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Interaction between *SELP* genetic polymorphisms with inflammatory cytokine interleukin-6 (*IL-6*) gene variants on cardiovascular disease in Chinese Han population

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Abstract The aim of the study is to investigate the impact of *SELP* and *IL-6* genetic single-nucleotide polymorphisms (SNPs) and its gene–gene interaction on cardiovascular disease (CVD) risk based on Chinese population. A total of 1082 subjects (519 males, 563 females), with a mean age of 53.9 ± 13.1 years, were selected, including 540 CVD patients and 542 normal control participants. Logistic regression model was used to examine the association between six SNPs 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–gene interaction. CVD risk was significantly higher in carriers with rs1800805-A allele than those with GG genotype (GA + AA vs. GG), adjusted OR (95% CI) = 1.69 (1.31–2.16), and CVD risk was also higher in carriers with rs6136-AC or CC genotype than those with AA genotype (AC + CC vs. AA), adjusted OR (95% CI) = 1.78 (1.28–2.26), and higher in carriers with rs1800796-GC or CC genotype than those with GG genotype (CC + GC vs. GG), adjusted OR (95% CI) = 1.67 (1.25–2.14). GMDR analysis suggested a significant two-locus model ($p = 0.0010$) involving rs1800805 and rs1800796. Overall, the cross-validation consistency of this model was 10/10, and the testing accuracy was 62.17%, and participants with rs1800805-GA or AA and rs1800796-GC or CC genotype have the highest CVD risk, compared to participants with rs1800805-GG and rs1800796-GG genotypes, and OR (95% CI) was 2.52 (1.81–2.66). Our results support an important association of rs1800805, rs6136 minor allele of *SELP* gene, rs1800796 within *IL-6* gene, and additional interaction between rs1800805 and rs1800796 with increased risk of CVD.

Introduction

Cardiovascular disease (CVD), including heart disease, vascular disease, and atherosclerosis, is the most critical global health threat, and in many countries the prevalence has been decreasing over the last decades (Nichols et al. 2012; Go et al. 2013). This widespread, addictive habit is now proven causal of many diseases, including CVD (U.S. Department of Health and Human Services 2004).

The human *SELP* gene maps on chromosome 1q22eq25 and is organized in 17 exons that span about 40 kb (Johnston et al. 1990). To date, polymorphic variants of *SELP* have been intensively studied in the pathogenesis of atherosclerotic and inflammatory diseases, including CVD and myocardial infarction (MI) (Ghazouani et al. 2009; Pasquali et al. 2010; Elmas et al. 2010). Large quantities of evidence have suggested that *SELP* genetic polymorphisms may contribute to an increased risk of CVD; however, the results of these studies were inconsistent (Carter et al. 2003; Kee et al. 2000). The *IL-6* gene was mapped to chromosome 7 at p21 (Ray et al. 1990). Studies have identified that single-nucleotide polymorphisms (SNPs) in the promoter regions of the *IL-6* gene were mediators for the circulation of mRNA and *IL-6* levels and the status of inflammation (Yeh et al. 2010; Pereira et al. 2011). Several studies have reported the association between the *IL-6* gene SNPs and CHD susceptibility in different populations (Basso et al. 2002; Humphries et al. 2001; Wei et al. 2006). However, these studies could not conclude a certain and definitive conclusion. In addition, the pathogenesis of CVD is diverse, including both genetic and

