

TPMT allele nomenclature committee

The table defines all the single-nucleotide polymorphisms (SNPs) in *TPMT* as of Nov 2022

Allele	dbSNP rsID and corresponding nucleotides on the positive chromosomal strand (for standardization) and ClinVar accession number if applicable	Nucleotide changes in the <i>TPMT</i> gene (given on the negative chromosomal strand, NCBI reference sequence NM_000367.2)	Gene location	Amino acid Change (NCBI reference sequence NP_000358.1)	References
<i>TPMT*1</i>	rs2842934 allele A ¹	Wild type 474T ¹			
<i>TPMT*1A</i>	ND, G>A	-178C>T	Exon I		[1]
<i>TPMT*1S</i>	A>G at rs2842934	474T>C	Exon VII	Ile158Ile	[2]
<i>TPMT*2</i>	C>G at rs1800462	238G>C	Exon V	Ala80Pro	[3, 4, 5, 6, 7]
<i>TPMT*3A</i>	C>T at rs1800460 T>C at rs1142345	460G>A 719A>G	Exon VII Exon X	Ala154Thr Tyr240Cys	[4, 5, 6, 7, 8]
<i>TPMT*3B</i>	C>T at rs1800460	460G>A	Exon VII	Ala154Thr	[4, 6, 7, 8]
<i>TPMT*3C</i>	T>C at rs1142345	719A>G	Exon X	Tyr240Cys	[4, 6, 7, 8]
<i>TPMT*3D</i>	C>A at s72552739 C>T at rs1800460 T>C at rs1142345	292G>T 460G>A 719A>G	Exon V Exon VII Exon X	Glu98Stop Ala154Thr Tyr240Cys	[9]
<i>TPMT*3E</i>	A>T at rs3931660 T>A at rs12529220 A>G at rs2518463 C>T at rs1800460 A>G at rs2842934 T>C at rs1142345	140+114T>A 141-101A>T 366+58T>C 460G>A 474T>C 719A>G	Intron III Intron III Intron IV Exon VII Exon VII Exon X	Ala154Thr Ile158Ile Tyr240Cys	[10]
<i>TPMT*4</i>	C>T at rs1800584	626-1G>A	Intron IX/ exon X in splice junction		[9, 11]

<i>TPMT*5</i>	A>G at rs72552740	146T>C	Exon IV	Leu49Ser	[4, 6, 9]
<i>TPMT*6</i>	T>A at rs75543815	539A>T	Exon VIII	Tyr180Phe	[4, 6, 9]
<i>TPMT*7</i>	A>C at rs72552736	681T>G	Exon X	His227Gln	[1, 4, 6, 9]
<i>TPMT*8</i>	C>T at rs56161402	644G>A	Exon X	Arg215His	[4, 6, 12]
<i>TPMT*9</i>	T>G at rs151149760	356A>C	Exon V	Lys119Thr	[4, 6, 13]
<i>TPMT*10</i>	C>G at rs72552737	430G>C	Exon VII	Gly144Arg	[4, 6, 14, 15]
<i>TPMT*11</i>	C>T at rs72552738	395G>A	Exon VI	Cys132Tyr	[4, 6, 16]
<i>TPMT*12</i>	G>A at rs200220210	374C>T	Exon VI	Ser125Leu	[4, 6, 15]
<i>TPMT*13</i>	T>A at rs72552742	83A>T	Exon III	Glu28Val	[4, 6, 15]
<i>TPMT*14</i>	T>C at rs9333569	1A>G	Exon III	Met1Val	[6, 17]
<i>TPMT*15</i>	C>T at rs9333570	495-1G>A	Intron VII/ exon VIII in splice junction		[17]
<i>TPMT*16</i>	C>T at rs144041067	488G>A	Exon VII	Arg163His	[6, 13, 18]
<i>TPMT*17</i>	ND, G>C	124C>G	Exon III	Gln42Glu	[6, 13]
<i>TPMT*18</i>	C>T at rs777686348	211G>A	Exon IV	Gly71Arg	[6, 13]
<i>TPMT*19</i>	ND, T>G	365A>C	Exon V	Lys122Thr	[6, 18]
<i>TPMT*20</i>	T>C at rs150900439	712A>G	Exon X	Lys238Glu	[6, 19]
<i>TPMT*21</i>	G>C at rs200591577	205C>G	Exon IV	Leu69Val	[6, 19]
<i>TPMT*22</i>	ND, C>G	488G>C	Exon VII	Arg163Pro	[6, 19]
<i>TPMT*23</i>	G>C at rs74423290	500C>G	Exon VIII	Ala167Gly	[20]
<i>TPMT*24</i>	C>A at rs6921269	537G>T	Exon VIII	Gln179His	[21]
<i>TPMT*25</i>	A>G at rs377085266	634T>C	Exon X	Cys212Arg	[21]
<i>TPMT*26</i>	A>G at rs72556347	622T>C	Exon IX	Phe208Leu	[22]
<i>TPMT*27</i>	ND, A>C	319T>G	Exon V	Tyr107Asp	[23]
<i>TPMT*28</i>	ND, C>G	349G>C ²	Exon V	Gly117Arg	[24]
<i>TPMT*29</i>	A>G at rs267607275	2T>C	Exon III	Met1Thr	[25]
<i>TPMT*30</i>	Old <i>TPMT*20</i> / <i>*24</i> , C>T at rs750424422	106G>A	Exon III	Gly36Ser	[6, 26]
<i>TPMT*31</i>	Old <i>TPMT*28</i> A>G at rs79901429	611T>C	Exon IX	Ile204Thr	[27]
<i>TPMT*32</i>	C>T at rs115106679	340G>A	Exon V	Glu114Lys	[28]
<i>TPMT*33</i>	G>A at rs112339338	487C>T	Exon VII	Arg163Cys	[28]
<i>TPMT*34</i>	G>A at rs111901354	244C>T	Exon V	Arg82Trp	[28]

