Genetic Risk for Ischemic and Hemorrhagic Stroke

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Objective—We performed an association study to identify gene polymorphisms for assessing the genetic risk of ischemic or hemorrhagic stroke.

Methods and Results—The study population comprised 3151 unrelated Japanese individuals: 1141 stroke patients (636 with atherothrombotic cerebral infarction, 282 with intracerebral hemorrhage, and 223 with subarachnoid hemorrhage) and 2010 controls. The genotypes for 202 polymorphisms of 152 genes were determined by suspension array technology. Multivariable logistic regression analysis with adjustment for conventional risk factors revealed that the −572G→C polymorphism of the interleukin-6 (IL-6) gene (IL6) was significantly (P<0.001) associated with both atherothrombotic cerebral infarction and intracerebral hemorrhage and that the −55C→T polymorphism of the uncoupling protein 3 gene (UCP3), the −863C→A polymorphism of the tumor necrosis factor (TNF) gene (TNF), and the G→A (Gly243Asp) polymorphism of the polycystic kidney disease 1–like gene (PKD1-like) were significantly associated with subarachnoid hemorrhage.

Conclusions—IL6 genotype may be useful in assessing the genetic risk for atherothrombotic cerebral infarction and intracerebral hemorrhage, and genotypes for UCP3, TNF, and PKD1-like may be similarly beneficial in assessment of the risk for subarachnoid hemorrhage. Validation of our findings will require additional studies with independent subject panels. (Arterioscler Thromb Vasc Biol. 2006;26:1920-1925.)

Key Words: atherothrombotic cerebral infarction ■ intracerebral hemorrhage ■ subarachnoid hemorrhage ■ polymorphism ■ genetics

Stroke is a common and serious disease, with ≈700 000 individuals experiencing a new or recurrent stroke and nearly 163 000 deaths attributable to stroke-related causes each year in the United States. The prevalence of stroke in the United States is 5.4 million. Of all such events, 88% are ischemic stroke, 9% are intracerebral hemorrhage, and 3% are subarachnoid hemorrhage.1 In Japan, the prevalence of stroke is 1.4 million (62% ischemic stroke, 23% intracerebral hemorrhage, and 11% subarachnoid hemorrhage), with nearly 132 000 deaths from this condition each year (Ministry of Health, Labor, and Welfare of Japan). Despite recent advances in acute stroke therapy, stroke remains the leading cause of severe disability and the third leading cause of death, after heart disease and cancer, in Western countries and Japan.2 Given the importance of prevention as a strategy to reduce the overall burden of stroke, the identification of markers of stroke risk is key, both for risk prediction and for potential intervention to avert future events.

Although genetic epidemiological studies have implicated several genetic variants as risk factors for ischemic or hemorrhagic stroke, the genetic determinants of these conditions remain largely unknown. We have now performed a large-scale association study for 202 polymorphisms of 152 candidate genes and ischemic or hemorrhagic stroke in 3151 Japanese individuals. The purpose of the present study was to identify gene polymorphisms that confer susceptibility to atherothrombotic cerebral infarction, intracerebral hemorrhage, or subarachnoid hemorrhage, and thereby to contribute to the primary and personalized prevention of these events.

Methods

Study Population

The study population comprised 3151 unrelated Japanese individuals (1484 men and 1667 women) who either visited outpatient clinics of or were admitted to one of the participating hospitals (Gifu Prefectural Gifu, Tajimi, and Gero Hot spring hospitals; Hiro saki University Hospital; Reimeikyo Rehabilitation Hospital; and Yokohama General Hospital) between October 2002 and March 2005. The 1141 stroke patients included 636 subjects (372 men and 264 women) with atherothrombotic cerebral infarction, 282 subjects (179 men and 103 women) with intracerebral hemorrhage, and 223 subjects (143 men and 80 women) with subarachnoid hemorrhage. The study population comprised 3151 unrelated Japanese individuals as characterized here: 1141 stroke patients (636 with atherothrombotic cerebral infarction, 282 with intracerebral hemorrhage, and 223 with subarachnoid hemorrhage) and 2010 controls. The genotypes for 202 polymorphisms of 152 genes were determined by suspension array technology. Multivariable logistic regression analysis with adjustment for conventional risk factors revealed that the −572G→C polymorphism of the interleukin-6 (IL-6) gene (IL6) was significantly (P<0.001) associated with both atherothrombotic cerebral infarction and intracerebral hemorrhage and that the −55C→T polymorphism of the uncoupling protein 3 gene (UCP3), the −863C→A polymorphism of the tumor necrosis factor (TNF) gene (TNF), and the G→A (Gly243Asp) polymorphism of the polycystic kidney disease 1–like gene (PKD1-like) were significantly associated with subarachnoid hemorrhage.

