Research Article

TPMT genotyping in 1000 Indian patients: 14-year experience from a tertiary-care hospital

Minal Umesh Paradkar[1], Swarup Arvind Vaishali Shah[1], Rani Deepak[1], Mihika Dave[1], Alpa Dherai[1,2], Dhanshri Shetty[2], Devendra Desai[3], Philip Abraham[3], Anand Joshi[3], Tarun Gupta[3], Tester F. Ashavaid[1,2*]

[1]*Research Laboratories, P. D. Hinduja Hospital and Medical Research Centre, V. S. Marg, Mahim, Mumbai, India*

[2]*Department of Biochemistry , P. D. Hinduja Hospital and Medical Research Centre, V. S. Marg, Mahim, Mumbai, India*

[3]*Department of Gastroenterology, P. D. Hinduja Hospital and Medical Research Centre, V. S. Marg, Mahim, Mumbai, India*

Article Info

[*]***Corresponding Author:***
Tester F. Ashavaid, PhD, FACB, CSci, FACBI
Department of Laboratory Medicine (Biochemistry),
P. D. Hinduja Hospital and Medical Research Centre,
Veer Savarkar Marg, Mahim, Mumbai – 400 016. India
Tel: +91 022 24447935 / Fax: +91 022 24442318
E-mail: dr_tashavaid@hindujahospital.com / tashavaid@gmail.com

Keywords

Thiopurine, TPMT, genetic testing, Indian patients, allele frequency

Abstract

Thiopurine methyltransferase (TPMT) enzyme plays a key role in the metabolism of the thiopurine drugs that are used for the treatment of inflammatory diseases. Mutations in the TPMT gene cause abnormal metabolism, resulting in toxicity; therefore, TPMT genetic analysis has been recommended for effective dose management. We retrospectively analysed data to determine the distribution of TPMT genotypes in a western Indian population. TPMT genotyping test was performed on 1000 patients with different inflammatory conditions between January 2009 and October 2023. The common TPMT genotypes *2, *3A, *3B and *3C were detected by amplification refractory mutation system - polymerase chain reaction (ARMS-PCR) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) techniques. TPMT mutants were detected in 36 (3.6%) patients, of whom 14 (39%) had TPMT*1/*3A, 19 (53%) had TPMT*1/*3C, two (5.5%) had TPMT*1/*3B, and one (2.8%) had TPMT*3B/*3B alleles; mutant allele frequencies were 0.7% for *3A, 0.2% for *3B and 1.65% for *3C. A sub-group analysis explained thiopurine toxicity in only 33% patients by TPMT gene polymorphism whereas in 67% the toxicity remained unexplained. The low prevalence of TPMT mutants (3.6%) along with unexplained thiopurine toxicity suggest that TPMT genotyping solely might be clinically less relevant in patients of Indian origin, underscoring the role of other genetic factors that may be involved in thiopurine toxicity in these patients.

Introduction

Thiopurine methyltransferase (TPMT) enzyme plays a key role in the metabolism of thiopurine drugs such as azathioprine (AZA) and 6-mercaptopurine (6-MP). These drugs are used as antimetabolite cytotoxic and immunosuppressive agents in the treatment of acute lymphoblastic leukaemia (ALL), inflammatory bowel disease (IBD), and autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune hepatitis, and generalized eczematous disorders. [1,2,] However, gastrointestinal disturbances, rashes, as well as more serious adverse drug reactions like bone marrow toxicity, hepatotoxicity, and pancreatitis can lead to discontinuation of therapy in some patients.[3] The wide inter-individual variations observed in the efficacy and toxicity of thiopurine drugs have been largely attributed to the presence of genetic polymorphisms in the TPMT gene affecting TPMT enzyme activity.[1,4,5] To date, over 40 TPMT variant alleles have been identified, of which four, i.e., TPMT*2, *3A, *3B and *3C, account for ~85%-95% of intermediate and low TPMT enzyme activity.[6,7]

The prevalence of TPMT variants varies across different populations. TPMT*2 is prevalent in European Caucasian populations, TPMT*3A is predominant in Caucasians and Latin Americans, and TPMT*3C is most common in East and South-East Asians and African populations.[8-14] The Indian population being heterogeneous shows ethnic differences in the distribution of these defective alleles.

Hence, we have retrospectively analysed our data to determine the TPMT allele frequencies as well as to assess the relevance of TPMT genotyping in Indian patients.

Patients and Methods

TPMT gene polymorphism was analysed in patients attending our hospital who had an indication for immunomodulator therapy. An informed consent was obtained from all the patients who underwent TPMT genotyping test. TPMT genotyping was performed as a test at our Molecular Diagnostic Laboratory that is accredited by the College of American Pathologists (CAP) and National Accreditation Board for testing and laboratories (NABL). 1000 samples for TPMT genotyping have been received over a period of 14 years from January 2009 until October 2023. The institutional ethics committee –II (IEC-II/IRB) had no objection to the publication of the manuscript.

TPMT genotyping assay had been standardized in-house using amplification refractory mutation system - polymerase chain reaction (ARMS-PCR) and polymerase chain reaction - restriction length polymorphism (PCR-RFLP), and further validated by DNA sequencing [15]. The methodology we used has been reported earlier [15] and the quality control measures, method validation (which includes repeatability, accuracy, sensitivity and specificity), inter-laboratory comparison (ILC) testing, and Sanger sequencing confirmation of the control samples have been followed, practised and documented over 14 years of the test performance. The assay included the common TPMT alleles, i.e. TPMT*2 (NM_000367.5:c.238G>C, p.Ala80Pro, rs18004622), TPMT*3B (NM_000367.5:c.460G>A, p.Ala154Thr, rs1800460), TPMT*3C (NM_000367.5:c.719A>G, p.Tyr240Cys, rs1142345), and TPMT*3A (which is characterized by the presence of TPMT*3B and TPMT*3C alleles).

TPMT allele frequencies were calculated using an online calculator (https://www.had2know.org/academics/hardy-weinberg-equilibrium-calculator-2-alleles.html). Diagnostic characteristics of the TPMT genotyping in thiopurine-intolerant and -tolerant patients were calculated using MedCalc® version 20.211 (https://www.medcal.org). Heatmaps were generated for comparative analysis between different populations using Microsoft Excel 2013 (https://www.ablebits.com/office-addins-blog/create-heat-map-excel/).

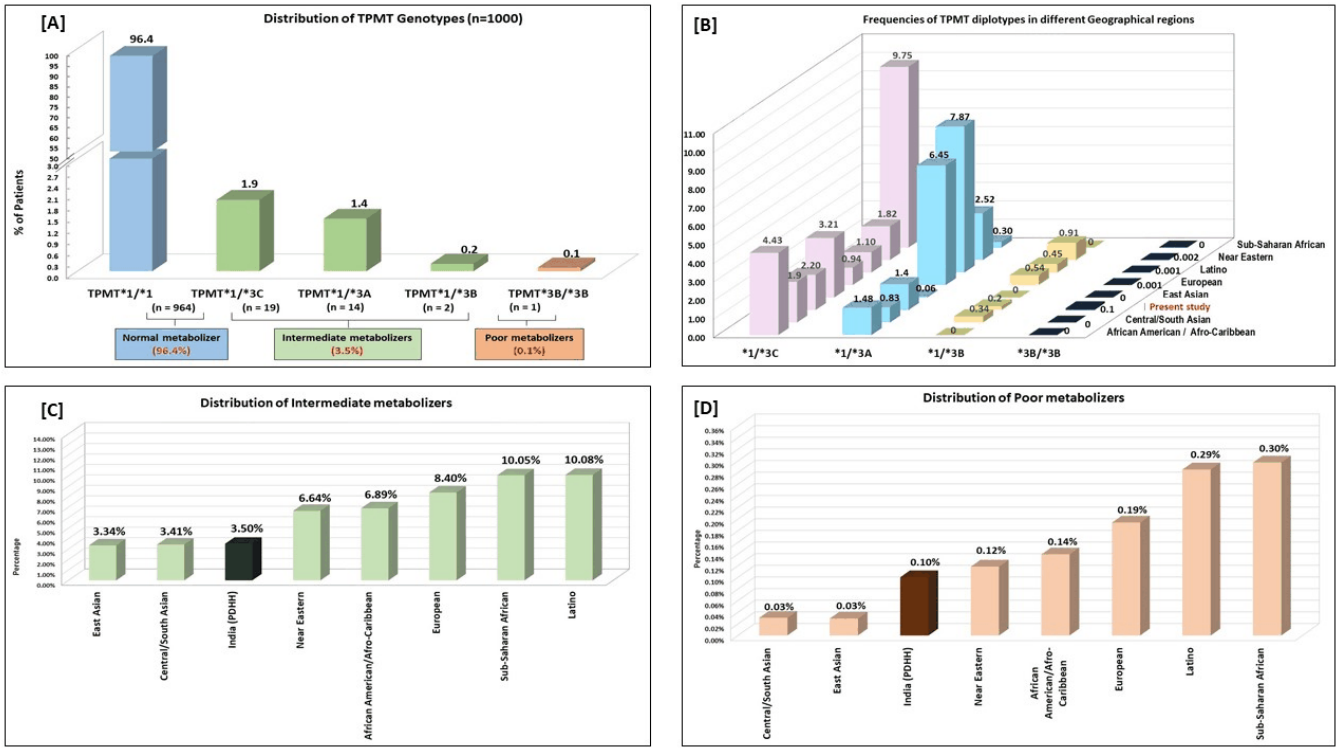
Results and Discussion

A total of 1000 samples were obtained from patients with mean age 38±17 years (range 03-87 years) of whom 535 patients were male. A majority of these were patients with IBD (76%, n=763), 5% (n=52) had ALL and 19% (n=185) had other indications such as rheumatology, nephrology, dermatology etc.