<i>TPMT*35</i>	ND	200T>C ³	Exon III	Phe67Ser	[29]
<i>TPMT*36</i>	ND	595G>A ₃	Exon VIII	Val199Ile	[29]
<i>TPMT*37</i>	A>T at rs398122996	648T>A	Exon X	Cys216Ter	[30]
<i>TPMT*38</i>	G>A at rs772832951	514T>C	Exon VIII	Ser172Pro	[31]
<i>TPMT*39</i>	A>G at rs281874771	218C>T	Exon VI	Ala73Val	[32]
<i>TPMT*40</i>	T>C at rs139392616	677G>A	Exon X	Arg226Q	[33]
<i>TPMT*41</i>	T>G at rs1142345	719A>C	Exon X	Tyr240Ser	[34]
<i>TPMT*42</i>	ins A at rs759836180, SCV000778513	95_96insA	Exon III	Lys32LysfsX58	[35]
<i>TPMT*43</i>	SCV000778514	234G>T	Exon V	Trp78Cys	[35]
	rs753545734, SCV000778515	262G>A	Exon V	Gly88Ser	
<i>TPMT*44</i>	rs201695576, SCV000778516	497A>G	Exon VIII	Tyr166Cys	[35]
<i>TPMT*45</i>	rs761990479	676C>T	Exon X	Arg226Stop	[36]
<i>TPMT*46</i>	C>T at rs56161402	644G>A	Exon X	Arg215His	[37]
	G>A at rs112339338	487C>T	Exon VII	Arg163Cys	

ND – Not reported to dbSNP, ¹dbSNP reports G>A at this position: however the TPMT nomenclature committee has defined wildtype as having allele A at this position (positive chromosomal strand) and the *1S allele as having allele G at this position (positive chromosomal strand): ² incorrect nucleotide substitutions given in reference 24: the corrected nucleotide substitution is included in the table (personal communication T. Marinaki).³ These alleles was numbered differently in the original publication [29].

1. Spire-Vayron de la Moureyre C, Debuysere H, Sabbagh N, Marez D, Vinner E, Chevalier ED, et al. Detection of known and new mutations in the thiopurine S-methyltransferase gene by single-strand conformation polymorphism analysis. *Hum Mutat* 1998; **12**: 177-185.
2. Yates CR, Krynetski EY, Loennechen T, Fessing MY, Tai HL, Pui CH, et al. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. *Ann Intern Med* 1997; **126**: 608-614.
3. Krynetski EY, Schuetz JD, Galpin AJ, Pui CH, Relling MV, Evans WE. A single point mutation leading to loss of catalytic activity in human thiopurine S-methyltransferase. *Proc Natl Acad Sci USA* 1995; **92**: 949-953.
4. Salavaggione OE, Wang L, Wiepert M, Yee VC, Weinshilboum RM. Thiopurine S-methyltransferase pharmacogenetics: variant allele functional and comparative genomics. *Pharmacogenet Genomics* 2005; **15**: 801-815.
5. Tai HL, Krynetski EY, Schuetz EG, Yanishevski Y, Evans WE. Enhanced proteolysis of thiopurine S-methyltransferase (TPMT) encoded by mutant alleles in humans (TPMT*3A, TPMT*2): mechanisms for the genetic polymorphism of TPMT activity. *Proc Natl Acad Sci U S A* 1997; **94**: 6444-6449.
6. Ujiie S, Sasaki T, Mizugaki M, Ishikawa M, Hiratsuka M. Functional characterization of 23 allelic variants of thiopurine S-methyltransferase gene (TPMT*2 - *24). *Pharmacogenet Genomics* 2008; **18**: 887-893.
7. Tai HL, Krynetski EY, Yates CR, Loennechen T, Fessing MY, Krynetskaia NF, et al. Thiopurine S-methyltransferase deficiency: two nucleotide transitions define the most prevalent mutant allele associated with loss of catalytic activity in Caucasians. *Am J Hum Genet* 1996; **58**: 694-702.

