Int J Clin Exp Pathol 2016;9(9):9612-9618
www.ijcep.com /ISSN:1936-2625/IJCEP0032024

Original Article

Association of SELP genetic polymorphisms and additional gene-smoking interaction on cardiovascular disease in Chinese Han population

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Received May 11, 2016; Accepted July 22, 2016; Epub September 1, 2016; Published September 15, 2016

Abstract: Aims: To investigate the impact of P-selectin (SELP) genetic polymorphisms and its interaction with smoking on cardiovascular disease (CVD) risk based on Chinese population. Methods: A total of 1082 subjects (519 males, 563 females), with a mean age of 53.9±13.1 years old, were selected, including 540 CVD patients and 542 normal control participants. Logistic regression model was used to examine the association between four SNP and CVD risk. Odds ratio (OR) and 95% confident interval (95% CI) were calculated. Generalized multifactor dimensionality reduction (GMDR) was employed to analyze the gene-smoking interaction. Results: Logistic regression analysis showed that CVD risk was significantly lower in carriers of A allele of the rs1800805 polymorphism than those with GG genotype (GA+AA *versus* GG), adjusted OR (95% CI)=1.69 (1.31-2.16). In addition, we also found CVD risk was also higher in carriers of AC genotype of the rs6136 polymorphism than those with AA genotype (AC+AA *versus* CC), adjusted OR (95% CI)=1.78 (1.28-2.26). GMDR analysis suggested a significant gene-environment interaction between rs1800805 and smoking. Overall, the two-locus models had a cross-validation consistency of 10 of 10, and had the testing accuracy of 62.17%, and smokers with GA or AA of rs1800805 genotype have the highest CVD risk, compared to never smokers with GG genotype, OR (95% CI) was 2.42 (1.83-3.16). Conclusions: Our results support an important association between rs1800805 and rs6136 minor allele of SELP and increased risk of CVD, and additional interaction between rs1800805 and smoking.

Keywords: Cardiovascular disease, SELP, polymorphism, interaction, smoking

Introduction

P-selectin (SELP) gene is a member of the selectin family of cell adhesion molecules which are involved in the transient attachment of leukocytes to endothelial cells, platelets and each other [1, 2]. The human SELP gene located on chromosome 1q22eq25 and was organized in 17 exons that span about 40 kb [3]. To date, polymorphic variants of SELP have been intensively reported to be involved in the pathogenesis of atherosclerotic and inflammatory diseases, including cardiovascular disease and MI [4-6]. Moreover, some studies have demonstrated that P-selectin may play a novel role in progression of both early and advanced stages of the atherosclerotic lesion development, and up-regulated expression of P-selectin on endothelial cells may promote the formation of atherosclerotic plaques, and increase the risk of atherosclerotic diseases [6, 7]. Several polymorphisms in the SELP gene [4, 8], which may influence the peptide sequence of this protein and its function, thereby contributing to susceptibility to CHD and MI, have been identified. Large quantities of evidence have suggested that SELP genetic polymorphisms may contribute to an increased risk of cardiovascular disease (CVD), however the results obtained from these studies were inconsistent [9, 10]. In addition, the pathogenesis of CVD is diverse, including both genetic and environmental factors, several risk factors we reported in previous studies, including age, obesity, high blood pressure, hyperlipidemia, diabetes mellitus, tobacco smoking, excessive alcohol consumption, lack of physical activity and so on. In these risk factors, smoking was an important factor for CVD, which has been reported in several studies [11, 12]. However, till now, no studies

Table 1. Description and Probe sequence for 3 SNPs used for Taqman fluorescence probe analysis

ID	SNP	Chromosome	Functional Consequence	Nucleotide substitution	Probe sequence
rs1800805	-1969G/A	1:169632043	Upstream variant 2 KB	G>A	5'-AACATGAGGCAATGCCAAAAAGAGG[A/G]GCTGGTGAGTGAAAGTAAGAACAGA-3'
rs1800808	-1817T/C	1:169631891	Upstream variant 2 KB	T>C	5'-CCTTACATGTCTATGTATTTGGTGA[C/T]TATTATCCTTATTATTCACATTGCT-3'
rs6136	Thr715Pro	1:169594713	Missense	A>C	5'-ATGCCAAGAGAATGGCCACTGGTCA[A/C]CTACCGTGCCAACCTGCCAAGGTAC-3'

focused on the gene-environment interaction between SELP gene and smoking on CVD were conducted. Given the interesting on SELP gene-CVD association and SELP gene-smoking interaction, we conducted this case-control study to investigate the impact of SELP genetic polymorphisms and its interaction with smoking on CVD risk based on Chinese population.

