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Original Article

Association between ErbB3 genetic polymorphisms and coronary artery disease in the Han and Uyghur populations of China

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Abstract: Background: ErbB3 is a member of the epidermal growth factor receptor (EGFR/ERBB) family of receptor tyrosine kinases. Recent research has shown that amplification of this gene is related to prostate, bladder and breast cancers, as well as low-density lipoprotein cholesterol (LDL-C) metabolism. LDL-C plays a considerable role in the development of cardiovascular disease. Thus, the present study assessed the association between human ErbB3 gene polymorphisms and coronary artery disease (CAD) in Han and Uygur populationsin China. Methods: We performed two independent case-control studies with a Han population (339 CAD patients and 395 control subjects) and a Uygur population (306 CAD patients and 325 control subjects). All of the CAD patients and controls were genotyped for the same three single nucleotide polymorphisms (rs877636, rs705708, and rs10783779) in the ErbB3 gene by real-time PCR. Results: In the Han population, rs877636 polymorphisms were associated with CAD on the basis of the genotypes, dominant model, additive model, and allele frequency (for genotypes: P = 0.008; for dominant model: P = 0.003; for additive model: P = 0.004; for allele: P = 0.008), and these significant difference was retained (all P < 0.05) after adjusting for the major confounding factors. Conclusion: The CT genotype and C allele of rs877636 in the ErbB3 gene could be a genetic marker of CAD risk for the Han population in China.

Keywords: ErbB3, case-control study, coronary artery disease, single nucleotide polymorphism, SREBF2

Introduction

Coronary artery disease (CAD) is a leading global cause of morbidity and mortality, which has both genetic and environmental components [1]. CAD is characterized by the accumulation of lipoproteins, inflammatory cells, and fibrous tissues in the walls of the arteries, which result in the development of lesions [2, 3]. CAD often occurs due to the development of atherosclerosis. Dyslipidemia is a major variable in the etiology of atherosclerosis and high plasma low-density lipoprotein cholesterol (LDL-C) concentrations are associated with a high risk of developing atherosclerosis in humans and experimental animals [4-6]. The genetic variation that underlies differences in individual LDL-C serum concentrations is an important determinant of atherosclerosis [7]. The genetic architecture of CAD has been studied widely, but significant information is available for only a few genes that influence LDL-C serum levels [8-10], where these genes account for a small percentage of the variation in LDL-C [11]. Thus, there is still lack of a comprehensive understanding of the underlying molecular and genetic mechanisms that regulate variation in the LDL-C serum concentrations, which impairs efforts to develop genetically informed, personalized treatment.

The Cox research group recently revealed that a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases, ErbB3, influences the variation in LDL-C in baboons and it is potentially a genetic mechanism that requires further investigation [12]. The human ErbB3 gene is located on the long arm of chromosome 12 (12q13), where it is encoded by 23,651 base pairs that translate into 1342 amino acids [13]. During human

development, ErbB3 is expressed in the skin, bone, muscle, nervous system, reproductive system, urinary tract, heart, lungs, and intestinal epithelium [14, 15]. The ErbB3 gene encodes a membrane-bound protein with a neuregulin-binding domain but no active kinase domain; therefore, it can bind a lig and but cannot convey a signal into the cell via protein phosphorylation. However, it forms heterodimers with other EGFR family members that possess kinase activities. Heterodimerization leads to the activation of pathways that mediate cell proliferation or differentiation. The amplification of this gene and/or over expression of its protein have been reported in numerous cancers, including prostate, bladder, and breast cancers (Ref Seq, July 2008).

According to previous research, the ErbB3 gene plays key roles in networks related to lipid metabolism, primarily by enhancing the transcription activity of sterol regulatory element-binding transcription factor 2 (SREBF2) [16]. Thus, we assume that the ErbB3 gene may participate in the process that leads to the occurrence and development of atherosclerosis, as well as coronary heart disease; therefore, we selected the ErbB3 gene as our research target. We assessed the association between ErbB3 gene polymorphisms and CAD in Han and Uygur populations in China. Thus, we determined the relationship between genetic variability in the ErbB3 gene and the susceptibility to CAD.

Methods

Ethical approval of the study protocol

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Urumqi, China). Written informed consent was obtained from all participants. All participants explicitly provided their permission for DNA analyses as well as for the collection of relevant clinical data. This study was conducted according to the standards of the Declaration of Helsinki.

