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CASE REPORT

Severe myelosuppression and alopecia after thiopurine initiation in a patient with *NUDT15* deficiency

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Thiopurines are a class of immunosuppressant and antineoplastic agents. They are widely used in the treatment of inflammatory bowel disease, haematological malignancies and autoimmune diseases, but can cause significant toxicity. Inherited gene mutations are now recognized as independent risk factors for severe adverse drug reactions to thiopurines even at 10-fold dose reductions. We present a case of thiopurine toxicity resulting in severe myelosuppression, hepatotoxicity and alopecia in an individual with homozygous *3/*3 loss-of-function alleles in the *NUDT15* gene. Our case highlights important differences in gene mutation frequencies between races that can help guide pharmacogenomic testing.

KEYWORDS
adverse drug reactions, NUDT15, thiopurine toxicity, TPMT

1 | INTRODUCTION

Thiopurines are a class of immunosuppressant and antineoplastic agents that include **mercaptopurine**, **azathioprine** (prodrug of mercaptopurine) and **thioguanine**. They are widely used in treating inflammatory bowel disease, haematological malignancies, autoimmune diseases and various dermatological conditions.[1] However, thiopurines are associated with significant adverse drug reactions, and 15–40% of patients will discontinue treatment due to intolerance. Well-documented adverse reactions include gastrointestinal symptoms, myelosuppression, infection and, rarely, secondary malignancy.[2]

Here, we present a case of severe thiopurine toxicity resulting in myelosuppression, hepatotoxicity and alopecia secondary to inherited loss-of-function mutations in the nudix hydrolase 15 (*NUDT15*) gene.

2 | CASE REPORT

A 41-year-old South Asian female initially presented with menorrhagia and was diagnosed with high-risk acute promyelocytic leukaemia (APL; PML-RARA positive). She was treated with induction chemotherapy consisting of prednisone, idarubicin, all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), followed by 2 cycles of consolidation therapy with ATRA and ATO alone. Her postconsolidation bone marrow aspirate showed complete disease remission with undetectable PML-RARA transcript levels, and she was subsequently started on maintenance therapy with ATRA, **methotrexate** and mercaptopurine administered every 3 weeks for a total of 8 planned cycles. Bloodwork at the time of starting maintenance therapy was haemoglobin (Hb) 97 g/L, white blood cell count (WBC) 6.7 $\times$ 10^9/L, platelet count (plt) 185 $\times$ 10^9/L and absolute neutrophil count (ANC) 4.43 $\times$ 10^9/L.

Seven weeks after starting maintenance therapy, she presented to hospital with a 2-week history of fatigue and malaise, anorexia, bruising, and recurrent menorrhagia. On examination, there was extensive alopecia, mucositis and oral ulcers, and petechiae of the lower extremities. On bloodwork, she was found to have severe pancytopenia (Hb 60 g/L, WBC 0.9 $\times$ 10^9/L, plt 4 $\times$ 10^9/L, ANC 0 $\times$ 10^9/L) and elevated liver enzymes (alanine transaminase 82 U/L [reference: 7–40 U/L], alkaline phosphatase 122 U/L [reference: 40–150 U/L], total bilirubin 14 µmol/L [reference: <22 µmol/L]).

Work-up identified mild iron deficiency anaemia and hepatosplenomegaly with fatty infiltration on abdominal ultrasound but otherwise normal haemolysis markers, infectious screen for hepatitis B and C, HIV, Epstein–Barr virus, cytomegalovirus, parvovirus, thyroid function, and vitamin B12 levels. A repeat bone marrow biopsy showed hypocellularity (<10% cells) but no evidence of APL recurrence.

Based on clinical features and the absence of a plausible alternative aetiology, a presumptive diagnosis of mercaptopurine toxicity was made. The patient underwent genetic testing and was found to have wildtype alleles in the thiopurine-S-methyltransferase (*TPMT*) gene, but homozygous loss-of-function alleles in the *NUDT15* gene (c.415C > T; *3/*3), resulting in complete loss of NUDT15 protein function. She was diagnosed with severe mercaptopurine toxicity secondary to an inherited NUDT15 protein deficiency, resulting in myelosuppression, hepatotoxicity and alopecia. While methotrexate toxicity can also cause hepatotoxicity and alopecia, in the context of the identified *NUDT15* mutations, this was favoured to be a less likely explanation for the patient's clinical presentation.