Materials and methods

Subjects

Participants were consecutively recruited between July 2012 and December 2014 from Tianjin Chest Hospital. All cases were confirmed by clinical diagnosis. CVD cases were diagnosed according to following events: interventional therapy of coronary artery (cardiac catheterization, percutaneous coronary intervention, or coronary artery bypass grafting), stable angina pectoris, unstable angina pectoris, the first occurrence of acute myocardial infarction, congestive heart failure caused by myocardial ischemia after baseline investigation, ischemic stroke, hemorrhagic stroke, and peripheral vascular disease, or cardiovascular death. A total of 1082 subjects (519 males, 563 females), with a mean age of 53.9±13.1 years old, were selected, including 540 CVD patients and 542 normal control participants. Healthy controls were randomly selected from a population screening program for risk factors of CVD in the same regions and matched to cases on the basis of age (±4 years). Participants with diabetes, hypertension, hyperlipidemia, missing data and participants with BMI<18.5 kg/m^2 were not included in the controls. Informed consent was obtained from all participants.

Body measurements

Body weight, height and waist circumference (WC) were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. WC was measured two times at 1 cm above the umbilicus at minimal respiration by trained observers; the mean of the two WC measurements was utilized in the analysis. Information on demographic, lifestyle risk factors for all participants was obtained using a standard questionnaire administered by trained staffs, including smoking and drinking status. Cigarette smokers were those who self-reported smoking cigarettes at least once a day for 1 year or more. Alcohol consumption was expressed as the sum of milliliters of alcohol per week from wine, beer, and spirits. Blood samples were collected in the morning after at least 8 hours of fasting. The concentrations of TC, FPG, HDL cholesterol and triglycerides were assessed enzymatically using an automatic biochemistry analyzer (Hitachi Inc., Tokyo, Japan) and commercial reagents.

Genomic DNA extraction and genotyping

Blood samples were collected from each participant. We selected SNPs within the SELP gene according to the following methods, including: 1) which have been reported associations with risk factors of CVD; 2) minor allele frequency (MAF) greater than 5%. At last, three SNPs of SELP gene were selected for genotyping in the study: rs1800805, rs1800808 and rs6136. Genomic DNA from participants was extracted from EDTA-treated whole blood, using the DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. All SNPs were detected by Taqman fluorescence probe. ABI Prism7000 software and allelic discrimination procedure was used for genotyping of fore-mentioned three SNPs. Probe sequences used for detection on all SNPs were shown in **Table 1**. A 25 μl reaction mixture including 1.50 ul SNP Genotyping Assays (20×), 12.25 μl Genotyping Master Mix

Table 2. General characteristics of 1082 study participants in case and control group

Variables	Cases group (n=540)	Control group (n=542)	*p*-values
Age (year)	53.8±14.2	54.1±15.1	0.736
Males N (%)	252 (46.7)	267 (49.3)	0.497
FPG (mmol/L)	5.5±1.3	5.3±1.2	0.009
TG (mmol/L)	1.5±0.7	1.2±0.8	<0.001
TC (mmol/L)	4.9±1.0	4.4±1.1	<0.001
HDL (mmol/L)	1.22±0.31	1.35±0.33	<0.001
WC (cm)	92.1±15.7	84.2±17.3	<0.001
BMI (kg/m^2)	25.8±9.3	23.2±9.7	<0.001
Smoke N (%)	186 (34.4)	131 (24.2)	<0.001
Alcohol consumption N (%)	198 (36.7)	175 (32.3)	0.130

Note: Means ± standard deviation for age, WC, BMI, FPG, TC, TG, HDL-C; TC, total cholesterol; HDL, high density lipoprotein; FPG, fast plasma glucose; TG, triglyceride.

(2×), 20 ng DNA, and the conditions were as follows: initial denaturation for 12 min and 92°C, denaturation for 20 s and 95°C, annealing and extension for 110 s and 60°C, 70 cycles.

Statistical analysis

The mean and SD were calculated for normally distributed continuous variables, and were compared using Student's t test. And percentages were calculated for categorical variable, and were compared using χ^2 test. Hardy-Weinberg equilibrium (HWE) was performed by using SNPStats (available online at http://bioinfo.iconcologia.net/SNPstats). Logistic regression was performed to investigate association between three SNP within SELP gene and CVD using gender, age, smoking and alcohol status, FPG, TC, TG and HDL as covariates in the model. Logistic regression was also performed to investigate gene-environment interaction between rs1800805 and smoking, and OR (95% CI) were calculated. Generalized multifactor dimensionality reduction (GMDR) [13] was used to analyze the impact of SELP gene-smoking interaction on CVD risk, cross-validation consistency, the testing balanced accuracy, and the sign test, to assess each selected interaction were calculated. The cross-validation consistency score is a measure of the degree of consistency with which the selected interaction is identified as the best model among all possibilities considered. The testing balanced accuracy is a measure of the degree to which the interaction accurately predicts case-control status with scores between 0.50 (indicating that the model predicts no better than chance) and 1.00 (indicating perfect prediction). Finally, a sign test or a permutation test (providing empirical *p*-values) for prediction accuracy can be used to measure the significance of an identified model.

