Risk and Severity of COPD Is Associated With the Group-Specific Component of Serum Globulin 1F Allele*

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Background: The finding that only 15 to 20% of cigarette smokers acquire COPD suggests that there is a genetic predisposition to the disease. Genetic polymorphism of the group-specific component of serum globulin (Gc-globulin), also known as vitamin-D–binding protein, is considered one of the candidates for the susceptibility to COPD. However, the role of Gc-globulin polymorphism in the development of COPD remains inconclusive.

Study objectives: To determine whether Gc-globulin gene polymorphism plays a role in the development of COPD in the Japanese population, and whether it is associated with the physiologic deterioration in COPD, and its radiologically detectable correlates.

Design: Association study.

Subjects and methods: One hundred three patients with COPD and 88 healthy smokers sampled from the Japanese population were genotyped for Gc-globulin by the restriction fragment-length polymorphism method. Based on the results of the genotyping, we investigated the relationship between Gc-globulin polymorphism and a physiologic/radiologic indicator of lung function, namely, the annual decline of FEV\textsubscript{1} (dFEV\textsubscript{1}) in 86 patients with COPD and 21 healthy smokers. Additionally, high-resolution CT parameters such as low-attenuation area percentage (LAA\%) and average CT number (mean CT score) were measured in 85 patients with COPD.

Results: There was an increased proportion of Gc\*1F homozygotes in the patients with COPD (32%) compared with the healthy smokers (17%) \([p = 0.01; \text{odds ratio}, 2.3; 95\% \text{ confidence interval}, 1.2 \text{ to } 4.6]\). Patients with COPD and the Gc\*1F allele showed a larger dFEV\textsubscript{1} \((p = 0.01)\), higher frequency with LAA\% > 60\% \((p = 0.01)\), and lower mean CT score than patients without this allele \((p = 0.03)\).

Conclusion: Gc-globulin polymorphism is significantly associated with susceptibility to COPD, and also with the severity of the disease. (CHEST 2004; 125:63–70)

Key words: Ge-globulin; high-resolution CT; low-attenuation area percentage; mean CT score; polymorphism; vitamin-D–binding protein

Abbreviations: bp = base-pair; CLA = continuous low-attenuation area; dFEV\textsubscript{1} = annual decline of FEV\textsubscript{1}; HRCT = high-resolution CT; HU = Hounsfield units; Gc-globulin = group-specific component of serum globulin; LAA\% = low-attenuation area percentage; MAF = macrophage-activating factor; PCR = polymerase chain reaction; RD = rapid decliner; sCLA = average size of continuous low-attenuation area units

Although the most critical factor for acquiring COPD is cigarette smoking,\textsuperscript{1} only 15 to 20\% of chronic smokers get this disease.\textsuperscript{2} Several epidemiologic studies\textsuperscript{3–6} have suggested familial clustering of the disease. This suggests that the genetic factors are likely to have a role in determining an individual’s susceptibility to COPD. Polymorphisms of several candidate genes have been investigated in relation to the development of COPD. One such candidate is the gene encoding the group-specific component of serum globulin (Gc-globulin), also called vitamin-D–binding protein.

Gc-globulin is a multifunctional, polymorphic, 55-kd protein,\textsuperscript{7} whose functions include being a precursor of macrophage-activating factor (MAF),\textsuperscript{8} and a co-chemotaxin for phagocytic cells.\textsuperscript{9} These functions suggest a role for this protein in the chronic inflammatory response in the lung.
Gc-globulin gene was localized to human chromosome 4q11-q13. There are three common polymorphisms in the structures of Gc-globulin that are encoded by one of three co-dominant alleles of the Gc-globulin gene, Gc*1F, Gc*1S, and Gc*2, and there are >124 rare variant alleles. Several studies have shown conflicting results in the relationship of Gc-globulin polymorphism and the risk for COPD. Thus, the role of its polymorphism relative to COPD susceptibility is not fully understood.

An important facet in investigating this protein is that the allele proportion varies considerably among populations. In the white population, the protein is reported to exhibit three major isotypes, namely, Gc-1F, Gc-1S, and Gc-2, with allele frequencies of 0.16, 0.56, and 0.28, respectively, whereas in the Japanese population, the same isotypes occur with the frequency of 0.49, 0.24, and 0.25. Ishii et al showed in the Japanese population that the proportion of Gc*1F homozygotes was significantly higher in patients with COPD than in healthy control subjects. This led us to hypothesize that a significant relationship may exist between Gc-globulin polymorphism and the risk for COPD in the Japanese population.

