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Nomenclature for alleles of the thiopurine methyltransferase gene

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Abstract

The drug-metabolizing enzyme thiopurine methyltransferase (TPMT) has become one of the best examples of pharmacogenomics to be translated into routine clinical practice. TPMT metabolizes the thiopurines 6-mercaptopurine, 6-thioguanine, and azathioprine, drugs that are widely used for treatment of acute leukemias, inflammatory bowel diseases, and other disorders of immune regulation. Since the discovery of genetic polymorphisms in the *TPMT* gene, many sequence variants that cause a decreased enzyme activity have been identified and characterized.

Increasingly, to optimize dose, pretreatment determination of TPMT status before commencing thiopurine therapy is now routine in many countries. Novel *TPMT* sequence variants are currently numbered sequentially using PubMed as a source of information; however, this has caused some problems as exemplified by two instances in which authors' articles appeared on PubMed at the same time, resulting in the same allele numbers given to different polymorphisms. Hence, there is

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Conflicts of interest M.V.R. and W.E. receive a portion of the income that St Jude Children's Research Hospital receives from licensing patent rights related to TPMT polymorphisms. E.S. and M.S. are holders of patent rights related to TPMT genetic variants. M.K. is a coinventor on a patent relating to a trinucleotide repeat polymorphism in the TPMT promoter. For the remaining authors there are no conflicts of interest.

an urgent need to establish an order and consensus to the numbering of known and novel *TPMT* sequence variants. To address this problem, a *TPMT* nomenclature committee was formed in 2010, to define the nomenclature and numbering of novel variants for the *TPMT* gene. A website (<http://www.imh.liu.se/tpmtalleles>) serves as a platform for this work. Researchers are encouraged to submit novel *TPMT* alleles to the committee for designation and reservation of unique allele numbers. The committee has decided to renumber two alleles: nucleotide position 106 (G > A) from *TPMT**24 to *TPMT**30 and position 611 (T > C, rs79901429) from *TPMT**28 to *TPMT**31. Nomenclature for all other known alleles remains unchanged.

Keywords

allele; nomenclature; pharmacogenetics; thiopurine methyltransferase

Introduction

The thiopurines 6-thioguanine, 6-mercaptopurine (6-MP), and its pro-drug azathioprine are purine based analogues. These drugs were synthesized in the early 1950's by Elion and Hitchings [1], and within a few years 6-MP was used to successfully treat children with childhood acute lymphoblastic leukemia (ALL) [2]. Today, thiopurines continue to be used extensively in clinical practice as anticancer and immunosuppressive agents despite having a narrow therapeutic index with potential life-threatening drug induced toxicity.

One of the main causes of toxicity is the way in which these prodrugs are metabolized to their active metabolites inside the cell [3,4]. They undergo extensive metabolism to form both active and inactive metabolites causing cell death by several different mechanisms [4]. The main causes of cytotoxicity are through the incorporation of thioguanine nucleotides (TGNs) into the DNA as base analogues [5], inhibition of *de novo* purine synthesis [6,7], and disturbances in intracellular signaling pathways. The latter of these contributes to the immunosuppressive properties of these agents [8–10]. Thiopurines are S-methylated by the enzyme thiopurine methyltransferase (TPMT, EC 2.1.1.67). This produces methylated metabolites such as S-methylmercaptopurine and S-methylthioguanine, both of which are believed to be inactive, and S-methyl-thioinosine monophosphate, an inhibitor of *de novo* purine synthesis, emphasizing the importance of TPMT activity in the metabolism of these drugs.

The first study measuring TPMT activity in humans by Weinshilboum and Sladek demonstrated trimodal distribution [11]. They reported that from a cohort of 298 randomly selected Caucasians, 11.1% had intermediate activity, 89.6% had high activity, and 0.3% had no activity. This was critical in helping to understand the role of TPMT activity in patients treated with thiopurines and was highlighted by Lennard [12], who showed that in children treated with 6-MP for ALL, the red blood cell TGN concentrations were inversely correlated to the TPMT activity, indicating that with high TPMT activity more drug was S-methylated to inactive metabolites.

Following the study of TPMT activity, the cloning and characterization of the human *TPMT* cDNA revealed that these phenotypic variations were primarily due to variation within the coding sequence of the gene itself [13,14]. The human *TPMT* gene maps to chromosome 6p22.3, which is 34 kb in length and consists of 10 exons. An untranscribed and untranslated pseudogene, homologous to 96% of the *TPMT* cDNA sequence, has been located to chromosome 18 [15]. To date, about 30 genetic variants have been shown to affect TPMT protein stability and/or enzymatic activity. Most are nonsynonymous single nucleotide

polymorphisms (SNPs, Table 1, Fig. 1). The most intensively studied alleles are *2, *3A, and *3C, which represent up to 95% of variant alleles found in most populations [16–18].

