G-Protein β3 Subunit Gene Variant is Unlikely to Have a Significant Influence on Serum Uric Acid Level in Japanese Workers

YASUSHI SUWAZONO, ETSUKO KOBAYASHI, MIREI UETANI, KATSUYUKI MIURA,¹ YUKO MORIKAWA,¹ MASAO ISHIZAKI,² TERUHIKO KIDO,³ HIDEAKI NAKAGAWA¹ and KOJI NOGAWA

Department of Occupational and Environmental Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan, ¹Department of Epidemiology and Public Health, ²Department of Hygiene, Kanazawa Medical University, Ishikawa, Japan, ³Department of Community Health Nursing, Kanazawa University School of Health Sciences, Kanazawa, Japan

SUWAZONO, Y., KOBAYASHI, E., UETANI, M., MIURA, K., MORIKAWA, Y., ISHIZAKI, M., KIDO, T., NAKAGAWA, H. and NOGAWA, K. G-Protein β3 Subunit Gene Variant is Unlikely to Have a Significant Influence on Serum Uric Acid Level in Japanese Workers. Tohoku J. Exp. Med., 2006, 209 (2), 149-157 — The C825T variant of the G-protein β3 subunit (GNB3) gene has attracted renewed attention as a candidate gene for obesity, hypertension and hyperuricemia. The main role of G-protein is to translate signals from the cell surface into a cellular response. The 825T allele is associated with a splice variant of GNB3 protein and enhanced G-protein activation. We examined the relationship between this variant and the risk of hyperuricemia in Japanese workers. The study subjects were 1,452 men and 1,169 women selected from 3,834 men and 2,591 women in 1997. On the basis of common clinical criteria, hyperuricemia I was defined as serum uric acid ≥ 7.0 mg/dl in men and 6.0 mg/dl in women or taking antihyperuricemic medication. The hyperuricemia I group consisted of 186 men and 20 women and its control of 1,266 men and 1,149 women. Hyperuricemia II was defined as serum uric acid > 5.7 mg/dl (median) in men and 3.9 mg/dl (median) in women or taking antihyperuricemic medication. The hyperuricemic II group consisted of 684 men and 570 women and its control of 768 men and 599 women. To replicate previous significant results in young Caucasian men, we selected these criteria because the authors of the study in young Caucasian men adopted the median in their subjects as a cut-off. The statistical power was estimated as 99% based on the significant results in Caucasians. Genotype and allele distributions in men and women with hyperuricemia I and II were not significantly different from those in the corresponding control groups. Logistic regression analysis on hyperuricemia I and II, and multiple regression on serum uric acid level demonstrated no significant effect of the C825T genotype. Despite the sufficient statistical power, this study could not demonstrate the significant influence of C825T on hyperuricemia or serum uric acid. The targeting of this polymorphism is unlikely to be beneficial in the prevention of hyperuricemia in the general Japanese population. ——— G protein; hyperuricemia; polymorphism; Japanese population; uric acid

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In recent years, many genetic variations have been identified and associated with acquired chronic diseases such as hypertension and diabetes mellitus as well as congenital hereditary diseases. Such chronic diseases are considered to be polygenic and have multifactorial traits. In other words, the onset of these diseases may be influenced by various genes interacting reciprocally with a combination of host factors such as lifestyle and environmental factors.