We also considered it important to test the contribution of Gc-globulin genotypes to the disease progression or severity in patients with COPD because, to our knowledge, this has not yet been investigated. The annual decline of FEV1 (dFEV1) is often taken to represent progressive airway obstruction and physiologic deterioration in smokers, and as an indication of disease progression in patients with COPD. Sandford et al investigated the relationship between various candidate gene genotypes, including Gc-globulin, and dFEV1 in a population of smokers; no relation was seen between Gc-globulin genotypes and decline in lung function. In addition to the evaluation of airway obstruction, it is also important to evaluate in patients with COPD the severity of parenchymal injury that is termed emphysema. Parameters such as low-attenuation area percentage (LAA%) and mean CT score in high-resolution CT (HRCT) have been shown to be useful in the assessment of emphysema. To test the hypothesis that Gc-globulin polymorphism has an important role in the susceptibility to COPD, we analyzed the polymorphism in patients with COPD and healthy smokers in a sample drawn from the Japanese population. We further examined the correlation between the genotypes and the extent of deterioration in the rate of airflow in patients with COPD presented by dFEV1. The correlation between the genotypes and the extent of emphysema was evaluated by several radiologic parameters assessed by HRCT.

**Materials and Methods**

**Subjects**

The study subjects for genotyping comprised 103 patients with COPD and 85 healthy smokers. Patients with COPD were recruited consecutively from the COPD clinic of Kyoto University Hospital if they had smoking history of >20 pack-years. The diagnosis of COPD was made according to the definition provided by the American Thoracic Society. Patients with reversible respiratory symptoms were considered to have a possibility of bronchial asthma and were excluded from the study. Healthy smokers with smoking history of >20 pack-years were recruited consecutively at the smokers’ clinic of Kyoto Disease Prevention Center (n = 68), or that of Ono Municipal Hospital (n = 20). Subjects were considered healthy smokers if they did not have COPD or other diseases, and their pulmonary function tests showed a FEV1/FVC ratio >70%. All subjects were of Japanese ancestry. This study was approved by the Ethics Committee of Kyoto University, and written informed consents were obtained from all subjects.

**Genotyping**

DNA for genotyping was extracted from blood using standard phenolchloroform method. To detect point mutations in exon XI (Glu/Asp 416 and Thr/Lys 420) of the Gc-globulin gene, polymerase chain reaction (PCR) was performed followed by restriction fragment-length polymorphism analysis. To amplify the region of interest that contains the point mutations, we used the upstream primer described by Schellenberg et al (5’TATGACCAAATGAAAGAAGS’), and we designed a downstream primer (5’TGACTAGATTGGAAGCATG’) according to the published Gc-globulin gene sequence. The PCR product is a fragment of 462 base-pairs (bp).

PCR was carried out with a thermal cycler (DNA Thermal Cycler; Perkin Elmer Cetus; Norwalk, CT). One hundred nanograms of genomic DNA was added to a mixture containing the following: 0.5 μmol/L of each primer; 3.75 U of Taq DNA polymerase (Amplitaq DNA Polymerase; Roche; Basel, Switzerland); 0.2 mM each of deoxyadenosine triphosphate, deoxycytidine triphosphate, deoxyguanosine triphosphate, and deoxythymidine triphosphate (Amersham Biosciences KK; Tokyo, Japan); 1.5 mM MgCl2; and 10 mM Tris Cl (pH 8.3) in a final volume of 150 μL. For amplification, the cycling parameters were 94°C for 30 s, 56°C for 30 s, and 72°C for 30 s, for 35 cycles. The PCR products were digested separately with restriction enzymes Hae III (Toyobo, Osaka, Japan) or Eco T14 I restriction enzymes (Takara Bio; Otsu, Japan) at 37°C overnight. Hae III cuts the Gc*1S allele at the point including the mutation Ghu (GTT, Gc*1S) → Asp (TGC, Gc*1F or Gc*2) into two bands of 295 bp and 167 bp, whereas Eco T14 I cuts Gc*2 allele into two bands of 302 bp and 156 bp including the mutation Thr (ACG, Gc*1F or Gc*1S) → Lys (AAG, Gc*2). Therefore, the PCR product from Gc*1F homozygotes alone remains uncut by either of the enzymes. The digested fragments were resolved on 3% agarose gels, stained with ethidium bromide (Invitrogen; Carlsbad, CA), and observed under ultraviolet light (Fig 1).
Low-attenuation area was defined as cut-off level between the normal lung density area and the analyzed. Each CT image was composed of 512 matrices (upper, middle, and lower lung) from each patient were analyzed automatically, and the total number of CLA and the continuous low-attenuation area (CLA) was recognized automatically, and the total number of CLA and the average size of CLA units (sCLA) of the three slices were calculated.