TPMT genotypes

TPMT wild-type genotype was present in 96.4% (n=964) of patients, whereas TPMT mutants were detected in only 3.6% (n=36). The distribution of TPMT genotypes (Figure 1A) showed predominance of TPMT*1/*1 genotype (96.4%; n=964), followed by TPMT*1/*3C (1.9%; n=19), TPMT*1/*3A (1.4%; n=14), TPMT*1/*3B (0.2%; n=2), and TPMT*3B/*3B (0.1%; n=1) patients. TPMT*2 variants were not detected in our patient population. The worldwide frequency of TPMT diplotypes as obtained from the updated Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (Figure 1B) showed TPMT*1/*3C genotype predominance in Sub-Saharan populations (9.75%), followed by African-American and Afro-Caribbean populations (4.43%) [5,6]; TPMT*1/*3A genotype was reported mainly from Latino (7.87%) and European (6.45%) populations.

Figure 1: [A] Allele frequencies of TPMT*3A, TPMT*3C, TPMT*3B and TPMT*2. Distribution of TPMT genotypes in total samples along with predicted phenotypes. [B] Frequencies of TPMT diplotypes in different geographical regions. [C] and [D] Comparison of Intermediate and poor metabolisers, respectively, with worldwide populations.



TPMT predicted metabolisers

TPMT genotype-based predicted metabolisers, according to the CPIC classification, showed 3.5% as intermediate metabolisers (Figure 1C) and 0.1% poor metabolisers (Figure 1D) in our population. The updated CPIC guidelines showed predominance of intermediate metabolisers in Latino (10.08%) and Sub-Saharan African (10.05%) populations followed by Europeans (8.4%) [5,6]. Poor metabolizers (Figure 1D) were detected in Sub-Saharan Africans (0.3%), Latinos (0.29%), and Europeans (0.19%).

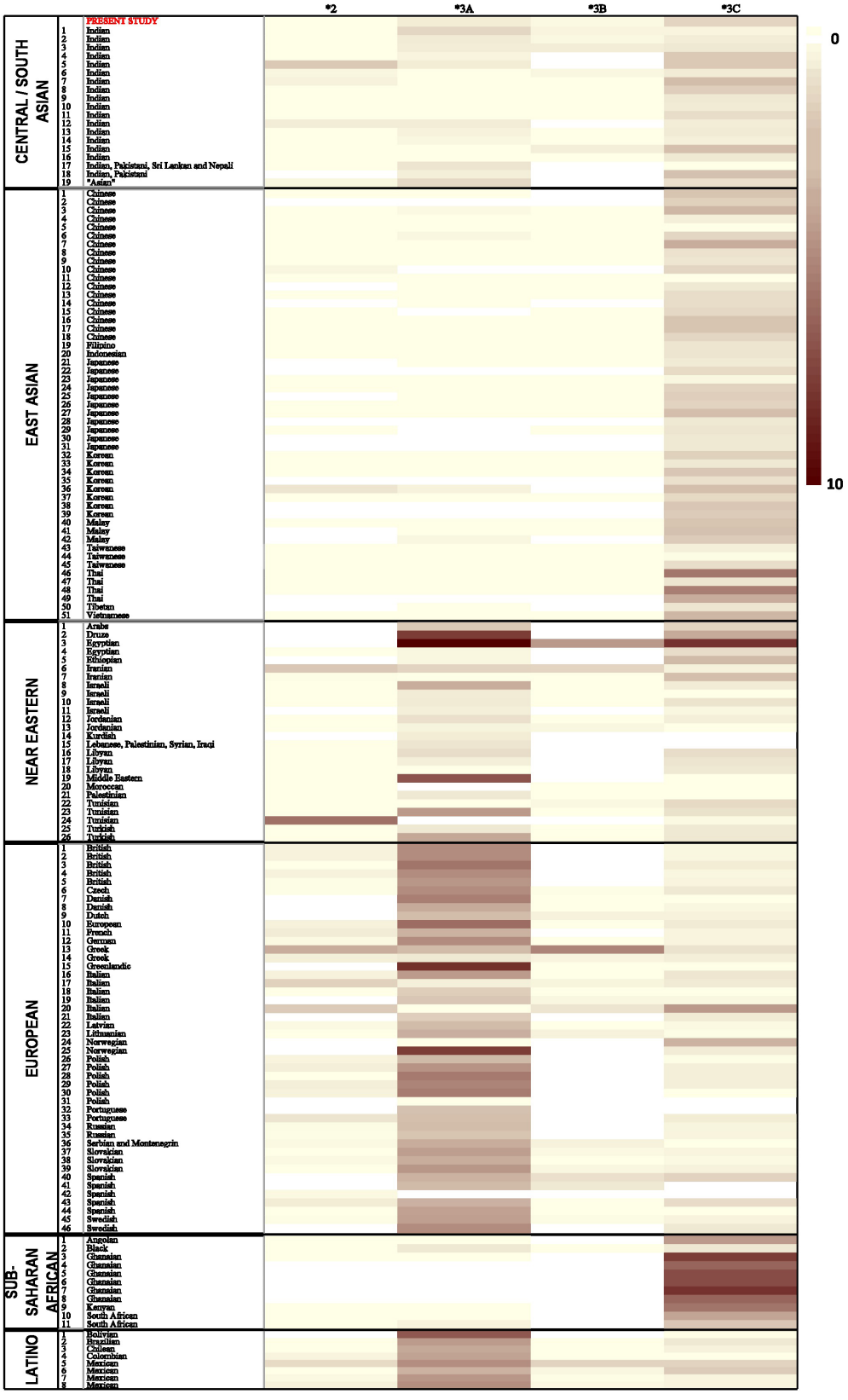
Comparison of TPMT allele frequencies

We observed TPMT mutant allele frequencies to be 0.7% for TPMT*3A, 0.2% for TPMT*3B, and 1.65% for TPMT*3C. Comparative analysis of allele frequencies with Indian and other geographical populations was performed using heatmap analysis. Data from different worldwide populations were selected from the updated CPIC guidelines [5,6] (Supplementary Table) and other worldwide reported studies.

TPMT*2 allele

Our data showed absence of TPMT*2 allele in our population. The non-functional TPMT*2 allele has low preponderance in worldwide populations. Low frequency has been reported in Europeans, the highest (3.19%) [5,6] (Supplementary Table) being reported from a Greek population (Figure 2). Its prevalence is low amongst Latinos while it is almost absent in East Asians and infrequent in South/Central Asians. Likewise, it is less frequent in the Indian population except for a study from southern India that reported a frequency of 3.1% [5,6] (Supplementary Table).

Figure 2: Heatmaps of allele frequencies (in %) of different geographical populations.



TPMT*3A allele

A 0.7% frequency of this allele was observed in our data from a western Indian population. Heatmap (Figure 2) shows characteristically distinctive patterns for TPMT*3A in Europeans and Americans. This allele is predominant in Latinos and Europeans, with frequencies of 3%-6.5% [5,6] (Suppl. Table) and 0%-8.1%, respectively [5,6,16-18] (Supplementary Table). Interestingly, in both these populations TPMT*3B and TPMT*3C alleles were infrequent; however compound variants were predominant. Conversely, this allele was scarcely present in East Asians, Africans, and near-Eastern populations. South/Central Asians showed low frequency and Indian populations also showed low frequencies from 0-1.6% [5,6,19-22] (Supplementary Table).

