LETTER TO THE EDITOR

TPMT gene in clinical practice: transforming research to clinical application

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To the Editor,

I would like to take this opportunity to emphasize the significance of pharmacogenetic variation in *TPMT*, the gene encoding thiopurine methyltransferase (TPMT). This enzyme is responsible for metabolizing thiopurine drugs, which are widely used in clinical practice, particularly for treating leukemias, autoimmune diseases, and preventing transplant rejection. TPMT enzyme activity varies among individuals based on their genotype. Some individuals carry genetic variants that result in low or no enzyme activity, while others exhibit intermediate activity, and some maintain normal levels. Patients with low TPMT activity are at an increased risk of severe adverse drug reactions (ADRs), such as myelosuppression and hepatotoxicity (1).

The *TPMT* gene exhibits a broad spectrum of genetic polymorphisms, with over 40 known allelic variants. These variants must be recorded in diplotypes (a combination of two haplotypes or alleles) for an accurate prediction of the patient's phenotype (2-4) (Figure 1).

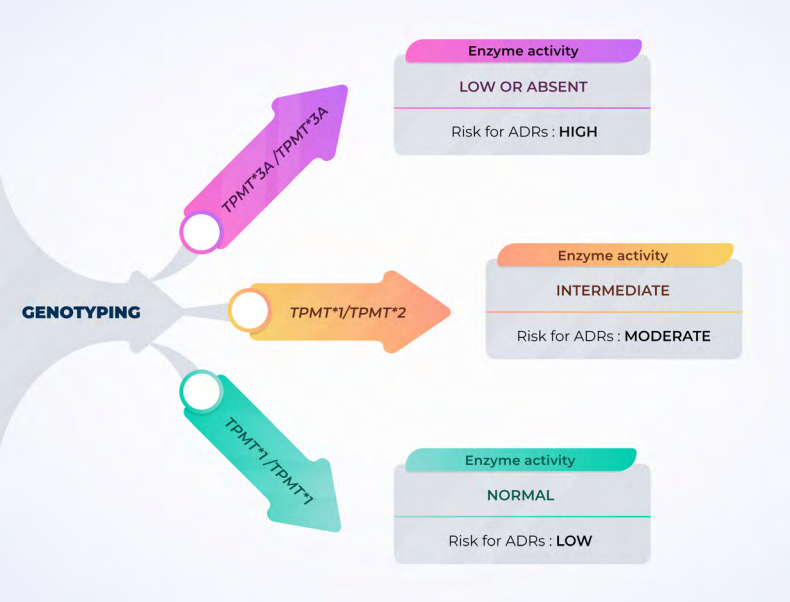

Figure 1. Each individual's *TPMT* genotype determines the phenotype (enzyme activity level) and the risk of developing adverse drug reactions (ADRs)

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an organization that unites experts in pharmacogenetics, pharmacogenomics, clinical pharmacology, genetics, and other related fields. Its primary goal is to enhance the safety and efficacy of drug therapies by tailoring treatments to the patient's genetic profile. CPIC develops guidelines that are regularly updated as new scientific and technological evidence emerges. For example, CPIC

Cite as:
Franco-Bustamante K, Poterico JA, Manassero-Morales G. TPMT gene in clinical practice: transforming research to clinical application. Investig Innov Clin Quir Pediatr. 2024;2(2):66-8. doi:10.59594/iicqp.2024.v2n2.105

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Received : 06/04/2024
Accepted : 07/20/2024
Published : 07/31/2024

recommends adjusting thiopurine doses or considering alternative therapies for patients with genetic variants that reduce TPMT or NUDT15 enzyme activity to prevent possible adverse reactions. Conversely, patients with normal enzyme activity can follow standard dosing treatment (Figure 2) (4,5).