However, large interethnic differences exist in the frequencies of these alleles, and in the prevalence of more rare alleles. Examples are *TPMT**8 and *TPMT**6, which occur at frequencies between 1.5 and 3.5% in some African and Asian populations [19,20], but very rarely, if at all, in other investigated populations. More detailed information about specific *TPMT* alleles can be found in Wang *et al.*'s [21] study. In the future, the application of routine exome or whole genome sequencing is likely to unveil many more rare *TPMT* sequence variants [22].

Patients inheriting two nonfunctional *TPMT* alleles are at the highest risk of hematopoietic toxicity if treated with conventional doses of thiopurines (essentially 100% risk), and convert more parent drug into active TGNs because they lack the methylation pathway, whereas patients who inherit one wild-type allele and one nonfunctional allele are at a significantly higher risk of hematopoietic toxicity (~35% cumulative incidence in one study of children with ALL) [23,24].

In contrast to this, ALL patients with high *TPMT* activity may have a higher risk of relapse if treated with conventional doses of 6-MP (depending on what other ALL therapy they receive); thus, they should be treated on full-dose thiopurine. Those with intermediate activity often require treatment with a lower dose to avoid toxicity. It has been shown that *TPMT* heterozygous ALL patients do not have a higher risk of ALL relapse if treated with a lower dose of 6-MP [25], and that heterozygous ALL patients have a significantly lower rate of minimal residual disease positivity for early treatment response to 6-MP, at least in the ALL Berlin-Frankfurt-Münster (BFM) trial [26].

Clearly, as this enzyme has such a profound effect on drug metabolism, it is critical that the *TPMT* status of a patient should be taken into account before commencing thiopurine treatment [27].

In 2011, a guideline from the Clinical Pharmacogenetics Implementation Consortium was published, with the purpose of providing information with which to interpret clinical *TPMT* genotype tests so that the results can be used successfully to guide the dosing of thiopurines [28].

Although there is still debate on genotype versus phenotype in assessing the *TPMT* status, it remains both timely and critical that a repository for the naming of these polymorphisms is created. This will have appropriate links to existing resources: thus, investigators in the field can easily identify polymorphisms that have been described previously and their effects on *TPMT* activity. It is to this end that a new *TPMT* nomenclature website (<http://www.imh.liu.se/tpmtalleles>) was launched by representatives from a worldwide group of researchers from the field of *TPMT* pharmacogenetic research.

The *TPMT* nomenclature website

Since the publication of the first *TPMT* variant (allele *2) in 1995 [13,14], many sequence variants in the *TPMT* gene have been identified and been given star (*) allele numbers (summarized in Table 1, Fig. 1). Currently, authors number alleles sequentially using PubMed as a source of information about the last published allele; however, this has caused some problems, as exemplified by two instances in which authors' articles appeared on PubMed at the same time, resulting in the same number being given to different polymorphisms.

To circumvent this in the future, there is a need for a unified nomenclature system, and therefore, in 2010, a TPMT nomenclature committee of representatives from around the world who work in the field was formed with the aim of creating a platform for a full description of known *TPMT* alleles and for the numbering of subsequent alleles. The TPMT nomenclature website (<http://www.imh.liu.se/tpmtalleles>) was launched in 2011 with the purpose of managing allele designations and providing a summary of published *TPMT* alleles. The nomenclature system chosen was based on the established star allele numbering system and on recommended genetic variant nomenclature guidelines [29–31].

Currently, the website covers the nomenclature for published *TPMT* alleles linked to a designated star allele number, as well as the functionality of the allele. In addition, links to the National Center for Biotechnology Information single nucleotide polymorphism database (dbSNP), as well as publications describing the original identification and/or the characterization of the allele are presented. Researchers are encouraged to submit their own validated novel genetic variants to dbSNP to obtain a reference SNP identification (rsID) to aid consistency in genetic variant mapping.

Inclusion criteria for *TPMT* alleles

The main function of the website is to encourage researchers worldwide to be confident of which *TPMT* allele they are referring and to avoid confusion in the literature in the future. The TPMT nomenclature committee has decided upon inclusion criteria that will help to maintain this goal, listed 1–8 in Table 2.

Renaming of existing *TPMT* alleles

To improve the existing nomenclature, the committee reviewed all existing allele numbers, and for those that are duplicated, the committee has agreed on the renumbering of two earlier identified and published alleles.