Measurement of Chest HRCT Parameters in Patients With COPD

The CT scans were taken in the supine position using a HRCT scanner (X-Vigor; Toshiba; Tokyo, Japan) with 2-mm collimation, scanning time of 1.0 s, 120-kilovolt electrical voltage, 200-mA electrical current, and 35-cm field of view. A high-resolution reconstruction algorithm for the lung (FC83; Toshiba) was employed. During scanning, the patients held their breath after a deep inspiration. Contrast medium was not used. Three slices (upper, middle, and lower lung) from each patient were analyzed. Each CT image was composed of 512 x 512 matrices with numerical data (CT numbers) in Hounsfield units (HU). The lung fields were automatically identified in each image. The cut-off level between the normal lung density area and the low-attenuation area was defined as ~960 HU. Considering that the LAA% of normal subjects was <30%, and LAA% of patients with COPD was 36.04 ± 60.8%, in our previous study, we defined the patients with LAA% of >60% as having severe emphysema at the outset of this study. The mean CT score was calculated as the average of the CT numbers in HU of all pixels in both lung fields in three slices. Each continuous low-attenuation area (CLA) was recognized automatically, and the total number of CLA and the average size of CLA units (sCLA) of the three slices were calculated.

Statistical Analysis

To test Gc-globulin phenotypic variance between patients with COPD and healthy smokers, and to compare the frequency of individuals over or under the threshold (dFEV₁ < 90 mL/yr, LAAS > 60%, or mean CT score < 940 HU) in the two populations, asymptotic normal tests for the equality of two population probabilities were performed. A Welch test was employed to test the difference of population averages in continuous variates between the two groups. StatView Version 5.0 (SAS Institute; Cary, NC) was used for the statistical calculations; p ≤ 0.05 was considered statistically significant.

Results

Subject Characteristics

The baseline characteristics and the results of baseline pulmonary function tests of 103 patients with COPD and 85 healthy smokers are shown in Table 1. In the initial evaluation of patients with COPD, 9 patients were classified in stage I, 38 patients were in stage IIA, 37 patients were in stage IIB, and 19 patients were in stage III. The evaluation was performed according to the Global Initiative for Chronic Obstructive Lung Disease guidelines.

Genotyping

Gc-globulin allele frequency and genotype frequency in each group are shown in Table 2. Allele frequency and genotype frequency for each group are shown in Table 2. Allele frequency and genotype frequency in each group are shown in Table 2. Allele frequency and genotype frequency in each group are shown in Table 2.
Data are presented as No. (%).

### Table 1—Baseline Characteristics of Study Subjects*

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Men/Women, No.</th>
<th>Age, yr</th>
<th>Smoking History, Pack-Years</th>
<th>FEV₁, L</th>
<th>FEV₁ % Predicted</th>
<th>FEV₁/FVC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with COPD (n = 103)</td>
<td>99/4</td>
<td>67.4 ± 7.8</td>
<td>58.3 ± 29.1</td>
<td>1.18 ± 0.49</td>
<td>45.3 ± 18.4</td>
<td>45.8 ± 10.4</td>
</tr>
<tr>
<td>Smoker control subjects (n = 88)</td>
<td>72/16</td>
<td>60.8 ± 12.0</td>
<td>41.1 ± 22.2</td>
<td>2.66 ± 0.56</td>
<td>88.4 ± 20.7</td>
<td>80.1 ± 7.8</td>
</tr>
</tbody>
</table>

*pData are presented as mean ± SD unless otherwise indicated.