Variants of the G-protein β3 subunit (GNB3) gene, such as C825T, have attracted renewed attention in recent years. The main role of G-protein is to translate signals from the cell surface into a cellular response (Siffert 2003). The 825T allele is associated with a splice variant of GNB3 protein and enhanced G-protein activation (Siffert et al. 1998) with ethnic distributions of the 825T allele frequency ranging from 20% to 80% (Siffert et al. 1999). Several studies have demonstrated that the 825T allele of the GNB3/C825T is associated with hypertension (Benjafield et al. 1998; Schunkert et al. 1998; Siffert et al. 1998; Beige et al. 1999; Dong et al. 1999; Hengstenberg et al. 2001). As obesity is an established major risk factor for hypertension, several studies investigated whether the 825T allele increases the risk for obesity (Siffert 2003) and demonstrated that this allele was associated with obesity or elevated body mass index (BMI) in several ethnic groups (Hegele et al. 1999; Siffert et al. 1999; Gutersohn et al. 2000; Brand et al. 2003; Dishy et al. 2003). However, little is known about the relationship between this polymorphism and serum uric acid level or hyperuricemia, despite the fact that hypertension and obesity are correlated to serum uric acid level or hyperuricemia (Li et al. 1997; Nakanishi et al. 1999; Rott and Agudelo 2003). To our knowledge, only one study has evaluated the relationship (Bührmann et al. 2004), showing that the serum uric acid level was significantly higher in carriers of the 825T allele (CT & TT, 321.3 μmol/l) than in individuals with the CC genotype (301.7 μmol/l). The odds ratios to display uric acid level above median (309.4 μmol/l) were significant in the CT (2.2) and TT genotype (3.1) with the CC genotype as reference group. However, they investigated only in young Caucasian men without consideration for other confounding variables. From an epidemiological point of view, in order to determine the influence of genetic polymorphisms in the occurrence of a specific disease, it is necessary to undertake large-scale studies in the general population. This prompted us to investigate in greater detail the relationship between the GNB3 gene (C825T) and serum uric acid or hyperuricemia in more than 2000 Japanese subjects. This included using multivariate analysis to examine whether polymorphism in this gene was independently associated with factors such as age, BMI, lifestyle, blood pressure and various clinical, biochemical and hematological data.

**Materials and Methods**

**Subjects**

The study was a cross-sectional design. The target subjects were 3,834 men and 2,591 women who worked in a zipper and sash factory in the Hokuriku district of Japan. All workers in this company underwent a legally required health check-up in 1997 that included measurement of height, weight and blood pressure together with analysis of blood samples and a self-administered questionnaire. After receiving ethics review board approval to carry out the proposed research, we sent a letter to each of the participants asking about their intention to participate in this study in 2001. Of the 2,008 males and 1,629 females who responded, 1,530 males and 1,213 females provided informed consent for study inclusion. After excluding subjects with missing data, analysis was carried out on 1,452 males and 1,169 females. In order to evaluate the influence of the C825T allele on serum uric acid level expressed as a continuous variable, subjects taking antihyperuricemic medication were excluded from the analyses. Using the above criteria, the final target population consisted of 1,443 men and 1,169 women. The study protocol was approved by the ethical review boards of Kanazawa Medical University and the Graduate School of Medicine, Chiba University.

**Genotyping**

 Buffy coats were isolated from venous blood samples collected from the subjects in 1997. The C825T genotype was determined by direct polymerase chain
reaction (PCR) amplification of the buffy coat using Ampdirect (Shimadzu, Kyoto) buffers and primers as described by Siffert et al. (1998). Ampdirect buffers allow PCR amplification directly from blood samples (Nishimura et al. 2002). The PCR sequence began with denaturation at 94°C for 5 min, followed by 40 cycles of denaturation at 94°C for 1 min, annealing at 60°C for 45 s, extension at 72°C for 1 min and a final extension at 72°C for 7 min. The PCR products were restricted with BseDl (Fermentas, Vilnius, Lithuania), separated on 2% agarose gels and then visualized under UV light by ethidium bromide staining. All genotyping had been completed in previous studies (Suwazono et al. 2004a, b).

Measurement of serum uric acid and diagnosis of hyperuricemia

The blood samples were collected randomly and non-fasting without any restrictions regarding meals. Serum uric acid level was measured by the uricase-peroxidase method (Pure Auto S UA; Daiichi Pure Chemicals, Tokyo) using an autoanalyzer (Hitachi 7700; Hitachi, Tokyo). Hyperuricemia was diagnosed and classified according to following criteria: (i) On the basis of common clinical criteria (Rathmann et al. 1998; Rott and Agudelo 2003), hyperuricemia I was defined as serum uric acid ≥ 7.0 mg/dl in men and 6.0 mg/dl in women or taking antihyperuricemic medication. The hyperuricemia I group consisted of 186 men and 20 women and its control of 1,266 men and 1,149 women. (ii) Hyperuricemia II was defined as serum uric acid > 5.7 mg/dl (median) in men and 3.9 mg/dl (median) in women or taking antihyperuricemic medication. The hyperuricemic II group consisted of 684 men and 570 women and its control of 768 men and 599 women. To replicate previous significant results in young Caucasian men (Bührmann et al. 2004), we selected these criteria because the authors of the study in young Caucasian men adopted the median in their subjects as a cut-off. This diagnosis of “Hyperuricemia” is not a strict medical diagnosis. The normal range of serum uric acid was 3.5 - 7.9 mg/dl in men and 2.6 - 6.0 mg/dl in women. A medical history was obtained using a self-administered questionnaire during the annual health examination. The responses in this questionnaire were confirmed by individual interviews with occupational physicians.