Subjects

The subjects were recruited from the Uygur and Han populations living in the Xinjiang Uygur Autonomous Region of China. All of the patients and controls received differential diagnoses for chest pain at the Cardiac Catheterization Laboratory of the First Affiliated Hospital of Xinjiang Medical University between 2011 and 2013. Highly skilled physicians performed all of the coronary angiography procedures using the Judkins approach [17]. At least two experienced imaging specialists interpreted the coronary angiography findings and the final CAD diagnosis was made on the basis of the angiography report. We randomly selected 339 Han patients and 306 Uygur patients with CAD, and control groups of 395 and 325 ethnically and geographically matched individuals, respectively. CAD diagnosed by angiography was defined as the presence of at least one significant coronary artery stenos is of ≥ 50% luminal diameter based on coronary angiography. All of the control subjects also underwent coronary angiography and had no coronary artery stenosesor clinical or electrocardiogram evidence of myocardial infarction or CAD. The control subjects were not healthy individuals, i.e., some had hypertension, diabetes mellitus (DM), or hyperlipidemia, and thus, the members of the control group were exposed to the same CAD risk factors, although their coronary angiogram results were normal. Data and information about traditional coronary risk factors, including hypertension, DM, and smoking, were collected from all study participants. Hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, or the use of any antihypertensive agent. DM was diagnosed according to the criteria of the American Diabetes Association [18]. In addition, individuals with fasting plasma glucose > 7.0 m mol/L or with a history of DM or insulin treatment were considered diabetic. Smoking was classified as smokers (including current and ex-smokers) or non-smokers. Patients with impaired renal function, malignancy, connective tissue disease, valvular disease, or chronic inflammatory disease were excluded.

Blood collection and DNA extraction

Before cardiac catheterization, a 5 mL sample of fasting venous blood drawn by venipuncture in the Cardiac Catheterization Laboratory was taken from all participants. The blood samples were collected in tubes containing ethylene diaminetetraacetic acid and the plasma content was separated by centrifugation at 4000 × *g* for 5 min. Genomic DNA was extracted from the peripheral leukocytes using the standard phenol-chloroform method. The DNA samples were stored at -80°C until use. DNA was diluted to a concentration of 50 ng/μL before use.

Table 1. Characteristics of the study participants among Han and Uygur populations

	Han			Uyghur		
	CAD	Control	*P*-value	CAD	Control	*P*-value
Number (n)	339	395		306	325	
Age (years)	58.60 ± 9.72	57.41 ± 10.52	0.112	54.75 ± 8.91	54.0 ± 8.51	0.275
BMI (kg/m^2)	25.78 ± 3.70	24.99 ± 3.33	0.002	27.14 ± 4.71	26.96 ± 4.17	0.62
Glu (m mol/L)	6.61 ± 2.49	5.52 ± 1.49	< 0.001*	6.88 ± 2.28	5.78 ± 1.69	< 0.001*
TG (m mol/L)	2.46 ± 1.76	1.87 ± 1.20	< 0.001*	2.45 ± 1.10	2.10 ± 0.65	< 0.001*
TC (m mol/L)	4.99 ± 1.29	4.21 ± 0.89	< 0.001*	3.93 ± 1.26	3.00 ± 1.09	< 0.001*
HDL (m mol/L)	1.09 ± 0.41	1.24 ± 0.55	< 0.001*	1.85 ± 1.40	2.72 ± 1.10	< 0.001*
LDL (m mol/L)	3.03 ± 0.90	2.36 ± 0.77	< 0.001*	2.81 ± 1.01	1.65 ± 1.04	< 0.001*
Cr (m mol/L)	79.02 ± 36.69	68.82 ± 16.05	< 0.001*	73.58 ± 37.91	59.79 ± 20.75	< 0.001*
BUN (m mol/L)	5.70 ± 1.88	5.18 ± 1.58	< 0.001*	6.54 ± 3.51	5.57 ± 1.09	< 0.001*
UA (m mol/L)	338.7 ± 92.79	305.78 ± 77.07	< 0.001*	265.36 ± 110.97	182.28 ± 119.42	< 0.001*
Diabetes, n (%)	103 (30.4%)	62 (15.7%)	< 0.001*	95 (31.0%)	54 (16.6%)	< 0.001*
Smoking, n (%)	158 (46.6%)	89 (22.5%)	< 0.001*	131 (42.86%)	95 (25.2%)	< 0.001*
Drinking, n (%)	105 (31.0%)	54 (13.7%)	< 0.001*	72 (23.5%)	48 (14.8%)	0.006
Hypertension, n (%)	153 (45.1%)	149 (33.7%)	0.002	134 (43.8%)	97 (29.8%)	< 0.001*

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages. BMI: body mass index; BUN: blood urea nitrogen; CAD: coronary artery disease; Cr: creatinine; DM: diabetes mellitus; Glu: glucose; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; EH: essential hypertension; UA: uric acid. *P*-values for continuous variables were calculated using independent samples *t*-tests. *P*-values for categorical variables were calculated using Pearson's exact test. *means p value <0.001, which is strongly significant.