frequencies for the healthy smokers were as follows: Ge*1F, 0.49; Ge*1S, 0.27; and Ge*2, 0.24. These values were similar to the reported allele frequencies from large studies in the Japanese population.16 Allele frequencies for the patients with COPD in the present study were as follows: Ge*1F, 0.58; Ge*1S, 0.22; and Ge*2, 0.19. Although there were no significant differences in allele frequencies between the two groups, there was an increased proportion of Ge*1F homozygotes in the patients with COPD (32%) compared with the healthy smokers (17%) \( [p = 0.01; \text{odds ratio}, 2.3; \text{95\% confidence interval, 1.2 to 4.6}] \). The baseline FEV₁ percentage predicted in patients with COPD and with Ge*1F alleles (ie, 1F-1F, 1F-1S, and 1F-2) was not significantly different from that in patients with COPD without it (ie, 1S-1S, 1S-2, and 2-2) \([44.8 ± 17.9\% \text{ vs } 48.4 ± 21.3\% , p = 0.54]\).

**dFEV₁**

Follow-up pulmonary function data for calculating dFEV₁ was available in 86 of the 103 patients with COPD, and 21 of the 88 smoker control subjects. There was no significant difference in age, smoking history, the baseline FEV₁ percentage predicted, and the distributions of Gc-globulin allele between subjects with 1-year follow-up data and those without them in either patients with COPD or control subjects. The dFEV₁ of patients with COPD (48.3 ± 62.7 mL) was significantly larger than that of control subjects (17.9 ± 32.5 mL, \( p < 0.0001 \)). There were 17 RDs (20%) in the group of patients with COPD, whereas there were no RDs in the smoker control group (\( p = 0.03 \)). There was no significant difference in dFEV₁ between Ge*1F homozygotic patients and patients with other genotypes (54.9 ± 66.4 mL vs 45.5 ± 60.7 mL, \( p = 0.54 \)); likewise, there was no significant difference in the frequency of RDs between the two groups (23% vs 20%, \( p = 0.78 \)).

### Table 2—Allele and Genotype Frequency in COPD Patients and Healthy Smoker Control Subjects*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients With COPD (n = 103)</th>
<th>Control Subjects (n = 88)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ge*1F</td>
<td>120 (58)</td>
<td>87 (49)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ge*1S</td>
<td>46 (22)</td>
<td>47 (27)</td>
<td>0.22</td>
</tr>
<tr>
<td>Ge*2</td>
<td>40 (19)</td>
<td>42 (24)</td>
<td>0.22</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1F-1F</td>
<td>33 (32)</td>
<td>15 (17)</td>
<td>0.014</td>
</tr>
<tr>
<td>1F-1S</td>
<td>29 (28)</td>
<td>27 (31)</td>
<td>0.70</td>
</tr>
<tr>
<td>1F-2</td>
<td>25 (24)</td>
<td>30 (34)</td>
<td>0.14</td>
</tr>
<tr>
<td>1S-1S</td>
<td>15 (11)</td>
<td>10 (11)</td>
<td>0.98</td>
</tr>
<tr>
<td>1S-2</td>
<td>3 (3)</td>
<td>5 (6)</td>
<td>0.35</td>
</tr>
<tr>
<td>2-2</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

*pData are presented as No. (%).

