RESEARCH NOTE

Association of *ACP1* gene polymorphisms and coronary artery disease in northeast Chinese population

TIANBAO LI[1], XUESONG XU[1,2], JIANZHUO LI[1], SHU XING[1,3], LIN ZHANG[3], WANNAN LI[1,3], JUNFENG MA[1,3]* and XUEQI FU[1,3]*

[1]*National Engineering Laboratory for AIDS Vaccine and* [3]*Key Laboratory for Molecular Enzymology and Engineering of Ministry of Education, Jilin University, Changchun 130012, People's Republic of China*
[2]*Clinical Laboratory of China-Japan Union Hospital of Jilin University, Changchun 130033, People's Republic of China*

[Li T., Xu X., Li J., Xing S., Zhang L., Li W., Ma J. and Fu X. 2015 Association of *ACP1* gene polymorphisms and coronary artery disease in northeast Chinese population *J. Genet.* **94**, 125–128]

Introduction

Coronary artery disease (CAD) is the major cause of death in most countries including China (He *et al.* 2005). A number of susceptible variants of candidate genes have been recognized as genetic risk factors that are associated with pathogenesis of coronary heart disease (Wu *et al.* 2001; Achour *et al.* 2011; Zhou *et al.* 2011). Recently, Banci *et al.* (2009) have reported acid phosphatase 1 (*ACP1*) gene *C allele as a risk factor for CAD in Caucasian (OR= 3.188). Here, we show that the genotype GA of rs79716074 (*ACP1* gene, exon 6) is associated with decreased risk of CAD in northeast Chinese population especially in females.

The *ACP1* gene is the only member of class II cysteine-based protein tyrosine phophatase (PTP) family in human and encodes the low molecular weight PTP (LMW-PTP), a group of 18-kDa proteins widely expressed in many tissues. LMW-PTP is involved in the regulation of important physiological processes including stress resistance and synthesis of the polysaccharide capsule, etc. (Souza *et al.* 2009).

There are three common codominant alleles of *ACP1*: *ACP1*A*, *ACP1*B* and *ACP1*C*. which contains single base substitutions located at specific sites. The *ACP1*C* allele differs from *ACP1*A* and *ACP1*B* alleles at rs11553742, while *ACP1*A* and *ACP1*B* alleles differ in an A–G transition at rs79716074. Previous studies reported that *ACP1* gene polymorphisms may be important pathogenic factors of immune dysregulation such as rheumatoid arthritis, systemic lupus erythematosis process, endometriosis and allergy (Ammendola *et al*. 2008, Teruel *et al.* 2011, 2012).

ACP1 is known to be associated with autoimmune diseases as well as atherosclerosis in Caucasian. However, no information is available regarding the interaction between *ACP1* gene polymorphism and CAD in Chinese. We conducted a hospital-based case–control study on 763 CAD patients and 657 controls suggesting that the genotype GA of rs79716074 in *ACP1* is a protective factor of CAD in Chinese northeast population.

Materials and methods

Subjects

The analysis involved 763 subjects admitted to the hospital for CAD and 657 blood donors as control from the Chinese northeast population. CAD is defined as angiographic evidence of at least one segment of a major coronary artery including the left anterior descending, left circumflex or right coronary artery with more than 50% organic stenosis. The other control subjects were randomly selected from outpatients who underwent regular physical examinations who came for regular health checkup. The control subjects were determined to be free of CAD and peripheral atherosclerotic arterial disease by medical history, clinical examinations and electrocardiography. Samples of CAD and control were collected at the same time, in the same hospital continuously in a period of six months. All the blood samples were collected from the clinical laboratory of China–Japan Union Hospital of Jilin University, Changchun, China, with approval of institutional Review Board obtained from Jilin University.

SNPs selection and genotyping

In all the samples detected, *ACP1*C* was not found in northeast Chinese population (methods according to Banci

*For correspondence. E-mail: Junfeng Ma, mjf@jlu.edu.cn; Xueqi Fu, fxq@jlu.edu.cn.
Tianbao Li and Xuesong Xu contributed equally to this work.

Keywords. acid phosphatase 1; polymorphisms; coronary artery disease; northeast Chinese.

et al. 2009). Therefore, SNP rs79716074 was selected for its ability of tagging *ACP1*A* and *ACP1*B* in northeast Chinese population.

Determination of ACP1g genotypes

PCR amplification: Genomic DNA was extracted from the whole blood by DNA extraction kit (Geneinn, Ningbo, China). A genomic DNA fragment containing exon 6 of the *ACP1* gene was amplified by polymerase chain reaction (PCR) with primers ACP1_F (5′-TTCAGAA CACCCTAGCAGATGTCC-3′) and ACP1_R (5′-GGACAG GAAAAAGAAGAAAATGGC-3′). PCR process was conducted following 40 cycles at 94°C for 30 s, 63°C for 30 s, and 72°C for 30 s with products of 320 bp DNA fragment.

