P-Selectin 1087G/A Polymorphism Is Associated With Neuropsychological Test Performance in Older Adults With Cardiovascular Disease

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Background and Purpose—There is growing evidence that the cell adhesion molecule P-selectin (SELP) contributes to the adverse vascular processes that promote cognitive impairment in individuals with cardiovascular disease. Previous research has shown that SELP genotypes moderate circulating levels of P-selectin and that patients undergoing coronary artery bypass graft with the SELP 1087A allele were less likely to show postoperative cognitive decline and more likely to exhibit lower levels of C-reactive protein than noncarriers. Thus, we expected that carriers of the 1087A allele (n = 43) would exhibit better cognitive functioning than persons with 2 1087G alleles (n = 77) and that C-reactive protein levels would be important for this relationship.

Methods—One hundred twenty older adults with diagnosed cardiovascular disease were recruited from outpatient cardiology clinics. Each participant underwent a comprehensive neuropsychological test battery and a blood draw.

Results—Participants with the SELP 1087A allele performed more poorly on tests of attention (Trail Making Test A: t[116] = 3.20, P = 0.002), executive function (Trail Making Test B: t[116] = 2.89, P = 0.005), psychomotor speed (Digit–Symbol Coding: t[117] = 2.54, P = 0.012), and memory (California Verbal Learning Test Discrimination: t[116] = 2.05, P = 0.04). There were no significant differences between the SELP genotype groups on demographic/medical variables or C-reactive protein levels.

Conclusions—Contrary to expectations, the present analyses showed that older patients with cardiovascular disease with the SELP 1087A allele performed more poorly on neuropsychological testing. Findings from the present study were counter to previous research with coronary artery bypass graft candidates. Further work using neuroimaging and alternative measures of cardiovascular function is needed to clarify the mechanisms of this association.

Key Words: cognitive function | heart disease | P-selectin

Cardiovascular disease (CVD) is a known risk factor for impairments in attention, executive function, memory, and other cognitive abilities.1–3 Numerous physiological consequences associated with CVD are known contributors to these cognitive deficits, including structural damage to the brain, systemic hypoperfusion, and inflammatory processes.4–7 Recent work suggests that changes in vascular structure and function are an important aspect of cognitive impairment associated with CVD. For example, recent work shows that indices of endothelial function, vascular smooth muscle function, and arterial stiffness are associated with cognitive function.8–11 Although the exact mechanism has yet to be determined, vascular markers of endothelial function are linked to the development and progression of white matter disease.12,13,14 There is growing evidence that the cell adhesion molecule P-selectin is an important contributor to the adverse vascular processes that promote cognitive impairment. P-selectin initiates cell activation and adhesion to platelets and endothelial cells, helps to mediate platelet–leukocyte interaction, and is expressed after exposure to inflammatory cytokines.15,16 Through leukocyte rolling and procoagulation, higher levels of P-selectin promote the development of atherosclerosis and are associated with CVD events17 and poor neurological outcomes, including greater white matter lesions and ischemic stroke.18,19

In turn, circulating levels of P-selectin (SELP) are moderated by SELP genotypes20,21 implicating SELP genotypes in the cognitive function of patients with CVD. Consistent with this notion, a recent study directly examined the association between
SELP 1087A allele and cognitive function in patients who underwent coronary bypass. More specifically, persons with the 1087A minor allele were less likely to show postoperative cognitive decline. Persons with the 1087A allele also exhibited lower levels of C-reactive protein (CRP); the authors raise the possibility that inflammatory processes may be an important contributor to the observed cognitive function.

Given the high prevalence of premorbid cognitive dysfunction in candidates for coronary artery bypass graft procedures, it appears likely that patients with CVD who carry the SELP 1087A allele would also have better cognitive function. We examined this possibility in a sample of older adults with CVD who completed a comprehensive neuropsychological test battery and blood draw to determine CRP levels. Based on this finding, we expected carriers of the 1087A allele would show better cognitive function than carriers of the 1087G allele alone and that CRP levels would be important for this relationship.