Renaming of *TPMT20/*24 (106G > A in exon III)**

The 106G > A SNP in exon 3 was identified during denaturing HPLC screening of the *TPMT* gene in 200 Japanese individuals [32] and was numbered *TPMT**20. At the same time, Schaeffeler *et al.* [33] identified a SNP at position 712 (A > G, rs150900439), and also numbered it *TPMT**20. To address this problem, in 2008 the 106 SNP was renumbered *TPMT**24 [34]. However, at the same time in 2008, Garat *et al.* [35] presented yet another SNP at position 537 (G > T), which was numbered *TPMT**24. The committee has decided that the SNP at position 106G > A should be designated by the unique star allele number *TPMT**30 (Table 1).

Renaming of *TPMT28 (611T > C in exon IX, rs79901429)**

The 611T > C (rs79901429) SNP was identified in a Swedish family with Italian ancestries, and was numbered *TPMT**28 in 2010 [36]. At the same time, Landy *et al.* [37] described the identification of a SNP at position 349 (G > C, see Table 1 for comments), which they also numbered *TPMT**28. The committee has decided that the SNP at position 611 should be assigned a novel star allele number – *TPMT**31 (Table 1).

Submission of new alleles

To avoid any confusion in the future, authors are encouraged to submit novel *TPMT* alleles (sequence and functionality if available), preferably after a manuscript has been accepted but before final proofing, to the nomenclature committee through the website for confidential designation and reservation of a novel allele number by the nomenclature committee, or to

contact the editor of the committee (corresponding author of the current paper) by ordinary mail.

To submit a novel *TPMT* allele to the committee, authors should fill in the form available on the *TPMT* nomenclature website, with information regarding, for example, the position of the variant, gene location (exon/intron, etc.), nucleotide position (e.g. 238), and SNP flanking sequence. Usage of star allele designations that have not been approved by the nomenclature committee is strongly discouraged, because of the risk of confusion when two different alleles are given the same star number. The editors of the *TPMT* nomenclature committee (and if appropriate the advisory board, details of which are found on the *TPMT* nomenclature website) will review the submission to evaluate whether there are enough data to support a new allele designation, and will await publishing before making the novel allele available, ensuring that only peer-reviewed data are published on the *TPMT* nomenclature website.

Conclusion

To maintain a common nomenclature system within the field, fellow scientists investigating *TPMT* polymorphisms are strongly encouraged to submit novel *TPMT* allelic variants to the *TPMT* nomenclature committee (<http://www.imh.liu.se/tpmtalleles>) by contacting the webmaster through the website for the designation and reservation of novel *TPMT* allele numbers confidentially.

The authors of this mini-review, some of whom have themselves identified novel *TPMT* alleles, are supportive of this new nomenclature system, and will use this system in their future work. This new nomenclature will also be used at www.pharmgkb.org for associations between *TPMT* alleles and drug responses reported in the literature [58] and at www.LOVD.nl/TPMT, a gene variant database, collecting and displaying all reported *TPMT* DNA variants.

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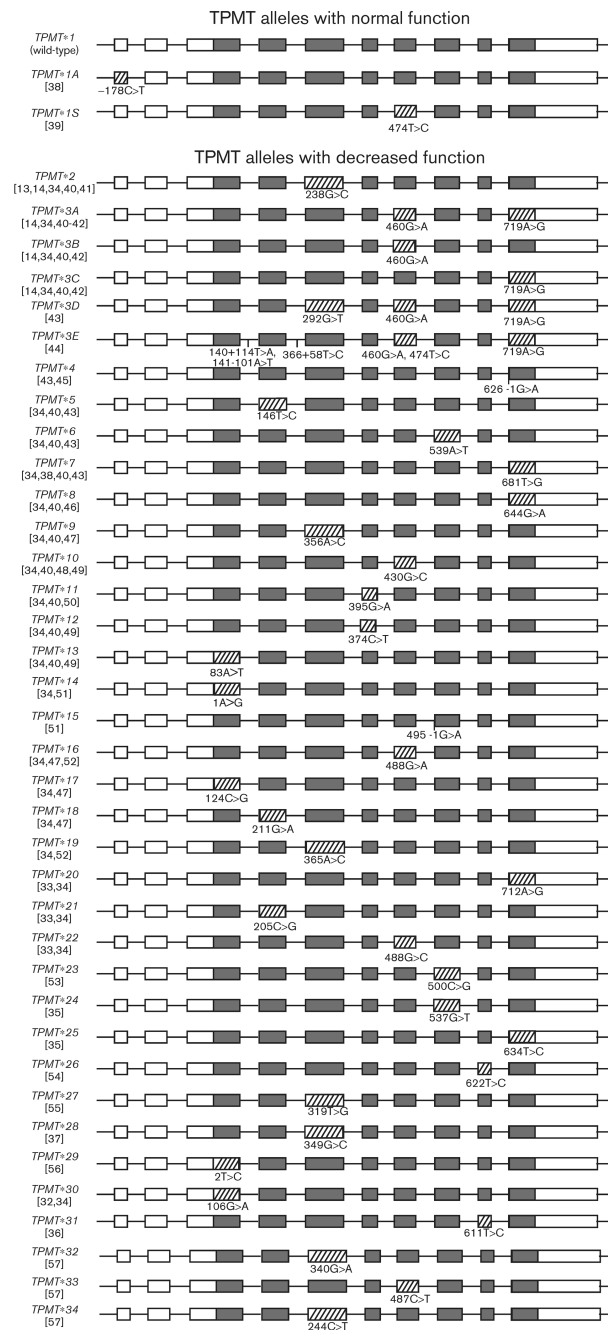