Mercaptopurine was stopped and the patient was treated with red blood cell and platelet transfusions, filgrastim, tranexamic acid and

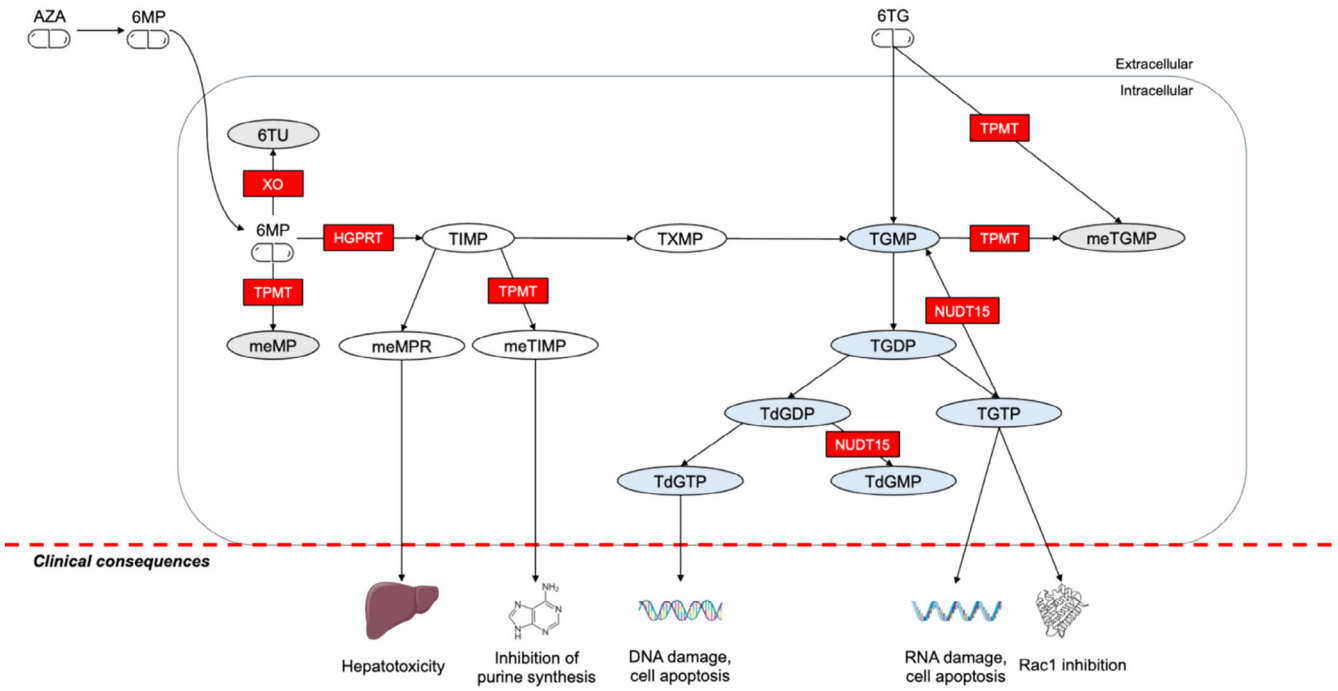

FIGURE 1 Thiopurine metabolism.[1] Thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) are enzymes primarily responsible for thiopurine metabolism within lymphocytes. TPMT catalyses the S-methylation of thiopurine drugs. NUDT15 converts cytotoxic triphosphate metabolites to less active monophosphate metabolites. Active thioguanine nucleotides are labelled in blue. Inactive metabolites are labelled in grey. 6MP, 6-mercaptopurine; 6TG, 6-thioguanine; 6TU, 6-thiouric acid; AZA, azathioprine; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; meMP, methylmercaptopurine; meMPR, methylmercaptopurine riboside; meTGMP, methylthioguanine monophosphate; meTIMP, methylthioinosine monophosphate; Rac1, Ras-related C3 botulinum toxin substrate 1; TdGDP, deoxy-thioguanine diphosphate; TdGMP, deoxy-thioguanine monophosphate. TdGTP, deoxy-thioguanine triphosphate; TGDP, thioguanine diphosphate; TGMP, thioguanine monophosphate; TGTP, thioguanine triphosphate; TIMP thioinosine monophosphate; TXMP, thioxanthine monophosphate; XO, xanthine oxidase.

leuprolide to suppress her menses. She had slow-to-recover cell counts and remained transfusion dependent until her discharge from hospital approximately 22 days later. Her discharge bloodwork showed Hb 78 g/L, WBC 2.2×10^9/L, plt 34×10^9/L, and ANC 0.82×10^9/L. Mercaptopurine was omitted from her subsequent therapy regimens given the risk of toxicity even with significant dose reductions.

3 | DISCUSSION

Inherited gene mutations in *TPMT* and *NUDT15* can substantially increase an individual's risk of severe thiopurine toxicity. Our case highlights a gap in current guidelines on pretreatment genetic screening for thiopurine initiation (particularly for *NUDT15* testing) and key racial differences in the population prevalence of mutations that can help guide individualized pharmacogenetic testing.