TPMT*3B allele

Our patient population had 0.2% frequency of this allele. The non-functional TPMT*3B allele is less commonly reported in worldwide populations (Figure 2). It is largely absent in East Asians and African populations and scarcely detected in the Middle East and South-Central Asians. Based on Heatmap, the reported frequency amongst Europeans varies from 0% in most populations to 1%, 3% and 4.78%, respectively, in the Italian, Spanish and Greek populations [5,6,18] (Supplementary Table). Studies from India have reported infrequent dissemination (0-0.67%) [5,6,19-22] (Supplementary Table).

TPMT*3C allele

Our data shows allele frequency of 1.65%. Heatmap (Figure 2) shows distinctive predominance of this allele in Africans, with highest frequency of 8% reported in the Ghanaian population [5,6] (Suppl. Table). East Asians show variability in frequency ranging from 0%-5.3% [5,6,23] (Suppl. Table). TPMT*3C variant is infrequent in major European populations except for the Norwegian and Italian populations that show frequencies of 3% and 4%, respectively [5,6] (Supplementary Table). Similarly, it is less frequently reported from the near Eastern, Latino and Central/South Asian populations. Amongst Indian populations it is reported in frequency from 0.4-2.6% [5,6,19-22] (Supplementary Table).

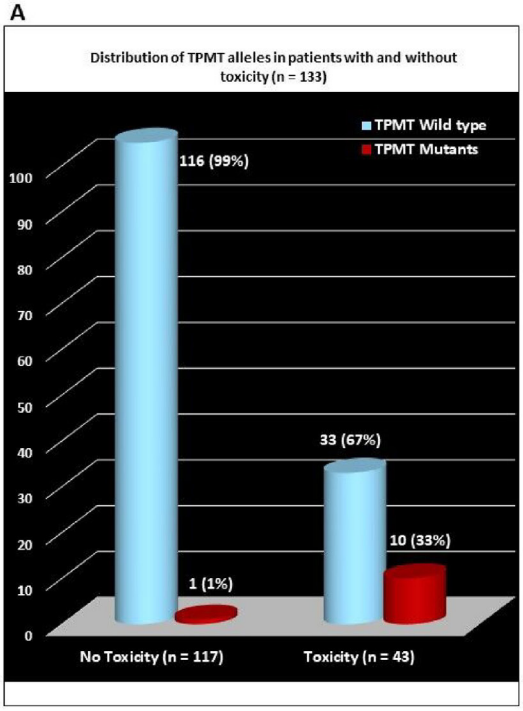
Overall, the comparative heatmap shows that there is low prevalence of TPMT alleles in Indian populations as compared with the European, Near Eastern, Sub-Saharan African and Latino populations. Indian populations shows similarity in the distribution of the TPMT alleles with the East Asian population wherein the TPMT*3C allele has been commonly reported as compared to other alleles. Based on the TPMT genotypes, the predicted intermediate metabolizers were detected in 3.5% patients in the present study (Figure 1A). Overall, the worldwide population shows more prevalence of intermediate metabolizers as compared to poor metabolizers (Figure 1C and 1D). Strong recommendations has been laid down by CPIC for the use of thiopurines in TPMT intermediate metabolizers wherein 30-80% reduction of doses is recommended to minimize the risk of thiopurine-related leukopenia, neutropenia and myelosuppression [5].

TPMT alleles and thiopurine toxicity

Genetic polymorphisms for enzymes involved in thiopurine metabolism have been recognised to predict toxicity. Leucopenia has been reported in 9%-27.7% of patients with IBD who were initiated on thiopurine treatment [20,24]. However, the important polymorphisms responsible for causing leucopenia vary amongst different populations: in Western countries, for example, TPMT gene polymorphisms have been recognised as an important cause. Hence, to further assess the role of TPMT gene polymorphisms in thiopurine-induced toxicity, we performed a sub-group analysis in 160 patients. Thiopurine toxicity was classified as reported [25]; based on this, 117 (73%)

Figure 3: [A] Sub-group analysis in patient with and without thiopurine toxicity. [B] The table depicts the clinical characteristics of TPMT genotyping test.

A



B

Statistics	Value	95% Interval	Significance
Sensitivity	23.26%	11.755% to 38.631%	
Specificity	99.15%	95.33% to 99.98%	
AUC	0.612	0.532 to 0.688	
Fischer's exact test		-	p = 0.000023
Chi-square test	24.6453	-	P < 0.00001
Odds ratio	35.1515	4.3403 to 284.686	z statistic = 3.326; p = 0.0009
Relative risk	27.2093	3.5888 to 206.2914	z statistic = 3.196; p = 0.0014
Positive Likelihood Ratio	27.21	3.59 to 206.29	
Negative Likelihood Ratio	0.77	0.66 to 0.91	
Disease prevalence	26.88%	20.18% to 34.45%	
Positive Predictive Value	90.91%	56.88% to 98.70%	
Negative Predictive Value	77.85%	74.87% to 80.57%	
Accuracy	78.75%	71.59% to 84.81%	

TPMT wild-type allele was predominant (99%) in the thiopurine-tolerant patient group while only one patient had TPMT mutant allele. TPMT mutant allele accounted for thiopurine toxicity in only 33% (n=10) of patients who exhibited thiopurine intolerance (Figure 3A). Genetic testing for TPMT did not provide any explanation for thiopurine toxicity in the remaining 67% (n=33). Diagnostic characteristics (Figure 3B) showed poor sensitivity (26.7%) and AUC (0.628), suggesting that TPMT genotyping alone is not adequate to predict thiopurine toxicity in Indian patients.

To summarize, the association between gene polymorphisms and thiopurine-related toxicity shows differences in different ethnic populations. It has been reported that Asians has lower TPMT mutation frequency than the Caucasians (~3% versus ~10%) [11,26], however the prevalence of thiopurine-induced toxicity is higher in Asians which is more often associated with the nucleoside diphosphatelinked moiety X-type motif 15 (NUDT15) genotype [27,28]. In the present study, the unexplained toxicity in 67% patients with normal TPMT genotypes could be attributed to other genetic variants (e.g. NUDT15, Inosine triphosphate pyrophosphatase (ITPA) and non-genetic factors such as environmental, drug-drug interactions, dietary and metabolic factors. The current study though limited to the traditional TPMT genetic marker over 14 years on a large sample size of 1000 patients, population-specific genetic markers (such as NUDT15) should be incorporated in the screening of thiopurine induced toxicity.

Conclusions

Our 14-year data on 1000 patient samples showed low prevalence of TPMT genetic variants in Indian patients. TPMT genotyping could not explain thiopurine toxicity in 67% of patients. Our data suggest that only TPMT genotyping might be clinically less relevant for patients of Indian origin, underscoring the need to include other genetic factors (e.g., NUDT15) to explain thiopurine toxicity in Indian patients.

Conflict of Interest

All authors have no conflict of interest to declare.

Supplemental material

One table containing TPMT allele frequency data, taken majorly from CPIC, used for generation of Heatmaps.

Credit Author Statement

Minal Paradkar: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing-original draft and Visualization. Swarup AV Shah: Methodology, Validation, Formal analysis, Investigation, and Writing-review and editing. Rani Deepak: Methodology, Investigation, Writing-review and editing. Mihika Dave: Investigation and Writing-review and editing. Alpa Dherai and Dhanashri Shetty: Writing-review and editing. Devendra Desai, Philip Abraham, Anand Joshi and Tarun Gupta: Resources and Writing-review and editing. Tester F Ashavaid: Conceptualization, Writing-review and editing, and Supervision.

Ethics approval and consent

An informed consent was obtained from all the patients who underwent TPMT genotyping test. The institutional ethics committee –II (IEC-II/IRB) had no objection to the publication of the manuscript. This study is in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki.

Research Funding

This study has not received any type of public or private funding.

Acknowledgement

This study includes retrospective data analysis of TPMT genotyping diagnostic test and hence no funding was required for the data analysis.