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environmental factors. However, till now, only a less number of studies have focused on the influence of gene–gene interaction among several SNPs on CVD susceptibility. Given the conflicting evidence on *SELP* and *IL-6* gene–CVD association and missing on gene–gene interaction, we conducted this case–control study to investigate the impact of *SELP* and *IL-6* genetic polymorphisms and its interactions 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 patients were confirmed by clinical diagnosis. CVD cases were diagnosed according to the 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 MI, congestive heart failure caused by myocardial ischemia after baseline investigation, ischemic stroke, hemorrhagic stroke, and peripheral vascular disease, or cardiovascular death. 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, and missing data and those 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 were measured, and 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 h 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* and *IL-6* gene according to the following criteria: (1) which have been reported associations with risk factors of CVD; (2) minor allele frequency (MAF) greater than 5%. At last, three SNPs within *SELP* gene and three SNPs within *IL-6* gene were selected for genotyping in the current study, including rs1800805, rs1800808, and rs6136 within *SELP* gene, and rs1800796, rs1800795, and rs1800797 within *IL-6* gene. 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. SNPs within *SELP* gene were detected by Taqman fluorescence probe, and the detailed methods and procedure have been well described in our previous study (Kou et al. 2016). Genotyping for three SNPs within *IL-6* was performed by polymerase chain reaction (PCR) restriction fragment length polymorphism (PCR-RELP) method. The nucleotide sequence of primers and description for the six SNPs are shown in Table 1. The PCR was carried out in a 25 μl reaction mixture containing 100 ng genomic DNA, 1.5 mM $MgCl_2$, 0.2 mM dNTPs, 1 mM each primer, reaction buffer, and 0.625 U Taq polymerase. The following cycling conditions were used: initial denaturation at 94 °C for 3 min, followed by 35 cycles of 94 °C for 30 s, 56 °C for 30 s (52 °C for 30 s for rs1800795), 72 °C for 20 s, and a final extension at 72 °C for 5 min.

Statistical analysis

The means and SDs were calculated for normally distributed continuous variables, which were analyzed using Student's *t* test. And percentages were calculated for categorical variables, which were analyzed using χ^2 test. Hardy–Weinberg equilibrium (HWE) was performed using SNPStats (available online at http://bioinfo.iconcologia.net/SNPstats). Logistic regression was performed to investigate the association between six SNPs within *SELP* and *IL-6* genes and CVD using gender, age, smoking and alcohol status, FPG, TC, TG, and HDL as covariates in the model. Generalized multifactor dimensionality reduction (GMDR) was used for gene–gene interaction, some parameters including cross-validation consistency, the testing-balanced accuracy, and the sign test, to assess each selected interaction were calculated. All reported *p* values were two-tailed, and to correct for multiple testing

Table 1 Probe and primer sequences for six SNPs used for genotyping

ID	SNP	Chromosome	Functional consequence	Nucleotide substitution	Probe/primer sequence
SELP gene					
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′
IL-6 gene					
rs1800795	−174G/C	7:22727026	Intron variant, upstream variant 2 KB	G > C	F: 5′-tgacttcagctttactctttgt-3′ R: 5′-ctgattggaaaccttattaag-3′
rs1800796	−572G/C	7:22726627	Intron variant, nc transcript variant, upstream variant 2 KB	G > C	F: 5′-gagacgccttgaagtaactg-3′ R: 5′-aaccaaagatgttctgaactga-3′
rs1800797	−597G/A	7:22726602	Intron variant, nc transcript variant, upstream variant 2 KB	G > A	F: 5′-ctcctctaagtgggctgaag-3′ R: 5′-caagcctgggattatgaaga-3′

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

Variables	Case 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

Means ± SD for age, WC, BMI, FPG, TC, TG, and HDL-C

TC total cholesterol, *HDL* high-density lipoprotein, *FPG* fast plasma glucose, *TG* triglyceride

we defined a Bonferroni-corrected threshold in different tables.

Results

A total of 1082 subjects (519 males, 563 females), with a mean age of 53.9 ± 13.1 years, 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 controls, and smoking rate was higher in cases than in controls. The mean values of WC, BMI, FPG, TG, and TC were also significantly higher in CVD cases than in controls. The concentration of HDL was lower in cases than in controls.

All genotypes were distributed according to HWE in controls (all p values were more than 0.05). The frequencies of rs1800805-A allele and AC genotype of rs6136 within *SELP* gene were significantly higher in CVD cases than in controls (29.6 vs. 22.1%; 40.2 vs. 31.2%), and rs1800796-G allele within *IL-6* gene was also significantly higher in CVD cases than in controls. Logistic regression analysis showed that CVD risk was significantly higher in carriers with rs1800805-A allele than those with GG genotype (GA + AA vs. GG), adjusted OR (95% CI) = 1.69 (1.31–2.16), and CVD risk was also higher in carriers with AC or CC genotype of the rs6136 polymorphism than those with AA genotype (AC + CC vs. AA), adjusted OR (95% CI) = 1.78 (1.28–2.26), and higher in carriers with GC or CC genotype of the rs1800796 polymorphism than those with GG genotype (CC + GC vs. GG), adjusted OR (95% CI) = 1.67 (1.25–2.14). (Table 3).

