**ABCG2 variant has opposing effects on onset ages of Parkinson’s disease and gout**

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**Funding Information**
Supported by grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, the Ministry of Health, Labour and Welfare of Japan, the Ministry of Defense of Japan, the Japan Society for the Promotion of Science, the Kawano Masanori Memorial Foundation for Promotion of Pediatrics, and the Gout Research Foundation of Japan.

Received: 6 November 2014; Accepted: 30 November 2014

**Annals of Clinical and Translational Neurology** 2015; 2(3): 302–306
doi: 10.1002/acn3.167

**Abstract**

Uric acid (urate) has been suggested to play a protective role in Parkinson’s disease onset through its antioxidant activity. Dysfunction of ABCG2, a high-capacity urate exporter, is a major cause for early-onset gout based on hyperuricemia. In this study, the effects of a dysfunctional ABCG2 variant (Q141K, rs2231142) were analyzed on the ages at onset of gout patients (N = 507) and Parkinson’s disease patients (N = 1015). The Q141K variant hastened the gout onset (P = 0.0027), but significantly associated with later Parkinson’s disease onset (P = 0.025). Our findings will be helpful for development of more effective prevention of Parkinson’s disease.

**Introduction**

Parkinson’s disease (PD) is a multifactorial disease characterized by selective cell death of dopaminergic neurons. Oxidative stress is well known to be one of the major causes of PD development.¹ On the other hand, uric acid (UA), which has an antioxidant effect on the central nervous system (CNS), may play a protective role in onset and development of PD.²,³ Gout, a consequence of hyperuricemia, is also associated with a lower risk of PD.⁴

Previously, common dysfunctional variants of ATP-binding cassette transporter, sub-family G, member 2 (ABCG2, also known as BCRP), a urate transporter gene,⁵,⁶ have been revealed to be a major cause of early-onset gout.⁷ The common variant (Q141K, rs2231142) of ABCG2 is proven to be a dysfunctional variant by in vitro functional studies.⁵,⁶

This study aimed to evaluate whether the Q141K variant of ABCG2 could delay the age at onset (AAO) of PD in a relatively large population of Japanese patients.
Patients and Methods

Study participants
This study was approved by the institutional ethical committees, and all procedures involved in this study were performed in accordance with the Declaration of Helsinki. Informed consent in writing was obtained from each subject participating in this study. A total of 1015 PD patients (464 male and 548 female) and 507 gout male patients was collected and then genetically analyzed. PD patients were collected in Juntendo University (Tokyo, Japan) and Kobe University (Kobe, Japan). Diagnosis of PD was made by board-certified neurologists of the Japanese Society of Neurology, based on the presence of at least two cardinal features of PD with no secondary cause, no levodopa unresponsiveness, or no early signs of more extensive nervous system involvement. Clinically defined gout cases were collected in the Kyoto Industrial Health Association (Kyoto, Japan).

Genetic analysis
Genomic DNA was extracted from whole peripheral blood cells. For PD patients, genotyping of Q141K (rs2231142) in ABCG2 gene was performed by direct sequencing using the following primers: forward, 5'-AT-GGAGTTAACTGTCAATTGCC-3', and reverse, 5'-CAC-GTTCATATATGTAACAAGCC-3'. DNA sequencing analysis was performed with a 3130xl Genetic Analyzer (Life Technologies Corporation, Carlsbad, CA). The genotyping data of PD patients collected in Kobe University were obtained from the result of previous GWAS using the Illumina Infinium HumanHap550 array (Illumina, Inc., San Diego, CA). For gout patients, genotyping of Q141K in ABCG2 gene was performed by TaqMan assay (Life Technologies Corporation) with a LightCycler 480 (Roche Diagnostics, Mannheim, Germany).

Statistical analysis
In the statistical analysis, SPSS v.17.0J (IBM Japan Inc., Tokyo, Japan) was used for all calculations. Regression analysis was used for the association analysis.

Table 1. Genotype of ABCG2 variant Q141K (rs2231142) for gout and PD patients.

| Q141K (rs2231142) | N (%)           |
|------------------|----------------|
|                  | C/C            | C/A          | A/A          | Total       | MAF          |
| Gout cases       | 131 (25.8)     | 257 (50.7)   | 119 (23.5)   | 507 (100.0) | 0.49         |
| PD cases         | 509 (50.1)     | 425 (41.9)   | 81 (8.0)     | 1015 (100.0)| 0.29         |

PD, Parkinson’s disease; MAF, minor allele frequency.

Results
The results of genotyping of gout and PD patients are shown in Table 1. Figure 1 shows the AAO of gout and PD participants of each genotype of ABCG2 Q141K. The AAO (mean ± standard error) of gout were 40.4 ± 1.1 years old, 42.0 ± 0.7 years old, and 45.0 ± 1.1 years old for patients with Q141K homozygous (A/A), heterozygous (C/A) mutation, and without Q141K mutation (C/C), respectively. On the other hand, the AAO of PD were 58.5 ± 1.1 years old, 58.2 ± 0.5 years old, and 56.6 ± 0.5 years for patients with Q141K homozygous, heterozygous mutation, and without mutation, respectively. The AAO of gout with homozygous mutation was 4.6 years younger than those without Q141K mutation, while the AAO of PD with homozygous mutation was 1.6 years older than those without Q141K mutation.

The Q141K mutation of ABCG2 hastened the onset of gout significantly (P = 0.0027; see Fig. 1A); on the contrary, this variant significantly delayed the PD onset (P = 0.025; see Fig. 1B).

