Polymorphism in the 5′-Flanking Region of Human Glutamate-Cysteine Ligase Modifier Subunit Gene Is Associated With Myocardial Infarction

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Background—Human glutamate-cysteine ligase (GCL) is a rate-limiting enzyme for the synthesis of glutathione that plays a crucial role in antioxidant defense mechanisms in most mammalian cells, including vascular cells. Oxidants transcriptionally upregulate GCL genes for glutathione synthesis, providing a protective mechanism against oxidative stress–induced cellular dysfunction. This study examined the hypothesis that variation in the GCL genes may be associated with coronary artery disease in which oxidative stress plays a pathogenetic role.

Methods and Results—We searched for the common variants in the 5′-flanking region of the GCL modifier subunit (GCLM) gene in patients with myocardial infarction (MI). We found a polymorphism (−588C/T) in which the T allele showed lower promoter activity (40% to 50% of C allele) in response to oxidants in the luciferase reporter gene assay. Allele frequencies were determined by polymerase chain reaction–based analysis of restriction fragment length polymorphism in 429 patients with MI and 428 control subjects (as defined by angiography) in Kumamoto Prefecture, Japan. The frequency of the T polymorphism was significantly higher in the MI group than in the control group (CT and TT genotypes: 31.5% in MI group versus 19.2% in control group; \(P=0.001\)). In multiple logistic regression analysis, the T polymorphism was a risk factor for MI independent of traditional coronary artery disease risk factors (odds ratio, 1.98; 95% confidence interval, 1.38 to 2.83; \(P=0.001\)).

Conclusions—These findings suggest that the −588T polymorphism of the GCLM gene may suppress GCLM gene induction in response to oxidants and that it is a genetic risk factor for MI. (Circulation. 2002;105:2968-2973.)

Key Words: antioxidants ■ genes ■ myocardial infarction ■ risk factors

Oxidative stress plays a crucial role in the pathogenesis of atherothrombotic complications in various occlusive vascular diseases including coronary artery disease (CAD).1–4 Cells have several antioxidant defense mechanisms, such as the induction of several cellular antioxidants, including glutathione (GSH).5,6 Thus, a weakened defense system against oxidative stress might partly contribute to the development of CAD. GSH (tripeptide thiols) is a major, naturally occurring antioxidant, and it has a predominant role in the regulation of the intracellular redox state and protects cells from oxidative injury in systems that scavenge radicals, eliminate lipid peroxidation products through GSH peroxidases, and repair oxidant damage.7 GSH is synthesized within most mammalian cells by the action of human glutamate-cysteine ligase (GCL) and GSH synthetase.7,8 GCL catalyzes the rate-limiting step in de novo GSH synthesis.7,8 GCL is a heterodimer composed of catalytic and modifier (GCLM) subunits.7,8 GSH production is paralleled with the induction of GCL gene expression, which is regulated primarily at the level of transcription.5,8–11 Both genes have putative oxidative stress-responsive elements in their promoter/enhancer regions.5–11 Thus, GCL genes are transcriptionally upregulated for GSH synthesis by oxidants through the cis-acting DNA elements, providing a protective mechanism against oxidative stress.5,8–11

We hypothesized that the ability of individuals to regulate antioxidant defense mechanisms, such as the increase in antioxidant levels in response to oxidants, may genetically vary because all of individuals with coronary risk factors, which impose oxidative stress as a common mechanism for their atherogenic effects, may not necessarily develop CAD. In the present study, we examined the hypothesis that functional variations in the 5′-flanking region of GCL genes may be present and that they may be implicated in myocardial...
infarction (MI). Previous reports showed that several mutations in the catalytic GCL gene caused hemolytic anemia and neurological disorders, but there was no description of cardiovascular changes in the patients with the gene mutations.12,13 Thus, the present study focused on the GCLM gene.