TPMT and *NUDT15* encode 2 eponymous enzymes that play essential roles in thiopurine metabolism. Thiopurine drugs are metabolized intracellularly to form active thioguanine nucleotides (TGNs; Figure 1). These nucleotides are cytotoxic to lymphocytes and induce cellular apoptosis through inhibition of purine synthesis, interruption of DNA and RNA transcription, and inhibition of **Rac1**, an antiapoptotic protein—thereby dampening the immune response. TPMT and NUDT15 convert active TGNs into noncytotoxic byproducts. Consequently, gene mutations can result in a loss of enzymatic activity, overproduction of active TGNs and end-organ toxicity.[3]

Mutations in the *TPMT* gene are commonly implicated in cases of severe thiopurine toxicity. These mutations are inherited in an autosomal codominant pattern, and individuals who possess 1 loss-of-function allele are considered intermediate metabolizers whereas individuals who possess 2 loss-of-function alleles are considered poor metabolizers.[4] Poor metabolizers almost universally develop severe thiopurine toxicity even at 10-fold dose reductions. Three polymorphisms (*2, *3A and *3C) account for over 90% of all intermediate and poor metabolizers in the general population, and this increases to over 95% with inclusion of a fourth variant (*3B), highlighting both the practicality and potential yield of genetic screening (Figure 2).[5] Pretreatment *TPMT* screening is supported by randomized control data; 1 study consisting of 783 individuals with inflammatory bowel disease (IBD) showed that pretreatment *TPMT* screening compared to weight-based dosing alone reduced the rate of adverse haematological events by 10-fold in at-risk individuals.[6] Accordingly, pretreatment *TPMT* testing is commonplace among patients with IBD and in other medical specialties including haematology, rheumatology and dermatology.[7–9]

However, individuals of Hispanic and Asian descent, who are more likely to develop thiopurine toxicity, rarely possess mutations in the *TPMT* gene. Pharmacoepidemiological data suggest that the loss-of-function *3 *NUDT15* mutation drives thiopurine intolerance in these patient populations. For example, a 2014 study showed that

