Note
Common variant of PDZ domain containing 1 (PDZK1) gene is associated with gout susceptibility: A replication study and meta-analysis in Japanese population

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ABSTRACT

PDZ domain containing 1 (PDZK1) is a scaffold protein that organizes a transportsome and regulates several transporters’ functions including urate and drug transporters. Therefore, PDZK1 in renal proximal tubules may affect serum uric acid levels through PDZK1-binding renal urate transporters. Two previous studies in Japanese male population reported that a PDZK1 single nucleotide polymorphism (SNP), rs12129861, was not associated with gout. In the present study, we performed a further association analysis between gout and rs12129861 in a different large-scale Japanese male population and a meta-analysis with previous Japanese population studies. We genotyped rs12129861 in 1210 gout cases and 1224 controls of a Japanese male population by TaqMan assay. As a result, we showed that rs12129861 was significantly associated with gout susceptibility (P = 0.016, odds ratio [OR] = 0.80, 95% confidence interval [CI] 0.67–0.96). The result of the meta-analysis among Japanese populations also showed a significant association (P = 0.013, OR = 0.85, 95% CI 0.75–0.97). Our findings show the significant association between gout susceptibility and common variant of PDZK1 which reportedly regulates the functions of urate transporters in the urate transportsome.

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1. Introduction

PDZ domain containing 1 (PDZK1) is a scaffold protein that binds to various transporters including drug transporters [1–3]. An example of such transporters is the organic anion transporting polypeptide 1A2 (OATP1A2), which is expressed in kidney and functions as a drug transporter [4]. In this scenario, PDZK1 regulates the transport function of OATP1A2 by modulating protein internalization via a clathrin-dependent pathway and by enhancing protein stability [1].

From a different perspective, rs12129861, a single nucleotide polymorphism (SNP), was reported to be associated with serum uric acid (SUA) levels in a genome-wide association study [5]. Rs12129861 is located near PDZK1 (approximately 2 kb upstream) and may affect the gene expression levels of PDZK1. However, in previous Japanese population reports [6,7] of clinically-defined male gout cases, rs12129861 has not shown a significant association with gout susceptibility.

In this study, we performed a further association study between gout and rs12129861 in a different large-scale Japanese population and a meta-analysis with previous Japanese population reports [6,7].

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2. Materials and methods

2.1. Patients and controls

This study was approved by the institutional ethical committees (National Defense Medical College and Nagoya University). All procedures were performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from each subject participating in the study. From the outpatients of Ryugoku East Gate Clinic (Tokyo, Japan), 1210 male Japanese patients with primary gout were recruited. All the patients were diagnosed with gout according to the criteria established by the American College of Rheumatology [8]. As the control group, 1224 Japanese men without gout history or hyperuricemia (SUA levels > 7.0 mg/dL) were selected from participants in the Shizuoka area in the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study) [9,10]. The mean age of cases and controls was 45.3 ± 10.4 and 53.1 ± 8.8 years old, respectively, and their mean body-mass index was 25.4 ± 3.7 and 23.3 ± 2.7 kg/m², respectively.

2.2. Genetic and statistical analyses

Genomic DNA was extracted from whole peripheral blood as previously described [11]. Genotyping of the PDZK1 polymorphism (rs12129861) was performed using a TaqMan assay (Thermo Fisher Scientific Inc., Waltham, MA) as previously described [7]. All of statistical analyses were performed with SPSS v.22.0 (IBM Japan Inc., Tokyo, Japan) and the software R (version 3.1.1) [12] with meta package [13]. Chi-square test was used for association and Hardy–Weinberg equilibrium analyses. A meta-analysis among present and previous studies [6,7] was performed by the DerSimonian and Laird [14] random-effects model. Cochran’s Q test and $I^2$ were used as measurements of heterogeneity among the present and two previous [6,7] studies. A $P$ value < 0.05 was considered statistically significant.

3. Results

The rs12129861 of PDZK1 genotyping results for 1210 gout cases and 1224 controls are shown in Table 1. The genotyping call rate for rs12129861 was 99.3%. In the control group, this variant was in Hardy–Weinberg equilibrium ($P > 0.05$).