Methods

Study Subjects

The study included 429 consecutive patients with previous MI and 428 consecutive control subjects who underwent coronary angiography and left ventriculography in Kumamoto University Hospital; all subjects were analyzed with regard to allele frequency. Clinical characteristics of the study patients and controls are shown in Table 1. All of the patients and controls were ethnic Japanese and partly overlapped with those studied in our previous reports.14 Criteria for MI included chest symptoms, characteristic ECG changes, and elevation of creatine kinase enzyme to more than twice the upper limit of normal. The findings in coronary angiography and left ventriculography supported the diagnosis of MI. Evaluation of risk factors was performed in the overall fasting condition in the chronic phase of MI in all MI patients. The control subjects underwent cardiac catheterization for atypical chest pain during a study period overlapping that of the patients with MI. The control subjects had angiographically documented normal coronary arteries (≤10% stenosis), normal ventriculography, and no clinical evidence of coronary artery spasm and syndrome X. All patients and subjects (n = 106) were used for HLA typing. The study protocol followed the national guidelines for genetic analysis in Japan and was approved by the ethics committee at Kumamoto University Hospital.

Identification of Polymorphisms in the Promoter Region

Genomic DNA was extracted from peripheral blood lymphocytes with the use of the phenol chloroform protocol.14 The promoter region of the GCLM gene was amplified by polymerase chain reaction (PCR) from genomic DNA obtained from 12 patients with MI and 12 control subjects using 10 sets of primer pairs covering the GCLM promoter sequence.10,11 The PCR products were sequenced with the Dye Terminator Cycle Sequencing Ready Reaction Kit (ABI PRISM) on an ABI Genetic Analyzer 373S (PE Biosystems). Sequences were analyzed and compared among the patients and the control subjects to detect polymorphisms.

Genotyping

We identified two polymorphisms, −588C/T and −23G/T, that were completely linked (Figure 2). Genotypes of each polymorphism were determined by PCR-based method of restriction fragment length polymorphism by investigators (S.S. and S.K.) who had no knowledge of the angiographic and clinical data of MI cases and control subjects. The −588C/T polymorphism creates a novel site for the MspI restriction enzyme (C/CGG) in the presence of the C allele. A set of primers was designed to amplify a 329-base pair (bp) fragment of the GCLM promoter by PCR (forward 5'-CTCAAGGGCAAAGACTCA-3'; reverse 5'-CCGGTCGGTGAGGTGACAC-3'), encompassing the −588C/T polymorphic site and an additional site for MspI as a control. Subjects with the CC genotype were identified by the presence of 200-, 84-, and 45-bp products on gel electrophoresis; those with the CT genotype were identified by 200-, 129-, 84-, and 45-bp bands; and those with TT genotypes were identified by 200- and 129-bp bands, as shown in Figure 2.

Similarly, the −23G/T polymorphism creates a novel site for the HinfI restriction enzyme (G/C), in the presence of the G allele. A set of primers was designed to amplify a 127-bp fragment of the GCLM promoter by PCR (forward 5'-GCTCCCTCTCGGCTCTCT-3'; reverse 5'-GCTGTCGGTGCCCATGGC-3'), encompassing the −23G/T polymorphic site. Subjects with the GG genotype were identified by the presence of 88- and 39-bp bands; those with the GT genotype were identified by 127-, 88-, and 39-bp bands; and those with TT genotypes were identified by 127-bp bands, as shown in Figure 2.

Cell Culture

HeLa (human cervical carcinoma cell line) cells and THP-1 (human monocyte cell line) cells were obtained from the Health Science Research Resources Bank. They were cultured in DMEM and RPMI 1640, respectively, with fetal calf serum. Primary cultures of human umbilical vein endothelial cells (HUVECs) were obtained as previously described.15 HUVECs at the second passage were used in the present study.