Other clinical factors

Various indices were used as potential explanatory factors for hyperuricemia and serum uric acid level including age, BMI, alcohol consumption, smoking habit, habitual exercise, menopausal status, mean blood pressure (mean BP), hematocrit, platelet count, glycosylated hemoglobin A1c (HbA1c) and plasma concentrations of alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), total serum cholesterol and creatinine. Alcohol consumption was classified into two categories as either (i) drinking at least six times a week or (ii) drinking less than six times a week. We adopted the same criterion in our previous studies (Suwazono et al. 2004a, b) because this seems to be very simple and sufficient to represent alcohol consumption as a covariate. Smoking habits were classified as either smoking or non-smoking, while habitual exercise was defined according to the presence or absence of regular exercise (at least light exercise once a week without shortness of breath or palpitations). Ex-smokers were categorized as “non-smokers.” Women were classified as pre- or post-menopausal. Mean BP was calculated by multiplying the diastolic pressure (DBP) by 2, adding the systolic pressure (SBP) and then dividing this sum by 3 (Cywinski 1980; Meaney et al. 2000).

Statistical analyses

In the univariate analyses, the genotypic and allelic frequencies of C825T were compared between subjects with hyperuricemia I or II and normal subjects using the Chi-square test (genotype) and Fisher’s exact test (allele). With regard to the power of the study, we calculated the genotypic frequencies in subjects with hyperuricemia II using the odds ratio (OR) of 2.2 for CT genotype and 3.1 for TT genotype as previously reported (Bührmann et al. 2004). The percentage prevalence of the CT or TT genotype in the hyperuricemic group was calculated from these ORs and the measured genotypic frequencies in normal subjects using the formula: (OR × 100 × percent CT or TT genotype in normal group) / (percent CC genotype in normal group + OR × percent CT or TT genotype in normal group) as described previously (Suwazono et al. 2004b). The power of the study was then calculated on the basis that 69% (n = 401) and 31% (n = 181) of normal men had the CT genotype and CC genotype respectively (Table 1). This represented 53% (n = 401 + 181 = 582) of men with the CT or CC genotype whilst the prevalence of hyperuricemia II was 47% (n = 177 + 348 = 525) of men with the CT and CC genotype. Assuming an OR of 2.2, the distribution of the genotypes in the hyperuricemia II group would be 83% for the CT genotype and 17% for the CC genotype. The criterion
for significance (alpha) was set at 0.05 (2-tailed). Therefore, with the sample size of 1,107 (582 normal and
525 subjects with hyperuricemia II), this study had
99.9% power to yield a statistically significant OR of 2.2
in men. In the normal women, the distribution was 67%
(n = 326) for the CT genotype and 33% (n = 159) for the
CC genotype, representing 52% (n = 326 + 159 = 485) of
the group. Forty-eight percent (n = 135 + 312 = 447) of
women with the CT or TT genotype exhibited hyperuri-
cemia II. With an odds ratio of 2.2, 82% of hyperurice-
mia II subjects would express the CT genotype and 18%
would express the CC genotype. Therefore, with the
sample size of 932, this study had more than 99.9%
power to yield a statistically significant OR in women.
Assuming OR of the TT genotype to CC genotype to be
3.1 (Bührmann et al. 2004), the statistical power was
99.9% or more in both men and women by similar calcu-
lation.

