[CASE REPORT]

Rare Genotype of His/His in *NUDT15* Codon 139 and Thiopurine-associated Adverse Events in a Case of Ulcerative Colitis

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Abstract:

Thiopurine drugs are commonly used to treat immunologic diseases. However, the narrow therapeutic safety margin demands evidence-based precision medicine approaches. *NUDT15* variants are associated with thiopurine-induced adverse events, particularly in Asians. We herein report a rare genotype of His/His in *NUDT15* codon 139 in a case of ulcerative colitis and review the relevant literature. The patient experienced severe thiopurine-associated adverse events, including leukopenia and alopecia. There is no literature on the His/His genotype in *NUDT15* codon 139, and our case suggests cautious use or the contraindication of thiopurines for patients with this genotype.

Key words: inflammatory bowel disease, His/His genotype, *NUDT15*, thiopurine, leukopenia, ulcerative colitis

(Intern Med 59: 1611-1613, 2020)

(DOI: 10.2169/internalmedicine.4261-19)

Introduction

Thiopurine drugs, including 6-mercaptopurine (6-MP) and its prodrug azathioprine (AZA), are commonly used for inflammatory bowel diseases (IBDs), rheumatic disease, acute lymphoblastic leukemia, and autoimmune hepatitis. However, *nucleoside diphosphate-linked moiety X-type motif 15* (*NUDT15*) variants are reported to show a significant association with thiopurine-induced adverse events, particularly in Asians.

NUDT15 is a 164-amino-acid protein that belongs to the nudix hydrolyses enzyme family, which mainly consists of pyrophosphohydrolases that act on nucleoside diphosphate. The function of this enzyme is to hydrolyze the thiopurine effector metabolites 6-thio-deoxy-GTP (dGTP) and 6-thio-GTP, thereby limiting the efficacy of thiopurines. The *NUDT15* genetic variants disrupt the function of *NUDT15* to varying degrees (1, 2).

We previously analyzed and established a method to accu-

rately identify the risk of codon 139 genotypes in adverse events associated with thiopurines in patients with IBDs, using the results of the MENDEL study in 2018 (3). However, cases with genetic variants of His/His in codon 139 were excluded. Owing to their rarity, cases with the His/His genetic variant in codon 139 have not been reported in Asian patients (Table) (1, 3-7). Therefore, the treatment strategy for patients with the His/His variant in codon 139 remains unclear.

Case Report

A 40-year-old man who had been diagnosed with ulcerative colitis 6 months earlier was referred to our unit, as he was resistant to induction therapy with 5-aminosalicylic acid, followed by prednisolone and leukocytapheresis. He was hospitalized and administered 4.0 mg/day tacrolimus to resolve abdominal pain and diarrhea and was discharged with the same dose of tacrolimus and 5.0 mg/day prednisolone. *NUDT15* genetic polymorphism testing (1) revealed

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Received: November 26, 2019; Accepted: February 26, 2020; Advance Publication by J-STAGE: April 9, 2020

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Figure 2. Star (★) allele-based haplotypes of *NUDT15* reported in patients. The diplotypes described in Table are combinations of the haplotypes.

All of the haplotypes (refer to Fig. 2) and diplotypes that induce thiopurine-associated leukopenia in Asian patients are summarized in Table. The estimated enzyme activity in haplotype cases with p.Arg139His is intermediate, whereas that in diplotype cases with the codon 139 His/His genotype is predicted to be low, regardless of the codon 18 genotype. Therefore, the codon 18 genotype may be ignored when determining the risk of adverse events (7).

We suggest cautious treatment with a low dose of 6-MP (5-10 mg/day) or the contraindication of thiopurines when the Arg/Arg genotype in codon 139 is replaced by Cys/His or Cys/Cys, respectively (3); such treatment lines are also recommended for patients with His/His. Further research will be required to clarify the risk of *NUDT15*-associated thiopurine-induced adverse events. Furthermore, although a case report may not determine the causal association, the accumulation of cases of this rare genotype is expected to help clarify the best management of unique cases.

The authors state that they have no Conflict of Interest (COI).

Financial Support

Sequence analyses were supported by AMED under Grant Number 19ek0410056 to Y. Kakuta.

References

1. Moriyama T, Nishii R, Perez-Andreu V, et al. NUDT15 polymor-

phisms alter thiopurine metabolism and hematopoietic toxicity. *Nat Genet* **48**: 367-373, 2016.

2. Valerie NC, Hagenkort A, Page BD, et al. NUDT15 hydrolyzes 6-thio-deoxyGTP to mediate the anticancer efficacy of 6-thioguanine. *Cancer Res* **76**: 5501-5511, 2016.
3. Kakuta Y, Kawai Y, Okamoto D, et al. NUDT15 codon 139 is the best pharmacogenetic marker for predicting thiopurine-induced severe adverse events in Japanese patients with inflammatory bowel disease: a multicenter study. *J Gastroenterol* **53**: 1065-1078, 2018.
4. Yang SK, Hong M, Baek J, et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. *Nat Genet* **46**: 1017-1020, 2014.
5. Chao K, Wang X, Cao Q, et al. Combined detection of NUDT15 variants could highly predict thiopurine-induced leukopenia in Chinese patients with inflammatory bowel disease: a multicenter analysis. *Inflamm Bowel Dis* **23**: 1592-1599, 2017.
6. Fan X, Yin D, Men R, Xu H, Yang L. NUDT15 polymorphism confer increased susceptibility to thiopurine-induced leukopenia in patients with autoimmune hepatitis and related cirrhosis. *Front Pharmacol* **10**: 346, 2019.
7. Kakuta Y, Izumiyama Y, Okamoto D, et al. High-resolution melt analysis enables simple genotyping of complicated polymorphisms of codon 18 rendering the NUDT15 diplotype. *J Gastroenterol* **55**: 67-77, 2020.
8. Tadaka S, Saigusa D, Motoike IN, et al. jMorp: Japanese Multi Omics Reference Panel. *Nucleic Acids Res* **46**: D551-D557, 2018.

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