

[CASE REPORT]

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

Kei Tomiyoshi¹, Hiroki Sato¹, Kentaro Tominaga¹, Yuzo Kawata¹, Daisuke Okamoto², Yoichi Kakuta², Junji Yokoyama¹ and Shuji Terai¹

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

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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

¹Division of Gastroenterology, Niigata University Medical and Dental Hospital, Japan and ²Division of Gastroenterology, Tohoku University Graduate School of Medicine, Japan

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Correspondence to Dr. Hiroki Sato, pyloki-sato@med.niigata-u.ac.jp

Table. NUDT15 Polymorphisms and Thiopurine-associated Leukopenia in Asian Patients.

Reference	Diagnosis†	Country	Number of patients	Reported haplotype	Possible diplotype and estimated enzyme activity‡
4	IBD	Korea	978	p.Arg139Cys	Normal: Arg/Arg, Intermediate: Arg/Cys, Low: Cys/Cys (codon 139)
1	ALL	Guatemala, Singapore, Japan	270	p.Arg139Cys p.Arg139His p.Val18Ile p.Val18_Val19insGlyVal	Normal: ★ 1/★ 1 Intermediate: ★ 1/★ 2, ★ 1/★ 3, ★ 1/★ 4, ★ 1/★ 5 Low: ★ 3/★ 5, ★ 2/★ 3, ★ 3/★ 3
5	IBD	China	732	p.Arg139Cys p.Val18_Val19insGlyVal p.Val18Ile	Normal: ★ 1/★ 1, Intermediate: ★ 1/★ 2, ★ 1/★ 3, ★ 1/★ 5, ★ 1/★ 6 Low: ★ 2/★ 3, ★ 2/★ 6, ★ 3/★ 3, ★ 3/★ 5
3	IBD	Japan	1,291	p.Arg139Cys p.Arg139His	Normal: Arg/Arg, Arg/His, Intermediate: Arg/Cys, Low: Cys/His, Cys/Cys (codon 139)
6	AIH	China	149	p.Arg139Cys	Normal: Arg/Arg, Intermediate: Arg/Cys, Low: Cys/Cys (codon 139)
7	IBD	Japan	1,245	p.Val18Ile p.Val18_Val19insGlyVal p.Gly17_Val18del	N+N: ★ 1/★ 1, N+I: ★ 1/★ 4, ★ 1/★ 5, ★ 1/★ 6, N+L: ★ 1/★ 2, ★ 1/★ 3, ★ 1/★ 9, I+L: ★ 3/★ 5, ★ 2/★ 6, ★ 2/★ 5, ★ 3/★ 4, ★ 2/★ 4, L+L: ★ 3/★ 3, ★ 2/★ 3, ★ 2/★ 2
Our case	IBD	Japan	1	p.Arg139His	His/His (codon 139)

†IBD: inflammatory bowel disease, ALL: acute lymphocytic leukemia, AIH: autoimmune hepatitis

‡N: Normal, I: Intermediate, L: Low enzyme activity; for star allele-based haplotyping, refer to Fig. 2

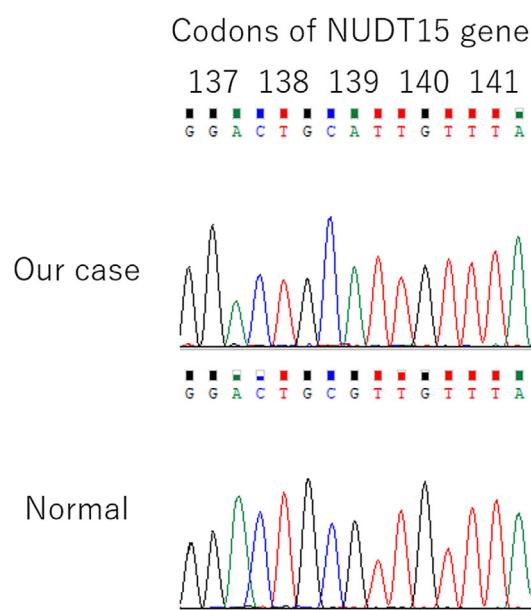


Figure 1. A Sanger sequence chromatogram around codon 139 of *NUDT15*. Exons 1-3 on *NUDT15* were analyzed. The homozygous mutation of c.416G>A leading to p.Arg139His was observed in our case.

the genetic variant of His/His in codon 139. Accordingly, as maintenance therapy, AZA was started at a low dose of 25 mg/day and increased to 50 mg/day after 2 weeks, based on a stable peripheral white blood cell count of 5,650/ μ L.