Recombinant Plasmid Constructions

Recombinant expression vectors were created by cloning restriction fragments isolated from the 5'-flanking sequences of the GCLM gene into pGL3-Basic (Promega) to determine promoter activity. Two DNA fragments covering the region from −1338 to 85 were amplified by PCR with genomic DNA (from −588/T−23G) wild-type homozygote and −588T/−23T variant homozygote and sequenced. The fragments were isolated by KpnI/XhoI restriction digestion and cloned into the KpnI/XhoI sites of pGL3-Basic, thus creating the recombinant plasmids pGL3-GCLMwild (with −588C/−23G) and pGL3-GCLMmut (with −588T/−23T). These plasmids were subjected to digestion with additional restriction enzymes to generate other constructs containing only 1 of the 2 polymorphisms.

TABLE 1. Clinical Characteristics of Control Subjects and Patients With MI

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n = 428)</th>
<th>Patients With MI (n = 429)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62 ± 12</td>
<td>68 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men/women, n</td>
<td>212/216</td>
<td>315/114</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>80 (18.7)</td>
<td>141 (32.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>133 (31.1)</td>
<td>196 (45.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>180 (42.1)</td>
<td>236 (55.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>116 (27.1)</td>
<td>155 (36.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.8 ±3.5</td>
<td>23.5 ±3.4</td>
<td>0.192</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number of patients (%).

Figure 1. Structure of 5'-flanking region of the GCLM gene (nucleotide position −1900 to 85) and polymorphic sites.

Figure 2. Ethidium bromide gels showing the 3 genotypes from polymorphisms −588C/T and −23G/T in the promoter region. 588 bases upstream (A) and 23 bases upstream (B) of GCLM.
The KpnI/SacII DNA fragment (−1338 to −345; containing −588C) from pGL3-GCLMwildtype was inserted into the KpnI/SacII–
digested pGL3-GCLMvariant (containing −23T) to create pGL3-
GCLM588C/-23T (containing the major C allele at −588 and the minor
T allele at −23). The SacII/PsrI DNA fragment (−345 to 62; containing −23G) from pGL3-GCLMwildtype was ligated into the
SacII/PsrI–digested pGL3-GCLMvariant (containing −588T) to create
pGL3-GCLM588T/-23G (containing the minor T allele at −588 and the
major G allele at −23).

Luciferase Reporter Gene Assay
DNA was introduced into the cells by the liposome-mediated
transfection method. Briefly, subconfluent cultures of HUVECs,
THP-1, and HeLa cells were transfected with cationic lipid reagent.
The transfection used 1 µg of pGL3 Luciferase Reporter Vector with
various GCLM promoters and 0.1 µg of pRL-TK control vector
(Promega) with the herpes simplex virus thymidine kinase promoter
to provide constitutive expression of Renilla luciferase expression.
LIPOFECTIN Reagent and PLUS Reagent (GIBCO BRL) were used
for the experiments with HeLa cells and HUVECs, and Effectene
Reagent (QIAGEN) was used with THP-1 cells. Twenty-four hours
after the transfection, the transfected cells were treated for 18 hours
with or without one of the following oxidants: 10 to 100 µmol/L of
tert-butylhydroquinone (tBHQ), 10 µmol/L of menadione, or 100
µmol/L of H₂O₂. The treated cells were harvested with passive lysis
buffer (Promega). Luciferase activity was measured with the dual-
luciferase assay system (Promega) and a luminometer. Luciferase
levels were expressed in arbitrary units after normalization to Renilla
luciferase levels.

Preparation and Culture of Human Monocytes
To examine the effects of −588C/T polymorphism on GCLM
mRNA expression, human peripheral blood monocytes were isolat-
ed[16] from 38 subjects (CC genotype, n=19; CT genotype, n=19)
who were selected from the subjects examined for allele frequency.
Coronary risk factors and frequencies of previous MI were matched
between the selected subjects with the CC genotype and CT
genotype. The mononuclear cells were plated in 6-well dishes for 2
hours. The nonadherent cells were then removed by washing. After
5 days of culture, the monocytes-macrophages were washed and then
treated for 18 hours with or without 50 µmol/L of tBHQ. The treated
cells were assayed for GCLM mRNA expression.