In order to evaluate the influence of genotype on
serum uric acid level, the means were calculated and
compared grouped according to gender, using one-way
analysis of variance (ANOVA) among three genotypes
and the \( t \)-test between CT & TT and CC genotypes. In
the previous study (Bührmann et al. 2004), the serum
uric acid level exhibited a significant 1.07-fold increase
in the CT & TT genotypes compared to the CC genotype.
Assuming that the same difference may exist in the pres-
ent study, the means of CT & TT genotypes would be 6.0
mg/dl in men and 4.2 mg/dl in women, i.e., 1.07 times
the measured mean uric acid levels in the CC genotype
(5.7 mg/dl in men and 3.9 mg/dl in women, Table 2).
With these means, measured standard deviations and
sample size, the statistical powers for the \( t \)-test in the
present study were calculated to be 99.2% in men and
99.9% in women.

In the multivariate analyses, logistic regression was
used to evaluate the effect of the C825T genotype on
hyperuricemia I and II using the following confounding
factors as the independent variables: age, BMI, alcohol
consumption, smoking habit, habitual exercise, hemato-
crit level, platelet count, ALT, \( \gamma \)-GTP, total serum choles-
terol, HbA1c, and creatinine. In women, menopause was
included and alcohol consumption was excluded from
the logistic model because there were only a small num-
ber of women (1.8%) who reported consuming alcohol
regularly. The same factors were used in multiple regres-
sion analyses in order to evaluate the effect of the C825T
genotype on serum uric acid level. Dummy variables for
alleles. The analyses were performed with SPSS 10.0J and
SamplePower 1.0 software (SPSS Inc., Chicago, IL,
USA). A \( p \) value < 0.05 was considered as statistically
significant.

**RESULTS**

The frequencies of genotype and allele in
hyperuricemia I or II and corresponding control
groups according to gender are shown in
Table 1. There was no significant difference in
the frequency of these genotypes or alleles.

The results of the one-way ANOVA and
\( t \)-test on serum uric acid level grouped according
to gender are summarized in Table 2. These data
shows that there was no significant difference in
either sex.

The results of the logistic regression analysis
on hyperuricemia I or II grouped according to
gender are shown in Table 3. While there was no
relationship between genotype and hyperuricemia
I or II in either sex, several other factors were
found to be determinants of the condition. In
men, age was negatively associated whilst BMI,
mean BP, \( \gamma \)-GTP, total serum cholesterol and cre-
atinine were positively associated with hyperuri-
cemia I. In women, BMI was positively associat-
ed with hyperuricemia I. Age was associated
negatively whilst BMI, mean BP, ALT and creati-
nine were associated positively with hyperurice-
mia II in both sexes. Alcohol consumption,
\( \gamma \)-GTP and total serum cholesterol in men and
menopause and hematocrit in women were posi-
tively associated with hyperuricemia II.

The results of the multiple regression analy-
ses on serum uric acid level are summarized in
Table 4 and show there was no significant rela-
tionship between the C825T allele and serum uric
acid level. Age was negatively associated whilst
BMI, mean BP, \( \gamma \)-GTP, total serum cholesterol and cre-
atinine were positively associated with serum uric
acid level in both sexes. Alcohol consumption
and \( \gamma \)-GTP in men and menopause, hematocrit
and ALT in women were positively associated
with the serum uric acid level.

**DISCUSSION**

In this study, no significant difference in
G-Protein C825T Gene and Hyperuricemia

The genotypic and allelic frequencies of GNB3/C825T was shown between the hyperuricemic and normal groups for both sexes in univariate analyses. Multiple logistic regression analysis confirmed that polymorphism in this gene was not associated with hyperuricemia, whereas several variables such as BMI and mean BP were significantly associated. The findings were less variable when subjects taking antihyperuricemic medication were excluded from the logistic regression analysis. Therefore, we consider that taking antihyperuricemic medication was not a significant confounding factor. Furthermore, one-way ANOVA, t-test and multiple regression analyses failed to reveal any significant influence of the C825T allele on serum uric acid level as a continuous