Digestion reaction: 4 μL of PCR products were fully digested by *Taq*I (MBI Fermentas, Vilnius, Lithuania) at 65°C for 1.5 h according to the manufacturer's instruction and then electrophoresed on 2% agarose gels. The digestion created two fragments of 219 and 101 bp for the rs79716074 GG or GA, while rs79716074 AA could not be cut (modified from Banci *et al.* 2009).

Statistical analysis

Statistical analyses were performed by use of the SPSS program ver. 19.0 (SPSS, Chicago, USA). Differences between two groups of samples were accessed by *t*-tests assuming unequal variances. *P* values less than 0.05 (2-tailed) were considered to be significant.

Results

The present study evaluated the association between coronary atherosclerosis and the rs79716074 polymorphism in the population of northeast China. Phenotype distribution in control case is in agreement with Hardy–Weinberg expectation ($P>0.05$).

ACP1 genotype and allele distributions in subjects with CAD and in control from the same population are shown in table 1. No significant difference in the *ACP1* allele frequencies was found when compared with the distribution of the *ACP1* alleles between CAD patients and control subjects. However, significant differences are discovered concerning rs79716074 the proportion of GA genotypes compared with AA and GG genotypes ($P = 0.025$, OR= 0.767 [0.609–0.967]). The difference remained statistically significant ($P = 0.020$, OR=0.760 [0.602–0.958]) after adjusting for age and gender by multivariate logistic regression model test. This result suggests that the genotype of GA may be a protective genotype against CAD (table 1).

In addition, we investigated the possible influence of *ACP1* polymorphisms on gender separately. Interestingly in CAD females, the proportion of GA genotype carriers was much lower than other genotypes (25.8%: 33.3%, $P =0.038$) (table 2). Moreover in females, the odds ratio of GA genotype carriers was 0.698 (95% CI: 0.498–0.978) related to AA+GG carries, while the odds ratio for the AA genotype versus other type was 1.403 (95% CI: 1.105–1.472). However, there is no significant difference in males among different genotypes.

To further explore the association between genotype of rs79716074 and CAD, we conducted blood analysis to evaluate the association of WBC, RBC, Hb and PLT with rs79716074 polymorphism between CAD patients and controls. No significant differences were found in comparison with the genotype of GA or other genotypes in the total samples. However, the GA genotype of rs79716074 in females was found to be associated with a relatively low platelet level (217.04 ± 60.34 of GA: 236.80 ± 72.64 of other genotypes, $P = 0.0092$*) in CAD patients but not connected in controls (212.96 ± 40.03 of GA: 224.88 ± 53.01 of other genotypes, $P = 0.13$).

Discussion

Previous studies reported that dysregulation of LMW-PTPs is involved in many common diseases, including allergies, asthma, obesity, cardiac hypertrophy and cancers. Further reports demonstrated the association of *ACP1* gene polymorphisms with atherogenesis and plaque rupture in rheumatoid arthritis (Teruel *et al.* 2011). Others also revealed the importance of different genotypes of LMW-PTPs in the

Table 1. Genotype and allele distribution of the rs79716074 polymorphism in cases and controls.

	Control (n =657)	Cases (n =763)	OR (95% CI)
Allele, *n*(%)			
A allele	1049 (79.8)	1246 (81.7)	NS
G allele	265 (20.2)	280 (18.3)	NS
Genotype, *n*(%)			
AA	421 (64.1)	524 (68.7)	1.237 (0.759–2.013)
GA	207 (31.5)	198 (26.0)	0.767 (0.609–0.967)*
GG	29 (4.4)	41 (5.3)	1.22 (0.978–1.521)

NS, no significant differences; CI, confidence interval; OR, odds ratio; *$P = 0.025$.
Distributions of rs79716074 in control group was in Hardy–Weinberg equilibrium ($P = 0.55$).

Table 2. Genotype and allele distribution of rs79716074 polymorphism in females.

	Control (n =285)	Case (n =375)	OR (95% CI)
Allele, *n* (%)			
A allele	445 (78.1)	615 (82.0)	NS
G allele	125 (21.9)	135 (18.0)	NS
Genotype, *n* (%)			
AA	175 (61.4)	259 (69.0)	1.403 (1.105–1.472) *
GA	95 (33.3)	97 (25.9)	0.698 (0.498–0.978)**
GG	15 (5.3)	19 (5.1)	0.961 (0.479–1.925)

NS, no significant differences; *$P = 0.038$; **$P = 0.047$.

predisposition/resistance to immunological disorders, showing the significant regulation of *ACP1* gene polymorphisms in autoimmune diseases (Rollin *et al.* 2013).