**Materials and Methods**

**Participants**
Participants were 120 older adults enrolled in a longitudinal examination of the neurocognitive consequences of CVD. Participants for the parent study were recruited from outpatient cardiology clinics and eligible if they had one or more of the following: myocardial infarction, cardiac surgery, heart failure, coronary artery disease, or hypertension. Individuals were excluded from enrolling in the parent study if they had a history of a major neurological disorder (eg, Alzheimer disease, stroke) or major psychiatric disorder (eg, schizophrenia, bipolar illness, substance abuse) and thus none were specifically excluded for the current set of analyses. All participants with genotype and CRP data in the parent study were included in these analyses; no differences emerged between persons who did and did not have these biomarkers in the parent study in key demographic characteristics (eg, age; \( P > 0.93 \)), medical conditions (eg, myocardial infarction; \( P > 0.35 \)), or cognitive function (Mini-Mental State Examination; \( P > 0.31 \)). Carriers of the 1087A allele were categorized into one group (n=43) and those with 2 copies of 1087G (n=77) were categorized into a second group. Demographic and medical characteristics of SELP groups are presented in Table 1.

**Measures**

**Neuropsychological Tests**
Neuropsychological tests were grouped into one of 5 neuropsychological domains to facilitate interpretation. Raw scores for each test were used in primary analyses. See Table 2 for neuropsychological test performance. Tests were administered in the following neuropsychological domains:

1. Global Functioning: Dementia Rating Scale;
2. Attention/Executive Function/Psychomotor Speed: Trail Making Tests A and B, Digit Symbol Coding, Controlled Oral Word Association Test;
3. Memory: California Verbal Learning Test learning, short free recall, long free recall, and discrimination;
4. Language: Boston Naming Test, Animal Naming;
5. Visual–Spatial: Block Design, Hooper Visual Organization Test; and

**Procedure**
Methods were approved by the local Institutional Review Board and all participants gave written informed consent. Participants provided medical history information through self-report, which was corroborated by medical records wherever possible. Participants then underwent blood draw and completed neuropsychological testing as administered by a trained researcher using standardized instructions. Blood samples were collected in tubes and refrigerated within 10 minutes of collection. Plasma was separated within 4 hours and samples were stored at −70°C until genetic analyses were performed.

All single nucleotide polymorphism determinations were performed using the fluorogenic 5′nuclease (TaqMan; Applied Biosystems, Foster City, Calif) method using reagents (VIC and FAM labeled probes and TaqMan Universal PCR Master Mix without AMPerase UNG) obtained from Applied Biosystems. Reactions were performed in an Applied Biosystems Prism 7300 Sequence Detection System using both absolute quantification and allelic discrimination modes as described in the instrument documentation. For rs6134, the TaqMan Genotyping assay C-11975296-10 was used. CRP was determined on a Beckman CX4 autoanalyzer using reagents obtained from Pointe Scientific, Inc (Lincoln Park, Mich). The assay range is 0.5 to 1.0 mg/dL and the interassay coefficient of variation is 2.0%. Laboratory values for the sample appear in Table 1.

**Statistical Analysis**
The association between SELP genotype and cognitive function was analyzed in several steps. First, the distributions of the primary variables were examined for violations of normality. All distributions were consistent with theoretical models and no variables required transformation. Detailed examination of cognitive tests identified several cases in which performance was \( > \pm 3 \) SD from the sample mean. However, Mahalanobis distance analyses indicated no outlier cases and thus no cases were excluded from analyses. Then, \( t \) tests and \( \chi^2 \) analyses were conducted to identify differences in demographic or medical characteristics between the genotype groups for use as covariates in primary analyses. No differences emerged and thus no demographic (eg, age, gender) or medical covariates (eg, cardiac surgery, hypertension) were used (Table 1). Of note, SELP groups did not differ in CRP levels. Finally, \( t \) tests were conducted to determine differences in neuropsychological test performance across groups.

**Results**
SELP genotype groups differed on several neuropsychological tests with medium effect sizes emerging for multiple tests in the attention/executive function/psychomotor speed domain, specifically Trail Making Test A (\( t (116) = 3.20, \)
Global function