Conclusions—IL6 genotype may be useful in assessing the genetic risk for atherothrombotic cerebral infarction and intracerebral hemorrhage, and genotypes for UCP3, TNF, and PKD1-like may be similarly beneficial in assessment of the risk for subarachnoid hemorrhage. Validation of our findings will require additional studies with independent subject panels. (Arterioscler Thromb Vasc Biol. 2006;26:1920-1925.)

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women) with intracerebral hemorrhage, and 223 subjects (89 men and 134 women) with subarachnoid hemorrhage. The stroke patients were recruited from consecutive individuals who either were admitted to the participating hospitals because of stroke events or visited outpatient clinics regularly. The diagnosis of ischemic or hemorrhagic stroke was based on the occurrence of a new and abrupt focal neurological deficit, with neurological symptoms and signs persisting for ≥24 hours. It was confirmed by positive findings in computed tomography or MRI (or both) of the head. The type of stroke was determined according to the Classification of Cerebrovascular Diseases III.1 Individuals with cardiogenic embolic infarction, lacunar infarction, transient ischemic attack, cerebrovascular malformations, brain tumors, or traumatic cerebrovascular diseases were excluded from enrollment in the study, as were those with atrial fibrillation in the absence or presence of valvular heart disease.

The 2010 control subjects (844 men and 1166 women) were recruited from consecutive individuals who visited outpatient clinics of the participating hospitals for an annual health checkup. These subjects either had or did not have conventional risk factors for ischemic or hemorrhagic stroke, including obesity (body mass index [BMI] ≥25 kg/m²), cigarette smoking (≥10 cigarettes daily), hypertension (systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg, or both), diabetes mellitus (fasting blood glucose of ≥6.93 mmol/L or hemoglobin A1C of ≥6.5%, or both), and hypercholesterolemia (serum total cholesterol of ≥5.72 mmol/L). They had no history of ischemic or hemorrhagic stroke or other cerebral diseases, coronary heart disease, peripheral arterial occlusive disease, or other atherosclerotic diseases, or other thrombotic, embolic, or hemorrhagic disorders. The study protocol complied with the Declaration of Helsinki and was approved by the committees on the ethics of human research of Mie University School of Medicine, Hirosaki University School of Medicine, Gifu International Institute of Biotechnology, and participating hospitals. Written informed consent was obtained from each participant.

Selection of Polymorphisms
With the use of public databases, we selected 152 candidate genes that might be associated with ischemic or hemorrhagic stroke on the basis of a comprehensive overview of vascular biology (from the viewpoint of regulation of the circulation, blood pressure, 5.72 mmol/L). They had no history of ischemic or hemorrhagic stroke in the absence or presence of valvular heart disease.

Genotyping of Polymorphisms
Venous blood (7 mL) was collected into tubes containing 50 mmol/L EDTA (disodium salt), and genomic DNA was isolated with a kit (G&G Science) by a method that combines the polymerase chain reaction and sequence-specific oligonucleotide probes with the use of suspension array technology (Luminex 100; Luminex). Primers, probes, and other conditions for genotyping are shown in supplemental Table II. Detailed methodology for genotyping was described previously.4

