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

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) 5, organic anion transporter 4 (OAT4/SLC22A11) 4, monocarboxylate transporter 9 (MCT9/SLC16A9) 1,2,3, glucose transporter 9 (GLUT9/SLC2A9) 5, organic anion transporter 4 (OAT4/SLC22A11) 4, monocarboxylate transporter 9 (MCT9/SLC16A9) 1,2,3, and leukine-rich repeat-containing 16 A (LRRC16a/CARMIL) 1,6.

PDZ domain containing 1 (PDZK1, also known as NHERF3) plays a pivotal role as a scaffolding protein that forms urate transportosomes5,7,8,9 with URAT1, ABCG2, and OAT4 (Figure 1). A single-nucleotide polymorphism (SNP), rs12129861, was first reported to have an association between PDZK1 gene and SUA 1, which was confirmed by a replication study 10. Although the minor allele of rs12129861 is shown to decrease SUA 1,10 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 Rheumatology 11. 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 was diagnosed according to the criteria established by the American College of Rheumatology 11. For the control group, 1302 male Japanese individuals were diagnosed as healthy controls without any history of gout.

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 SUA 1,10.

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 transportosomes 6,7,8, 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 SUA 1, has an association with gout susceptibility attributable to the transportosome failure 6. PDZK1 is, therefore, thought to play a role in urate transport through this stabilization and/or anchoring effect of urate transporters 7,8. Together with the fact that PDZK1 is expressed in the kidney 7, 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 transportosome involving PDZK1 because the association between rs12129861 and SUA 1,10, as well as the molecular interaction among PDZK1 and urate transporters 6,7,8,9, 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 direct morphological evidence. Moreover, our study analyzed the association between clinically defined patients with gout and rs12129861.

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![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). Together with NHERF1, which also scaffolds urate transporters (OAT4, NPT1, and MRP4), PDZK1 plays a pivotal role in forming a urate-transporting multimeric complex (urate transportosomes) in humans.](https://www.jrheum.org)
acknowledges Dr. Takada and Dr. Matsuo contributed equally to this work.

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

<table>
<thead>
<tr>
<th>rs12129861</th>
<th>Genotypes</th>
<th>p</th>
<th>MAF</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
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<td>Case</td>
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<tr>
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<tr>
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<td>8</td>
<td>0.90</td>
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</table>

MAF: minor allele frequency; Ref: reference.

REFERENCES


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