GMDR analysis was used to find the best gene–gene interaction combination among six SNPs within *SELP* and *IL-6* genes in this study. It can be suggested from Table 4 a significant two-locus model ($p=0.0010$) involving rs1800805 and rs1800796, indicating a potential gene–gene interaction between rs1800805 and rs1800796. Overall, the cross-validation consistency of this model was 10/10, the testing

Table 3 Logistic regression analysis of the association between 6 SNPs and CVD risk

SNPs	Genotypes and alleles	Frequencies *N* (%)		OR (95% CI)*	*p* values	*p* values for HWE test for controls
		Control group ($n=542$)	Case group ($n=540$)			
SELP gene						
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)	<0.001	
	AA	31 (5.7)	54 (10.0)	1.88 (1.34–2.31)	<0.001	
	GA + AA	209 (38.6)	266 (49.3)	1.69 (1.31–2.16)	<0.001	
	Allele, 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)	0.441	
	CC	35 (6.5)	45 (8.3)	1.38 (0.84–2.05)	0.642	
	CC + TC	222 (41.0)	250 (46.3)	1.29 (0.93–1.86)	0.562	
	Allele, 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)	<0.001	
	CC	31 (5.7)	47 (8.7)	1.18 (0.91–1.66)	0.423	
	CC + AC	200 (36.9)	264 (48.9)	1.78 (1.28–2.26)	<0.001	
	Allele, C (%)	231 (21.3)	311 (28.8)			
IL-6 gene						
rs1800795	GG	311 (57.4)	277 (51.3)	1.00 (ref)		0.217
	GC	192 (35.4)	209 (38.7)	1.20 (0.78–1.76)	0.528	
	CC	39 (7.2)	54 (10.0)	1.43 (0.74–2.20)	0.619	
	GC + CC	231 (42.6)	263 (48.7)	1.27 (0.80–1.91)	0.507	
	Allele, C (%)	270 (24.9)	317 (29.4)			
rs1800796	GG	355 (65.5)	273 (50.6)	1.00 (ref)		0.465
	GC	164 (30.3)	216 (40.0)	1.51 (1.27–1.89)	<0.001	
	CC	23 (4.2)	51 (9.4)	2.12 (1.43–2.88)	<0.001	
	GC + CC	187 (34.5)	267 (49.4)	1.67 (1.25–2.14)	<0.001	
	Allele, C (%)	210 (19.4)	318 (29.4)			
rs1800797	GG	345 (63.6)	303 (56.1)	1.00 (ref)		0.225
	GA	169 (31.2)	189 (35.0)	1.33 (0.91–1.83)	0.609	
	AA	28 (5.2)	48 (8.9)	1.50 (0.81–2.32)	0.804	
	GA + AA	197 (36.3)	237 (43.9)	1.36 (0.89–1.85)	0.725	
	Allele, A (%)	225 (20.8)	285 (26.4)			

*Adjusted for gender, age, smoking and alcohol status, FPG, TC, TG, and HDL. Bonferroni-corrected threshold: $p<0.00417$

Table 4 Best gene–gene interaction models, as identified by GMDR

Locus No.	Best combination	Cross-validation consistency	Testing accuracy	*p* values*
2	rs1800805 rs1800796	10/10	0.6217	0.0010
3	rs1800805 rs1800796 rs6136	8/10	0.5399	0.0547
4	rs1800805 rs1800796 rs6136 rs1800795	7/10	0.4958	0.1719
5	rs1800805 rs1800796 rs6136 rs1800795 rs1800797	5/10	0.4958	0.3770
6	rs1800805 rs1800796 rs6136 rs1800795 rs1800797 rs1800808	6/10	0.5399	0.4258

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

accuracy was 62.17%, and participants with rs1800805-GA or AA genotype and rs1800796-GC or CC have the highest CVD risk, compared to participants with rs1800805-GG and rs1800796-GG genotypes, and OR (95% CI) was 2.52 (1.81–2.66), after adjustment for gender, age, smoking and alcohol status, FPG, TC, TG, and HDL (Table 5).