**HRCT Parameters**

Chest HRCT examination was performed in 85 patients with COPD. The relationship between genotypes and the value of each HRCT parameter is shown in Figures 2–4. There was no significant difference between Ge*1F homozygotes and Ge*1F heterozygotes (1F-1S and 1F-2) in any HRCT parameters (data not shown). Therefore, we compared the HRCT parameters between Ge*1F(+) patients and Ge*1F(−) patients. The number of subjects in each group was 72 and 13, respectively. Although the difference in the mean LAA% between the two patient groups did not reach significance (51.5 ± 13.3% vs 45.5 ± 10.5%, \( p = 0.07 \)), severely emphysematous patients with LAA% > 60% showed a significant association with Ge*1F(+) genotype (22 of 72 Ge*1F(+) vs 1 of 13 Ge*1F(−), \( p = 0.01 \); Fig 2). There was a significant difference in the mean CT score between the two patient groups (−929.6 ± 23.1 HU vs −918.0 ± 16.2 HU, \( p = 0.027 \); Fig 3). Simple linear regression analysis was used for studying correlations between LAA% and HRCT parameters.
and mean CT score. Mean CT score was linearly correlated with LAA% \( (R^2 = 0.97, p < 0.001) \), with a simple linear regression model as follows: mean CT score (HU) = \(-1.69 \times \text{LAA}\% - 842\). Patients with mean CT score < -940 HU were defined as having severe emphysema based on this model. Again, severely emphysematous patients with mean CT score < -940 HU were more frequently seen in the \( Gc^*1F(+) \) group than in the \( Gc^*1F(-) \) group (26 patients vs 0 patients, \( p < 0.0001; \) Fig 3). Additionally, sCLA was larger in \( Gc^*1F(+) \) patients than \( Gc^*1F(-) \) patients \((35.9 \pm 26.2 \text{ pixels vs } 22.7 \pm 12.1 \text{ pixels}, p = 0.004; \) Fig 4). There was no significant difference in total number of CLAs between the two groups \((5,005 \pm 2,117 \text{ vs } 4,267 \pm 2,135, p = 0.25)\).

**DISCUSSION**

This study showed that \( Gc^*1F \) homozygosity was significantly associated with COPD in a cohort of Japanese smokers, and that this genotype was less frequent in healthy smokers. Previous studies on \( Gc \)-globulin polymorphism have shown varied results in association of this polymorphism and the risk of COPD. Kueppers et al\(^{13} \) showed that the frequency of homozygous \( Gc-2 \) phenotype was only 0.01 in patients with COPD compared with 0.05 in control subjects, but the study performed by Kauffmann et al\(^{14} \) failed to confirm this result. Subsequently, Horne et al\(^{15} \) showed that the frequency of homozygous \( Gc-1F \) phenotype in patients with COPD was 0.06, and was greater than that in control subjects \((0.01; \text{relative risk, } 4.8)\). They also found that the phenotypes containing the \( Gc-2 (2-1F, 2-1S, \text{ and } 2-2) \) had a protective effect.\(^{15} \) More recently, Schellenberg et al\(^{12} \) again replicated the result showing decreased frequency of homozygous \( Gc*2 \) genotype in patients with COPD \((0.03) \) compared to control subjects \((0.14)\). However, they could not verify the results shown by Horne et al\(^{15} \) that \( Gc-1F \) homozygotes had an increased risk for COPD. They concluded that the reason was due to the insufficient number of subjects needed to verify the hypothesis that \( Gc*1F \) homozygotes had an increased risk.\(^{12} \) These studies were based on white populations in which the frequencies of the three alleles were 0.16, 0.56, and 0.28 for \( Gc*1F, Gc*1S \) and \( Gc*2 \), respectively.\(^{17} \) It has been noted that the frequency of the \( Gc \) allele varies with ethnicity; in the Japanese
population, it has been reported to be 0.49, 0.24, and 0.25 for Gc*1F, Gc*1S, and Gc*2, respectively. This distribution has a larger frequency of Gc*1F compared to that in whites. Our results and those of Ishii et al corroborate that Gc*1F homozygotes have an increased risk for COPD, at least in the Japanese population.

There are a few studies on the relationship between genetic factors and decline of lung function. As regards Gc-globulin genotypes among smokers, there was no difference reported between the fast decliners and nondecliners. Contrary to this finding, we have shown that patients with Gc*1F allele had notably larger dFEV1 than those without it, on the basis of equal baseline FEV1 percentage predicted between the two groups. The reason for this disparity in the results is not clear; however, there seem to be several differences in the study parameters. First, we applied a different definition of rapid decline, that is, dFEV1 > 90 mL as described previously, whereas the other study defined a dFEV1 > 3.0% predicted. Second, we investigated patients who already had COPD; this population would be expected to have a larger dFEV1 than smoker control subjects regardless of Gc-globulin genotypes.

In this study, the dFEV1 of the patients with COPD and Gc*1F allele was larger than that of the subjects without this allele, though the two groups showed no differences in the mean age, smoking history, and the baseline FEV1 percentage predicted. We interpret this to mean that the Gc*1F allele had some role in the deterioration of dFEV1 in patients with COPD. The reason why subjects with Gc*1F allele did not acquire the disease at a younger age compared with those without the allele may be related to other factors possibly involved in the development of COPD.

