of *ABCA1* polymorphisms and plasma lipid levels on the risk of CHD were also estimated by unconditional logistic regression analysis. Statistical analyses were performed using the SPSS17.0 software and the SNPStats program [28]. A *P*-value (two-sided test) less than 0.05 was considered statistically significant.

Results

Characteristics of study subjects and ABCA1 SNPs

The demographic and clinical data and plasma lipid levels of 1514 participants enrolled in this study are presented in **Table 1**. There were no significant differences in age and sex between CHD patients and control subjects ($P > 0.05$). Patients with CHD had higher levels of TG, TC, and LDL-C, but lower levels of HDL-C than controls. There were more smokers and drinkers in CHD patients than in control subjects.

Table 2 presents gene position, major and minor alleles, MAF, genotyping rates, and HWE test results of four *ABCA1* SNPs. The genotype distributions of all SNPs did not deviate from HWE in control subjects ($P > 0.05$).

Associations between ABCA1 polymorphisms and plasma lipid levels

Plasma lipid changes in carriers of different genotypes or alleles are shown in **Table 3**. Nonsynonymous SNP rs2230808 was found to be associated with TC levels. Individuals who were carriers of the A allele of SNP rs2230808 had a higher TC level than noncarriers. Regarding the effect of SNPs rs363717 and rs4149339 on HDL-C levels, there was a borderline significant trend in the difference of HDL-C levels between carriers and noncarriers of the major allele of these two SNPs ($P = 0.066$ for rs363717, $P = 0.090$ for rs4149339).

Associations between ABCA1 polymorphisms and CHD risk

The genotype distribution and allelic frequency of each SNP between CHD patients and control subjects are shown in **Table 4**. For SNP rs363717, a significant difference in genotype distributions was observed between CHD patients and control subjects ($x^2 = 8.43$, $P = 0.015$). And the frequency of the G allele in CHD patients was lower than in controls. Genotype distributions and allelic frequencies of three other *ABCA1*SNPs were not significantly different between CHD patients and control subjects ($P > 0.05$).

As shown in **Table 5**, SNP rs363717 was found to have a protective effect on CHD risk. Under the codominant and dominant models of inheritance, carriers of the G allele had a significantly decreased risk of CHD as compared to those with the wild-type genotype AA (OR = 0.70, 95% CI 0.55-0.89, $P = 0.003$ for AG, OR = 0.71, 95% CI 0.56-0.89, $P = 0.003$ for AG + GG). The above *P* values remained significant after Bonferroni corrections. There was no significant association between three other *ABCA1* SNPs and CHD risk under the three genetic models.

Table 5. Analysis of the association of four *ABCA1* SNPs with CHD risk

SNPs	Models	OR	95% CI	*P*	AIC
rs363717	Codominant	**0.70**	**0.55-0.89**	**0.003**	1799.4
		0.81	0.47-1.39	0.447	
	Dominant	**0.71**	**0.56-0.89**	**0.003**	1797.7
	Recessive	0.92	0.54-1.56	0.750	1806.0
rs4149339	Codominant	0.95	0.75-1.19	0.646	1810.7
		0.89	0.56-1.42	0.633	
	Dominant	0.94	0.75-1.18	0.587	1808.8
	Recessive	0.92	0.58-1.44	0.704	1809.0
rs4149338	Codominant	0.93	0.74-1.18	0.568	1807.1
		0.80	0.51-1.26	0.337	
	Dominant	0.92	0.73-1.14	0.438	1805.5
	Recessive	0.83	0.53-1.29	0.398	1805.4
rs2230808	Codominant	1.18	0.93-1.50	0.171	1806.0
		1.00	0.69-1.45	0.982	
	Dominant	1.14	0.91-1.44	0.252	1804.8
	Recessive	0.91	0.64-1.29	0.585	1805.8

Data were analyzed by unconditional logistic regression analyses adjusted for age, sex, smoking, and alcohol drinking; OR, odds ratio; CI, confidence interval; AIC, Akaike information criterion; Codominant model, homozygote for the major allele serves as the reference; Dominant model (minor allele homozygote + heterozygote *vs*. major allele homozygote); Recessive model (minor allele homozygote *vs*. major allele homozygote + heterozygote); Bold values are statistically significant.

Linkage disequilibrium (LD) and haplotype analysis

Pairwise LD extent (D') and correlation coefficient (r^2) among the four *ABCA1* SNPs are presented in **Table 6**.

Haplotype analysis results are summarized in **Table 7**. Only one LD block was constructed by the Gabriel algorithm [29]. It was comprised of three SNPs (rs363717, rs4149339, and rs4149338). The GCC haplotype was significantly more frequent in control subjects than in CHD patients, thus potentially playing a protective role in CHD (OR = 0.80, 95% CI 0.65-0.97, *P* = 0.027). Compared to the ATT haplotype, the ACC haplotype was associated with a significantly increased risk of CHD (OR = 1.59, 95% CI 1.15-2.20, *P* = 0.005).