Biochemical analyses

High-density lipoprotein cholesterol (HDL-C), LDL-C, total cholesterol (TC), triglyceride (TG), serum glucose concentration (GLU), blood urea nitrogen (BUN), creatinine (Cr), and uric acid (UA) were all measured using standard methods in the Central Laboratory of the First Affiliated Hospital at Xinjiang Medical University, as described previously.

Genotyping

In this study, we obtained three tag single nucleotide polymorphisms (SNPs) (rs877636, rs705708, and rs10783779) using Haplo view 4.2 and the Hap Map phase II database, with a minor allele frequency ≤ 0.5 and linkage disequilibrium patterns with r2 ≥ 0.5 as a cutoff. Genotyping was confirmed using a Taq Man SNP Genotyping Assay (Applied Bio systems, Foster City, CA). The primers and probes used in the Taq Man® SNP Genotyping Assays (ABI) were selected on the basis of information from the ABI website (http://myscience.appliedbiosystems.com). Thermal cycling was performed using an Applied Bio systems 7900HT Standard Real-Time PCR System. Plates were read using Sequence Detection Systems (SDS) automation controller software v 2.3 (ABI). PCR amplification was performed using 2.5 μL of Taq Man Universal Master Mix, 0.15 μL of probes, and 1.85 μL of double-distilled H_2O in a final reaction volume of 6 μL containing 1 μL DNA. The thermal cycling conditions were as follows: 95°C for 5 min, 40 cycles at 95°C for 15 s, and 60°C for 1 min. All of the 96-well plates were read using SDS automation controller software v 2.3 (ABI).

Statistical analysis

Differences in continuous variables [age, body mass index (BMI), TC, TG, HDL-C, LDL-C, GLU, BUN, Cr, UA] were analyzed using means ± standard deviations (SDs). Differences between the CAD and control groups were analyzed using an independent sample t-test. Differences in the frequencies of smoking, drinking, hypertension, DM, and ErbB3 genotypes were analyzed using a χ^2 test or Pearson's exact test, as appropriate. Hardy-Weinberg equilibrium was assessed by χ^2 analysis. Logistic regression analyses with effect ratios [odds ratio (OR) and 95% confidence intervals (CI)] were used to assess the contributions of major risk factors. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) v. 17.0 for Windows (SPSS Institute, Chicago, USA). Statistically significant differences were accepted at $P < 0.05$.

Table 2. Genotype and allele distributions in patients with CAD and control participants