### Table 1. Frequencies (%) of genotype and allele in hyperuricemia I or II subjects and corresponding control groups.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group I (UA &lt; 7.0 mg/dl)</td>
<td>Control group I (UA ≥ 7.0 mg/dl)</td>
<td>Control group I (UA &lt; 6.0 mg/dl)</td>
<td>Control group I (UA ≥ 6.0 mg/dl)</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia I (UA ≥ 7.0 mg/dl)</td>
<td>Hyperuricemia I (UA ≥ 6.0 mg/dl)</td>
<td>Hyperuricemia I (UA &gt; 5.7 mg/dl)</td>
<td>Hyperuricemia I (UA &gt; 3.9 mg/dl)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>312 (24.6%)</td>
<td>46 (24.7%)</td>
<td>287 (25.0%)</td>
<td>7 (35.0%)</td>
</tr>
<tr>
<td>CT</td>
<td>650 (51.3%)</td>
<td>99 (53.2%)</td>
<td>628 (54.7%)</td>
<td>10 (50.0%)</td>
</tr>
<tr>
<td>TT</td>
<td>304 (24.0%)</td>
<td>41 (22.0%)</td>
<td>234 (20.4%)</td>
<td>3 (15.0%)</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1,274 (50.3%)</td>
<td>191 (51.3%)</td>
<td>1,202 (52.3%)</td>
<td>24 (60.0%)</td>
</tr>
<tr>
<td>T</td>
<td>1,258 (49.7%)</td>
<td>181 (48.7%)</td>
<td>1,096 (47.7%)</td>
<td>16 (40.0%)</td>
</tr>
<tr>
<td></td>
<td>Control group II (UA ≤ 5.7 mg/dl)</td>
<td>Hyperuricemia II (UA &gt; 5.7 mg/dl)</td>
<td>Control group II (UA ≤ 3.9 mg/dl)</td>
<td>Hyperuricemia II (UA &gt; 3.9 mg/dl)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>181 (23.6%)</td>
<td>177 (25.9%)</td>
<td>159 (26.5%)</td>
<td>135 (23.7%)</td>
</tr>
<tr>
<td>CT</td>
<td>401 (52.2%)</td>
<td>348 (50.9%)</td>
<td>326 (54.4%)</td>
<td>312 (54.7%)</td>
</tr>
<tr>
<td>TT</td>
<td>186 (24.2%)</td>
<td>159 (23.2%)</td>
<td>114 (19.0%)</td>
<td>123 (21.6%)</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>763 (49.7%)</td>
<td>702 (51.3%)</td>
<td>644 (53.8%)</td>
<td>582 (51.1%)</td>
</tr>
<tr>
<td>T</td>
<td>773 (50.3%)</td>
<td>666 (48.7%)</td>
<td>554 (46.2%)</td>
<td>558 (48.9%)</td>
</tr>
</tbody>
</table>

Significant difference was not observed. UA, uric acid.

### Table 2. Results of one-way ANOVA and t-test on serum uric acid.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (S.D.)</td>
<td>n</td>
<td>Mean (S.D.)</td>
</tr>
<tr>
<td>CC</td>
<td>356</td>
<td>5.68 (1.15)</td>
<td>294</td>
<td>3.94 (0.84)</td>
</tr>
<tr>
<td>CT</td>
<td>744</td>
<td>5.70 (1.12)</td>
<td>638</td>
<td>3.96 (0.81)</td>
</tr>
<tr>
<td>TT</td>
<td>343</td>
<td>5.68 (1.08)</td>
<td>237</td>
<td>4.00 (0.80)</td>
</tr>
<tr>
<td>CC</td>
<td>356</td>
<td>5.68 (1.15)</td>
<td>294</td>
<td>3.94 (0.84)</td>
</tr>
<tr>
<td>CT+TT</td>
<td>1,087</td>
<td>5.69 (1.11)</td>
<td>875</td>
<td>3.97 (0.80)</td>
</tr>
</tbody>
</table>

S.D., standard deviation. Significant difference was not observed. No subjects were taking antihyperuricemic medication.
variable. This finding was contrary to the previously reported result in young Caucasian men (Bührmann et al. 2004). In the present study, no significant odds ratio was obtained. Therefore, we could not determine whether the discrepancy was due to a different effect of \( \text{GNB3/C825T} \) in each of the ethnic groups, or to insufficient power of detection in the present study. As the observed genotype distribution was not shown in the previous study (Bührmann et al. 2004), we could not evaluate the difference in genotype distributions. Accordingly, we calculated statistical power in the present study, assuming the effect (i.e., OR of \( \text{GNB3/C825T} \) in \( \gamma \)-GTP) was the same as that in the previous study. As a result, the statistical power was proven sufficient for detection. Consequently, we concluded that the effect of \( \text{GNB3/C825T} \) was smaller than that in the previous study (Bührmann et al. 2004). Thus, we consider that such an assumption is necessary to interpret the result in the present study. On the other hand, the observed genotype distribution was in Hardy-Weinberg equilibrium in men \( (p > 0.05) \), but not in women \( (p < 0.05) \). Conceivably, this discrepancy between men and women may be due to differences in the migration of married women in different populations. However, this explanation could not be determined because the detailed data were not available in the present study. Nevertheless we did not think that this discrepancy affected the negative findings in the present study.