Fig. 1. Schematic representation of thiopurine methyltransferase (TPMT) alleles showing affected exons in stripe pattern, unaffected exons in dark gray, and untranslated parts of exons in white. The sizes of the exons are proportional to base pair length, whereas the introns are not. Nucleotide changes in the *TPMT* gene (given on the negative chromosomal strand, NCBI reference sequence NM_000367.2) are numbered such that the A in the ATG is + 1.

Table 1

TPMT allele nomenclature

Allele	dbSNP rsID and corresponding nucleotides on the positive chromosomal strand (for standardization)	Nucleotide changes in the TPMT 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 ^a	Wild type 474T ^a	–	–	–
<i>TPMT*1A</i>	ND, G> A	– 178C>T	Exon I	–	[38]
<i>TPMT*1S</i>	A >G at rs2842934	474T >C	Exon VII	Ile158Ile	[39]
<i>TPMT*2</i>	C>G at rs1800462	238G>C	Exon V	Ala80Pro	[13,14,34,40,41]
<i>TPMT*3A</i>	C> T at rs1800460	460G>A	Exon VII	Ala154Thr	[14,34,40–42]
	T >C at rs1142345	719A >G	Exon X	Tyr240Cys	–
<i>TPMT*3B</i>	C> T at rs1800460	460G>A	Exon VII	Ala154Thr	[14,34,40,42]
<i>TPMT*3C</i>	T >C at rs1142345	719A >G	Exon X	Tyr240Cys	[14,34,40,42]
<i>TPMT*3D</i>	C>A at s72552739	292G > T	Exon V	Glu98Sto	[43]
	C> T at rs1800460	460G>A	Exon VII	Ala154Thr	–
	T >C at rs1142345	719A >G	Exon X	Tyr240Cys	–
<i>TPMT*3E</i>	A > T at rs3931660	140+ 114T > A	Intron III	–	[44]
	T>A at rs12529220	141–101A> T	Intron III	–	–
	A >G at rs2518463	366 + 58T >C	Intron IV	–	–
	C> T at rs1800460	460G>A	Exon VII	Ala154Thr	–
	A >G at rs2842934	474T >C	Exon VII	Ile158Ile	–
	T >C at rs1142345	719A >G	Exon X	Tyr240Cys	–
<i>TPMT*4</i>	C>T at rs1800584	626-1G> A	Intron IX/exon X in splice junction	–	[43,45]
<i>TPMT*5</i>	A >G at rs72552740	146T >C	Exon IV	Leu49Ser	[34,40,43]
<i>TPMT*6</i>	T >A at rs75543815	539A > T	Exon VIII	Tyr180Phe	[34,40,43]
<i>TPMT*7</i>	A >C at rs72552736	681T >G	Exon X	His227Gln	[34,38,40,43]
<i>TPMT*8</i>	C>T at rs56161402	644G>A	Exon X	Arg215His	[34,40,46]
<i>TPMT*9</i>	T>G at rs151149760	356A >C	Exon V	Lys119Thr	[34,40,47]
<i>TPMT*10</i>	C>G at rs72552737	430G>C	Exon VII	Gly144Arg	[34,40,48,49]
<i>TPMT*11</i>	C>T at rs72552738	395G > A	Exon VI	Cys132Tyr	[34,40,50]
<i>TPMT*12</i>	ND, G> A	374C >T	Exon VI	Ser125Leu	[34,40,49]
<i>TPMT*13</i>	T> A at rs72552742	83A >T	Exon III	Glu28Val	[34,40,49]
<i>TPMT*14</i>	T>C at rs9333569	1A >G	Exon III	Met1Val	[34,51]
<i>TPMT*15</i>	C>T at rs9333570	495-1G > A	Intron VII/exon VIII in splice junction	–	[51]
<i>TPMT*16</i>	C> T at rs144041067	488G>A	Exon VII	Arg163His	[34,47,52]
<i>TPMT*17</i>	ND, G>C	124C >G	Exon III	Gln42Glu	[34,47]
<i>TPMT*18</i>	ND, C> T	211G >A	Exon IV	Gly71Arg	[34,47]
<i>TPMT*19</i>	ND, T>G	365A>C	Exon V	Lys122Thr	[34,52]
<i>TPMT*20</i>	T>C at rs150900439	712A >G	Exon X	Lys238Glu	[33,34]