GCLM mRNA Expression in Human
Monocytes-Macrophages
Total RNA was extracted from the treated human monocytes-
macrophages with a Qiagen RNeasy kit and DNAse I (QIAGEN).
The expression of GCLM mRNA was quantified by a real-time one-step
reverse transcriptase PCR assay based on the 5′ flanking region of the GCLM
gene (Figure 1). The luciferase activity was defined as
the ratio of luciferase activity in the treated cells to that of the
untreated cells. The luciferase activity was measured with a luminometer.

Plasma GSH Assay
EDTA-plasma was obtained after an overnight fast and stored at
−80°C until assay after the addition of 50 µmol/L of acivicin (γ-
glutamyltranspeptidase inhibitor). Plasma GSH levels were mea-
sured by the high performance liquid chromatography–electro-
chemical method[17] in 84 subjects (CC genotype, n=48; CT
genotype, n=34; TT genotype, n=2). These subjects were selected
from the study subjects examined for allele frequency to match the
risk factors and frequency of previous MI between patients with CT
and TT genotypes and those with the CC genotype.

Statistical Analysis
To evaluate the −588T polymorphism as an independent risk factor
between patients with MI and control subjects, multiple logistic
regression analysis was performed with the following factors as
categorical covariates: age (≥70 years), sex (men), smoking history
(defined as smoking ≥10 cigarettes per day for ≥10 years),
hypertension (≥140/90 mm Hg or taking antihypertensive medica-
tion), diabetes mellitus (according to American Diabetes Association
guidelines[16]), hypercholesterolemia (>220 mg/dl or the use of
lipid-lowering medications), body mass index (>25 kg/m²), and
−588T polymorphisms (TT and CT genotypes). Mean values of
continuous variables with normal distributions and frequencies
between groups were compared with an unpaired t test and χ²
analysis or Fisher’s exact test, respectively. Statistical significance
was defined as P<0.05. Statistical analysis was performed with
StatView 5.0 (SAS Institute, USA).

Results
Identification of GCLM Polymorphism and
GCLM Genotypes
Two novel polymorphisms (−588C/T and −23G/T) were iden-
tified in the 5′-flanking region of the GCLM gene (Figure 1). The
2 polymorphisms were completely linked. The −588TTT, TT, and CC
genotypes were present in 16 (3.7%), 119 (27.8%), and 294 (68.5%) of 429 patients
with MI, respectively, and they were present in 2 (0.5%), 80
(18.7%), 346 (80.8%) of 428 control subjects, respectively.
The genotype distribution was consistent with the population
being in Hardy-Weinberg equilibrium. In the analysis of the
recessive, additive, and dominant effects of the −588T
polymorphism, each frequency was significantly higher in the
MI group than in the control group (P<0.001 in all), as
shown in Table 2. The −588T polymorphism (TT and CT
genotypes), male sex, high age (≥70 years), hypercholester-
olemia, diabetes mellitus, and hypertension were variables
differing significantly and independently between patients
with MI and control subjects in multiple logistic regression
analysis, as shown in Table 3. This polymorphism remained
a significant risk factor for MI independently of other
traditional risk factors in multivariate statistical analysis after
matching sex and age between cases and controls (data not
shown).

Promoter Activities of the GCLM Gene
HUVECs, THP-1 cells, and HeLa cells transfected with
pGL3-GCLMvariant (−588T/−23T) had luciferase levels com-
parable to those transfected with pGL3-GCLMwildtype (−588C/
−23G) at the nontreated control condition, as shown in
Figure 3. The luciferase levels were induced in cells with
pGL3-GCLMwildtype but not those with pGL3-GCLMvariant
when cells were incubated with 10 to 100 µmol/L of tBHQ
for 18 hours, as shown in Figure 3. Similar results were
obtained with the experiments that used other oxidants (ie,
menadione or H₂O₂; data not shown). The induced luciferase
levels in response to tBHQ were significantly lower in cells
transfected with pGL3-GCLM588T/-23G (containing the minor T
allele at −588 and the major G allele at −23) than those with