Important features of this study include the fact that data was collected from more than 2000 subjects and were examined for the influence of a wide range of confounding variables on hyperuricemia and uric acid level by using multivariate analyses. Previous study on this gene polymorphism has incorporated univariate analyses only (Bührmann et al. 2004). We therefore consider

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Hyperuricemia I</th>
<th>Hyperuricemia II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Genotype (TT/CC)</td>
<td>0.91 (0.56, 1.48)</td>
<td>0.34 (0.07, 1.75)</td>
</tr>
<tr>
<td>Genotype (CT/CC)</td>
<td>1.14 (0.76, 1.71)</td>
<td>0.69 (0.23, 2.08)</td>
</tr>
<tr>
<td>Smoking habit (smoker/non-smoker)</td>
<td>0.78 (0.55, 1.11)</td>
<td>5.62 (0.97, 32.63)</td>
</tr>
<tr>
<td>Alcohol consumption (6 times a week or more/less than 6 times a week)</td>
<td>1.23 (0.85, 1.78)</td>
<td>1.01 (0.99, 1.05)</td>
</tr>
<tr>
<td>Habitual exercise (absence/presence)</td>
<td>1.26 (0.89, 1.79)</td>
<td>0.37 (0.13, 1.02)</td>
</tr>
<tr>
<td>Menopausal status (post-/pre-menopausal)</td>
<td>1.00 (0.04, 3.22)</td>
<td>1.01 (0.90, 1.60)</td>
</tr>
<tr>
<td>Age</td>
<td>0.96** (0.94, 0.98)</td>
<td>1.04 (0.97, 1.12)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.12** (1.05, 1.19)</td>
<td>1.31** (1.16, 1.49)</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>1.04** (1.02, 1.05)</td>
<td>0.98 (0.94, 1.03)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>0.96 (0.90, 1.02)</td>
<td>1.15 (0.97, 1.37)</td>
</tr>
<tr>
<td>Platelet count (10⁴/mm³)</td>
<td>1.02 (0.99, 1.05)</td>
<td>1.00 (0.91, 1.09)</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>1.00 (0.99, 1.01)</td>
<td>0.97 (0.91, 1.03)</td>
</tr>
<tr>
<td>( \gamma )-GTP (IU/l)</td>
<td>1.01** (1.00, 1.01)</td>
<td>1.02 (0.99, 1.05)</td>
</tr>
<tr>
<td>Total serum cholesterol (mg/dl)</td>
<td>1.01 (1.00, 1.01)</td>
<td>1.02 (1.00, 1.03)</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>1.00 (0.66, 1.52)</td>
<td>1.03 (0.40, 2.66)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>69.82 (17.08, 285.48)</td>
<td>27.02 (0.36, 2,026.69)</td>
</tr>
</tbody>
</table>

\* Two-sided \( p < 0.05 \), \** two-sided \( p < 0.001 \). OR, odds ratio: The ratio of the former to the latter was CI, confidence intervals; BMI, body mass index; ALT, alanine aminotransferase; \( \gamma \)-GTP, \( \gamma \)-glutamyl transpeptidase;
on hyperuricemia I and II.