The previous studies on *ACP1* gene polymorphisms attract our attention to its possible association with CAD. Our results showed that the GA genotype carriers with medium *ACP1* activity reveal a low risk in CAD among Chinese northeast people. A 23.3% decreased risk of CAD was observed in subjects with the rs79716074 GA genotype in comparison with the AA and GG carriers, indicating that the GA genotype may have the protective effect against CAD. Further, GA genotype displays a 30.2% protective function of developing CAD in females, while AA genotype was associated with a 40.3% increased risk in females. However, no significant difference has been discovered in males. The observed differences between males and females are probably derived from the difference in their hormonal patterns, which has also been reported in the study of *ACP1* to account for the gender difference in type I diabetes and allergy of Th2 class (Bottini *et al.* 2002; Gloria-Bottini *et al.* 2007).

The protection of rs79716074 polymorphism was found to be associated with a balanced activity in CAD patients. CAD progression always accompanies with enhanced thrombin-induced platelet aggregation. In addition, this polymorphism of GA was related to normal levels of platelet in comparison with controls, which may be one of the reasons to prevent CAD.

In this study, CAD may not be completely excluded in controls, though we carefully selected individuals without history of angina, no symptoms or other atherosclerotic vascular disease signs and no adverse coronary angiography as healthy control. In addition, our data were obtained at the time of diagnosis, thus there may be a requirement for the analysis of the association between the rs79716074 polymorphism and the CAD prognosis due to certain followed-up clinical outcomes including severe cardiac events. Our study is confined to Chinese northeast population, therefore, the data have to be extrapolated to other regions and people with caution.

In conclusion, our study demonstrates that the rs79716074 genotype of GA polymorphism in *ACP1* associated with the decreased risk of CAD in Chinese northeast population especially in females. This understanding will stimulate further investigation into targeting functions of *ACP1* so as to reduce the risk of CAD.

Acknowledgement

This work was sponsored by the National Natural Science Foundation of China (grant no. 81000202 for S. Xing, 31000358 for J. Ma and 81102859 for W. Li).

References

Achour A., Zaag I., Gueddah L., Trimeche B., Slama F. B. and Zemni R. 2011 Role of CYP1A1 (T6235C) polymorphism and cigarette smoking in the development of coronary heart disease in Tunisian population. *J. Genet.* **90**, 303–307.

Ammendola M., Pietropolli A., Saccucci P., Piccione E., Bottini E. and Gloria-Bottini F. 2008 Acid phosphatase locus 1 genetic polymorphism, endometriosis, and allergy. *Fertil. Steril.* **90**, 1203–1205.

Banci M., Saccucci P., D'Annibale F., Dofcaci A., Trionfera G., Magrini A. *et al.* 2009 ACP1 genetic polymorphism and coronary artery disease: an association study. *Cardiology* **113**, 236–242.

Bottini N., Meloni G. F., Borgiani P., Giorgini A., Buzzetti R., Pozzilli P. *et al.* 2002 Genotypes of cytosolic low-molecular-weight protein-tyrosine-phosphatase correlate with age at onset of type 1 diabetes in a sex-specific manner. *Metabolism* **51**, 419–422.

Gloria-Bottini F., Bottini N., Renzetti G. and Bottini E. 2007 ACP1 and Th class of immunological disease: evidence of interaction with gender. *Int. Arch. Allergy Immunol.* **143**, 170–176.

He J., Gu D., Wu X., Reynolds K., Duan X., Yao C. *et al.* 2005 Major causes of death among men and women in China. *N. Engl. J. Med.* **353**, 1124–1134.

Rollin J., Claire P., Leroux D., May M. A. and Gruel Y. 2013 Impact of polymorphisms affecting the ACP1 gene on levels of antibodies to platelet factor 4/heparin complexes. *J. Thromb. Haemost.* **11**, 1609–1611.

Souza A. C., Azoubel S., Queiroz K. C., Peppelenbosch M. P. and Ferreira C. V. 2009 From immune response to cancer: a spot on the low molecular weight protein tyrosine phosphatase. *Cell Mol. Life Sci.* **66**, 1140–1153.

Teruel M., Martin J. E., Gonzalez-Juanatey C., Lopez-Mejias R., Miranda-Filloy J. A., Blanco R. *et al.* 2011 Association of acid

phosphatase locus 1*C allele with the risk of cardiovascular events in rheumatoid arthritis patients. *Arthritis Res. Ther.* **13**, R116.

Teruel M., Martin J. E., Ortego-Centeno N., Jimenez-Alonso J., Sanchez-Roman J, de Ramon E. *et al.* 2012 Novel association of acid phosphatase locus 1*C allele with systemic lupus erythematosus. *Hum. Immunol.* **73**, 107–110.

Wu K. K., Aleksic N., Ahn C., Boerwinkle E., Folsom A. R., Juneja H. *et al.* 2001 Thrombomodulin Ala455Val polymorphism and risk of coronary heart disease. *Circulation* **103**, 1386–1389.

Zhou X., Xu W. and Chen J. 2011 The 981C>T polymorphism in protein tyrosine phosphatase 1B is associated with decreased risk of coronary artery disease in Chinese Han population. *Atherosclerosis* **218**, 147–150.

Received 11 May 2014, in revised form 24 July 2014; accepted 19 August 2014
Unedited version published online: 26 August 2014
Final version published online: 16 February 2015