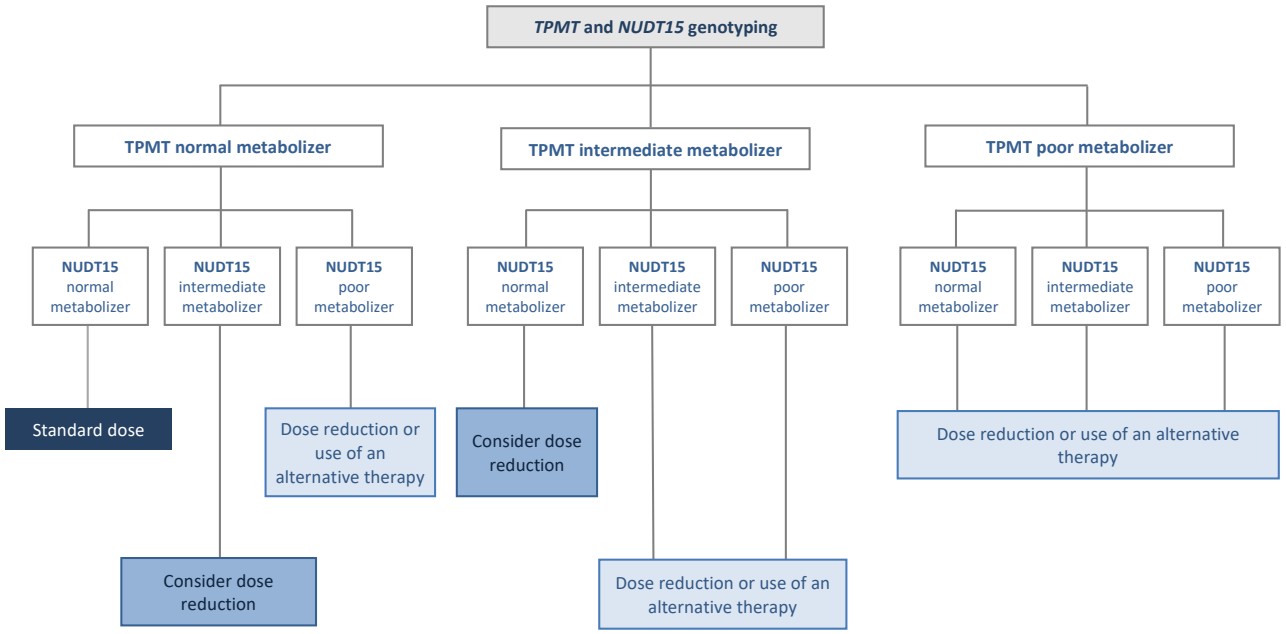

Figure 2. Recommended dosing algorithm for thiopurine drugs based on the combined predictive phenotype determined by the *TPMT* and *NUDT15* diplotypes (5)

Studies in Latin America have documented *TPMT* diplotypes in patients with leukemia, revealing significant variability in their frequency. Potential intermediate metabolizers represent 8.7% and 27.2% of the studied populations, while potential poor metabolizers account for up to 0.8% (6-10).

An analysis of *TPMT* polymorphisms was conducted in a cohort of 112 pediatric patients diagnosed with type B acute lymphoblastic leukemia at the Instituto Nacional de Salud del Niño San Borja (INSN-SB). The identification of polymorphisms was performed using allele-specific polymerase chain reaction (PCR) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) techniques, utilizing peripheral blood samples. Preliminary results indicate that 35.7% of the patients exhibited phenotypes associated with intermediate enzyme activity, while none showed phenotypes consistent with low activity. These findings have spurred new research collaborations with the Hematopoietic Progenitor Transplant Sub-Unit - Clinical Hematology, advancing pharmacogenetics research. Additionally, our institution has successfully implemented *TPMT* genotyping in routine clinical practice for acute lymphoblastic leukemia patients.

In conclusion, we highlight the importance of *TPMT* genotyping before initiating thiopurine treatment. This practice not only enables informed decisions on drug dosing but also ensures treatment safety through effective monitoring. We are confident that this recommendation, if widely adopted, will significantly enhance clinical outcomes and improve the quality of life for our patients.

Author contributions

All authors confirm their contributions to the conceptualization, design, data collection, analysis, interpretation, and preparation of the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest related to the content of this manuscript.

Funding

This study was self-funded.

Ethical considerations

Not applicable.

REFERENCES

1. Relling M, Gardner E, Sandborn W, Schmiegelow K, Pui CH, Yee S, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther. 2011;89(3):387–91. doi: 10.1002/cpt.1304
2. Appell ML, Berg J, Duley J, Evans WE, Kennedy MA, Lennard L, et al. Nomenclature for alleles of the thiopurine methyltransferase gene. Pharmacogenet Genomics. 2013;23(4):242–8. doi: 10.1097/FPC.0b013e32835f1cc0
3. PharmGKB [Internet]. Gene-specific information tables for TPMT. [cited 2022 Oct 21]. Available from: https://www.pharmgkb.org/page/tpmtRefMaterials
4. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011;89(3):464–7. doi: 10.1038/clpt.2010.279
5. Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther. 2019;105(5):1095–105. doi: 10.1002/cpt.1651
6. Taja-Chayeb L, Vidal-Millán S, Gutiérrez O, Ostrosky-Wegman P, Dueñas-González A, Candelaria M. Thiopurine S-methyltransferase gene (TPMT) polymorphisms in a Mexican population of healthy individuals and leukemic patients. Med Oncol. 2008;25(1):56–62. doi: 10.1007/s12032-007-9002-6
7. Moreno-Guerrero SS, Ramírez-Pacheco A, Dorantes-Acosta EM, Medina-Sanson A. Análisis de los polimorfismos génicos de tiopurina S-metiltransferasa (TPMT) en pacientes pediátricos mexicanos con cáncer. Rev Invest Clin [Internet]. 2013 [cited 2022 Oct 21];65(2):156–64. Available from: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=43713
8. Garrido C, Santizo VG, Müllers P, Soriano DR, Avila GB, Dean M, et al. Frequency of thiopurine S-methyltransferase mutant alleles in indigenous and admixed Guatemalan patients with acute lymphoblastic leukemia. Med Oncol. 2013;30(1):474. doi: 10.1007/s12032-013-0474-2
9. Farfan MJ, Salas C, Canales C, Silva F, Villarroel M, Kopp K, et al. Prevalence of TPMT and ITPA gene polymorphisms and effect on mercaptopurine dosage in Chilean children with acute lymphoblastic leukemia. BMC Cancer. 2014;14(1):299. doi: 10.1186/1471-2407-14-299
10. Jiménez-Morales S, Ramírez-Florencio M, Mejía-Aranguré JM, Núñez-Enríquez JC, Bekker-Mendez C, Torres-Escalante JL, et al. Analysis of thiopurine S-methyltransferase deficient alleles in acute lymphoblastic leukemia patients in Mexican patients. Arch Med Res. 2016;47(8):615–22. doi: 10.1016/j.arcmed.2016.11.018