References

1. Kotur N, Dokmanovic L, Janic D, et al. TPMT gene expression is increased during maintenance therapy in childhood acute lymphoblastic leukemia patients in a TPMT gene promoter variable number of tandem repeat-dependent manner. Pharmacogenomics. 2015;16(15):1701–1712. doi: 10.2217/pgs.15.109
2. Chouchana L, Narjoz C, Beaune P, Loriot MA, Roblin X. Review article: the benefits of pharmacogenetics for improving thiopurine therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2012;35(1):15–36. doi: 10.1111/j.1365-2036.2011.04905.x
3. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. Gut. 2002;50(4):485–489. doi: 10.1136/gut.50.4.485
4. Chouchana L, Narjoz C, Roche D, et al. Interindividual variability in TPMT enzyme activity: 10 years of experience with thiopurinepharmacogenetics and therapeutic drug monitoring. Pharmacogenomics. 2014;15(6):745–757. doi: 10.2217/pgs.14.32
5. CPIC® Guideline for Thiopurines and TPMT and NUDT15. https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/ (accessed: 13/06/2024)
6. Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi: 10.1002/cpt.1304.
7. Asadov C, Aliyeva G, Mustafayeva K. Thiopurine S-Methyltransferase as a pharmacogenetic biomarker: significance of testing and review of major methods. Cardiovasc Hematol Agents Med Chem 2017;15: 23–30. doi: 10.2174/1871525715666170529091921
8. Gallardo-Cóndor J, Naranjo P, Atarihuana S, Coello D, Guevara-Ramírez P, Flores-Espinoza R, Burgos G, López-Cortés A, Cabrera-Andrade A. Population-Specific Distribution of TPMT Deficiency Variants and Ancestry Proportions in Ecuadorian Ethnic Groups: Towards Personalized Medicine. Ther Clin Risk Manag. 2023;19:1005-1018. doi: 10.2147/TCRM.S432856.
9. Otterness D, Szumlanski C, Lennard L, et al. Human thiopurine methyltransferase pharmacogenetics: gene sequence polymorphisms. Clin Pharmacol Ther. 1997;62(1):60–73. doi:10.1016/S0009-9236(97)90152-1.
10. Isaza C, Henao J, Lopez AM, Cacabelos R. Allelic variants of the thiopurine methyltransferase (TPMT) gene in the Colombian population. Methods Find Exp Clin Pharmacol. 2003;25(6):423–429. doi:10.1358/mf.2003.25.6.769646
11. Collie-Duguid ES, Pritchard SC, Powrie RH, et al. The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations. Pharmacogenetics. 1999;9(1):37–42. doi:10.1097/00008571-199902000-00006
12. Ameyaw MM, Collie-Duguid ES, Powrie RH, Ofori-Adjei D, McLeod HL. Thiopurine methyltransferase alleles in British and Ghanaian populations. Hum Mol Genet. 1999;8(2):367–370. doi:10.1093/hmg/8.2.367
13. Chang JG, Lee LS, Chen CM, et al. Molecular analysis of thiopurine S-methyltransferase alleles in South-East Asian populations. Pharmacogenetics. 2002;12(3):191–195. doi:10.1097/00008571-200204000-00003
14. Garrido C, Santizo VG, Mullers P, 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
15. Ashavaid TF, Raghavan R, Shah S, Kapadia A, Almel S, Desai D. TPMT and DPD polymorphisms: Efficient screening method for Indian patients considering taking Thiopurine and 5-FU drugs. Dis Markers. 2009;27(5):231-238. doi: 10.3233/DMA-2009-0668
16. Zalizko P, Stefanovics J, Sokolovska J, Paramonova N, Klavina E, Erts R, Rovite V, Klovins J, Pukitis A. Thiopurine S-methyltransferase genetic polymorphisms in adult patients with inflammatory bowel diseases in the Latvian population. Therap Adv Gastroenterol. 2020;13:1756284820937426. doi: 10.1177/1756284820937426.
17. Casajús A, Zubiaur P, Méndez M, Campodónico D, Gómez A, Navares-Gómez M, Villapalos-García G, Soria-Chacartegui P, Novalbos J, Román M, Mejía-Abril G, Ochoa D, Abad-Santos F. Genotype-Guided Prescription of Azathioprine Reduces the Incidence of Adverse Drug Reactions in TPMT Intermediate Metabolizers to a Similar Incidence as Normal Metabolizers. Adv Ther. 2022;39(4):1743-1753. doi: 10.1007/s12325-022-02067-8.
18. Díaz-Villamarín X, Fernández-Varón E, Rojas Romero MC, Callejas-Rubio JL, Cabeza-Barrera J, Rodríguez-Nogales A, Gálvez J, Morón R. Azathioprine dose tailoring

based on pharmacogenetic information: Insights of clinical implementation. Biomed Pharmacother. 2023;168:115706. doi: 10.1016/j.biopha.2023.115706.
19. Ambar G, Vandana A, Lalit D, Jyoti K. Thiopurine S-methyltransferase (TPMT) Mutation Prevalence and Myelosuppression Frequency in North Indian Patients with Autoimmune Disorders. J Assoc Physicians India. 2018;66(5):39-44. PMID: 30477053.
20. Banerjee R, Ravikanth VV, Pal P, Bale G, Avanthi US, Goren I, Girish BG, Mitnala S, Reddy DN. NUDT15 C415T variant compared with TPMT genotyping in predicting azathioprine-induced leucopenia: prospective analysis of 1014 inflammatory bowel disease patients in India. Aliment Pharmacol Ther. 2020;52(11-12):1683-1694. doi: 10.1111/apt.16137.
21. Shah, Swarup A.V., Paradkar, Minal U., Desai, Devendra C. and Ashavaid, Tester F.. "Preemptive NUDT15 genotyping: redefining the management of patients with thiopurine-induced toxicity" Drug Metabolism and Personalized Therapy, vol. 33, no. 1, 2018, pp. 57-60. https://doi.org/10.1515/dmpt-2017-0038
22. Davavala SK, Desai DC, Abraham P, Ashavaid T, Joshi A, Gupta T. Prevalence of TPMT polymorphism in Indian patients requiring immunomodulator therapy and its clinical significance. Indian J Gastroenterol. 2014;33(1):41-45. doi: 10.1007/s12664-013-0374-6.
23. Chen ZY, Zhu YH, Zhou LY, Shi WQ, Qin Z, Wu B, Yan Y, Pei YW, Chao NN, Zhang R, Wang MY, Su ZH, Lu XJ, He ZY, Xu T. Association Between Genetic Polymorphisms of Metabolic Enzymes and Azathioprine-Induced Myelosuppression in 1,419 Chinese Patients: A Retrospective Study. Front Pharmacol. 2021;12:672769. doi: 10.3389/fphar.2021.672769.
24. Grover N, Bhatia P, Kumar A, Singh M, Lad D, Mandavdhare HS, Samanta J, Prasad KK, Dutta U, Sharma V. TPMT and NUDT15 polymorphisms in thiopurine induced leucopenia in inflammatory bowel disease: a prospective study from India. BMC Gastroenterol. 2021 Aug;21(1):327. doi: 10.1186/s12876-021-01900-8.
25. Coelho T, Andreoletti G, Ashton JJ, Batra A, Afzal NA, Gao Y, Williams AP, Beattie RM, Ennis S. Genes implicated in thiopurine-induced toxicity: Comparing TPMT enzyme activity with clinical phenotype and exome data in a paediatric IBD cohort. Sci Rep. 2016;6:34658. doi: 10.1038/srep34658.
26. Takatsu N, Matsui T, Murakami Y, et al. Adverse reactions to azathioprine cannot be predicted by thiopurine S-methyltransferase genotype in Japanese patients with inflammatory bowel disease. J Gastroenterol Hepatol 2009;24:1258-1264.
27. Yang SK, Hong M, Baek J, et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nat Genet 2014; 46:1017-1020.
28. Shah SA, Paradkar M, Desai D, Ashavaid TF. Nucleoside diphosphate-linked moiety X-type motif 15 C415T variant as a predictor for thiopurine-induced toxicity in Indian patients. J Gastroenterol Hepatol. 2017;32(3):620-624. doi: 10.1111/jgh.13494. PMID: 27416873.