8. Szumlanski C, Otterness D, Her C, Lee D, Brandriff B, Kellsell D, et al. Thiopurine methyltransferase pharmacogenetics: human gene cloning and characterization of a common polymorphism. *DNA Cell Biol* 1996; **15**: 17-30.

9. Otterness D, Szumlanski C, Lennard L, Klemetsdal B, Aarbakke J, Park-Hah JO, et al. Human thiopurine methyltransferase pharmacogenetics: gene sequence polymorphisms. *Clin Pharmacol Ther* 1997; **62**: 60-73.
10. Colleoni L, Kapetis D, Maggi L, Camera G, Canioni E, Cavalcante P, et al. A New Thiopurine S-Methyltransferase Haplotype Associated With Intolerance to Azathioprine. *J Clin Pharmacol* 2013; **53**: 67-74.
11. Otterness D, Szumlanski C, Weinshilboum R. Human thiopurine methyltransferase pharmacogenetics: identification of a novel variant allele. *J Invest Med* 1996; **44**: 248A.
12. Hon YY, Fessing MY, Pui CH, Relling MV, Krynetski EY, Evans WE. Polymorphism of the thiopurine S-methyltransferase gene in African-Americans. *Hum Mol Genet* 1999; **8**: 371-376.
13. Schaeffeler E, Fischer C, Brockmeier D, Wernet D, Moerike K, Eichelbaum M, et al. Comprehensive analysis of thiopurine S-methyltransferase phenotype-genotype correlation in a large population of German-Caucasians and identification of novel TPMT variants. *Pharmacogenetics* 2004; **14**: 407-417.
14. Colombel JF, Ferrari N, Debuysere H, Marteau P, Gendre JP, Bonaz B, et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. *Gastroenterology* 2000; **118**: 1025-1030.
15. Hamdan-Khalil R, Allorge D, Lo-Guidice JM, Cauffiez C, Chevalier D, Spire C, et al. In vitro characterization of four novel non-functional variants of the thiopurine S-methyltransferase. *Biochem Biophys Res Commun* 2003; **309**: 1005-1010.
16. Schaeffeler E, Stanulla M, Greil J, Schrappe M, Eichelbaum M, Zanger UM, et al. A novel TPMT missense mutation associated with TPMT deficiency in a 5-year-old boy with ALL. *Leukemia* 2003; **17**: 1422-1424.
17. Lindqvist M, Haglund S, Almer S, Peterson C, Taipalensu J, Hertvig E, et al. Identification of two novel sequence variants affecting thiopurine methyltransferase enzyme activity. *Pharmacogenetics* 2004; **14**: 261-265.
18. Hamdan-Khalil R, Gala JL, Allorge D, Lo-Guidice JM, Horsmans Y, Houdret N, et al. Identification and functional analysis of two rare allelic variants of the thiopurine S-methyltransferase gene, TPMT*16 and TPMT*19. *Biochem Pharmacol* 2005; **69**: 525-529.
19. Schaeffeler E, Eichelbaum M, Reinisch W, Zanger UM, Schwab M. Three novel thiopurine S-methyltransferase allelic variants (TPMT*20, *21, *22) - association with decreased enzyme function. *Hum Mutat* 2006; **27**: 976.
20. Lindqvist M, Skoglund K, Karlgren A, Soderkvist P, Peterson C, Kidhall I, et al. Explaining TPMT genotype/phenotype discrepancy by haplotyping of TPMT*3A and identification of a novel sequence variant, TPMT*23. *Pharmacogenet Genomics* 2007; **17**: 891-895.
21. Garat A, Cauffiez C, Renault N, Lo-Guidice JM, Allorge D, Chevalier D, et al. Characterisation of novel defective thiopurine S-methyltransferase allelic variants. *Biochem Pharmacol* 2008; **76**: 404-415.
22. Kham SK, Soh CK, Aw DC, Yeoh AE. TPMT*26 (208F-->L), a novel mutation detected in a Chinese. *Br J Clin Pharmacol* 2009; **68**: 120-123.
23. Feng Q, Vannaprasaht S, Peng Y, Angsuthum S, Avihingsanon Y, Yee VC, et al. Thiopurine S-methyltransferase pharmacogenetics: functional characterization of a novel rapidly degraded variant allozyme. *Biochem Pharmacol* 2010; **79**: 1053-1061.
24. Landy J, Bhuva N, Marinaki A, Mawdsley J. Novel thiopurine methyltransferase variant TPMT*28 results in a misdiagnosis of TPMT deficiency. *Inflamm Bowel Dis* 2010.
25. Lee CK, Loh TP, Wong ST, Lee HK, Huan PT, Chiu LL, et al. Detection of a novel single nucleotide polymorphism of the human thiopurine s-methyltransferase gene in a Chinese individual. *Drug Metab Pharmacokinet* 2012; **27**: 559-561.
26. Sasaki T, Goto E, Konno Y, Hiratsuka M, Mizugaki M. Three novel single nucleotide polymorphisms of the human thiopurine S-methyltransferase gene in Japanese individuals. *Drug Metab Pharmacokinet* 2006; **21**: 332-336.
27. Appell ML, Wennerstrand P, Peterson C, Hertvig E, Martensson LG. Characterization of a novel sequence variant, TPMT*28, in the human thiopurine methyltransferase gene. *Pharmacogenet Genomics* 2010; **20**: 700-707.