			Han			Uyghur		
Variants			CAD n (%)	Control n (%)	*P*-value	CAD n (%)	Control n (%)	*P*-value
Rs877636 (SNP1)	Genotype	TT	175 (51.60%)	248 (62.80%)		173 (56.50%)	204 (62.80%)	
		CT	140 (41.30%)	122 (30.90%)		110 (35.90%)	103 (31.70%)	
		CC	24 (7.10%)	25 (6.30%)	0.008	23 (7.50%)	18 (5.50%)	0.239
	Dominant model	TT	175 (51.60%)	248 (62.80%)		173 (56.50%)	204 (62.80%)	
		CC+CT	164 (48.40%)	147 (37.20%)	0.003	133 (43.50%)	121 (37.20%)	0.123
	Recessive model	CC	24 (7.10%)	25 (6.30%)		23 (7.50%)	18 (5.50%)	
		TT+CT	315 (92.90%)	370 (93.70%)	0.767	283 (92.50%)	307 (94.50%)	0.336
	Additive model	CT	140 (41.30%)	122 (30.90%)		110 (35.90%)	103 (31.70%)	
		CC+TT	199 (58.70%)	273 (69.10%)	0.004	196 (64.1%)	222 (68.3%)	0.274
	Allele	T	490 (72.30%)	618 (78.20%)		456 (74.50%)	511 (78.60%)	
		C	188 (27.70%)	172 (21.80%)	0.008	156 (25.50%)	139 (21.40%)	0.085
Rs705708 (SNP2)	Genotype	AA	33 (9.70%)	44 (11.10%)		52 (17.00%)	49(15.10%)	
		AG	142 (41.90%)	147 (37.20%)		140 (45.80%)	134 (41.20%)	
		GG	164 (48.40%)	204 (51.60%)	0.424	114 (37.30%)	142 (43.70%)	0.258
	Dominant model	GG	164 (48.40%)	204 (51.60%)		114 (37.30%)	142 (43.70%)	
		AG+AA	175 (51.60%)	191 (48.40%)	0.415	192 (62.70%)	183 (56.30%)	0.105
	Recessive model	AA	33 (9.70%)	44 (11.10%)		52 (17.00%)	49 (15.10%)	
		GG+AG	306 (90.30%)	351 (88.90%)	0.549	254 (83.00%)	276 (84.90%)	0.517
	Additive model	AG	142 (41.90%)	147 (37.20%)		140 (45.80%)	134 (41.20%)	
		AA+GG	197 (58.10%)	248 (62.80%)	0.199	166 (54.20%)	191 (58.80%)	0.261
	Allele	G	470 (69.3%)	555 (70.30%)		368 (60.1%)	418 (64.30%)	
		A	208 (30.7%)	235 (29.70%)	0.698	244 (39.9%)	232 (35.70%)	0.126
Rs10783779 (SNP3)	Genotype	GG	38 (11.20%)	48 (12.20%)		36 (11.80%)	28 (8.60%)	
		GT	151 (44.50%)	168 (42.50%)		137 (44.80%)	139 (42.80%	
		TT	150 (44.20%)	179 (45.30%)	0.851	133 (43.50%)	158 (48.60%)	0.276
	Dominant model	GG	38 (11.20%)	48 (12.20%)		36 (11.80%)	28 (8.60%)	
		GT+TT	301 (88.80%)	347 (87.80%)	0.731	270 (88.20%)	297 (91.40%)	0.235
	Recessive model	TT	150 (44.20%)	179 (45.30%)		133 (43.50%)	158 (48.60%)	
		GG+GT	189 (55.80%)	216 (54.70%)	0.823	173 (56.50%)	167 (51.40%)	0.202
	Additive model	GT	151 (44.50%)	168 (42.50%)		137 (44.80%)	139 (42.80%	
		TT+GG	188 (55.50%)	227 (57.50%)	0.602	169 (55.20%)	186 (57.20%)	0.631
	Allele	G	227 (33.5%)	264 (33.40%)		209 (34.20%)	195 (30.00%)	
		T	451 (66.5%)	526 (66.60%)	0.979	403 (65.80%)	455 (70.00%)	0.114

CAD: coronary artery disease; *n*: number of participants; SNP: single nucleotide polymorphism.

Results

Characteristics of the study participants

As shown in **Table 1**, there were no significant differences in age between the CAD patients and control subjects for the Han and Uygur populations, which indicated that the study was an age-matched case-control study.

In the Han population, BMI, plasma concentrations of GLU, TG, TC, LDL, Cr, BUN, and UA, and the prevalence of essential hypertension, DM, smoking, and drinking were significantly higher in patients with CAD than the control subjects.

In the Uyghur population, the plasma concentrations of GLU, TG, TC, LDL, Cr, BUN, and UA, and the prevalence of essential hypertension, DM, smoking, drinking were significantly higher in subjects with CAD compared with the controls. There was no significant difference in BMI between the CAD patients and the control subjects. In both the Han and Uyghur groups, the serum concentration of HDL-C was significantly lower in CAD patients than the control subjects.

Distributions of ErbB3 genotypes

As shown in **Table 2**, the genotype distributions for each SNP were in good agreement with the predicted Hardy-Weinberg equilibrium values (data not shown). In the Han population, the distribution of SNP1 (rs877636) genotypes dif-

Table 3. Multivariate logistic regression analysis if CAD patients and control subjects (rs877636) from the Han population

	Han		
	OR	95% CI	*P*-value
Dominant model (TT/CC+CT)	0.605	0.427-0.858	0.005
Smoking	2.147	1.44-3.119	< 0.001*
Drinking	1.395	0.863-2.257	0.174
Hypertension	1.301	0.915-1.849	0.143
Glu	1.29	1.163-1.43	< 0.001*
BUN	1.027	0.919-1.148	0.638
Cr	1.011	1.000-1.023	0.042
UA	1.001	0.999-1.004	0.227
TG	1.009	0.887-1.158	0.897
TC	1.359	1.01-1.829	0.043
HDL	0.34	0.213-0.543	< 0.001*
LDL	1.778	1.223-2.586	0.003

CAD: coronary artery disease; OR: odds ratios; 95% CI: 95% confidence interval; BUN: blood urea nitrogen; Cr: creatinine; Glu: glucose; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UA: uric acid. *means p value <0.001, which is strongly significant.