Discussion

In the present study, we found that the CVD risks were higher in the rs1800805-A allele, C allele of rs6136 within *SELP*, and rs1800796-G allele within *IL-6* carriers, suggesting that variants in three SNPs were associated with increased CVD risk. The human *SELP* gene maps on chromosome 1q22eq25 and is organized in 17 exons that span about 40 kb (Johnston et al. 1990), and many SNPs distributed in the promoter and coding sequences have been reported previously (Ay et al. 2007; Herrmann et al. 1998) with some other diseases, such as MI and IS (Tregouet et al. 2002; Nadar et al. 2004); however, the association of SNPs within *SELP* gene and susceptibility to CVD still remains controversial. A study (Barbaux et al. 2001) suggested a significant association between *SELP* gene polymorphisms and serum P-selectin levels, which was associated with coronary artery disease (CAD) risk as reported previously (Bielinski et al. 2015). Ghazouani et al. (2009) suggested that −2123C/G in *SELP* gene was associated with increased CHD risk in Tunisians. However, the inconsistent results were also obtained in some other studies. Volcik et al. (2006) indicated that *Thr715Pro* polymorphism is not associated with incident CHD or ischemic stroke (IS) in either whites or African-Americans, although genotypes carrying the P-selectin Pro715 variant allele are associated with decreased P-selectin levels compared to the homozygous wild-type genotype in whites. Zhou et al. (2014) also suggested no significant associations between *SELP* genetic polymorphisms and the risk of CHD and MI among Africans.

Several similar studies were also performed on the relationship between *IL-6* SNP and CHD- or CVD-related diseases risk; however, these studies could not conclude consolidated results. Gigante et al. (2015) indicate no significant association of *IL6R* haplotypes with the risk of CHD in European populations. A meta-analysis (Song et al. 2015) suggested that the *IL-6*-572G > C polymorphism may play a protective role on the risk of CHD. Another Chinese study in Han Chinese population (Jia et al. 2010) indicated a significant association between the −572G/C polymorphism within *IL-6* gene and pathogenesis of CHD. Tong et al. (2013) suggested that *IL-6* SNPs were associated with increased CAD risk in the Chinese population and may be useful predictive markers for CAD susceptibility. Another Chinese case–control study (Fan et al. 2011) also suggested that *IL-6* 572C/G polymorphism was associated with susceptibility to CHD after adjustment for several other risk factors, and they concluded that *IL-6*-572C/G polymorphism might be a potential risk factor for CHD in Chinese population. A meta-analysis (Yin et al. 2012) also suggested a positive association between *L-6* gene polymorphism and increased CHD risk among Asians.

The pathogenesis of CVD is diverse, including too many genetic factors, gene–gene and gene–environment interactions. However, till now, no studies focused on the impact of gene–gene interactions between *SELP* gene and *IL-6* gene on CVD risk. In this study, GMDR analysis was used to investigate gene–gene interaction among these six SNPs in this study; we found a significant gene–gene interaction between rs1800805 and rs1800796, and participants with rs1800805-GA or AA genotype and rs1800796-GC or CC have the highest CVD risk, compared to participants with rs1800805-GG and rs1800796-GG genotype. To our knowledge, this is the first study focused on the impact of gene–gene interaction between *SELP* gene and *IL-6* gene on CVD risk. The underlying mechanism of this interaction was not well known. The influence of this interaction on sP-selectin levels may be the possible explanation for this interaction on CVD risk.

Several limitations of this study should be considered. Firstly, more SNPs within *SELP* or *IL-6* gene should be included in the gene–gene interaction analysis. Secondly, the sample size was relatively small, and the results obtained from this study should be checked in the future studies with a larger sample size.

In conclusion, we found an important association of rs1800805, rs6136 minor allele of *SELP* gene, rs1800796 within *IL-6* gene, and additional interaction between rs1800805 and rs1800796 with increased risk of CVD.

Table 5 Stratified analysis of interaction between rs1800805 and rs1800796 using logistic regression

rs1800805	rs1800796	OR (95% CI)*	*p* values
GG	GG	1.00	–
GA or AA	GG	1.49 (1.08–1.92)	0.020
GG	GC or CC	1.35 (1.05–1.78)	0.038
GA or AA	GC or CC	2.52 (1.81–2.66)	<0.001

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

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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