28. Lennard L, Cartwright CS, Wade R, Richards SM, Vora A. Thiopurine methyltransferase genotype-phenotype discordance, and thiopurine active metabolite formation, in childhood acute lymphoblastic leukaemia. *Br J Clin Pharmacol* doi 10.1111/bcp.12066 2012.
29. Skrzypczak-Zielinska M, Borun P, Milanowska K, Jakubowska-Burek L, Zakerska O, Dobrowolska-Zachwieja A, et al. High-resolution melting analysis of the TPMT gene: a study in the Polish population. *Genet Test Mol Biomarkers* 2013; **17**: 153-159.
30. Roberts R, Wallace M, Drake J, Stamp L. IdentificationDOI:10.1097/FPCofanovel.000000000000049thiopurinemethyltransferase allele (TPMT*37). *Pharmacogenetics and genomics* 2014
31. Kim HY, Lee SH, Lee MN, Kim JW, Kim YH, Kim MJ, et al. Complete sequence-based screening of TPMT variants in the Korean population. *Pharmacogenet Genomics*. 2015. DOI 10.1097/FPC.0000000000000117.
32. Coelho, T. *et al.* Genes implicated in thiopurine-induced toxicity: Comparing TPMT enzyme activity with clinical phenotype and exome data in a paediatric IBD cohort. *Scientific reports* **6**, 34658, doi:10.1038/srep34658 (2016).
33. Liu, C. *et al.* Genomewide Approach Validates Thiopurine Methyltransferase Activity Is a Monogenic Pharmacogenomic Trait. *Clin Pharmacol Ther* **101**, 373-381, doi:10.1002/cpt.463 (2017).
34. Iu, Y. P. H. *et al.* One amino acid makes a difference-Characterization of a new TPMT allele and the influence of SAM on TPMT stability. *Scientific reports* **7**, 46428, doi:10.1038/srep46428 (2017).
35. Zimdahl Kahlin A, Helander S, Skoglund K, Soderkvist P, Martensson LG, Appell ML. Comprehensive study of thiopurine methyltransferase genotype, phenotype, and genotype-phenotype discrepancies in Sweden. *Biochem Pharmacol*. 2019;**164**:263-72.
36. Ha C, Kim ES, Kwon Y, Choe YH, Kim MJ, Lee SY. The Identification of a Novel Thiopurine S-Methyltransferase Allele, TPMT*45, in Korean Patient with Crohn's Disease. *Pharmgenomics Pers Med*. 2020;13:665-71.
37. Pratt VM, Wang WY, Boone EC, Broeckel U, Cody N, Edelmann L, et al. Characterization of Reference Materials for TPMT and NUDT15: A GeT-RM Collaborative Project. *J Mol Diagn*. 2022;24(10):1079-88.