Statistical Analysis
Clinical data were compared between subjects with atherothrombotic infarction, intracerebral hemorrhage, or subarachnoid hemorrhage and controls by the unpaired Student t test. Qualitative data were compared by the χ² test. Allele frequencies were estimated by the gene counting method, and the χ² test was used to identify departure from Hardy–Weinberg equilibrium. In the initial screen, the genotype distribution of each autosomal polymorphism was compared by

the χ² test (3×2) between subjects with atherothrombotic infarction, intracerebral hemorrhage, or subarachnoid hemorrhage and controls. For gene polymorphisms located on the X chromosome, allele frequencies were compared by the χ² test (2×2). Polymorphisms related (P<0.01) to atherothrombotic infarction, intracerebral hemorrhage, or subarachnoid hemorrhage were further examined by multivariable logistic regression analysis with adjustment for covariates, with each of these conditions as a dependent variable and independent variables including age, sex (0=woman; 1=man), BMI, smoking status (0=nonsmoker; 1=smoker), metabolic variables (0=no history of hypertension, diabetes mellitus, or hypercholesterolemia; 1=positive history), and genotype of each polymorphism. Each genotype was assessed according to dominant (0= wild-type homozygote; 1=heterozygote=variant homozygote), recessive (0= wild-type homozygote=heterozygote; 1=variant homozygote), and additive ((0,0)=wild-type homozygote; (1,0)=heterozygote; (0,1)=variant homozygote) genetic models, and the P value, odds ratio, and 95% CI were calculated. Additive models included additive 1 and 2 models: heterozygotes versus wild-type homozygotes for the additive 1 model, and variant homozygotes versus wild-type homozygotes for the additive 2 model. The false discovery rate (FDR) was calculated by the method of Benjamini and Hochberg.5 Calculation of the FDR is an approach to dealing with the problems associated with multiple comparisons and provides a measure of the expected proportion of false positives among data. The FDR threshold is determined from the observed P value distribution and is adaptive to the signal level in data. The FDR differs from a P value, and much higher FDRs than P values can be tolerated. In the present study, the χ² test was used as an initial screen, and multivariable logistic regression analysis was subsequently applied in a more rigorous evaluation of association. In the initial screen (the χ² test), the FDR was calculated from the distribution of P values for 202 polymorphisms in each type of stroke. In multivariable logistic regression analysis, the FDR was calculated from the distribution of P values for dominant, recessive, and additive genetic models of selected polymorphisms in each type of stroke. Given that a total of 40 tests was performed in multivariable logistic regression analysis, the P value for significant association that resulted in an FDR of 0.05 was 0.00125. We therefore adopted a level of P<0.001 for significant association in multivariable logistic regression analysis. For other clinical background data, we adopted a level of P<0.05 for significant association, given that comparisons of these data between cases and controls were performed for reference. Statistical significance was examined by 2-sided tests, and statistical analyses were performed with JMP software version 5.1 (SAS Institute).

Results
The characteristics of the 3151 study subjects are shown in Table 1. Age, the frequency of men, and the prevalence of hypertension, diabetes mellitus, and hypercholesterolemia were greater in subjects with atherothrombotic infarction than in controls. Age, BMI, and the prevalence of hypercholesterolemia were lower, whereas the frequency of men and the prevalence of smoking and hypertension were higher in subjects with intracerebral hemorrhage than in controls. Age, BMI, and the prevalence of hypercholesterolemia were lower, and the prevalence of smoking was higher in subjects with subarachnoid hemorrhage than in controls.

Evaluation of genotype distributions by the χ² test revealed that 2, 4, and 5 polymorphisms were related (P<0.01) to the prevalence of atherothrombotic infarction, intracerebral hemorrhage, or subarachnoid hemorrhage, respectively (Table 2). These polymorphisms were further analyzed for their relations to each disorder. Multivariable logistic regression analysis with adjustment for age, sex, BMI, and the prevalence of smoking, hypertension, diabetes mellitus, and hyperchole-

