Polymorphism of the Lipoprotein Lipase Gene and Risk of Atherothrombotic Cerebral Infarction in the Japanese

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Background and Purpose—Lipid and lipoprotein abnormalities have been implicated in the pathogenesis of ischemic cerebrovascular disease and atherosclerosis. Lipoprotein lipase (LPL) plays an important role in plasma lipoprotein metabolism. Several studies have recently reported the presence of a relationship between Ser447Stop mutation of LPL and coronary artery disease. Other polymorphisms (HindIII and PvuII) of the LPL gene have already been shown to correlate significantly with dyslipidemia. We investigated whether these polymorphisms are associated with increased risk of ischemic cerebrovascular disease (CVD).

Methods—We recruited 177 CVD patients (atherothrombotic infarction, n=71; cardioembolic infarction, n=30; lacunar infarction, n=76) and 177 healthy control subjects. Subjects were genotyped for the Ser447Stop mutation and for HindIII/PvuII restriction fragment length polymorphisms of the LPL gene, and the findings were investigated for associations with the clinical subtypes of CVD and with lipid levels.

Results—The Ser447Stop mutation correlated significantly with CVD (0.107 versus 0.158; P=0.035). For the CG+GG versus CC genotype, the odds ratio between control subjects and CVD patients with atherothrombotic infarction was 0.42 (95% CI, 0.18 to 0.99) (P=0.046). Serum HDL cholesterol and triglyceride levels did not correlate significantly with the Ser447Stop genotype. HindIII polymorphism correlated significantly with CVD (0.234 versus 0.169; P=0.031), but the frequency of PvuII polymorphism was not significantly different between groups.

Conclusions—Our results suggest that the Ser447Stop mutation of the LPL gene is a novel genetic marker for low risk of atherothrombotic cerebral infarction. (Stroke. 2001;32:1481-1486.)

Key Words: atherosclerosis ■ cerebral infarction ■ lipids ■ polymorphism ■ risk factors

The etiology of ischemic cerebrovascular disease (CVD) is heterogeneous, but the contribution of genetic as well as environment factors has been proposed. Age, smoking, hypertension, and diabetes have been established as independent risk factors for ischemic CVD.1-4 Although no gene has been convincingly shown to be of importance for ischemic CVD, obvious candidate genes are those with an established or potential role in atherosclerosis. The relationship between hyperlipidemia and CVD is controversial.5,6 Disorders of lipid metabolism associated with high levels of LDL cholesterol or low levels of HDL cholesterol have been recently recognized as risk factors for atherosclerotic vascular disease. Lipoprotein lipase (LPL) plays a key role in lipoprotein metabolism as an enzyme that hydrolyzes triglycerides from VLDL and chylomicrons, as well as in the removal of lipoproteins from the circulation.7-9 LPL influences the interaction of atherogenic lipoproteins with the cell surface and with receptors on the vascular wall.10-12

The human LPL gene is localized to chromosome 8p22, spanning approximately 30 kb and containing 10 exons.13 Several DNA variants of the LPL gene have been found and reported to underlie changes in plasma lipoprotein levels and to be important cardiovascular risk factors. For example, HindIII polymorphism of intron 8 of this gene is associated with elevated triglyceride levels,14,15 low HDL cholesterol levels,16,17 and premature coronary artery disease (CAD).15,18 PvuII polymorphism of intron 6 is also associated with elevated triglyceride levels14 and severity of CAD and with type II diabetes in CAD patients.19 The Ser447Stop mutation has been identified just 635 bp downstream from the HindIII polymorphism. This mutation is a consequence of a C to G transversion at nucleotide 1595 in exon 9, which converts the serine 447 codon (TCA) to a premature termination codon (TGA).20,21 Recent studies have suggested that risk of CAD is decreased by Ser447Stop polymorphism, which underlies increased HDL cholesterol levels and decreased triglyceride levels.
levels, suggesting that it is a beneficial genetic variant with respect to lipoprotein metabolism. Thus, Ser447Stop polymorphism should have a protective effect against the development of atherosclerosis and subsequent CAD.

To our knowledge, no studies have previously examined the clinical significance of these polymorphisms in patients with ischemic CVD. In the present study we used restriction fragment length polymorphism (RFLP) analysis to investigate the importance of polymorphisms of the LPL gene as risk factors for ischemic CVD. We also examined the relationship between these polymorphisms and the clinical subtype of ischemic CVD and serum lipid levels.