Discussion
This study revealed for the first time that a common dysfunctional variant of ABCG2 (Q141K, rs2231142) has surprisingly differential effects on two common diseases, significantly delaying the AAO of PD, while hastening that of gout.

ABCG2 encodes ATP-dependent transporter for urate excretion both in gut and kidney. Molecular functional studies revealed that ABCG2 dysfunction elevates serum UA levels. As UA is the strong antioxidant, ABCG2 dysfunction might have a neuroprotective effect. In fact, our study showed that the dysfunctional variant of this UA-related gene, ABCG2, could have a protective effect against PD, which is wholly consistent with the previous studies suggesting that the higher levels of serum UA are negatively correlated with the risk of PD and its rate of progression.

So far, only a few genetic analyses have been performed about the association between PD onset and UA-related genes. However, there is no report demonstrating that...
a single variant of ABCG2 could significantly affect the AAO of PD.

Together with the antioxidant effect of UA, our results strongly support the hypothesis that UA should reduce the risk of PD as an antioxidant, because oxidative stress is involved in the pathogenesis of PD. In addition to its expression in gut and kidney, ABCG2 highly expresses in the blood brain barrier (BBB).\textsuperscript{21} Therefore, we propose a physiological model that ABCG2 exports urate from the brain side to the blood side at BBB (see Fig. 2). Since ABCG2 dysfunction decreases urate excretion via gut\textsuperscript{14,15} and kidney\textsuperscript{16} which results in serum UA elevation,\textsuperscript{5,6,14,16} it therefore has a pathogenic effect on earlier onset of gout. Elevated serum UA also should result in elevated UA levels in CNS. In addition, ABCG2 dysfunction could decrease urate excretion via BBB that enhances the

![Bar chart showing the age at onset of gout and PD for different genotypes of ABCG2 Q141K](image)

**Figure 1.** ABCG2 dysfunctional variant (Q141K) and the age at onset (AAO) of gout/PD. The AAO of gout was significantly hastened as the number of minor alleles of Q141K increased ($P = 0.0027$); on the contrary, the AAO of PD was significantly delayed as the number of minor alleles of Q141K increased ($P = 0.025$). The AAO of gout with homozygous mutation (A/A) was 4.6 years younger than those without Q141K mutation (C/C). And the AAO of PD with homozygous mutation was 1.6 years older than those without Q141K mutation. Each bar represents the mean with standard error.

![Diagram showing the role of ABCG2 in urate excretion](image)

**Figure 2.** Contrary effects of ABCG2 dysfunction on PD and gout. ABCG2 is expressed in gut, kidney, and blood brain barrier (BBB) and exports urate. ABCG2 dysfunction in gut and kidney elevates the serum uric acid (UA) levels and subsequently causes gout. In this proposed model, ABCG2 dysfunction in BBB plays an important role on increasing UA levels in central nervous system (CNS), together with increased serum UA by ABCG2 dysfunction in gut and kidney.
elevation of UA levels in CNS as shown in our proposed model (see Fig. 2). In this model, ABCG2 dysfunction coordinately increases UA levels in CNS by the combined two differential mechanisms shown in Figure 2, although other UA-related gene variants have not been reported to have such differential mechanisms to elevate UA levels in CNS. Thus, the dysfunction of ABCG2 both in gut/kidney and BBB could cooperatively contribute to the elevated UA levels in CNS. These proposed differential mechanisms are consistent with our present result, which showed the differential effects on AAO of two common diseases, gout and PD. By these two differential mechanisms, therefore, ABCG2 dysfunction could have a significant neuroprotective effect for later onset of PD through increased UA, the strong antioxidant (see Fig. 2). That is why ABCG2 dysfunction could have significant effects on PD and be important in PD pathogenesis. Furthermore, the regulation of UA levels in serum and CNS could be applicable for prevention and therapy of PD.22

Acknowledgments

Supported by grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, the Ministry of Health, Labour and Welfare of Japan, the Ministry of Defense of Japan, the Japan Society for the Promotion of Science, the Kawano Masanori Memorial Foundation for Promotion of Pediatrics, and the Gout Research Foundation of Japan. The authors thank all the participants involved in this study. We are also indebted to Y. Takada, T. Nakamura, H. Nakashima, Y. Sakurai, J. Abe, K. Gotanda, Y. Morimoto, H. Inoue, H. Ogata, S. Tatsukawa, Y. Shichijo, Y. Tanahashi, and A. Akashi, National Defense Medical College, Tokorozawa, Japan, for genetic analysis and enlightening discussion, and to Y. Takada, T. Nakamura, H. Nakashima, Y. Sakurai, J. Abe, K. Gotanda, Y. Morimoto, H. Inoue, H. Ogata, S. Tatsukawa, Y. Shichijo, Y. Tanahashi, and A. Akashi, National Defense Medical College, Tokorozawa, Japan, for genetic analysis and enlightening discussion, and to T. Takada, the University of Tokyo Hospital, Tokyo, Japan, and Kimiyoshi Ichida, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan, for their helpful discussion.

Author Contribution

H. M., W. S., T. C., Y. K., A. N., S. S., M. S., T. T., and N. S. performed genetic analyses. H. T., W. S., H. O., M. F., K. N., T. S., K. Kaida., K. Kamakura., T. T., and N. H. performed clinical evaluations and medical record reviews. H. M. and T. C. wrote the paper. All authors contributed to data interpretation and manuscript preparation.

Conflicts of Interest

None declared.

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