Interactions of ABCA1 polymorphisms and plasma lipids on CHD risk

Significant interactions were observed between TG levels and three *ABCA1* SNPs (*P* = 0.010 for rs363717, *P* = 0.010 for rs4149339, *P* = 0.020 for rs4149338). The odds ratios for subjects with different genotypes and TG levels are shown in **Table 8**. Subjects with wild-type homozygotes of each polymorphism and TG < 1.70 mmol/L were defined as the reference group. For each of the three *ABCA1* SNPs, the OR to develop CHD was largest among subjects who were homozygous for the major allele and had a plasma TG level between 1.70 mmol/L and 2.26 mmol/L (OR = 15.1 for rs363717; OR = 17.7 for rs4149339; and OR = 17.6 for rs4149338). In subjects with TG < 1.70 mmol/L, the ORs to develop CHD were similar in those subjects homozygous for the major allele and carriers of the minor allele (1.00 *vs*. 0.80 for rs363717; 1.00 *vs*. 1.00 for rs4149339; and 1.00 *vs*. 1.00 for rs4149338). There were no significant interactions between the four polymorphisms and other plasma lipids on the risk of CHD (data not shown).

Discussion

Nonsynonymous SNP rs2230808 results in an amino acid change at codon 1,587 from arginine (R) to lysine (K), thus potentially altering the sequence, structure, and function of ABCA1 [9]. The three 3' UTR SNPs may affect mRNA stability or interact with microRNAs [30], and ultimately influence the expression of *ABCA1*.

We found that the nonsynonymous SNP rs2230808 was associated with plasma TC levels but not with the risk of CHD. The frequency of the G allele was 63.8% in CHD patients and 64.2% in control subjects. Similarly, the frequency was 68% in the normal Greek population [6]. Previous studies have investigated the effect of *ABCA1* SNP rs2230808 on plasma lipids and CHD risk, but their findings are inconsistent. Kolovou et al. [6] found that *ABCA1* SNP rs2230808 was associated with plasma lipid levels, and subjects with heterozygous genotype GA had higher TC levels compared to those with the GG genotype. Clee et al. [31] reported that *ABCA1* SNP rs2230808 was not a modifiable risk factor for CHD. The study by Tregouet et al. [9] showed that this SNP was not associated with CHD risk. In accordance with the above findings, we also did not find a significant association of SNP rs2230808 and CHD

Table 6. Pairwise linkage disequilibrium extent (D') and correlation coefficient (r^2) among four *ABCA1* SNPs

SNP	Linkage disequilibrium extent (D')			
	rs363717	rs4149339	rs4149338	rs2230808
Correlation coefficient (r^2)				
rs363717	-	1.0	1.0	0.35
rs4149339	0.66	-	0.99	0.26
rs4149338	0.64	0.94	-	0.26
rs2230808	0.06	0.05	0.05	-

risk. Nevertheless, we found that individuals who were carriers of the A allele had a significantly higher level of TC than noncarriers of the A allele. On the contrary, a prospective study showed that SNP rs2230808 predicted an increased risk of CHD in the Danish population, and this SNP remained to be a significant factor for the prediction of CHD after adjustment for age, smoking, hypertension, and diabetes [21]. It is likely that the effects of *ABCA1* variation on CHD risk may be modified by ethnic background or environmental factors [17, 32].

We found a significant association of *ABCA1* 3'UTR SNPs *via* both single SNP and haplotype analyses. Regarding the three 3'UTR SNPs in *ABCA1*, there is limited information on the effect of these SNPs on CHD risk and plasma lipid levels. In our study, two SNPs (rs363717 and rs4149339) were shown to be associated with plasma levels of HDL-C, with the major allele being associated with decreased HDL-C levels. Both single-locus and haplotype effects on the risk of CHD were observed in our study. By single-locus analysis, only SNP rs363717 was associated with CHD risk, with the G allele being associated with a decreased risk of CHD. It is believed that low levels of plasma HDL-C were major risk factors for CHD [9, 10, 21, 33, 34]. Therefore, the association between SNP rs363717 and CHD risk could account for its association with HDL-C. Haplotype analysis has the ability to provide extra power in association studies of complex diseases such as CHD, and it can reduce the numbers of statistical tests when evaluating the interaction between gene variants [9, 10]. In the present study, the GCC haplotype generated from the three 3'UTR SNPs (rs363717, rs4149339, and rs4149338) was overrepresented in controls and was associated with a decreased risk of CHD, while the ACC haplotype was overrepresented in cases and thus associated with an increased risk of CHD. Our study suggest that *ABCA1* 3'UTR SNP rs363717 and 3'UTR haplotypes may be critical contributors to CHD risk, and this finding needs to be validated in further genetic association studies with a larger sample.