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terolemia revealed that the \(-572G\rightarrow C\) polymorphism of the interleukin 6 (IL-6) gene (IL6; recessive genetic model) was significantly \((P<0.001)\) associated with the prevalence of atherothrombotic infarction or intracerebral hemorrhage, and that the \(-55C\rightarrow T\) polymorphism of the uncoupling protein 3 gene (UCP3; additive 1 model), the \(-863C\rightarrow A\) polymorphism of the tumor necrosis factor (TNF) gene (TNF; dominant, recessive, and additive 2 models), and the G\(\rightarrow\)A (Gly243Asp) polymorphism of the polycystic kidney disease 1--like gene (PKD1-like; dominant and additive 1 models) were significantly associated with the prevalence of subarachnoid hemorrhage (Table 3). The genotype distributions of these polymorphisms among controls and subjects with atherothrombotic infarction, intracerebral hemorrhage, or subarachnoid hemorrhage are shown in Table 4, with those in controls being in Hardy--Weinberg equilibrium.

### Table 1. Characteristics of the 3151 Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atherothrombotic Infarction</th>
<th>Intracerebral Hemorrhage</th>
<th>Subarachnoid Hemorrhage</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>636</td>
<td>282</td>
<td>223</td>
<td>2010</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.2(\pm)11.1*</td>
<td>60.6(\pm)11.3*</td>
<td>55.8(\pm)12.6*</td>
<td>63.0(\pm)11.4</td>
</tr>
<tr>
<td>Sex (male/female, %)</td>
<td>58.5/41.5*</td>
<td>63.5/36.5*</td>
<td>39.9/60.1</td>
<td>42.0/58.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3(\pm)3.1</td>
<td>22.8(\pm)3.2½</td>
<td>23.0(\pm)2.8½</td>
<td>23.5(\pm)3.0</td>
</tr>
<tr>
<td>Current or former smoker (%)</td>
<td>16.0</td>
<td>22.7½</td>
<td>26.5*</td>
<td>15.4</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>69.3*</td>
<td>57.5*</td>
<td>40.8</td>
<td>40.5</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>39.0*</td>
<td>18.4</td>
<td>14.8</td>
<td>18.9</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>34.4§</td>
<td>17.0*</td>
<td>18.8†</td>
<td>28.8</td>
</tr>
</tbody>
</table>

Age and BMI values are means\(\pm\) SD. Smoker indicates smoking \(\geq\)10 cigarettes daily; hypertension, systolic blood pressure of \(\geq\)140 mm Hg or diastolic blood pressure of \(\geq\)90 mm Hg (or both), or taking antihypertensive medication; diabetes mellitus, fasting blood glucose of \(\geq\)6.93 mmol/L (126 mg/dL) or glycated hemoglobin of \(\geq\)6.5% (or both), or taking antidiabetes medication; hypercholesterolemia, serum total cholesterol of \(\geq\)5.72 mmol/L (220 mg/dL) or taking lipid-lowering medication. \(*P<0.05; \#P<0.01\) vs controls.

### Table 2. Polymorphisms Related \((P<0.01)\) to Atherothrombotic Infarction, Intracerebral Hemorrhage, or Subarachnoid Hemorrhage Evaluated by the \(\chi^2\) Test

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Polymorphism</th>
<th>(P)</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
<td>(-572G\rightarrow C)</td>
<td>&lt;0.001</td>
<td>0.182</td>
</tr>
<tr>
<td>MTHFR</td>
<td>677C(\rightarrow)T (A1222Val)</td>
<td>0.002</td>
<td>0.162</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL6</td>
<td>(-572G\rightarrow C)</td>
<td>0.003</td>
<td>0.606</td>
</tr>
<tr>
<td>GJB4</td>
<td>C(\rightarrow T) (Arg103Cys)</td>
<td>0.004</td>
<td>0.384</td>
</tr>
<tr>
<td>CCL5</td>
<td>(-28C\rightarrow G)</td>
<td>0.007</td>
<td>0.458</td>
</tr>
<tr>
<td>CPB2</td>
<td>529G(\rightarrow A) (A147Thr)</td>
<td>0.008</td>
<td>0.394</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCP3</td>
<td>(-55C\rightarrow T)</td>
<td>&lt;0.001</td>
<td>0.016</td>
</tr>
<tr>
<td>TNF</td>
<td>(-863C\rightarrow A)</td>
<td>0.001</td>
<td>0.121</td>
</tr>
<tr>
<td>PKD1-like</td>
<td>G(\rightarrow A) (Gly243Asp)</td>
<td>0.002</td>
<td>0.114</td>
</tr>
<tr>
<td>CAPN10</td>
<td>4852G(\rightarrow A)</td>
<td>0.003</td>
<td>0.157</td>
</tr>
<tr>
<td>PAX4</td>
<td>567C(\rightarrow T) (Arg121Trp)</td>
<td>0.004</td>
<td>0.154</td>
</tr>
</tbody>
</table>