Subjects and Methods

Subjects

The study population consisted of 177 patients with ischemic CVD who had been admitted to Juntendo University Hospital or Ebara Metropolitan Hospital and 177 control subjects. All subjects enrolled in the study were Japanese. Brain CT and/or brain MRI, B-mode carotid ultrasonography, and electrocardiography were performed in all patients. On the basis of the Classification of Cerebrovascular Disease III by the committee of the National Institute of Neurological Disorders and Stroke, 24 ischemic CVD patients were divided into 3 clinical subtypes: (1) cardioembolic infarction caused by nonvalvular atrial fibrillation, (2) atherothrombotic infarction, and (3) lacunar infarction. CVD patients with transient ischemic attack and cerebral hemorrhage were not included in this study. Patients with significant internal carotid artery stenosis (>70%) on B-mode carotid ultrasonography were included in the category of atherothrombotic infarction (n = 30). All patients were investigated at least 2 months after the occurrence of stroke. Blood samples for genotyping were taken after determination of the clinical subtype of CVD, and the mean interval between the onset of CVD and genotyping was 1.6 ± 0.8 months. The examiner who performed the genotyping was blinded to the clinical subtype of ischemic CVD. The control group was randomly selected from the inpatients of the hospitals and matched with CVD patients for age and sex. Control subjects had no symptoms or history of ischemic stroke, CAD, or peripheral atherosclerotic disease. Brain CT and/or MRI and B-mode carotid ultrasonography were not performed in all control subjects. Informed consent was obtained from all subjects after they received a full explanation of the study. The Ethics Committee of Juntendo University approved this study.

Hypertension was defined as systolic arterial blood pressure >140 mm Hg and/or diastolic pressure >90 mm Hg or as current treatment with antihypertensive drugs. Diabetes was defined by the diagnostic criteria of the World Health Organization or as current treatment for diabetes.

Determination of LPL Ser447Stop Polymorphism by RFLP

Oligonucleotides

Polymerase chain reaction (PCR)–RFLP was used to detect Ser447Stop polymorphism in exon 9 of the LPL gene, with the use of the primers described previously. Two polymorphisms, identified by restriction enzyme cleavage with HindIII (intron 8) and PvuII (intron 6) of a PCR-amplified segment of the LPL gene, were studied according to the previously reported protocol. Primer sets were as follows: Ser447Stop mutation: forward primer, 5'-CATCCATTTTTTCACCAGGG-3'; reverse primer, 5'-AGTCTGGTGAGCATTCTGGGCTA-3'; HindIII RFLP: forward primer, 5' -GATGCTACCTGGATAATCATCAAAG-3'; reverse primer, 5'-CTGCAAGGTAGCTGTGCTACTG-3'; PvuII RFLP: forward primer, 5'-ATGACAGCAGATCTCTTAGAC-3'; reverse primer, 5'-GAGACACAGATCTCTTAGAC-3'.

Amplification of Genomic DNA

Each amplification reaction was performed with 250 ng of genomic DNA; 10 pmol of each primer; 2 μL of 10× buffer solution; 200 μmol/L each of dATP, dCTP, dGTP, and dTTP; and 1 U of Taq polymerase in a total volume of 20 μL. Amplification was performed in a GeneAmp PCR system 9700 (Perkin Elmer–Cetus). In the case of amplification of exon 9, initial denaturation at 94°C for 5 minutes was followed by 30 cycles of denaturation at 94°C for 1 minute, annealing at 57°C for 1 minute, and extension at 72°C for 1 minute, with final extension at 72°C for 10 minutes. For amplification of intron 8, initial denaturation at 94°C for 5 minutes was followed by 30 cycles of denaturation at 94°C for 1 minute, annealing at 57°C for 1 minute, and extension at 72°C for 1 minute, with final extension at 72°C for 10 minutes. For intron 6, initial denaturation at 94°C for 5 minutes was followed by 30 cycles of denaturation at 94°C for 1 minute, annealing at 57°C for 1 minute, and extension at 72°C for 1 minute, with final extension at 72°C for 10 minutes.