Many studies have demonstrated that interactions between genetic variation and environmental factor play a critical role in the development of multifactorial diseases [33, 35]. If the interactions exist, the effects of environmental factors on the risk of these diseases will be modified by genotypes. CHD is influenced by multiple factors and their interactions, and the causes are not fully understood [1, 3, 4, 36]. Conventional risk factors such as altered lipid levels, smoking, hypertension, and diabetes may only explain about two-thirds of the presence of CHD [1]. Genetic factors and gene-environment interactions are also essential in the etiology of CHD [1, 17]. The metabolism of plasma lipids is complex. In general, high TG levels often accompany low HDL-C levels [1, 31, 37]. Several remnant particles in TG-rich lipoprotein metabolism are essential for the formation of HDL-C. Cholesteryl ester in HDL-C is mainly transferred to VLDL particles, which increase TG levels but lower HDL-C levels in the blood. The above two processes are often modulated by *ABCA1* polymorphisms, resulting in increased TG and VLDL levels, and reduced formation of HDL-C [1, 33, 38]. Therefore, we supposed that the effect of high TG levels on CHD risk could be modified by *ABCA1* polymorphisms. These *ABCA1* SNPs may serve as markers to identify those with a high risk for CHD in subjects with high TG levels. In subjects with borderline high TG levels, TG levels should be controlled by mediations if they are homozygous for the major allele of these three *ABCA1* SNPs.

Our study has several limitations, and thus the findings from the present study should be interpreted with caution. Because of ethnic differences, we cannot necessarily generalize our results to other populations with different races and ethnicities. Further studies with a large cohort and in other ethnic populations are needed to confirm the role of *ABCA1* polymorphism in plasma lipid variability and CHD risk.

Table 7. Association of *ABCA1* haplotypes and CHD risk

	Haplotypes			Frequencies			OR (95% CI)	*P*
	rs363717	rs4149339	rs4149338	Total	CHD	Controls		
1	A	T	T	0.703	0.711	0.695	1.00	-
2	G	C	C	0.210	0.189	0.230	0.80 (0.65-0.97)	**0.02**
3	A	C	C	0.076	0.098	0.054	1.59 (1.15-2.20)	0.005
rare	-	-	-	0.011	0.002	0.021	0.11 (0.03-0.38)	<0.001

The analysis was adjusted by age, sex, smoking, and drinking; Bold *P* values were statistically significant; The reference group was the most common haplotype (ATT); Rare haplotypes: haplotypes with frequencies below 0.01.

Table 8. Odds ratios (ORs) for CHD in subjects with different genotypes and plasma TG levels

Lipid levels[a] (mmol/L)	rs363717		rs4149339		rs4149338	
	AA	AG/GG	TT	CT/CC	TT	CT/CC
TG<1.70	1.0[b]	0.8 (0.6-1.0)	1.0[b]	1.0 (0.8-1.3)	1.0[b]	1.0 (0.8-1.3)
1.70≤TG<2.26	**15.1 (7.1-32.1)**	**2.6 (1.3-5.1)**	**17.7 (7.4-42.2)**	**4.2 (2.3-7.8)**	**17.6 (7.4-42.1)**	**4.2 (2.3-7.8)**
TG≥2.26	**5.1 (2.9-8.9)**	**5.1 (2.5-10.1)**	**4.9 (2.7-9.0)**	**6.5 (3.5-12.2)**	**5.2 (2.8-9.6)**	**6.1 (3.3-11.2)**
*P**	**0.01**		**0.01**		**0.02**	

[a]Lipid levels were divided into three groups: low (TG<1.70), borderline high (1.70≤TG<2.26), and high (TG≥2.26); [b]This group serves as the reference group; **P*, Interaction between three polymorphisms and plasma TG levels; Odds ratios, 95% CI, and *P* values of interactions were calculated by unconditional logistic regression analyses, adjusted for age, sex, smoking, and alcohol drinking; Bold *P* values were statistically significant.

In addition, our study cannot rule out the potential role of other untested SNPs within *ABCA1* in affecting plasma lipid variability and CHD risk.

In conclusion, our study demonstrated that *ABCA1* polymorphisms influences plasma lipid levels and CHD risk in a Chinese Han population. The three 3'UTR SNPs in *ABCA1* interacted with high triglyceride levels to affect the risk of CHD, and they could serve as markers to identify high risk patients for CHD in subjects with high triglyceride levels.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (No. 30870952), the Science and Technology Department of Jilin Province (No. 20080735), the Health Department of Jilin Province (No. 2001R009), the Bethune B Project of Jilin University (No. 2013102009), and the International Cooperation of Science and Technology Department of Jilin Province (No. 20140413-016GH).

Disclosure of conflict of interest

None.

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