The genotype distributions of each polymorphism were compared between subjects with atherothrombotic infarction, intracerebral hemorrhage, or subarachnoid hemorrhage and controls by the \(\chi^2\) test \((3\times2)\).

### Discussion

We examined the independent relations of 202 polymorphisms in 152 candidate genes to atherothrombotic infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. Our large-scale association study showed that the \(-572G\rightarrow C\) polymorphism of \(IL6\) was significantly associated with both atherothrombotic infarction and intracerebral hemorrhage and that the \(-55C\rightarrow T\) polymorphism of \(UCP3\), the \(-863C\rightarrow A\) polymorphism of \(TNF\), and the \(G\rightarrow A\) (Gly243Asp) polymorphism of \(PKD1\)-like were significantly associated with subarachnoid hemorrhage.

Atherothrombotic cerebral infarction is the most common type of stroke and, in most patients, is caused by atherosclerosis. Several genetic determinants contribute to the risk of atherothrombotic infarction. We have now shown that the \(-572G\rightarrow C\) polymorphism of \(IL6\) was significantly associated with the prevalence of atherothrombotic infarction, with the \(-572C\) allele representing a risk factor for this condition. IL-6 plays a key role in promotion of the acute inflammatory response and in regulation of the production of acute phase proteins such as C-reactive protein. It contributes to the inflammatory response by activating endothelial cells and stimulating the synthesis of fibrinogen. This cytokine is thus likely important in the pathogenesis of vascular inflammation. The \(-174G\rightarrow C\) polymorphism of \(IL6\) was shown previously to be associated both with intima-media thickness of the carotid artery, an important predictor of new myocardial infarction and stroke, and with coronary heart disease. This polymorphism was also found to be associated with a history of ischemic stroke and with the severity of ischemic stroke in young patients, with the \(G\) allele being a risk factor for this condition. However, this polymorphism has not been detected in the Japanese population. Cerebral ischemia induces the expression of IL-6 in neurons and astrocytes. The serum concentration of IL-6 also increases within several days after an ischemic stroke. The ischemic brain appears to be a major source of IL-6, given that the serum concentration of this cytokine correlates with infarct size and that its concentration in cerebrospinal fluid is greater than that in serum.
various observations suggest that gene variants of IL6 play an important role in the development and outcome of ischemic stroke.

Intracerebral hemorrhage has been shown to have environmental and genetic risk factors, including hypertension and a polymorphism of the apolipoprotein E gene. We have now shown that the –572G→C polymorphism of IL6 was also significantly associated with the prevalence of intracerebral hemorrhage, with the –572C allele being a risk factor for this condition. The –174G→C polymorphism of IL6 was found previously to be associated with intracerebral hemorrhage at brain arteriovenous malformations. Furthermore, a high plasma level of IL-6 was shown to be an independent predictor of early hematoma growth of intracerebral hemorrhage. These observations suggest that IL-6 plays a role in the onset and progression of intracerebral hemorrhage. The association of the –572G→C polymorphism of IL6 with intracerebral hemorrhage implicates inflammatory processes in the pathophysiology of this condition. Cytokines induce the production of matrix metalloproteinases (MMPs), which degrade the extracellular matrix around blood vessels and may damage the vascular wall. Local release of IL-6 by...
endothelial cells may therefore contribute to vascular wall instability by stimulating the release and activation of MMPs. The association of the −572G→C polymorphism of IL6 with intracerebral hemorrhage might thus be attributable to MMP-mediated weakening of vascular walls already compromised by hemodynamic stress.