SUPPLEMENTARY TABLE: TPMT ALLELE FREQUENCY IN DIFFERENT WORLDWIDE POPULATIONS

No.	Authors	Year	PMID	Population group	Population	Add'l population info	Subject type	N subjects genotyped	Allele frequency					Allele frequency in %				
									*1	*2	*3A	*3B	*3C	*1	*2	*3A	*3B	*3C
Central/South Asian																		
1	Davavala Sandeep Kirit	2014	23996738	Central/South Asian	Indian	Western India	Gastrointestinal disease patients	126	0.976	0.0	0.016	0.004	0.004	97.6	0.0000	1.6000	0.4000	0.4000
2	Shah SAV	2018	29470173	Central/South Asian	Indian	Western India	IBD patients	370	0.9824	0	0.0081	0.0027	0.0068	98.24	0.0000	0.8100	0.2700	0.6800
3	Iyer Sandhya N	2012	22580794	Central/South Asian	Indian		Healthy individuals	225	0.9777	0.0	0.0067	0.0067	0.0089	97.77	0.0000	0.6700	0.6700	0.8900
4	Kapoor Gauri	2009	19675376	Central/South Asian	Indian	North Indian	Healthy individuals	120	0.975	0.0	0.004	-	0.021	97.5	0.0000	0.4000		2.1000
5	Kapoor Gauri	2010	20153897	Central/South Asian	Indian	North Indian	Pediatric ALL patients	71	0.951	0.021	0.007	-	0.021	95.1	2.1000	0.7000		2.1000
6	Murugesan Raju	2010	23136604	Central/South Asian	Indian	Southern Indian	Healthy individuals	326	0.9862	0.0031	0.0	0.0031	0.0076	98.62	0.3100	0.0000	0.3100	0.7600
7	Desire Salamun	2010	19830600	Central/South Asian	Indian	South Indian	ALL patients	98	0.969	0.005	0.0	0.0	0.026	96.9	0.5000	0.0000	0.0000	2.6000
8	Umamaheswaran Gurusamy	2012	22318545	Central/South Asian	Indian	Andhrite	Healthy individuals	158	0.981	0.0	0.0	0.0	0.019	98.1	0.0000	0.0000	0.0000	1.9000
9	Umamaheswaran Gurusamy	2012	22318545	Central/South Asian	Indian	Kannadiga	Healthy individuals	161	0.991	0.0	0.0	0.0	0.009	99.1	0.0000	0.0000	0.0000	0.9000
10	Umamaheswaran Gurusamy	2012	22318545	Central/South Asian	Indian	Keralite	Healthy individuals	177	0.992	0.0	0.0	0.0	0.008	99.2	0.0000	0.0000	0.0000	0.8000
11	Umamaheswaran Gurusamy	2012	22318545	Central/South Asian	Indian	Tamilian	Healthy individuals	112	0.987	0.0	0.0	0.0	0.013	98.7	0.0000	0.0000	0.0000	1.3000
12	Linga Vijay Gandhi	2014	25538405	Central/South Asian	Indian	South Indian	Pediatric ALL patients	72	0.9793	0.0069	0.0069	-	0.0069	97.93	0.6900	0.6900		0.6900
13	Kham S K Y	2002	12142782	Central/South Asian	Indian	Singaporean	Healthy individuals and pediatric ALL patients	200	0.987	0.0	0.005	0.0	0.008	98.7	0.0000	0.5000	0.0000	0.8000
14	Ambar G	2018	30477053	Central/South Asian	Indian	North Indian	Autoimmune disease patients	176	0.9916	0	0.0028	0	0.0056	99.16	0.0000	0.2800	0.0000	0.5600
15	Banerjee R	2020	33111378	Central/South Asian	Indian	Hyderabad, South India	IBD patients	81	0.9691	0	0	0.0062	0.0247	96.91	0.0000	0.0000	0.6200	2.4690
16	Kham Shirley Kow Yin	2008	18193212	Central/South Asian	Indian	Singaporean	Healthy individuals	163	0.991	0.0	0.0	0.0	0.009	99.1	0.0000	0.0000	0.0000	0.9000
17	Collie-Duguid E S	1999	10208641	Central/South Asian	Indian, Pakistani, Sri Lankan and Nepali		Healthy individuals	99	0.99	0.0	0.01	-	0.0	99	0.0000	1.0000		0.0000
18	Marinaki Anthony M	2003	12563179	Central/South Asian	Indian and Pakistani	British	Gastroenterology patients	85	0.97	-	0.006	-	0.024	97		0.6000		2.4000
19	Lennard Lynne	2015	25940902	Central/South Asian	"Asian"	from Britain	Pediatric ALL patients	164	0.97	0.003	0.015	-	0.012	97	0.3000	1.5000		1.2000
East Asian																		
1	Collie-Duguid E S	1999	10208641	East Asian	Chinese	Han Chinese	Healthy individuals	192	0.977	0.0	0.0	-	0.023	97.7	0.0000	0.0000		2.3000
2	Chen ZY	2021	34084143	East Asian	Chinese			1419	0.9821	-	-	-	0.0179	98.21				1.7900
3	Kham S K Y	2002	12142782	East Asian	Chinese	Singaporean	Healthy individuals and pediatric ALL patients	271	0.97	0.0	0.002	0.0	0.028	97	0.0000	0.2000	0.0000	2.8000
4	Zhang Jian-ping	2004	15255798	East Asian	Chinese	Han Chinese	Healthy individuals	87	0.994	0.0	0.0	0.0	0.006	99.4	0.0000	0.0000	0.0000	0.6000
5	Zhang Jian-ping	2004	15255798	East Asian	Chinese	Yao Chinese	Healthy individuals	126	1	0.0	0.0	0.0	0.0	100	0.0000	0.0000	0.0000	0.0000
6	Zhang Jian-Ping	2004	14985891	East Asian	Chinese	Uygur Chinese	Healthy individuals	160	0.981	0.0	0.003	0.0	0.016	98.1	0.0000	0.3000	0.0000	1.6000
7	Song D-K	2006	17176368	East Asian	Chinese	Han Chinese	Healthy individuals and renal transplant recipients	332	0.968	0.0	0.0	0.0	0.032	96.8	0.0000	0.0000	0.0000	3.2000
8	Zhang Jian-Ping	2006	16223474	East Asian	Chinese	Han Chinese	Healthy individuals	312	0.989	0.0	0.0	0.0	0.011	98.9	0.0000	0.0000	0.0000	1.1000
9	Zhang Jian-Ping	2006	16223474	East Asian	Chinese	Jing Chinese	Healthy individuals	103	0.9903	0.0	0.0	0.0	0.0097	99.03	0.0000	0.0000	0.0000	0.9700
10	Zhang Jian-Ping	2006	16223474	East Asian	Chinese	Uygur Chinese	Healthy individuals	160	0.981	0.003	-	-	0.016	98.1	0.3000			1.6000
11	Zhang Jian-Ping	2006	16223474	East Asian	Chinese	Yao Chinese	Healthy individuals	126	1	0.0	0.0	0.0	0.0	100	0.0000	0.0000	0.0000	0.0000
12	Lu Yi	2007	17113562	East Asian	Chinese	Singaporean	Healthy individuals	166	0.991	-	0.0	0.0	0.009	99.1		0.0000	0.0000	0.9000
13	Zhang Li-Rong	2007	16952345	East Asian	Chinese	Han Chinese	Renal failure patients and healthy individuals	278	0.987	0.0	0.0	0.0	0.013	98.7	0.0000	0.0000	0.0000	1.3000
14	Kham Shirley Kow Yin	2008	18193212	East Asian	Chinese	Singaporean	Healthy individuals	153	0.987	-	0.0	-	0.013	98.7		0.0000		1.3000
15	Cao Qian	2009	19252404	East Asian	Chinese	Han Chinese	Healthy individuals and inflammatory bowel disease patients	462	0.985	0.0	-	0.0	0.015	98.5	0.0000		0.0000	1.5000

