



Decoding genetic divergence: TPMT and NUDT15 polymorphisms in north India mirror Caucasian ancestry

Arshdeep Singh¹, Renu Moti Pandita², Manjeet Kumar Goyal³, Barjinderjit K. Dhillon², Vandana Midha⁴, Ajit Sood¹

¹Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, India; ²Molecular Genetics Laboratory, Dayanand Medical College and Hospital, Ludhiana, India; ³Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, India; ⁴Department of Medicine, Dayanand Medical College and Hospital, Ludhiana, India

Thiopurines such as azathioprine and mercaptopurine, have been integral to management of inflammatory bowel disease (IBD) since their inception in late 1960s.¹ Thiopurines have proven efficacy as steroid sparing agents for maintenance of remission in IBD, with remission rates ranging from 40.00% to 60.00%.² Additionally, they enhance the effectiveness of biologics by reducing immunogenicity and preventing the formation of anti-drug antibodies. However, their clinical utility is hampered by potential adverse effects, including bone marrow suppression, hepatotoxicity, gastrointestinal intolerance and increased risk of infections.³

The advent of personalized medicine has transformed therapeutic paradigms, enabling pharmacogenetically informed interventions. Genetic polymorphisms in enzymes such as thiopurine S-methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) have been extensively studied, given their critical roles in thiopurine metabolism. Variations in these genes have implications for drug safety, influencing susceptibility to thiopurine-induced myelosuppression. TPMT, exhibits an inverse relationship with intracellular 6-thioguanine levels, with polymorphisms predicting cytopenia risk. Similarly, NUDT15 variants have been implicated in dose-dependent cytopenia.⁴

Ethnic and regional diversity has been observed in the distribution of TPMT and NUDT15 polymorphisms. In Cauca-

sian populations, approximately 90.00% exhibit normal TPMT activity, while 10.00% have intermediate activity and a mere 0.30% lack enzyme function entirely. Conversely, NUDT15 variants, which are infrequent in Caucasians, are notably more common in East Asians, where mutant genotypes necessitate thiopurine dose reductions. Such variability underscores the necessity of region-specific pharmacogenetic data to guide clinical practice.^{2,5}

We evaluated the prevalence of NUDT15 and TPMT polymorphisms in north Indian IBD cohort. This study was approved by the Institutional Review Board of Dayanand Medical College and Hospital (IRB No. DMCH/R & D/2020/23). Written informed consent was waived. Peripheral blood samples (2 mL) were collected in EDTA vials, and DNA was isolated using the QIAamp DNA Mini Kit. Samples (200 µL) were processed with proteinase K, lysis buffer, and ethanol, followed by centrifugation through QIAamp spin columns. The eluted DNA was stored in autoclaved tubes, and quality was verified using a NanoDrop spectrophotometer. Polymerase chain reaction amplification targeted TPMT (c.238 G>C, c.460 G>A, c.719 A>G) and NUDT15 polymorphisms (c.415 C>T;R139C). Digestion with restriction enzymes (Hpy10F) and restriction fragment length polymorphism analysis were performed, and products were visualized using agarose gel electrophoresis with ethidium bromide staining under ultraviolet light.³

Among 454 patients (mean age 45.00 ± 29.69 years, 251 males [55.40%]), 1 patient (0.22%) was heterozygous for NUDT15 polymorphism with rest all having wild type gene. Twenty patients (4.40%) had TPMT polymorphisms, out of which 4

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Correspondence to Ajit Sood, Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana, Punjab 1410001, India.

E-mail: ajitsood10@gmail.com

(0.88%), 9 (1.98%), 16 (3.52%), and 13 (2.86%) patients had heterozygous variant of TPMT*2A, TPMT*3A, TPMT*3B, and TPMT*3C polymorphisms, respectively. Eight patients (1.76%) were compound heterozygotes for both TPMT*3A and TPMT*3C, and 6 patients (1.32%) were compound heterozygous for TPMT*3B and TPMT*3C. Despite these polymorphisms, only 9 patients (1.98%) developed leukopenia.

Our data diverge from South Asian trends, highlighting a higher prevalence of TPMT polymorphisms and a negligible frequency of NUDT15 variants in north India. Previous studies have reported the frequency of TPMT polymorphisms varying from 10.10% in Caucasians, to 2.00% in South East Asians and 4.70% in Chinese populations with data from India ranging between 1.70% to 7.50% (Supplementary Table 1). A recent systematic review concluded that NUDT15 c.415C>T(p. R139C) polymorphism was found in 16.50% (95% confidence interval, 13.09–20.58) Asians whereas it was rare in Caucasians and Africans, with allele frequencies of 0.12 and <0.01, respectively.^{6,7} The NUDT-15 polymorphism prevalence in our cohort was 0.22%, much lower than previous studies.

The plausible explanation of these differences can stem from genetic studies, which reveal that the Punjabi population, particularly in northwest India, shares significant genetic affinities with European and Central Asian populations. Historical migrations, such as those involving Indo-Aryan and Indo-Scythian tribes, may have introduced substantial West Eurasian genetic components into Punjabi communities. Microsatellite marker analyses demonstrate that Punjabi groups like Jat Sikhs exhibit a distinct clustering pattern, aligning more closely with Caucasoid populations than with other South Asian groups.⁸ Furthermore, studies on mitochondrial DNA and Y-chromosome markers indicate greater admixture with European lineages in north Indian population.⁸⁻¹⁰

In conclusion, our study reveals a distinct pharmacogenetic profile in north India, characterized by higher prevalence of TPMT polymorphisms and a negligible frequency of NUDT15 variants, diverging from broader South Asian trends, highlighting the need for region-specific pharmacogenetic data in clinical practice. Relying solely on NUDT15 screening in Asian populations may be inadequate; instead, combined TPMT and NUDT15 genotyping is essential for optimizing resource allocation and enhancing patient safety. The genetic parallels between north Indians and Caucasians highlight the need for further insights into historical and evolutionary influences, which could inform more personalized and effective therapeutic strategies for IBD and beyond.

ADDITIONAL INFORMATION

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Conflict of Interest

Sood A is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Author Contributions

Conceptualization: Singh A, Goyal MK, Midha V. Data curation: Sood A, Midha V. Formal analysis: Pandita RM, Dhillon BK, Goyal MK. Investigation: Singh A, Midha V. Methodology: Singh A, Pandita RM, Dhillon BK, Sood A. Supervision: Sood A. Writing - original draft preparation: Singh A, Sood A, Goyal MK. Writing - review & editing: Singh A, Pandita RM, Dhillon BK, Goyal MK, Midha V, Sood A. Approval of final manuscript: all authors.

Additional Contributions

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ORCID

Singh A	https://orcid.org/0000-0001-7163-0454
Pandita RM	https://orcid.org/0009-0002-3358-0673
Goyal MK	https://orcid.org/0000-0002-5511-2099
Dhillon BK	https://orcid.org/0000-0002-1071-4459
Midha V	https://orcid.org/0000-0003-0192-3969
Sood A	https://orcid.org/0000-0001-6961-6389

Supplementary Material

Supplementary materials are available at the Intestinal Research website (<https://www.irjournal.org>).

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