Digestion and Electrophoresis

The C-G mutation at the LPL Ser447stop polymorphism site creates a MnlI recognition site (New England Biolabs). The PCR product of 488 bp contains 2 MnlI restriction sites, of which 1 is polymorphic and reveals the Ser447Stop mutation. Digestion of the PCR product results in 3 fragments of 285, 246, and 203 bp, which were confirmed on 3% agarose gel. The products obtained by digestion with HindIII and PvuII were electrophoresed on 2% agarose gel. After HindIII digestion, the presence of the restriction site (HindIII+) resulted in fragments of 140 and 210 bp, while the presence of the PvuII site (PvuII+) yielded fragments of 222 and 209 bp.

Serum Lipid Measurements

Blood samples for the evaluation of lipid levels were obtained from subjects between 8 and 11 AM, after at least 12 hours of fasting, from a forearm vein after venous occlusion for few seconds in a sitting position. Serum levels of total cholesterol (TC), HDL cholesterol, and triglycerides were measured by standard enzymatic methods. LDL cholesterol levels were calculated with the Friedewald formula.

Statistical Analysis

Serum triglyceride values were log transformed to remove positive skewness before analysis. The Hardy-Weinberg equilibrium for the LPL genotype distribution was assessed by χ² analysis. Data on age and lipid levels were presented as mean ± SEM, and differences between groups were analyzed by the unpaired Student’s t test. The frequencies of the alleles and the relations of genotype between the study groups were analyzed by constructing 2×2 and 2×3 contingency tables followed by χ² analysis. Odds ratios and 95% CIs for relative risk of CVD associated with LPL Ser447Stop GG+CG genotypes were determined by Pearson’s χ² test and multiple logistic regression analysis after adjustment for age, sex, hypertension, and diabetes. A P value <0.05 was considered significant. Statistical analysis was performed with StatView version 5.0 for the Macintosh computer (SAS Institute).

Results

The characteristics of the subjects are summarized in Table 1. There were no significant differences in age and sex between CVD patients and controls. The risk factors examined (ie, hypertension and diabetes) were significantly more commonly seen in CVD patients than in controls. Serum cholesterol and triglyceride levels tended to be higher in patients than in controls. Of 57 of 177 patients (32.2%) had hyperlipidemia, and 31 (54.4%) of these patients had already been treated with hypolipidemic agents. However, only 11 (35.5%) of these 31 treated patients showed improvement of lipid levels at that time.
The genotype distribution and the allele frequency for LPL gene polymorphism are summarized in Table 2. The observed frequencies of the 3 genotypes did not differ from the expected frequencies according to the Hardy-Weinberg equilibrium for both the control group (χ² = 1.03, df = 2, P = 0.60) and CVD patients (χ² = 3.33, df = 2, P = 0.19). The G allele frequencies of the Ser447Stop polymorphism in CVD patients and control subjects were 0.107 and 0.158, respectively. The prevalence of Ser447Stop showed a significant difference between CVD patients and control subjects. The genotype distribution and the allele frequency for LPL Ser447Stop polymorphism and HindIII/PvuII polymorphism in CVD patients and control subjects are shown in Table 3. There were no significant differences in the serum levels of TC, triglycerides, HDL cholesterol, and LDL cholesterol between CC and CG+GG genotypes. HindIII and PvuII alleles did not correlate significantly with plasma levels of TC, triglycerides, HDL cholesterol, or LDL cholesterol (data not shown).

The odds ratios of the CG+GG genotype for atherothrombotic infarction between atherothrombotic infarction patients and control subjects were 0.45 (95% CI, 0.22 to 0.93; P = 0.031) and, after adjustment for conventional risk factors, 0.42 (95% CI, 0.18 to 0.99; P = 0.046). Linkage disequilibriums between the 3 polymorphisms of LPL were determined in normal subjects. HindIII and PvuII alleles were in strong linkage disequilibrium (D = 0.157, Dmax = 94%; P < 0.001). A signific-

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**Table 1. Characteristics of Case Patients and Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patients</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>177</td>
<td>177</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.22±9.10</td>
<td>62.23±10.79</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex, % (M:F)</td>
<td>64.4 (114:63)</td>
<td>70.1 (124:53)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>8.05</td>
<td>65.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>13.56</td>
<td>27.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.88±0.17</td>
<td>5.18±0.08</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.38±0.06</td>
<td>1.38±0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.37±0.12</td>
<td>1.53±0.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. *Student’s t test and χ² test were used to compare the values of patients and control subjects.