SUPPLEMENTARY TABLE: TPMT ALLELE FREQUENCY IN DIFFERENT WORLDWIDE POPULATIONS

No.	Authors	Year	PMID	Population group	Population	Add'l population info	Subject type	N subjects genotyped	Allele frequency					Allele frequency in %				
									*1	*2	*3A	*3B	*3C	*1	*2	*3A	*3B	*3C
16	Xin Hua-Wen	2009	19048245	East Asian	Chinese		Renal transplant recipients	150	0.977	0.0	0.0	0.0	0.023	97.7	0.0000	0.0000	0.0000	2.3000
17	Xiong Hui	2010	19682085	East Asian	Chinese		Renal transplant recipients	155	0.977	0.0	0.0	0.0	0.023	97.7	0.0000	0.0000	0.0000	2.3000
18	Chen Dongying	2014	24322830	East Asian	Chinese	Han Chinese	Lupus patients	126	0.984	0.0	0.0	0.0	0.016	98.4	0.0000	0.0000	0.0000	1.6000
19	Chang Jan-Gowth	2002	11927834	East Asian	Filipino		Healthy individuals	100	0.99	0.0	0.0	0.0	0.01	99	0.0000	0.0000	0.0000	1.0000
20	Chang Jan-Gowth	2002	11927834	East Asian	Indonesian		Healthy individuals	100	0.99	0.0	0.0	0.0	0.01	99	0.0000	0.0000	0.0000	1.0000
21	Hiratsuka M	2000	10751626	East Asian	Japanese		Healthy individuals	192	0.992	-	0.0	0.0	0.008	99.2		0.0000	0.0000	0.8000
22	Ando M	2001	11337943	East Asian	Japanese		Pediatric ALL patients	71	0.979	-	-	-	0.014	97.9				1.4000
23	Kubota T	2001	11422006	East Asian	Japanese		Healthy individuals	151	0.997	0.0	0.0	0.0	0.003	99.7	0.0000	0.0000	0.0000	0.3000
24	Kumagai K	2001	11337944	East Asian	Japanese		Rheumatic disease patients and healthy individuals	507	0.983	0.0	0.0	0.0	0.017	98.3	0.0000	0.0000	0.0000	1.7000
25	Kubota Takahiro	2004	15167635	East Asian	Japanese		Healthy individuals	157	0.981	-	0.0	0.0	0.019	98.1		0.0000	0.0000	1.9000
26	Okada Yuko	2005	16272700	East Asian	Japanese		Healthy individuals and lupus patients	242	0.983	0.0	0.0	0.0	0.017	98.3	0.0000	0.0000	0.0000	1.7000
27	Tamori Akihiro	2007	17241387	East Asian	Japanese		Liver disease patients	236	0.975	0.0	0.0	0.0	0.025	97.5	0.0000	0.0000	0.0000	2.5000
28	Ban Hiromitsu	2008	18827410	East Asian	Japanese		Healthy individuals and inflammatory bowel disease patients	111	0.991	-	-	-	0.009	99.1				0.9000
29	Takatsu Noritaka	2009	19682195	East Asian	Japanese		Inflammatory bowel disease patients	147	0.99	0.0	-	0.0	0.01	99	0.0000		0.0000	1.0000
30	Ban Hiromistu	2010	20393862	East Asian	Japanese		Healthy individuals and inflammatory bowel disease patients	279	0.991	-	-	-	0.009	99.1				0.9000
31	Osaki Rie	2011	22977575	East Asian	Japanese		Healthy individuals and inflammatory bowel disease patients	279	0.991	-	-	-	0.009	99.1				0.9000
32	Jun J B	2005	16396707	East Asian	Korean		Lupus patients	342	0.975	0.0	0.0	0.0	0.018	97.5	0.0000	0.0000	0.0000	1.8000
33	Lee Sang Seop	2008	18775689	East Asian	Korean		Healthy individuals	400	0.988	0.0	0.0	0.0	0.009	98.8	0.0000	0.0000	0.0000	0.9000
34	Jung Yoon Suk	2010	19960028	East Asian	Korean		Inflammatory bowel disease patients	204	0.978	0.0	0.0	0.0	0.022	97.8	0.0000	0.0000	0.0000	2.2000
35	Kim Jae Hak	2010	20308917	East Asian	Korean		Inflammatory bowel disease patients	286	0.988	-	-	-	0.012	98.8				1.2000
36	Kim Hyery	2012	23029095	East Asian	Korean		Pediatric ALL patients	100	0.96	0.01	0.005	-	0.025	96	1.0000	0.5000		2.5000
37	Kim Hyun-Young	2015	25564374	East Asian	Korean		Hospital patients	900	0.9832	0.0	0.0	0.0	0.0144	98.32	0.0000	0.0000	0.0000	1.4400
38	Lee Mi-Na	2015	25851563	East Asian	Korean		Pediatric inflammatory bowel disease patients	137	0.97	-	-	-	0.022	97				2.2000
39	Lee Minseok	2017	28966507	East Asian	Korean		Dermatology patients	123	0.976	-	-	-	0.02	97.6				2.0000
40	Kham S K Y	2002	12142782	East Asian	Malay	Singaporean	Healthy individuals and pediatric ALL patients	217	0.975	0.0	0.0	0.0	0.023	97.5	0.0000	0.0000	0.0000	2.3000
41	Lu Yi	2007	17113562	East Asian	Malay	Singaporean	Healthy individuals	104	0.976	-	0.0	0.0	0.024	97.6		0.0000	0.0000	2.4000
42	Kham Shirley Kow Yin	2008	18193212	East Asian	Malay	Singaporean	Healthy individuals	163	0.977	-	0.003	-	0.02	97.7		0.3000		2.0000
43	Chang Jan-Gowth	2002	11927834	East Asian	Taiwanese		Healthy individuals	249	0.994	0.0	0.0	0.0	0.006	99.4	0.0000	0.0000	0.0000	0.6000
44	Lu H-F	2006	16476125	East Asian	Taiwanese	Han Taiwanese	Healthy individuals	117	0.9988	0.0	0.0	0.0	0.0012	99.88	0.0000	0.0000	0.0000	0.1200
45	Lu H-F	2006	16476125	East Asian	Taiwanese	Taiwan aborigines	Healthy individuals	409	0.9872	0.0	0.0	0.0	0.0128	98.72	0.0000	0.0000	0.0000	1.2800
46	Hongeng S	2000	11025471	East Asian	Thai		Pediatric ALL patients	75	0.947	0.0	0.0	0.0	0.053	94.7	0.0000	0.0000	0.0000	5.3000
47	Chang Jan-Gowth	2002	11927834	East Asian	Thai		Healthy individuals	100	0.99	0.0	0.0	0.0	0.01	99	0.0000	0.0000	0.0000	1.0000
48	Srimartpirom Somrudee	2004	15206995	East Asian	Thai	Northeastern Thai	Healthy individuals	200	0.95	0.0	0.0	0.0	0.05	95	0.0000	0.0000	0.0000	5.0000
49	Vannaprasaht Suda	2009	19695401	East Asian	Thai		Renal transplant recipients	139	0.968	-	-	-	0.032	96.8				3.2000
50	Lu H-F	2005	16164497	East Asian	Tibetan		Healthy individuals	50	0.99	-	0.0	-	0.01	99		0.0000		1.0000
51	Lee Sang Seop	2008	18775689	East Asian	Vietnamese	Viet Kinh	Healthy individuals	159	0.972	0.0	0.0	0.0	0.028	97.2	0.0000	0.0000	0.0000	2.8000