Results

A total of 1082 subjects (519 males, 563 females), with a mean age of 53.9±13.1 years old, were selected, including 540 CVD patients and 542 normal control participants. **Table 2** shows the characteristics of cases and controls. The distribution of smoking was significantly different between CVD cases and normal controls, smoking rate was higher in cases than that in controls. The mean of WC, BMI, FPG, TG and TC were also significantly higher in CVD cases than that in normal controls. The concentration of HDL was lower in cases than that in controls.

All genotypes were distributed according to Hardy-Weinberg equilibrium in controls (all *P* values were more than 0.05). The frequencies of rs1800805- A allele was significantly higher in CVD cases than that in controls (29.6% *vs* 22.1%), and AC genotype of rs6136 was also significantly higher in CVD cases than that in controls (40.2% *vs* 31.2%). Logistic regression analysis showed that genotypes of variants in rs1800805 and rs6136 were associated with increased CVD risk, after adjustment for gender, age, smoking and alcohol status, FPG, TC, TG and HDL. CVD risk was significantly higher in carriers of rs1800805- A allele than those with GG genotype (GA+AA *versus* GG, adjusted OR (95% CI)=1.69 (1.31-2.16). In addition, we also found CVD risk was also higher in carriers of ACor CC genotype of the rs6136 polymorphism than those with AA genotype (AC+AA *versus* CC), adjusted OR (95% CI)=1.78 (1.28-2.26) (**Table 3**).

GMDR analysis was used to investigate SELP gene-smoking interaction in this study. **Table 4** shows the results obtained from GMDR models. There was a significant two-locus model (P=0.0010) involving rs1800805 and smoking, indicating a potential gene-environment interaction between rs1800805 and smoking.

Table 3. Logistic analysis on the association between 3 SNP and CVD risk

SNPs	Genotypes and Alleles	Frequencies N (%) Control group (n=542)	OR (95% CI)* Cases group (n=540)	H-W test for controls	
rs1800805					
	GG	333 (61.4)	274 (50.7)	1.00	0.269
	GA	178 (32.8)	212 (39.3)	1.62 (1.29-2.04)	
	AA	31 (5.7)	54 (10.0)	1.88 (1.34-2.31)	
	GA+AA	209 (38.6)	266 (49.3)	1.69 (1.31-2.16)	
	G	844 (77.9)	760 (70.4)		
	A	240 (22.1)	320 (29.6)		
rs1800808					
	TT	320 (59.0)	290 (53.7)	1.00	0.102
	TC	187 (34.5)	205 (38.0)	1.26 (0.95-1.73)	
	CC	35 (6.5)	45 (8.3)	1.38 (0.84-2.05)	
	CC+TC	222 (41.0)	250 (46.3)	1.29 (0.93-1.86)	
	T	827 (76.3)	785 (72.7)		
	C	257 (23.7)	295 (27.3)		
rs6136					
	AA	342 (63.1)	276 (51.1)	1.00	0.102
	AC	169 (31.2)	217 (40.2)	1.85 (1.32-2.41)	
	CC	31 (5.7)	47 (8.7)	1.18 (0.91-1.66)	
	CC+AC	200 (36.9)	264 (48.9)	1.78 (1.28-2.26)	
	A	853 (78.7)	769 (71.2)		
	C	231 (21.3)	311 (28.8)		

*Adjusted for gender, age, smoking and alcohol status, FPG, TC, TG and HDL.

Table 4. Best gene-smoking interaction models, as identified by GMDR

Locus no.	Best combination	Cross-validation consistency	Testing accuracy	*p-values**
2	rs1800805 Smoking	10/10	0.6217	0.0010
3	rs1800805 rs6136 Smoking	9/10	0.5399	0.0547
4	rs1800805 rs6136 rs1800808 Smoking	8/10	0.4958	0.1719

*Adjusted for gender, age, smoking and alcohol status, FPG, TC, TG and HDL.

Table 5. Gene environment interaction analysis for rs1800805 and smoking by using logistic

rs1800805	Smoking	OR (95% CI)*	*P-values*
GG	Never	1.00	-
GA or AA	Current	1.59 (1.18-2.02)	0.010
GG	Never	1.38 (1.04-1.98)	0.038
GA or AA	Current	2.42 (1.83-3.16)	<0.001

*Adjusted for gender, age, smoking and alcohol status, FPG, TC, nal Article.

Overall, the two-locus models had a cross-validation consistency of 10 of 10, and had the testing accuracy of 62.17%, and smokers with GA or AA of rs1800805 genotype have the highest CVD risk, compared to never smokers with GG genotype, OR (95% CI) was 2.42 (1.83-3.16), after adjustment for gender, age, smoking and alcohol status, FPG, TC, TG and HDL (**Table 5**).