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TABLE 2. Genotype Frequencies of GCLM Promoter Polymorphisms in Control Subjects and Patients With MI

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=428)</th>
<th>Patients With MI (n=429)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>−588C/T and −23G/T, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCLM/TT-TT</td>
<td>2/428 (0.5)</td>
<td>16/429 (3.7)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>GCLM/CT-GT</td>
<td>80/428 (18.7)</td>
<td>119/429 (27.8)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>GCLM/CC-GG</td>
<td>346/428 (80.8)</td>
<td>294/429 (68.5)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>−588T allele vs C allele</td>
<td></td>
<td></td>
<td>1.96 (1.41–2.65)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>−588TT and CT vs CC</td>
<td></td>
<td></td>
<td>1.94 (1.47–2.61)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>−588TT and CT and CC</td>
<td></td>
<td></td>
<td>8.25 (1.89–36.11)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are presented as number of patients (%). CI indicates confidence interval; OR, odds ratio.
*Fisher’s exact test.

TABLE 3. Multiple Logistic Regression Analysis for Variables Differing Between Controls and Patients With MI

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>SEM</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−588T polymorphism</td>
<td>0.68</td>
<td>0.18</td>
<td>&lt;0.001</td>
<td>1.98 (1.38–2.83)</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>1.06</td>
<td>0.19</td>
<td>&lt;0.001</td>
<td>2.89 (1.99–4.22)</td>
</tr>
<tr>
<td>Age (≥70 y)</td>
<td>0.77</td>
<td>0.17</td>
<td>&lt;0.001</td>
<td>2.15 (1.55–3.00)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.74</td>
<td>0.18</td>
<td>&lt;0.001</td>
<td>2.09 (1.48–2.96)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.63</td>
<td>0.18</td>
<td>&lt;0.001</td>
<td>1.88 (1.32–2.68)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.51</td>
<td>0.16</td>
<td>0.002</td>
<td>1.66 (1.21–2.28)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>0.31</td>
<td>0.18</td>
<td>0.088</td>
<td>1.37 (0.96–1.96)</td>
</tr>
<tr>
<td>Body mass index (&gt;26 kg/m²)</td>
<td>0.04</td>
<td>0.19</td>
<td>0.832</td>
<td>1.04 (0.72–1.51)</td>
</tr>
<tr>
<td>Constant</td>
<td>−1.95</td>
<td>0.22</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
</tbody>
</table>

−588T polymorphism indicates −588TT and −588CT combined; other abbreviations as in Table 2.

Discussion

The present study found 2 polymorphisms (−588C/T and −23G/T), which are completely linked, in the 5′-flanking region of GCLM gene. The present reporter gene assay showed that the variants in the GCLM gene suppressed promoter activity in response to oxidants and that the −588T polymorphism was responsible for the functional change between the 2 polymorphisms. The association study showed that the frequency of the −588T polymorphism was significantly higher in the MI group than in the control group and that this polymorphism was an independent risk factor for MI. Furthermore, the present study showed that GCLM mRNA expression in the cultured human monocytes-macrophages was increased in response to oxidants, but the induction was less in the cells from CT subjects compared with CC subjects. Thus, these data indicate that the −588T polymorphism may suppress the increase in GCLM gene expression to oxidative stress and that it is a genetic risk factor for MI. In addition,

![Figure 3. Effects of polymorphisms on the promoter activity of GCLM gene. The promoter activity is expressed as relative luciferase activity normalized to Renilla activity. The transfected cells were incubated for 18 hours with or without tBHQ (100 μmol/L for HUVECs and HeLa cells; 10 μmol/L for THP-1 cells). Wild-type indicates the promoter construct containing major alleles (−588C and −23G alleles); variant, the construct containing minor alleles (−588T and −23T alleles); −588C/−23T, the construct containing the major C allele at −588 and the minor T allele at −23; and −588T/−23G, the construct containing the minor T allele at −588 and the major G allele at −23. Data are expressed as the means ± SEM (bars) from 8 independent experiments.](http://circ.ahajournals.org/)

pGL3-GCLM*-subtype (HeLa cells), as shown in Figure 3. The induced levels were comparable between cells with pGL3-GCLM*-588CT/23T (containing the major C allele at −588 and the minor T allele at −23) and those with pGL3-GCLM*-subtype. Thus, the −588T polymorphism reduced the promoter activity of the GCLM gene at the condition exposed to tBHQ, whereas the −23T polymorphism did not have a significant effect.