- Dementia Rating Scale

<table>
<thead>
<tr>
<th></th>
<th>1087G/G (n=77)</th>
<th>1087G/A or 1087A/A (n=43)</th>
<th>t Statistic</th>
<th>P Value</th>
<th>Cohen’s d</th>
<th>Effect Size</th>
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<tr>
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<tr>
<td>Trail Making Test A</td>
<td>36.35±10.42</td>
<td>43.86±15.33</td>
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<td>92.64±40.07</td>
<td>119.93±62.59</td>
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<td>Controlled Oral Word Association Test</td>
<td>40.84±10.91</td>
<td>36.55±13.60</td>
<td>1.88</td>
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<td>Digit–Symbol Coding</td>
<td>57.61±14.20</td>
<td>50.81±13.60</td>
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<td>Digit Span</td>
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<td>California Verbal Learning Test: Learning</td>
<td>46.08±12.36</td>
<td>45.30±11.86</td>
<td>0.33</td>
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<td>California Verbal Learning Test: short free recall</td>
<td>9.04±3.70</td>
<td>8.40±2.83</td>
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<td>California Verbal Learning Test: long free recall</td>
<td>9.20±3.84</td>
<td>8.95±3.14</td>
<td>0.36</td>
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<td>California Verbal Learning Test: discrimination language</td>
<td>92.19±6.94</td>
<td>89.37±7.57</td>
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<td>Boston Naming Test</td>
<td>55.15±4.59</td>
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<td>1.91</td>
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<td>Animal Naming</td>
<td>19.47±5.52</td>
<td>19.40±5.37</td>
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<td>0.95</td>
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<td>Block Design</td>
<td>32.77±11.14</td>
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<td>Hooper Visual Organization Test</td>
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<td>22.93±3.87</td>
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<td>Grooved Pegboard–Dominant</td>
<td>92.47±20.99</td>
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</table>

P=0.002), Trail Making Test B (t[116]=2.89, P=0.005), and Digit Symbol Coding (t[117]=2.54, P=0.012). Medium effect sized differences also emerged on a memory index, specifically California Verbal Learning Test Discrimination (t[116]=2.05, P=0.04; Table 2). Contrary to expectations, persons with the 1087A allele had poorer neuropsychological test performance for each test.

Discussion

Contrary to expectations and previous work,22 the present analyses showed that older patients with CVD with the SELP 1087A allele performed more poorly on several neuropsychological tests assessing attention/executive function/psychomotor speed and a memory index. These medium effect size differences emerged despite SELP genotype groups being similar in demographic and medical conditions. Notably, SELP groups did not differ in CRP levels. Several aspects of these findings warrant brief discussion.

Levels of soluble P-selectin have been associated with increased periventricular white matter lesions.18 As such, it is possible that genetic predispositions to adhesion molecule levels (eg, P-selectin) and the causative effect of vascular changes on brain lesions may account for the pathophysiology of cognitive difficulties observed in patients with CVD. However, the current literature is still in the early stages of identifying which specific polymorphisms predict phenotypes associated with CVD. A comprehensive investigation of genetic correlates of P-selectin in a large community-based study identified specific SELP genotypes that increase or decrease soluble P-selectin, thereby promoting or preventing CVD, respectively.33 Thus, although contrary to findings from previous studies, the current results may illustrate the possible synergistic effects of SELP alleles; the presence of other SELP genotypes may moderate the influence of the SELP 1087A allele or may interact with the presence of other CVD risk factors such as hypertension. Further work is needed to clarify this possibility.

An important limitation of the present study is the sole use of the SELP 1087G/A genotype. As noted, it is not yet entirely clear which genetic polymorphisms predict phenotypes associated with CVD and use of other SELP single nucleotide polymorphisms in isolation or in combination with other genetic factors with known cognitive effects (eg, apolipoprotein E) may produce different results. Similarly, soluble levels of P-selectin were not available as part of this cohort and would help to clarify the unexpected findings. Another potential limitation involves the use of cross-sectional methodology, which does not permit examination of the relationship between SELP and cognitive function over time. Given the progressive nature of cognitive decline associated with CVD,34 longitudinal study will be important to investigation of the relationship between SELP genotypes and cognitive function in participants who develop cognitive decline in the future versus those who remain cognitively stable or intact. Furthermore, in light of the known relationship between P-selectin and white matter lesions and ischemic stroke,18,19 future studies should also include neuroimaging of cerebrovascular functioning to help clarify possible mechanisms for the relationship between SELP and neuropsychological function. Finally, because the SELP genotype
groups did not differ on demographic or medical variables, statistical analyses were not adjusted. However, larger studies are needed to determine whether possible combinations of these variables interact with the SELP genotype to influence cognitive test performance.

Summary
Findings from the present study indicate that the SELP 1087G/A single nucleotide polymorphism is associated with cognitive function in older adults with CVD. Findings were counter to those from candidates for coronary artery bypass graft procedures and further work is needed to clarify the mechanisms for this association, particularly prospective studies that include neuroimaging and alternate measures of cerebrovascular function.

Disclosures
None.

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