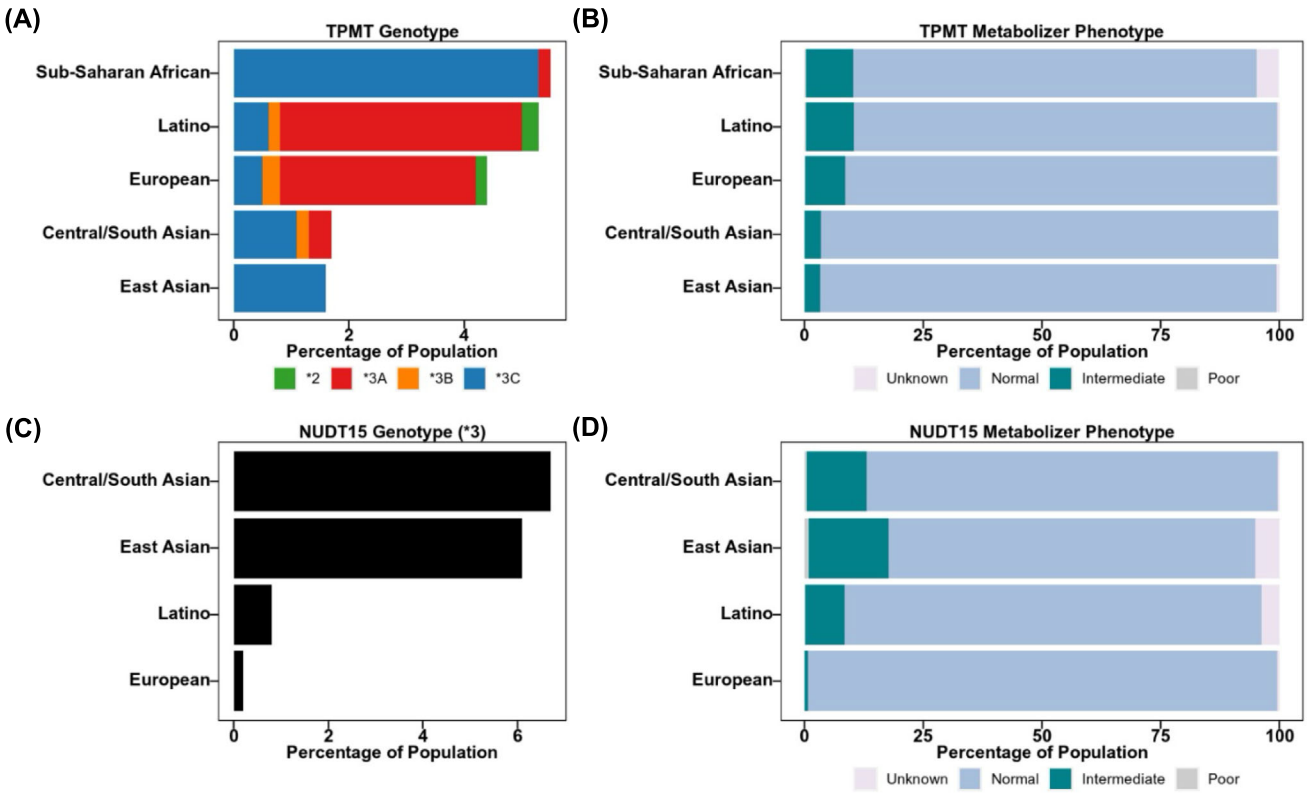

FIGURE 2 Prevalence of *TPMT* and *NUDT15* genotypes and phenotypes.[4] (A) Population allele frequency of the 4 most common *TPMT* genotypes. (B) Distribution of *TPMT* metabolizer phenotypes. (C) Population allele frequency of *NUDT15* *3 genotype. (D) Distribution of *NUDT15* metabolizer phenotype.

individuals homozygous for the *3 *NUDT15* mutation tolerated only 8% of the standard mercaptopurine dose prior to significant toxicity, similar to individuals who are homozygous for *TPMT* gene mutations.[10] Furthermore, the proportion of Asians and Hispanics who possess 1 *NUDT15* loss-of-function allele is double that of Europeans and Africans who possess 1 *TPMT* loss-of-function allele (21 *vs.* 10%), and this difference increases to 10-fold among individuals with 2 loss-of-function alleles (2 *vs.* 0.3%; Figure 2).[4] However, *NUDT15* mutation screening and subsequent thiopurine dose adjustments remain inconsistently recommended by clinical practice guidelines, and often differ by medical specialty. For example, most IBD practice guidelines in North America and Europe provide recommendations for *TPMT* screening but infrequently discuss *NUDT15* testing.[11–13] In contrast, all paediatric patients with acute lymphoblastic anaemia are recommended to have both *TPMT* and *NUDT15* genotyping completed prior to initiation of thiopurines.[14] Furthermore, clinical practice guidelines from Asia preferentially recommend *NUDT15* testing over *TPMT*.[15]

Our case also adds to a handful of existing reports suggesting that alopecia may be an early manifestation of thiopurine toxicity. While alopecia was previously thought to be a marker of thiopurine toxicity seen only in individuals with *NUDT15* mutations, there is new evidence to suggest that alopecia may also occur in individuals who do not possess *NUDT15* variant alleles.[16] Furthermore, as similarly observed in our case, hair loss often precedes organ toxicity and myelosuppression.[17] Thus, recognition of this clinical manifestation may help facilitate prompt early thiopurine withdrawal and pharmacogenetic testing.

We present a patient with severe myelosuppression, hepatotoxicity and alopecia following mercaptopurine initiation who was found to have homozygous *3/*3 loss-of-function alleles in the *NUDT15* gene. Inherited mutations in the *NUDT15* and *TPMT* genes can increase an individual's risk of severe adverse drug reactions to thiopurine medications. These mutations, however, occur at different frequencies based on an individual's racial background, yet few clinical guidelines directly reference these distinctions when providing recommendations for pretreatment genetic screening. Clinician recognition of these important pharmacogenomic differences is crucial to guide appropriate pretreatment screening, increase the yield of genetic testing and reduce the risk of adverse drug reactions.

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander *et al*., 2021).[18]

AUTHOR CONTRIBUTIONS

Annie Siyu Wu conducted the literature review and drafted the initial manuscript. Lee Mozessohn led data collection and provided expertise on the use of thiopurines in hematological malignancies as well as applications for gene mutation screening within the field. Richard B. Kim contributed to data collection, led genotyping and provided expertise in clinical pharmacology and adverse drug reactions. Jonathan S. Zipursky supervised the project, contributed to data collection, participated in drafting of the initial manuscript, and provided expertise in clinical pharmacology and adverse drug reactions. All authors revised and approved the final manuscript.

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CONFLICTS OF INTEREST STATEMENT

J.S.Z. is a Medical Advisor for the First Exposure program. J.S.Z. reports payments from law firms for medicolegal opinions on the safety and effectiveness of drugs unrelated to this work.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

PRIOR PRESENTATIONS

This paper was presented as an oral presentation at the Canadian Society of Internal Medicine Annual Meeting, October 2024.

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