However, on day 40 from the initiation of AZA therapy, he returned to our unit with severe fatigue and anorexia; a blood test showed severe leukopenia, 1,650/ μ L (neutrophil count: 21.5/ μ L). The 6-thioguanine nucleotide level was

within the therapeutic range at 72 pmol/ 8×10^8 red blood cells. He suffered from severe alopecia. Upon hospitalization, all medications, including AZA, were ceased, and granulocyte colony-stimulating factor was used to increase his white blood cell count to 4,440/ μ L. He was discharged on day 18 and commenced vedolizumab therapy at a starting dose of 300 mg per 2 weeks that was gradually tapered to 300 mg per 8 weeks. He remains in remission.

We analyzed the exonic sequences of *NUDT15* and identified only the His/His variant (Fig. 1); no functional variants in coding regions besides His/His on codon 139 were identified.

All procedures performed in the subject were in accordance with the 1964 Declaration of Helsinki. Informed consent was obtained from the participant involved in the study.

Discussion

We herein report a rare case of ulcerative colitis with a His/His mutation; the patient had acute and severe leukopenia (white blood cell count <2,000/ μ L, <8 weeks) along with severe alopecia. In the MENDEL study, which involved 1,291 patients with IBD with a history of thiopurine usage, Arg/Arg, Arg/His, Arg/Cys, Cys/His, and Cys/Cys genotypes in codon 139 were found in 74.2%, 0.5%, 21.3%, 0.2%, and 3.8%, respectively (3). The His/His genotype was not observed, so the frequency of this genotype was considered even rarer than those observed. According to the sequence data of 4,700 Japanese individuals in the Tohoku Medical Megabank Organization, the allele frequency of p.Arg139 His is 0.0008, so the genotype frequency of His/His is even lower (estimated at 0.00000064) (8).

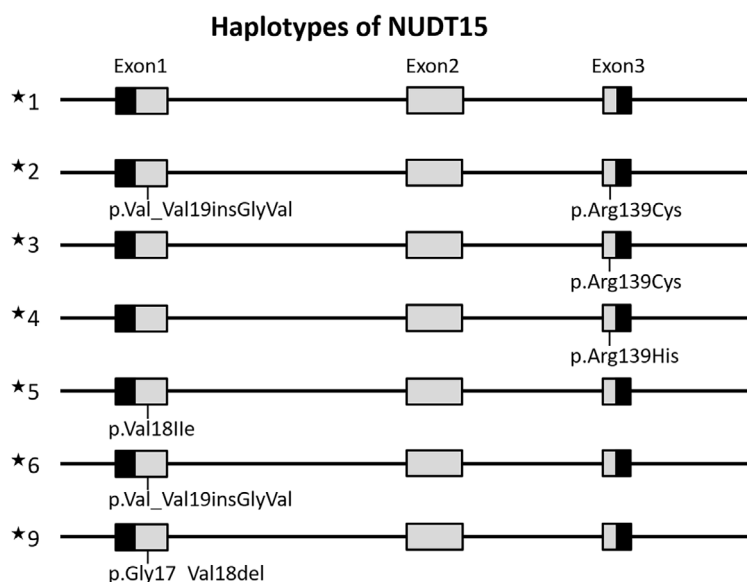


Figure 2. Star (*) allele-based haplotypes of *NUDT15* reported in patients. The diplotypes described in Table are combinations of the haplotypes.

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).

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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, Hagenkott 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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