SUPPLEMENTARY TABLE: TPMT ALLELE FREQUENCY IN DIFFERENT WORLDWIDE POPULATIONS

No.	Authors	Year	PMID	Population group	Population	Add'l population info	Subject type	N subjects genotyped	Allele frequency					Allele frequency in %				
									*1	*2	*3A	*3B	*3C	*1	*2	*3A	*3B	*3C
Near Eastern																		
1	Ronen Ofri	2010	21348397	Near Eastern	Arabs	Israeli	Healthy individuals	118	0.962	-	0.021	-	0.017	96.2		2.1000		1.7000
2	Ronen Ofri	2010	21348397	Near Eastern	Druze	Israeli	Healthy individuals	46	0.891	-	0.076	-	0.033	89.1		7.6000		3.3000
3	El-Rashedy Farida H	2015	26811598	Near Eastern	Egyptian		Pediatric ALL patients	25	0.44	-	0.44	0.04	0.08	44		44.0000	4.0000	8.0000
4	Hamdy Samar I	2003	12814450	Near Eastern	Egyptian		Healthy individuals	200	0.984	0.0	0.003	-	0.013	98.4	0.0000	0.3000		1.3000
5	Ronen Ofri	2010	21348397	Near Eastern	Ethiopian	Jewish/Israeli	Healthy individuals	169	0.97	-	0.003	-	0.027	97		0.3000		2.7000
6	Bahari Ali	2010	20408054	Near Eastern	Iranian	Southeastern Iranian	Healthy individuals	832	0.94	0.0216	0.0168	0.0162	0.0054	94	2.1600	1.6800	1.6200	0.5400
7	Moini Maryam	2012	21938428	Near Eastern	Iranian	Southern Iran	Healthy individuals	500	0.974	0.001	0.0	0.0	0.025	97.4	0.1000	0.0000	0.0000	2.5000
8	Efrati Edna	2009	19048244	Near Eastern	Israeli	Druze	Healthy individuals	156	0.9606	0.0	0.0319	0.0	0.0075	96.06	0.0000	3.1900	0.0000	0.7500
9	Efrati Edna	2009	19048244	Near Eastern	Israeli	Jewish	Healthy individuals	531	0.9927	0.0	0.0073	0.0	0.0	99.27	0.0000	0.7300	0.0000	0.0000
10	Efrati Edna	2009	19048244	Near Eastern	Israeli	Moslem	Healthy individuals	194	0.9816	0.0	0.0079	0.0	0.0105	98.16	0.0000	0.7900	0.0000	1.0500
11	Ronen Ofri	2010	21348397	Near Eastern	Israeli	Jewish	Healthy individuals	164	0.991	-	0.006	-	0.003	99.1		0.6000		0.3000
12	Hakooz Nancy	2010	20521035	Near Eastern	Jordanian		Healthy individuals	169	0.982	0.0	0.012	0.0	0.006	98.2	0.0000	1.2000	0.0000	0.6000
13	Elawi Asma M	2013	23398787	Near Eastern	Jordanian		Healthy individuals and rheumatoid arthritis patients	360	0.993	0.0	0.0042	0.0028	0.0	99.3	0.0000	0.4200	0.2800	0.0000
14	Ronen Ofri	2010	21348397	Near Eastern	Kurdish	Israeli	Healthy individuals	73	0.993	-	0.007	-	-	99.3		0.7000		
15	Phillips Paul H	2007	17577869	Near Eastern	Lebanese, Palestinian, Syrian, Iraqi		Pediatric ALL patients	143	0.99	0.0	0.01	-	-	99	0.0000	1.0000		
16	Zeglam Hamza Ben	2015	25819542	Near Eastern	Libyan	Tawargha	Healthy individuals	38	0.974	0.0	0.013	-	0.013	97.4	0.0000	1.3000		1.3000
17	Zeglam Hamza Ben	2015	25819542	Near Eastern	Libyan	Tripoli	Healthy individuals	154	0.984	0.0	0.006	-	0.01	98.4	0.0000	0.6000		1.0000
18	Zeglam Hamza Ben	2015	25819542	Near Eastern	Libyan	Yefren	Healthy individuals	54	0.991	0.0	0.0	-	0.009	99.1	0.0000	0.0000		0.9000
19	Lennard Lynne	2015	25940902	Near Eastern	Middle Eastern	from Britain	Pediatric ALL patients	15	0.933	0.0	0.067	-	0.0	93.3	0.0000	6.7000		0.0000
20	Janati Idrissi Meryem	2015	25573490	Near Eastern	Moroccan		Healthy individuals	103	1	0.0		0.0	0.0	100	0.0000	0.0000	0.0000	0.0000
21	Ayesh Basim Mohammad	2013	24499706	Near Eastern	Palestinian		Pediatric ALL patients	56	0.9911	0.0	0.0089	0.0	0.0	99.11	0.0000	0.8900	0.0000	0.0000
22	Melaouhia Salma	2012	22225964	Near Eastern	Tunisian		Crohn's disease patients	208	0.9832	0.0	0.0	0.0024	0.0144	98.32	0.0000	0.0000	0.2400	1.4400
23	Ben Salah Lynda	2013	23553048	Near Eastern	Tunisian		Crohn's disease patients	88	0.949	0.0	0.0397	0.0	0.0113	94.9	0.0000	3.9700	0.0000	1.1300
24	Ouerhani Slah	2013	23065291	Near Eastern	Tunisian		Healthy individuals and ALL patients	206	0.942	0.056	-	-	0.002	94.2	5.6000			0.2000
25	Tumer Tugba Boyunegmez	2007	17617792	Near Eastern	Turkish		Pediatric ALL patients	106	0.982	0.0	0.009	0.0	0.009	98.2	0.0000	0.9000	0.0000	0.9000
26	Albayrak Meryem	2011	21400026	Near Eastern	Turkish		Pediatric ALL patients	58	0.957	0.0	0.034	0.0	0.009	95.7	0.0000	3.4000	0.0000	0.9000
European																		
1	Ameyaw M M	1999	9931345	European	British		Healthy individuals	199	0.947	0.005	0.045	-	0.003	94.7	0.5000	4.5000		0.3000
2	Collie-Duguid E S	1999	10208641	European	British		Healthy individuals	199	0.947	0.005	0.045	-	0.003	94.7	0.5000	4.5000		0.3000
3	McLeod H L	1999	10354134	European	British		Pediatric ALL patients	147	0.939	0.0	0.054	-	0.007	93.9	0.0000	5.4000		0.7000
4	McLeod H L	1999	10634140	European	British		Healthy individuals	199	0.947	0.005	0.045	-	0.003	94.7	0.5000	4.5000		0.3000
5	Lennard Lynne	2015	25940902	European	British	White	Pediatric ALL patients	1965	0.9539	0.0008	0.041	-	0.004	95.39	0.0800	4.1000		0.4000
6	Slanar Ondrej	2008	18600549	European	Czech		Healthy individuals and inflammatory bowel disease patients	696	0.9443	0.001	0.045	0.0007	0.009	94.43	0.1000	4.5000	0.0700	0.9000
7	Reuther L O	2003	12492733	European	Danish		Crohn's disease patients	120	0.95	-	0.05	0.0	0.0	95		5.0000	0.0000	0.0000
8	Toft Nina	2006	17129980	European	Danish		Healthy individuals	200	0.964	-	0.033	0.0	0.003	96.4		3.3000	0.0000	0.3000
9	Corominas H	2000	11007234	European	Dutch		Healthy individuals and ulcerative colitis patients	190	0.964	-	0.026	0.005	0.005	96.4		2.6000	0.5000	0.5000
10	Spire-Vayron de la Moureyre C	1998	9831928	European	European		Healthy individuals and patients receiving thipurine therapy	191	0.927	0.005	0.057	0.0	0.008	92.7	0.5000	5.7000	0.0000	0.8000

SUPPLEMENTARY TABLE: TPMT ALLELE FREQUENCY IN DIFFERENT WORLDWIDE POPULATIONS

No.	Authors	Year	PMID	Population group	Population	Add'l population info	Subject type	N subjects genotyped	Allele frequency					Allele frequency in %				
									*1	*2	*3A	*3B	*3C	*1	*2	*3A	*3B	*3C
11	Ganiere-Monteil Catherine	2004	15022030	European	French										0.7500	3.0000		0.4000
12	Schaeffeler Elke	2004	15226673	European	German		Healthy individuals	1214	0.947	0.002	0.045	0.0	0.004	94.7	0.2000	4.5000	0.0000	0.4000
13	Gazouli M	2010	20175817	European	Greek		Pediatric inflammatory bowel disease patients	97	0.8831	0.0319	0.0266	0.0478	0.0106	88.31	3.1900	2.6600	4.7800	1.0600
14	Coucoutsi Constantina	2017	28857898	European	Greek	Cretan	Healthy individuals and inflammatory bowel disease patients	342	0.975	0.006	0.009	0.004	0.006	97.5	0.6000	0.9000	0.4000	0.6000
15	Toft Nina	2006	17129980	European	Greenlandic		Outpatient patients	142	0.919	-	0.081	0.0	0.0	91.9		8.1000	0.0000	0.0000
16	Rossi A M	2001	11372592	European	Italian		Healthy individuals	103	0.9464	0.0049	0.039	0.0	0.0097	94.64	0.4900	3.9000	0.0000	0.9700
17	Rossino R	2006	16789994	European	Italian	Sardinian	Healthy individuals	259	0.9652	0.0174	0.0058	0.0039	0.0077	96.52	1.7400	0.5800	0.3900	0.7700
18	Christensen A F	2009	19473573	European	Italian		Autoimmune disease patients	78	0.9808	0.0	0.0192	0.0	0.0	98.08	0.0000	1.9200	0.0000	0.0000
19	Serpe Loredana	2009	19891552	European	Italian		Healthy individuals	943	0.972		0.022	0.003	0.003	97.2	0.0000	2.2000	0.3000	0.3000
20	Larussa Tiziana	2012	22385887	European	Italian		Inflammatory bowel disease patients	51	0.93	0.02	0.0	0.01	0.04	93	2.0000	0.0000	1.0000	4.0000
21	Di Salvo Angela	2016	27665263	European	Italian	Sicilian	Patients with inflammatory bowel disease, autoimmune or hematologic diseases	184	0.973	-	0.019	-	0.008	97.3		1.9000		0.8000
22	Zalizko P	2020	32704308	European	Latvian		Inflammatory bowel disease patients	244	0.9692	0.0021	0.0266	0	0.0021	96.92	0.2100	2.6600	0.0000	0.2100
23	Steponaitiene Ruta	2016	26674571	European	Lithuanian		Inflammatory bowel disease patients	551	0.963	0.0	0.031	0.005	0.001	96.3	0.0000	3.1000	0.5000	0.1000
24	Loennechen T	2001	11503013	European	Norwegian	Saami	Cardiology patients	194	0.97	-	0.0	-	0.03	97		0.0000		3.0000
25	Loennechen T	2001	11503013	European	Norwegian	White	Cardiology patients	66	0.9164	-	0.076	-	0.0076	91.64		7.6000		0.7600
26	Kurzawski Mateusz	2004	15385838	European	Polish		Healthy individuals	358	0.968	0.004	0.027	-	0.001	96.8	0.4000	2.7000		0.1000
27	Kurzawski Mateusz	2005	16044099	European	Polish		Renal transplant recipients	180	0.946	0.006	0.042	-	0.006	94.6	0.6000	4.2000		0.6000
28	Chrzanowska Maria	2006	17220558	European	Polish		Hemodialysis patients	87	0.942	0.0	0.052	-	0.006	94.2	0.0000	5.2000		0.6000
29	Kurzawski Mateusz	2009	19229528	European	Polish		Renal transplant recipients	157	0.94	0.006	0.048	-	0.006	94	0.6000	4.8000		0.6000
30	Chrzanowska Maria	2012	22594254	European	Polish		Pediatric ALL patients and healthy individuals	98	0.944	0.005	0.051	-	0.0	94.4	0.5000	5.1000		0.0000
31	Skrzypczak-Zielinska Marzena	2013	23252704	European	Polish		Healthy individuals and inflammatory bowel disease patients	274	0.9982	-	0.0	-	-	99.82		0.0000		
32	Alves S	1999	10376773	European	Portuguese	Northern Portuguese	Healthy individuals	310	0.976	-	0.024	-	-	97.6		2.4000		
33	Alves S	2001	11503011	European	Portuguese		Healthy individuals	143	0.958	0.01	0.025	-	0.007	95.8	1.0000	2.5000		0.7000
34	Nasedkina Tatyana V	2006	16724002	European	Russian		Healthy individuals and pediatric hematology patients	700	0.969	0.0014	0.026	-	0.0036	96.9	0.1400	2.6000		0.3600
35	Samochatova Elena V	2009	19034904	European	Russian		Pediatric hematology patients, other pediatric patients and healthy adults	995	0.972	0.001	0.023	-	0.004	97.2	0.1000	2.3000		0.4000
36	Dokmanovic Lidija	2006	17164697	European	Serbian and Montenegrin		Healthy individuals and pediatric ALL patients	200	0.961	0.002	0.032	0.005	0.0	96.1	0.2000	3.2000	0.5000	0.0000
37	Chocholova Alica	2013	23581716	European	Slovakian		Healthy individuals and pediatric inflammatory bowel disease patients	395	0.956	0.0	0.038	0.002	0.004	95.6	0.0000	3.8000	0.2000	0.4000
38	Desatova B	2013	23731044	European	Slovakian		Inflammatory bowel disease patients	330	0.964	0.002	0.032	0.0	0.002	96.4	0.2000	3.2000	0.0000	0.2000