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**Table 2. Allele and Genotype Frequencies of LPL Ser447Stop Polymorphism and HindIII/PvuII Polymorphism in CVD Patients and Control Subjects**

<table>
<thead>
<tr>
<th>LPL Ser447Stop</th>
<th>Genotype, n (%)</th>
<th>Allele Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=177)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>126 (71.2%)</td>
<td>0.158</td>
</tr>
<tr>
<td>G</td>
<td>140 (79.1%)</td>
<td>0.107</td>
</tr>
<tr>
<td>CG + GG</td>
<td>37 (20.9%)</td>
<td>0.029</td>
</tr>
<tr>
<td>HindIII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H−/−</td>
<td>13 (7.3%)</td>
<td>0.234</td>
</tr>
<tr>
<td>H−/+</td>
<td>57 (32.2%)</td>
<td>0.169</td>
</tr>
<tr>
<td>H+/+</td>
<td>107 (60.5%)</td>
<td>0.031</td>
</tr>
<tr>
<td>PvuII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P−/−</td>
<td>18 (10.2%)</td>
<td>0.285</td>
</tr>
<tr>
<td>P−/+</td>
<td>65 (36.7%)</td>
<td>0.237</td>
</tr>
<tr>
<td>P+/+</td>
<td>94 (53.1%)</td>
<td>0.146</td>
</tr>
</tbody>
</table>

H indicates lacunar infarction; ATI, atherothrombotic infarction; and CI, cardioembolic infarction.

*χ² tests were used to compare allele frequencies between control and CVD patients or between control and each group of CVD patients.
TABLE 3. Serum Concentrations of TC, HDL Cholesterol, Triglycerides, and LDL Cholesterol in Various Genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>TC, mmol/L</th>
<th>HDL cholesterol, mmol/L</th>
<th>Triglycerides, mmol/L</th>
<th>LDL cholesterol, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser447Stop</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>5.04±0.16</td>
<td>1.41±0.05</td>
<td>1.35±0.11</td>
<td>3.36±0.15</td>
</tr>
<tr>
<td>Absent</td>
<td>5.14±0.08</td>
<td>1.37±0.03</td>
<td>1.50±0.06</td>
<td>3.47±0.08</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. Triglyceride values were log transformed before analysis, but untransformed values are presented.

Discussion

In this study the frequency of the G allele was significantly higher in control subjects than in patients with atherothrombotic infarction. With the use of meta-analyses, previous studies showed that the odds ratio for ischemic heart disease was 0.8 (95% CI, 0.7 to 1.0), indicating a cardioprotective effect of this LPL gene variant. As was previously reported for patients with myocardial infarction, mutation of the Ser447Stop seems to be associated with a reduced risk of atherothrombotic cerebral infarction. The present study also demonstrated that patients with carotid stenosis had a lower G allele frequency. Therefore, the Ser447Stop allele was associated with a decreased risk of atherosclerotic disease of the internal carotid artery. However, Sass et al reported no difference in the carotid wall intima-media thickness between carriers and noncarriers of the Ser447Stop mutation among normal middle-aged individuals. The observed discrepancies between studies could be explained by differences in the age and background of examined subjects. Sass et al recruited individuals aged 33 to 50 years who had no history of cardiovascular disease and were not on any antihypertensive or hypolipidemic agents, whereas our subjects were selected from CVD patients. It is possible that the effect of the LPL Ser447Stop polymorphism is age dependent and may be low at baseline in healthy young people. Finally, the differences in results may be due to differences in the genetic and environmental background, ie, Japanese versus European population. The effect of this gene may be modulated or stimulated by different factors, such as individual lifestyles.

In contrast to the patients with atherothrombotic infarction, the frequency of this mutation was not different among patients with lacunar infarction, cardioembolic infarction, and control subjects, indicating a lack of association between lacunar or cardioembolic infarction and this polymorphism. Lacunar infarction is caused by several distinct mechanisms, including lipohyalinosis, microatheroma, atherosclerosis, embolism, and hemodynamic hyperperfusion. Cardioembolic infarction is caused by embolism in patients with nonvalvular atrial fibrillation, and there is no distinct role for atherosclerotic mechanisms. Therefore, the relationship between atherothrombotic infarction and this polymorphism may be stronger than in other types of CVD. Our results indicate that the Ser447Stop mutation in atherothrombotic infarction may protect against the development of atherosclerosis.