Table 4. Multivariate logistic regression analysis of CAD patients and control subjects (rs877636) from the Han population

	Han		
	OR	95% CI	*P*-value
Additive model (CT/CC+TT)	1.643	1.142-2.338	0.007
Smoking	2.161	1.451-3.218	< 0.001*
Drinking	1.387	0.858-2.243	0.181
Hypertension	1.297	0.913-1.843	0.147
Glu	1.291	1.165-1.431	< 0.001*
BUN	1.024	0.916-1.144	0.681
Cr	1.011	1.001-1.022	0.039
UA	1.02	0.999-1.04	0.206
TG	1.077	0.889-1.22	0.922
TC	1.359	1.011-1.829	0.042
HDL	0.354	0.222-0.564	< 0.001*
LDL	1.774	1.220-2.579	0.003

CAD: coronary artery disease; OR: odds ratios; 95% CI: 95% confidence interval; BUN: blood urea nitrogen; Cr: creatinine; Glu: glucose; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UA: uric acid. *means p value <0.001, which is strongly significant.

fered significantly between the CAD and control subjects (P = 0.008). The distributions of SNP1 (rs877636) alleles, the dominant model (TT vs. CC+CT), and additive model (CT vs. CC+TT) differed significantly between the CAD and control subjects (for alleles: P = 0.008; for dominant model: P = 0.003; for additive model: P = 0.004). The C allele in rs877636 was significantly more frequent in CAD patients than in control subjects (27.70% vs. 21.80%) and the T allele in rs877636 was significantly less frequent in CAD patients than in the control subjects (72.3% vs. 78.2%).

The additive model (CT vs. CC+TT) for rs877636 was more significant in CAD patients compared with that in the control subjects (41.30% vs. 30.90%). The dominant model (TT vs. CC+CT) of rs877636 was less significantin CAD patients compared with that in the control subjects (51.60% vs. 62.80%). In the Uygur population, the distribution of the three SNP genotypes and alleles did not differ significantly between the CAD patients and control subjects.

Logistic regression analyses

Tables 3 and **4** shows the multivariate logistic regression analysis combined the genotypes with the following variables: the incidence of hypertension, smoking, and drinking, and the GLU, TG, TC, HDL-C, LDL-C, UA, Cr, and BUN levels (**Table 3**: in the dominant model; **Table 4**: in the additive model). In the Han population, after multivariate adjustment, rs877636 was still significantly associated with CAD in both models (for dominant model, OR: 0.605, 95% CI: 0.427-0.858, P = 0.005; for additive model, OR: 1.643, 95% CI: 1.142-2.338, P = 0.007).

Discussion

Cholesterol is an essential component of most biological membranes and a precursor in the synthesis of steroid hormones and bile acids. However, high levels of LDL-C cause severe health problems, including coronary heart disease [19]. The EGFR/ERBB family of membrane-bound tyrosine kinase receptors comprises Egfr, ErbB2, ErbB3, and ErbB4, which activate potent signaling pathways [20]. All four of the receptors are expressed in cervical cancer [21-24], and the over expression of ERBB family members and the expression of

alternative Egfr isoforms are associated with advanced stage cancers and more aggressive cancers [25-27].

Compared with other members of the ERBB family, ErbB3 receptor has been investigated less frequently because it was initially identified as an inactive kinase receptor, where its function depends on interactions with ErbB partners, primarily via heterodimerization. Therefore, functional polymorphisms in ErbB3 have been neglected for this pseudo-kinase (Shi et al., 2010).

The Cox research group established a well-characterized atherosclerosis model in a pedigree baboon population [2, 6] and performed hepatic whole-genome expression profiling of LDL-C-discordant baboons, which were fed a high-cholesterol/high-fat diet for seven weeks. They successfully identified a cluster of QTLs on baboon chromosome 11, which encodes variation in multiple quantitative traits influenced by the serum LDL-C levels [28]. Thus, they suggested that the ErbB3 gene is responsible for variation in the LDL-C serum concentration and that this gene may be pleiotropic, participating in networks related to lipid metabolism [12].

