Common Variant of PDZK1, Adaptor Protein Gene of Urate Transporters, is Not Associated with Gout

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To the Editor:

Gout, a multifactorial disease characterized by acute inflammatory arthritis, is caused as a consequence of hyperuricemia. Previous genetic studies have revealed that gout and serum uric acid (SUA) levels have associations with various genes such as ATP-binding cassette transporter, subfamily G, member 2 (ABCG2/BCRP)1,2,3, glucose transporter 9 (GLUT9/SLC2A9)4, organic anion transporter 4 (OAT4/SLC22A11)5,6, monocarboxylate transporter 9 (MCT9/SLC16A9)7,8, and leukine-rich repeat-containing 16 A (LRRC16A/CARMIL)9,10.

PDZ domain containing 1 (PDZK1, also known as NHERF3) plays a pivotal role as a scaffolding protein that forms urate transportosomes6,7,8,9 with URAT1, ABCG2, and OAT4 (Figure 1). A single-nucleotide polymorphism (SNP), rs12129861, was first reported to have an association between PDZK1 gene and SUA1, which was confirmed by a replication study10. Although the minor allele of rs12129861 is shown to decrease SUA1,10, to the best of our knowledge, no study to date has investigated its association with clinically defined patients with gout.

In our present study, we therefore investigated the association between clinically defined gout and rs12129861 of PDZK1 with male Japanese subjects.

As the case group, 741 male Japanese patients with primary gout were collected from the outpatients of Midorigaoka Hospital (Osaka, Japan) and Jikei University Hospital (Tokyo, Japan). All patients were diagnosed according to the criteria established by the American College of Rheumatology11. For the control group, 1302 male Japanese individuals were collected from the Japan Multi-Institutional Collaborative Cohort Study, because they had normal SUA levels (≤ 7.0 mg/dl) without any gout history. The mean ages with SD of case and control groups were 55.0 ± 13.2 and 52.7 ± 8.4 years, respectively, and their respective mean body mass index was 24.6 ± 3.5 and 23.2 ± 2.8 kg/m². Each subject participating in our study provided written informed consent. Our study was approved by the institutional ethical committees, and all procedures involved were performed in accordance with the Declaration of Helsinki. Genomic DNA was extracted from whole peripheral blood cells3. Genotyping of rs12129861 was performed by the TaqMan method (Life Technologies Corp.) with a LightCycler 480 (Roche Diagnostics)3. To confirm their genotypes, more than 50 samples were subjected to direct sequencing with the following primers: forward 5′-TGT TTA TTA GTA AGT C-3′, and reverse 5′-CAG TAG AAG TAG GGT TTC ACC-3′. DNA sequencing analysis was performed with a 3130xl Genetic Analyzer (Life Technologies)2. The chi-square test was used for association analysis with SPSS v.22.0 (IBM Japan Inc.).

Table 1 shows the genotyping result of rs12129861 for 741 patients with gout and 1302 controls. The call rate for rs12129861 was 97.4%. The p value for Hardy-Weinberg equilibrium was 0.73. A p value that suggested mistyping was not obtained. The minor allele frequencies of the variant rs12129861 showed no significant association with gout in the allele frequency mode (p = 0.30; Table 1). Therefore, we indicated that rs12129861, a common SNP of PDZK1, had no association with gout susceptibility, even though it was reported to have an association with SUA1,10.

PDZK1 is a scaffolding protein which has 4 PDZ domains. Similar to another scaffolding protein Na⁺/H⁺ exchanger regulatory factor 1 (NHERF1), PDZK1 is one of the key molecules for urate transportosomes6,7,8, and is known to bind urate transporters at its PDZ domains and to mediate the subcellular localization of those proteins (Figure 1). In addition, our previous study indicated that LRRC16A, which was reported to have an association with SUA1, has an association with gout susceptibility attributable to the transportosome failure6. PDZK1 is, therefore, thought to play a role in urate transport through this stabilization and/or anchoring effect of urate transporters6,7. Together with the fact that PDZK1 is expressed in the kidney7, it seems reasonable that the SNP of PDZK1 would have an association with SUA levels and subsequently with gout as a result of transportosome failure.

However, our present study showed that rs12129861 of PDZK1 has no association with gout. This may be partly because of the difference of the investigated population and/or because of the limited sample (2043 individuals). Our result with patients with gout does not deny the presence of urate transportosomes involving PDZK1 because the association between rs12129861 and SUA1,10, as well as the molecular interaction among PDZK1 and urate transporters6,7,8,9, has already been reported. Nevertheless, the advantage of our study is the quality of the cases: all of the patients with gout who participated in our study were diagnosed by

![Figure 1. Urate transportosome in the renal tubular cells. PDZK1 (also known as NHERF3) is a scaffolding protein that binds to several urate transporters such as URAT1, OAT4, and NPT1. As for ABCG2, the interaction with PDZK1 is shown to be weak (dotted line)7. Together with NHERF1, which also scaffolds urate transporters (OAT4, NPT1, and MRP4), PDZK1 plays a pivotal role in forming a urate-transporting multimolecular complex (urate transportosomes) in humans.](Image 110x146 to 470x332)
expert physicians as primary gout at gout clinics. In our present study, it would be adequate to analyze the relationship between an SNP and gout susceptibility with only male patients, because female patients are rare in Japan. Indeed, only 10 female cases (1.3%) were collected at the same clinics in the same period. Therefore, the reliability of the result with our case population would be higher than those with self-reported case populations to identify the genetic factor of gout. Although further studies of PDZK1 are necessary to reveal the relationship between PDZK1 variants and gout, our study at least revealed that rs12129861 of PDZK1 is not a strong genetic risk factor for gout.

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ACCREDITATION

Dr. Takada and Dr. Matsuo contributed equally to this work.

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REFERENCES


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Table 1. Association analysis of rs12129861 of PDZK1 gene in gout cases and controls.

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Case</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>G/G</td>
<td>575</td>
<td>951</td>
</tr>
<tr>
<td>G/A</td>
<td>156</td>
<td>281</td>
</tr>
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<td>19</td>
</tr>
<tr>
<td>p</td>
<td>0.54</td>
<td>—</td>
</tr>
<tr>
<td>MAF</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>OR</td>
<td>0.30</td>
<td>0.90</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.74–1.10</td>
<td>—</td>
</tr>
</tbody>
</table>

MAF: minor allele frequency; Ref: reference.