Discussion

In the present study, we found that there was a significant association between rs1800805 and rs6136 in SELP with increased CVD risk. The CVD risks were higher in the A allele of rs1800805 and C allele of rs6136 carriers, suggesting that variants in two SNP could increase CVD risk. The human SELP gene located on chromosome 1q22eq25 and is organized in 17 exons that span about 40 kb [3]. SELP,

also called granule membrane protein 140 (GMP-140), antigen CD62, or platelet activation dependent granule-external membrane protein (PADGEM), is a 140-kD adhesion molecule that mediates the interaction of stimulated endothelial cells or platelets to leukocytes in the vascular surface [1, 2, 14]. SELP splicing variant forms and a number of SNPs distributed in the promoter and coding sequence have been described [3, 15, 16]. The distribution of these allelic variants in the population have been investigated in association studies with myocardial infarction and stroke [9, 17, 18], however the association of SELP polymorphisms and cardiovascular diseases remains controversial. Barbaux et al [19] indicated a strong association between P-selectin gene polymorphisms and serum P-selectin levels and a complex age-dependent relation between soluble P-selectin levels and coronary artery disease, which suggests that this molecule might have different roles in the atherothrombotic process. A recent study conducted by Bielinski et al [20] indicated that there was a positive linear association between P-selectin levels and rate of incident CHD after adjustment for traditional risk factors in non-Hispanic white Americans. Ghazouani et al [4, 8] suggested that -2123C/G in SELP gene was associated with increased CHD risk in Tunisians. Reiner et al [21] also suggested that common SELP polymorphisms were associated with soluble P-selectin and carotid IMT in young adults, but the patterns of association differed between EAs and AAs. These results support the role of P-selectin in the preclinical stages of atherosclerosis. However, some studies suggested inconsistent results. Volcik et al [22] conducted a study and indicated that the SELP Thr715Pro polymorphism is not associated with incident CHD or ischemic stroke in either whites or African-Americans, although genotypes carrying the SELP Pro715 variant allele are associated with decreased P-selectin levels compared to the homozygous wild-type genotype in whites. Zhou et al [23] also suggested a significant relationship between SELP genetic polymorphisms and the pathogenesis of CHD among Asians and Caucasians. However, they observed no significant associations between SELP genetic polymorphisms and the risk of CHD and MI among Africans.

The pathogenesis of CVD is diverse, including both genetic and environmental factors, several risk factors we reported in previous studies, including age, obesity, high blood pressure, hyperlipidemia, diabetes mellitus, tobacco smoking, excessive alcohol consumption, lack of physical activity and so on. In these risk factors, smoking was an important risk factor for CVD and has been reported in several studies [11, 12]. However, till now, no studies focused on the gene-environment interaction between SELP gene and smoking on CVD were conducted. For this reason, an analysis on impact of gene-environment interaction between SELP gene and smoking on CVD risk was necessary. GMDR analysis was used to investigate SELP gene-smoking interaction in this study, we found a potential gene-environment interaction between rs1800805 and smoking, smokers with GA or AA of rs1800805 genotype have the highest CVD risk, compared to never smokers with GG genotype. To our knowledge, this is the first study focused on the impact of gene-environment interaction between SELP gene and smoking on CVD risk. The underlying mechanism of this interaction remains unclear. The influence of gene-smoking interaction on sP-selectin levels maybe the possible explanation for this interaction on CVD risk. Two previous studies have confirmed the impact of SELP gene-smoking interaction on sP-selectin levels. Barbaux et al [19] have confirmed the finding of a significant interaction of Thr715Pro and smoking in determining sP-selectin levels. Carter et al [9] concluded the similar results that the Pro715 allele was associated with decreased sP-selectin in non-smokers whereas in current smokers and there was no difference in the levels of sP-selectin by genotype.

Several limitations of this study should be considered. Firstly, more environmental factors should be included in the SELP-environment interaction studies, including lifestyle, diet and activity factors. Secondly, More SNPs in SELP gene should be included in the future study, not only in SELP gene, but also in others metabolic related gene, and additional gene-gene interaction should be investigated in the further studies.

In conclusion, we found a significant association between SNP in SELP with increased CVD risk. The CVD risks were higher in the A allele of rs1800805 and C allele of rs6136 carriers, suggesting that variants in two SNP could increase CVD risk. We also found a potential

gene-environment interaction between rs1800805 and smoking, smokers with GA or AA of rs1800805 genotype have the highest CVD risk, compared to never smokers with GG genotype.

Acknowledgements

The writing of this paper was supported by Tianjin Chest Hospital. We thank all the partners and staffs who help us in the process of this study.

Disclosure of conflict of interest

None.

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