Several lines of evidence indicate that ErbB3 plays a central role in the AKT1/GSK3β pathway. The AKT1/GSK3β pathway influences key cell biology processes, including cholesterol homeostasis, inflammation, cell growth, and proliferation. Moreover, many complex diseases such as various types of cancer are related to the deregulation of this pathway [16, 29]. Related studies have shown that the AKT1/GSK3β pathway is regulated by switching of the phosphatidylinositol biphosphate (PIP2) lipid molecule to phosphatidylinositol triphosphate (PIP3) and vice versa via phosphorylation and dephosphorylating, respectively. In this pathway, aSrc tyrosine kinase receptor is stimulated by growth factors and binding to diacylglycerol kinaseα, which phosphorylates the diacylglycerol lipid molecule to yield PIP2 [30].

An epidermal growth factor stimulates the ErbB3 receptor, recruits and forms a heteromeric complex with ErbB2, which possesses an intrinsic kinase activity, and assists in generating the AKT1 substrate, PIP3 [31].

The heteromeric complex binds and activates phosphoinositide 3-kinase, which phosphorylates and converts PIP2 into PIP3. PIP3 is an activator of AKT1, which phosphorylates and inactivates GSK3β [32]. After the inactivation of GSK3β, the stability of SREBF2 and the lipid production transcription activity are promoted and enhanced [16, 33]. SREBF2 is a transcription factor that activates the expression of genes involved in the biosynthesis of cholesterol, fatty acid, and Triglyceride [28]. In general, the activity of SREBF2 is inhibited by GSK3β, which leads to phosphorylation, proteasomal degradation, and the triggered targeting of ubiquitination [34]. The ability of GSK3β to inhibit the transcription activity of SREBF2 is consequently reduced, which results in increased lipid production and low serum LDL-C levels [12].

In this study, we hypothesized that variability in the ErbB3 gene may affect the risk of CAD by activating the expression of genes involved in lipid and cholesterol biosynthesis [35], as well as promoting the stability and enhancing the transcription activity of sterol regulatory element-binding proteins, which influence the LDL-C level. We genotyped three SNPs of the ErbB3 gene in the Uygur and Han populations from China, and assessed the associations between these ErbB3 polymorphisms and CAD in a case-control analysis.

In the Han population, there was a significant difference in the genotypic distribution of SNP1 (rs877636) between CAD patients and control subjects. The distributions of SNP1 (rs877636) alleles, the dominant model (TT vs. CC+CT), and the additive model (CT vs. CC+TT) differed significantly between the CAD and control participants. The C allele and the additive model (CT vs. CC+TT) for rs877636 were significantly more frequent in CAD patients than the control subjects. The T allele and the dominant model (TT vs. CC+CT) for rs877636 were significantly less frequent in the CAD patients than in the control subjects.

The significant differences between the two SNP1 models in the CAD patients and control subjects was retained after multivariate adjustment for confounding factors such as the plasma concentrations of TG, UA, HDL, LDL-C, GLU, and Cr, as well as the incidence of hypertension, DM, drinking, and smoking (**Table 4**).

Thus, in the Han population, the C allele is a CAD risk factor and the T allele may protect against CAD. The risk of CAD was increased

with the CT genotype of rs877636, whereas the TT genotype of rs877636 reduced the risk of CAD.

We found no significant differences between the patients with CAD and the controls in terms of the distributions of the rs705708 (SNP2) and rs10783779 (SNP3) genotypes, the dominant model, the recessive model, or the allele frequency among the Han and Uygur populations.

The present study was limited by the relatively small sample size, which may have led to weak statistical power and wide CIs when estimating the ORs.

Conclusion

This study is the first to demonstrate the importance of ErbB3 gene polymorphisms in CAD. The C allele of rs877636 may be a genetic risk marker and the T allele may be a protective genetic marker of CAD in Han subjects. The TT genotype of rs877636 could be a protective genetic marker of CAD in the Han population in China, which supports the hypothesis that ErbB3 gene variations are involved in the pathogenesis of CAD. Further studies are required to replicate our results and to elucidate the underlying biological mechanism involved.

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Disclosure of conflict of interest

None.

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