Intracranial aneurysm, which accounts for most of the incidence of subarachnoid hemorrhage, has a genetic component. First-degree relatives of patients with subarachnoid hemorrhage have a risk of experiencing ruptured intracranial aneurysms that is ≈4× that of the general population. We have now shown that the −863C→A polymorphism of TNF was significantly associated with the prevalence of subarachnoid hemorrhage, with the −863A allele being a risk factor for this condition. The amounts of TNF mRNA and protein as well as that of a proapoptotic downstream target, Fas-associated death domain protein, were found to be increased in human intracranial aneurysms. TNF and Fas-associated death domain protein may have deleterious effects on cerebral arteries by promoting inflammation and subsequent apoptosis in vascular and immune cells, thereby weakening vessel walls. TNF induces apoptosis in cultured cerebral endothelial cells by activating the protease caspase 3. Furthermore, the TNF concentration in the hemorrhagic cerebrospinal fluid of individuals who had experienced subarachnoid hemorrhage was greater for those with an unfavorable outcome than for those with a good outcome. In addition, individuals with the A allele of the −863C→A polymorphism of TNF have a higher risk of a poor outcome after subarachnoid hemorrhage. These previous observations and our present data suggest that TNF may play important roles in the development of intracranial aneurysm and outcome after subarachnoid hemorrhage.

We have also shown that the G→A (Gly243Asp) polymorphism of PKD1-like and the −55C→T polymorphism of UCP3 were significantly associated with the prevalence of subarachnoid hemorrhage, with the A and T alleles, respectively, of these polymorphisms representing risk factors for this condition. Genome-wide linkage analysis of intracranial aneurysm revealed significant linkage (logarithm of odds score = 4.2) to a single locus at 1p34.3. Several candidate genes for intracranial aneurysm, including PKD1-like, are located in this region. The localization of PKD1-like within this susceptibility locus for intracranial aneurysm together with the association of this gene with subarachnoid hemorrhage in the present study thus implicate PKD1-like as a candidate gene for subarachnoid hemorrhage. The T allele of the −55C→T polymorphism of UCP3 was shown to be associated with an atherogenic lipid profile and a lower risk for the development of type 2 diabetes mellitus. However, the relation of this polymorphism to subarachnoid hemorrhage has not been described previously.

Given the multiple comparisons of genotypes with atherothrombotic infarction, intracerebral hemorrhage, or subarachnoid hemorrhage in the present study, we adopted a level of P < 0.001 for significant association in multivariable logistic regression analysis, given that such P values resulted in an FDR of < 0.05 in the analysis. However, in the initial screen (Table 2), only the disease association of UCP3 satisfied the condition of FDR < 0.05; the disease associations of IL6, TNF, and PKD1-like should thus be interpreted with caution. The chances of a false-positive association of the IL6 polymorphism with atherothrombotic infarction and intracerebral hemorrhage were 18.2% and 60.6%, respectively, whereas the corresponding values for the TNF and PKD1-like polymorphisms and subarachnoid hemorrhage were 12.1% and 11.4%, respectively. In addition, the statistical evaluation by multivariable logistic regression analysis was not independent of that by the χ² test in the initial screen because the same set of genotyping data and disease phenotypes were used in both analyses. Given that the results of the present study may not be definitive, validation of our findings will require their replication with independent subject panels. It is also possible that ≈1 of the polymorphisms associated with each disorder in our study are in linkage disequilibrium with polymorphisms of other nearby genes that are actually responsible for the development of these conditions. Functional relevance of the identified polymorphisms to gene transcription or to protein structure or function has also not been determined in the present study. In conclusion, although our present results suggest that IL6 is a susceptibility locus for both atherothrombotic infarction and intracerebral hemorrhage, and that UCP3, TNF, and PKD1-like constitute susceptibility loci for subarachnoid hemorrhage, the lack of replication and the high FDRs for IL6, TNF, and PKD1-like in the initial screen are limitations of our study.

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Disclosures

None.

References


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