In contrast to previous Japanese studies’ results [6,7], the present study shows a statistically significant association between gout and rs12129861 ($P = 0.016$, odds ratio (OR) with 95% confidence interval (CI) 0.80 [0.67–0.96]). In the meta-analysis among the present and previous Japanese studies [6,7] was performed by the DerSimonian and Laird [14] random-effects model. Cochran’s Q test and $I^2$ were used as measurements of heterogeneity among the present and two previous [6,7] studies. A $P$ value < 0.05 was considered statistically significant.

4. Discussion

As a component of a transportsome, PDZK1 regulates the function of several transporters including drug [15–17]. A transportsome is a transporting multicomplex composed of transporters and scaffold proteins [15–17]. In human kidney, the urate transportsome is located at the apical membrane of proximal tubular cells and contains several urate transporters [15–17], such as ATP-binding cassette transporter, subfamily G, member 2 (ABCG2/BCRP), organic anion transporter 4 (OAT4/SLC22A11), urate transporter 1 (URAT1/SLC22A12), type 1 sodium-dependent phosphate transporter (NPT1/SLC17A1), and multidrug resistance protein 4 (MRP4/ABCC4). Common variants of ABCG2 [18] significantly increase gout [19–21] and hyperuricemia risks [22,23]. Additionally, OAT4 [24], URAT1 [25–28], and NPT1 [27–30] genes are associated with gout susceptibility. PDZK1 and sodium protein exchanger regulatory factor 1 (NHERF 1) assemble the scaffolding network connecting these transporters in the transportsome [16,17].

To date, two previous reports showed lack of association between the PDZK1 rs12129861 polymorphism and gout susceptibility in the Japanese population; however, as shown in Fig. 1, the direction of the effect was similar in both studies [6,7]. Therefore, we performed an additional association analysis in a different larger Japanese population. A significant association between rs12129861 and gout susceptibility was evidenced by the present replication study and the meta-analysis with previous reports [6,7]. These findings imply that lack of association between rs12129861 and gout susceptibility was due to the limited number of samples in the previous studies [6,7]. Moreover, other studies report the association between gout and PDZK1 polymorphisms in Han Chinese [27,31] and New Zealand population [28]. Two of these reports [28,31] showed positive association consistently with the present study results. Since previous genome-wide association studies showed that common variant of PDZK1 are associated with SUA [5,32], PDZK1 variants could be associated with SUA levels [15–17], such as ATP-binding cassette transporters [15–17].

In conclusion, the PDZK1 rs12129861 showed the association with gout susceptibility which might lead to individual differences in urate transport through the urate transportsome. Our findings also suggest that this PDZK1 variant might be associated with individual differences in drug transport through the drug transportsome.

Table 1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Allele frequency mode</th>
<th>$P$ value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G</td>
<td>0.02</td>
<td>0.016</td>
<td>0.80 (0.67–0.96)</td>
</tr>
<tr>
<td>G/A</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAF</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>972</td>
<td>212</td>
<td>14</td>
</tr>
<tr>
<td>Control</td>
<td>939</td>
<td>261</td>
<td>18</td>
</tr>
</tbody>
</table>

CI, confidence interval; MAF, minor allele frequency; OR, odds ratio.

Fig. 1. Meta-analysis of PDZK1 rs12129861 polymorphism for gout in Japanese male populations. The meta-analysis was performed among results of the present and two previous Japanese male population studies (Urano et al., 2013 [6] and Takada et al., 2014 [7]) by the random-effects (DerSimonian and Laird) model. The sizes of the black boxes are proportional to the inverse of the squared standard error. The horizontal lines indicate the 95% CIs of ORs. The diamond shows the summary OR, and the width indicates the 95% CI. The summary OR was 0.85 (95% CI 0.75–0.97), which was statistically significant ($P_{meta} = 0.003$).

Conflict of interest

The authors declare that they have no conflict of interest.
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References