Previous studies showed that the Ser447Stop mutation was associated with increased HDL cholesterol and decreased triglyceride levels. Plasma and vascular wall LPLs have different roles in atherosclerosis. Clee et al demonstrated that increased plasma LPL activity alone, in the absence of an increase in vascular wall LPL, is associated with a reduced susceptibility to atherosclerosis. On the other hand, decreased plasma LPL activity is associated with high triglycerides and low HDL phenotype, which is often observed in patients with premature vascular disease. The Ser447Stop mutation is reported to be associated with higher plasma LPL activity. Kozaki et al investigated the expression of C-terminal truncated LPLs by assessing their activity and mass in culture media and in cells. The level of LPL Ser447Stop mutant was approximately twice as high as that of normal LPL in the medium. Therefore, this mutation increases HDL cholesterol levels and decreases triglyceride levels. However, we did not find any relationship between Ser447Stop mutation and serum lipid levels. Several reasons may account for these conflicting results. All CVD patients in the present study were selected from patients who had been admitted to the hospital at least 2 months after the occurrence of stroke. Therefore, the bias between selection and the time point of lipid measurements after stroke onset cannot be ignored in the present study. Variations in lipid and lipoprotein levels and composition have been observed during the acute period after ischemic cerebrovascular events. Woo et al compared the serum lipid profile within 48 hours of the onset of stroke and 3 months later. They found significantly lower TC and LDL cholesterol levels as well as a significantly higher triglyceride level at 3 months after stroke compared with the data obtained within 48 hours after the onset. In our study a number of CVD patients had already been treated with hypolipidemic drugs, and some of them did not show any improvement in lipid levels. Therefore, it is likely that the difference in the timing of lipid measurement and treatment with lipid-lowering drugs could underestimate the correlation between this mutation and serum lipid levels.

The present study demonstrated that HindIII polymorphism is associated with increased risk of atherothrombotic infarction. Chen et al reported that carotid artery atherosclerosis correlates significantly with the HindIII polymorphism in white male subjects. Likewise, Thorn et al found that white patients with severe coronary atherosclerosis had a higher frequency of the H+ allele than healthy controls and suggested that HindIII polymorphism of LPL influences atherosclerotic disease. Both HindIII and PvulI polymorphism have been found in all racial groups, but Chamberlain et al indicated that there were differences in the frequencies of both the HindIII and the PvulI alleles between whites and Japanese. The frequencies of HindIII and PvulI allele detected in the present study were similar to those described in healthy Japanese populations. The frequency of the G allele of LPL Ser447Stop polymorphism was similar to that reported in other countries. In fact, Murano et al suggested that the Ser447Stop mutation might be distributed worldwide. In some studies, a strong linkage disequi-
librium among the 3 polymorphisms of LPL was found. Our
data also show that the Ser447Stop mutation is in significant
linkage disequilibrium with HindIII and PvuII.
In addition to the Ser447Stop mutation, other studies have
investigated the association between other LPL mutations and
atherosclerosis or ischemic CVD.37–39 Asn291Ser polymor-
phism of the LPL gene is associated with reduced HDL
cholesterol levels and premature atherosclerosis.37 Only 2
studies have evaluated the relationship between other LPL
gene mutations and ischemic CVD. Huang et al38 reported
that Asn291Ser polymorphism of LPL, similar to HindIII and
PvuII polymorphism, did not significantly contribute to the
risk of ischemic stroke. Wittrup et al39 showed that
Asn291Ser polymorphism was not associated with nonfatal
ischemic CVD in men but was possibly associated with a
2-fold increased risk in women. However, they did not
analyze the associations between the clinical subtypes of
ischemic CVD and control subjects. To our knowledge, our
study provides the first evidence of the relationship between
clinical subtypes of ischemic CVD and the Ser447Stop
polymorphism of LPL gene related to lipid metabolism.

In conclusion, G allele of Ser447Stop polymorphism is
significantly less frequent in patients with ischemic CVD
than in control subjects. Moreover, HindIII polymorphism is
associated with increased risk of atherothrombotic infarction.
The Ser447Stop mutation is in significant linkage disequilib-
rium with HindIII. The LPL Ser447Stop mutation appears to
have a protective effect against the development of athero-
sclerosis and subsequent atherothrombotic cerebral infarction.
Our results suggest that the Ser447Stop mutation of the
LPL gene is a novel genetic factor for atherothrombotic
cerebral infarction. Further prospective investigations in a
large population among various races are required to confirm
these findings.

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