SUPPLEMENTARY TABLE: TPMT ALLELE FREQUENCY IN DIFFERENT WORLDWIDE POPULATIONS

No.	Authors	Year	PMID	Population group	Population	Add'l population info	Subject type	N subjects genotyped	Allele frequency					Allele frequency in %				
									*1	*2	*3A	*3B	*3C	*1	*2	*3A	*3B	*3C
39	Milek M	2006	16691038	European	Slovenian		Healthy individuals	194	0.951	0.0	0.041	0.003	0.005	95.1	0.0000	4.1000	0.3000	0.5000
40	Corominas H	2000	11007234	European	Spanish		Healthy individuals and ulcerative colitis patients	169	0.941	-	0.03	0.012	0.017	94.1		3.0000	1.2000	1.7000
41	Corominas H	2003	12509611	European	Spanish		Rheumatoid arthritis patients	111	0.964	-	0.027	0.009	-	96.4		2.7000	0.9000	
42	Bosó Virginia	2014	24232128	European	Spanish		Solid organ transplant donors and recipients	569	0.998	0.002	-	-	-	99.8	0.2000			
43	Díaz-Villamarín X	2023	37857254	European	Spanish			149	0.9494	0.007	0.0302	0	0.0134	94.94	0.7000	3.0200	0.0000	1.3400
44	Casajús A	2022	35192152	European	Spanish			109	0.9633	0	0.0367	0	0	96.33	0.0000	3.6700	0.0000	0.0000
45	Haglund Sofie	2004	14656901	European	Swedish		Healthy individuals	800	0.95633	0.0006	0.0375	0.0012	0.00437	95.63	0.0600	3.7500	0.1200	0.4370
46	Hindorf U	2004	15545169	European	Swedish	Blekinge County	Inflammatory bowel disease patients	55	0.946	-	0.045	-	0.009	94.6		4.5000		0.9000
Sub-Saharan African																		
1	Oliveira E	2007	17473918	Sub-Saharan African	Angolan	Cabinda	Healthy individuals	103	0.937	0.0	0.0	-	0.039	93.7	0.0000	0.0000		3.9000
2	Lennard Lynne	2015	25940902	Sub-Saharan African	Black	from Britain	Pediatric ALL patients	55	0.982	0.0	0.009	0.0	0.009	98.2	0.0000	0.9000	0.0000	0.9000
3	Ameyaw M M	1999	9931345	Sub-Saharan African	Ghanaian		Healthy individuals	217	0.924	0.0	0.0	-	0.076	92.4	0.0000	0.0000		7.6000
4	Yen-Revollo J L	2009	19546880	Sub-Saharan African	Ghanaian	Akwapim	Healthy individuals	90	0.94	-	-	-	0.06	94				6.0000
5	Yen-Revollo J L	2009	19546880	Sub-Saharan African	Ghanaian	Ashanti	Healthy individuals	103	0.93	-	-	-	0.07	93				7.0000
6	Yen-Revollo J L	2009	19546880	Sub-Saharan African	Ghanaian	Ewe	Healthy individuals	183	0.93	-	-	-	0.07	93				7.0000
7	Yen-Revollo J L	2009	19546880	Sub-Saharan African	Ghanaian	Fanti	Healthy individuals	160	0.92	-	-	-	0.08	92				8.0000
8	Yen-Revollo J L	2009	19546880	Sub-Saharan African	Ghanaian	Ga	Healthy individuals	183	0.94	-	-	-	0.06	94				6.0000
9	McLeod H L	1999	10634140	Sub-Saharan African	Kenyan		Healthy individuals	101	0.946	0.0	0.0	-	0.054	94.6	0.0000	0.0000		5.4000
10	Heckmann Jeannine M	2005	15792824	Sub-Saharan African	South African	Black	Healthy individuals and neurology patients	227	0.965	0.0	0.0	-	0.035	96.5	0.0000	0.0000		3.5000
11	Heckmann Jeannine M	2005	15792824	Sub-Saharan African	South African	Mixed ancestry	Healthy individuals and neurology patients	272	0.974	0.0	0.004	-	0.022	97.4	0.0000	0.4000		2.2000
Latino																		
1	Lu H-F	2005	16164497	Latino	Bolivian		Healthy individuals	115	0.9348	-	0.0652	-	0.0	93.48		6.5200		0.0000
2	Silva Marcilene Rezende	2008	19057372	Latino	Brazilian		Pediatric ALL patients	116	0.952	0.0	0.039	0.0	0.009	95.2	0.0000	3.9000	0.0000	0.9000
3	Farfan Mauricio J	2014	24774509	Latino	Chilean		Pediatric ALL patients	103	0.961	0.0	0.034	0.0	0.005	96.1	0.0000	3.4000	0.0000	0.5000
4	Isaza C	2003	12949626	Latino	Colombian	Mestizo	Healthy individuals	140	0.96	0.004	0.036	0.0	0.0	96	0.4000	3.6000	0.0000	0.0000
5	Taja-Chayeb Lucia	2008	18188716	Latino	Mexican		Healthy individuals and ALL patients	147	0.908	0.014	0.044	0.017	0.017	90.8	1.4000	4.4000	1.7000	1.7000
6	Ramos Marco A	2011	21254844	Latino	Mexican	Baja California	Healthy individuals	150	0.947	0.0	0.03	0.003	0.02	94.7	0.0000	3.0000	0.3000	2.0000
7	Jiménez-Morales Silvia	2016	28476189	Latino	Mexican		Healthy individuals and pediatric ALL patients	849	0.952	0.002	0.041	0.001	0.004	95.2	0.2000	4.1000	0.1000	0.4000
8	Ramirez-Florencio Mireya	2018	29264794	Latino	Mexican		Lupus patients and rheumatoid arthritis patients	553	0.945	0.005	0.044	0.002	0.004	94.5	0.5000	4.4000	0.2000	0.4000