Previous studies have shown that LAA% and sCLA correlated well with FEV1 percentage predicted and FEV1/FVC. In HRCT examinations, patients with Gc*1F allele had a higher LAA%, lower mean CT score, and larger sCLA than patients without the allele, whereas no difference was observed in the baseline FEV1 percentage predicted. This result may suggest that patients with the Gc*1F allele tend to acquire a more severe emphysema than patients without the Gc*1F allele. There have been few attempts to define a correlation between genetic factors and emphysematous changes in HRCT. HRCT is less frequently used in clinical practice for the management of COPD than pulmonary function tests. We suppose the reason may be due to its higher cost and lack of feasibility of setting up the equipment. Further investigation is needed to clarify whether Gc-globulin polymorphism contributes to an early development of pathologic emphysematous lesions that are difficult to detect by pulmonary function tests.

Gc-globulin has two different biological functions related to inflammation. This protein enhances the chemotactic activity of C5a and C5a des-Arg for neutrophils. However, there were no differences between the three Gc-globulin isoforms in terms of their potency to induce neutrophil chemotaxis. Another function is to undergo conversion to a potent MAF by the removal of specific glycosylated moieties from the protein. The Gc-2 protein has no glycosylated Lys at residue 420 and is unable to be converted to MAF. This raises the possibility that in homozygous Gc*2 individuals, cigarette smoking may cause less pulmonary inflammation because of reduced MAF activity. We could not replicate the protective effect of Gc*2 allele shown by Horne et al, presumably because there is a relatively small frequency of Gc*2 allele in this patient cohort.

There are several limitations in our study. First, the age and smoking history in pack-years of the control group were not exactly equivalent to the COPD patient group. Considering that some sub-
jects in the control group might subsequently acquire COPD, with or without additional smoking exposure, the possibility remains that the different background of the two groups could influence the results of the genotyping. Ideally, the age and smoking history of the two groups should be exactly matched. Then the results of genotyping would be more clearly differentiated between the two groups. Secondly, only a small number of smoker control subjects were successfully followed up for > 1 year, and we obtained dFEV_{1} data in a segment of this group. This was because they stopped visiting the clinic on cessation of smoking. Thirdly, data on HRCT parameters were not collected in the healthy smoker group because the facilities where the healthy smokers were recruited were not equipped with the same imaging technique that was available for the patients with COPD. If healthy smokers with Ge^{*}1F allele could be shown to have larger dFEV_{1} and higher LAA% than those without the allele, our conclusion that the Ge^{*}1F allele is related to the development of COPD would be more clearly substantiated. The role of this allele in the early development of COPD remains to be investigated.

Though only Ge^{*}1F homozygotes were significantly associated with COPD and not the control subjects, we could not confirm a difference in dFEV_{1} or HRCT parameters between the patients with COPD and Ge^{*}1F homozygotes and those of Ge^{*}1F heterozygotes. From the data we obtained, we infer that the presence of a single Ge^{*}1F allele caused a rapid decline of FEV_{1} in patients who already had COPD. However, we were not able to demonstrate that Ge^{*}1F homozygosity was more likely to be associated with further rapid decline of FEV_{1} than Ge^{*}1F heterozygosity. As mentioned above, if dFEV_{1} and HRCT parameters were available in a sufficiently large control group, the role of Ge^{*}1F homozygosity or heterozygosity in deterioration of lung function or HRCT findings would have been clearly elucidated.

In conclusion, we showed that the incidence of Ge^{*}1F homozygosity was significantly higher in patients with COPD than in healthy smokers. Patients with COPD and the Ge^{*}1F allele had a faster decline of FEV_{1} than patients without the allele. Moreover, HRCT parameters indicated that patients with COPD with this allele had a more severe emphysema. The role of Gc-globulin genotypes in acquiring COPD remains to be elucidated.

ACKNOWLEDGMENT: The authors thank Dr. Kimio Morimune of the Graduate School of Economics, Kyoto University, for statistical analyses, and Dr. Koichi Nishimura, Department of Respiratory Medicine, Kyoto University Hospital, for clinical work on patients with COPD, and clinical data. An English-language scientific editor provided linguistic help for this article.

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