GCLM mRNA Expression in Human Cultured Monocytes-Macrophages

GCLM mRNA expression levels in monocytes-macrophages from patients with the CT genotype were comparable to those from the risk factor–matched patients with the CC genotype at the nontreated control condition. The mRNA levels were induced in both genotypes in response to 50 μmol/L of tBHQ for 18 hours, but the induced levels were significantly lower in cells with the CT genotype than those with the CC genotype after incubation with tBHQ, as shown in Figure 4.

Plasma GSH Levels

Plasma GSH levels were significantly lower in CT and TT genotypes than in the CC genotype, as shown in Figure 5.
plasma GSH levels were significantly lower in subjects with the T allele than in those without the T allele. The T allele may possibly weaken the intracellular production of GSH in response to oxidative stress, leading to the increase in susceptibility to the oxidant-induced vascular injury that is thought to occur as part of the pathogenesis of CAD.

GSH is synthesized from its constituent amino acids in 2 sequentials by GCL and GSH synthetase. 7,8 GCL is the rate-limiting enzyme in de novo GSH synthesis, whereas GSH synthetase apparently has no regulatory role. The GCLM gene has several putative oxidative stress-responsive elements in the promoter/enhancer region.10,11 When cells are challenged with sublethal oxidative stress or GSH depletion, GCLM mRNA expression was induced through activation of oxidative stress-responsive elements in the promoter region.10,11,19 These result in de novo GSH synthesis and provide a protective/adaptive mechanism against oxidative stress. Although there is no putative enhancer element that contains the −588 position on the computer-based data research, Moinova et al10 showed that the nucleotides −718 to −344 contribute to the increase in the promoter activity in response to β-naphthoflavone, a potent inducer of several phase II enzymes. Thus, it is possible that the −588T allele might modify the binding of nuclear proteins to unidentified cis-elements around the −588 position, leading to suppression of oxidant-induced expression of the GCLM gene.

A recent study showed that low serum levels of GSH are a risk factor for CAD. 20 Previous in vitro studies demonstrated that GSH depletion inhibits nitric oxide production in endothelial cells. 21 We and others previously showed that GSH supplementation improves endothelial vasmotor dysfunction, an early event observed in atherosclerotic arteries, in the coronary arteries of patients with coronary risk factors or coronary spastic angina that imposes oxidative stress.22–24 Furthermore, GSH suppresses the induction of proatherothrombotic molecules in the cultured human monocytes exposed to oxidative stress.15 These atheroprotective effects of GSH support the hypothesis that low GSH levels may potentially contribute to the development of atherosclerotic CAD.

The present study is limited by the relatively small number of studied patients. Furthermore, the precise mechanisms by which −588C/T polymorphism in the GCLM gene is linked to the genesis of MI remain largely undefined. We cannot exclude the possibility that this polymorphism is a marker for another functional variant within this or adjacent genes. In addition, only survivors of acute MI were enrolled as MI patients in the present study. A longitudinal study with a large number of study patients with homogeneous risk is thus required to assess the precise role of this gene variant in the pathogenesis of CAD.

In conclusion, the present study demonstrated that 2 polymorphisms (−588C/T and −23G/T) occur in the 5’ flanking region of the GCLM gene, that the −588T polymorphism in the GCLM gene suppresses the induction of the GCLM gene expression to oxidative stress, and that this polymorphism is significantly associated with MI. Thus, the −588T polymorphism in the GCLM gene is a genetic risk factor for MI.

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References


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