<table>
<thead>
<tr>
<th>Hyperuricemia II</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>0.89</td>
<td>0.65, 1.23</td>
<td>1.30</td>
</tr>
<tr>
<td>0.92</td>
<td>0.70, 1.21</td>
<td>1.15</td>
</tr>
<tr>
<td>0.84</td>
<td>0.66, 1.07</td>
<td>1.22</td>
</tr>
<tr>
<td>1.60''</td>
<td>1.25, 2.05</td>
<td></td>
</tr>
<tr>
<td>0.98</td>
<td>0.78, 1.24</td>
<td>0.88</td>
</tr>
<tr>
<td>2.68''</td>
<td></td>
<td>1.49, 4.80</td>
</tr>
<tr>
<td>0.97''</td>
<td>0.96, 0.98</td>
<td>0.97''</td>
</tr>
<tr>
<td>1.09''</td>
<td>1.04, 1.14</td>
<td>1.09''</td>
</tr>
<tr>
<td>1.02''</td>
<td>1.01, 1.03</td>
<td>1.02''</td>
</tr>
<tr>
<td>1.01</td>
<td>0.96, 1.05</td>
<td>1.17''</td>
</tr>
<tr>
<td>1.02</td>
<td>1.00, 1.04</td>
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<tr>
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<td>1.01, 1.03</td>
<td>1.04''</td>
</tr>
<tr>
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</tr>
<tr>
<td>0.90</td>
<td>0.68, 1.18</td>
<td>1.29</td>
</tr>
<tr>
<td>17.97''</td>
<td>6.66, 48.48</td>
<td>42.09''</td>
</tr>
</tbody>
</table>

estimated for categorical variables. HbA\textsubscript{ic}, glycosylated hemoglobin A\textsubscript{ic}.

the design of our study may improve epidemiological accuracy. Furthermore, as far as we know, other polymorphic genes for human urate transporter 1 (Ichida et al. 2004; Graessler et al. 2006), endothelial constitutive nitric oxide synthase (Lee et al. 2003), alpha2-adrenoceptor (Masuo et al. 2005), tumor necrosis factor-alpha (Schulz et al. 2004), 5-hydroxytryptamine receptor 2A (Suwazono et al. 2006), and methylene tetrahydrofolate reductase (Zuo et al. 2000) have been associated with uric acid levels or its metabolism. Another notable feature of this study was that it investigated gene polymorphism in Japanese workers which included both sexes and a wide age range. From an epidemiological point of view, it is important to establish the genotypic distribution and association of polymorphism with hyperuricemia or serum uric acid level in the general population.

We have evaluated the influence of the \textit{GNB3/C825T} allele on hypertension and obesity (Suwazono et al. 2004a, b) and found a lack of associations that had been previously reported in different ethnic groups. A similar discrepancy to the result in young Caucasian men was also found in this study. Rosskopf and colleagues characterized the entire \textit{GNB3} gene and defined new polymorphisms (Rosskopf et al. 2000, 2002), some of which almost demonstrated linkage disequilibrium with C825T. Siffert (2003) pointed out that the complex of these polymorphisms appeared to cause alternative splicing of the 825T allele. Recently, an association of the \textit{GNB3/C825T} polymorphism with the autonomic nervous system was demonstrated in young healthy Japanese men (Matsunaga et al. 2005). G-proteins play an important role along with the major autonomic neurotransmitter receptors in autonomic transmission (Schnabel and Bohm 1996; Kirstein and Insel 2004). Because the 825T allele of \textit{GNB3} is associated with enhanced G-protein activation (Siffert et al. 1998), different functions in sympathetic and parasympathetic system activities may result from modification of G protein-coupled receptor-mediated signaling in the autonomic system (Matsunaga et al. 2005). Therefore, the pathology of the C825T polymorphism may be an altered autonomic nervous system.

There is also evidence that the haplotype of C825T polymorphism with other polymorphisms of the \textit{GNB3} (i.e., C1429T) differ between ethnic groups (Rosskopf et al. 2002). This difference may explain the different association of C825T with hypertension, obesity and hyperuricemia between different ethnic groups. Our study does not exclude the possibility that other variants around C825T polymorphism may influence uric acid levels and the prevalence of hyperuricemia in the Japanese population. Therefore, future investigations should also investigate whether haplotypes of C825T and other polymorphisms in \textit{GNB3} are associated with hyperuricemia or serum uric acid level.

In conclusion, this study indicated that the \textit{GNB3/C825T} polymorphism is not a significant factor for hyperuricemia or serum uric acid level in Japanese people and that targeting this poly-
G-Protein C825T gene and hyperuricemia in the general Japanese population.

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References
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