Allele	dbSNP rsID and corresponding nucleotides on the positive chromosomal strand (for standardization)	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</i> *21	G>C at rs200591577	205C >G	Exon IV	Leu69Val	[33,34]
<i>TPMT</i> *22	ND, C>G	488G>C	Exon VII	Arg163Pro	[33,34]
<i>TPMT</i> *23	G>C at rs74423290	500C >G	Exon VIII	Ala167Gly	[53]
<i>TPMT</i> *24	C> A at rs6921269	537G> T	Exon VIII	Gln179His	[35]
<i>TPMT</i> *25	ND, A >G	634T >C	Exon X	Cys212Arg	[35]
<i>TPMT</i> *26	A >G at rs72556347	622T>C	Exon IX	Phe208Leu	[54]
<i>TPMT</i> *27	ND, A >C	319T >G	Exon V	Tyr107Asp	[55]
<i>TPMT</i> *28	ND, C>G	349G>C ^b	Exon V	Gly117Arg	[37]
<i>TPMT</i> *29	A >G at rs267607275	2T >C	Exon III	Met1Thr	[56]
<i>TPMT</i> *30	Old <i>TPMT</i> *20/*24, ND, C> T	106G> A	Exon III	Gly36Ser	[32,34]
<i>TPMT</i> *31	Old <i>TPMT</i> *28 A >G at rs79901429	611T>C	Exon IX	Ile204Thr	[36]
<i>TPMT</i> *32	C> T at rs115106679	340G>A	Exon V	Glu114Lys	[57]
<i>TPMT</i> *33	G> A at rs112339338	487C>T	Exon VII	Arg163Cys	[57]
<i>TPMT</i> *34	G> A at rs111901354	244C>T	Exon V	Arg82Trp	[57]

The table defines all the single nucleotide polymorphisms (SNPs) in *TPMT* as of January 2013.

dbSNP, single nucleotide polymorphism database; ND, not reported to dbSNP; *TPMT*, thiopurine methyltransferase.

^adbSNP reports G> A at this position: however, the *TPMT* nomenclature committee has defined wild type as having allele A at this position (positive chromosomal strand) and the *1S allele as having allele G at this position (positive chromosomal strand).

^bIncorrect nucleotide substitutions are given in Landy *et al.*'s [37] study: the corrected nucleotide substitution is included in the table (T. Marinaki, 14 September 2012, personal communication).

Table 2

Inclusion criteria for *TPMT* alleles to be assigned a unique identity and to be included on the TPMT website^a

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- (1) On the TPMT nomenclature website, only human *TPMT* alleles are considered
 - (2) The gene and allele are separated by an asterisk followed by Arabic numerals (e.g. *TPMT*1*, *TPMT*3*)
 - (3) Additional nucleotide changes and combinations of nucleotide changes, including silent mutations in the gene, will be assigned letters (e.g. **1A*, **1S*)
 - (4) To be assigned as a unique allele, it should contain nucleotide changes that have been shown to affect transcription, splicing, translation, post-transcriptional or post-translational modifications or result in at least one amino acid change
 - (5) Numbering of nucleotides in the allele should be as described in Antonarakis and the Nomenclature Working Group [30]. In the cDNA sequence, the base A in the initiation codon ATG is denoted as + 1 and the base before A is numbered as – 1
 - (6) Submission of new alleles should be done with information sufficient to fulfill the criteria to be assigned a unique allele (as under criterion 4 above) or letter (as described under criterion 3 above). For incorporation into the website as a unique allele, all exons and exon–intron borders should have been sequenced. If a new allele has been detected on the cDNA level, verification of the mutation(s) on the genomic level is necessary. For acceptance of a new SNP given a separate letter (criterion 3), evidence for its presence on the genomic level is necessary
 - (7) No temporary allelic numbers or letters are provided, and information about any new allele submitted will continuously be published on the website. In case an author does not want to release the information on the website before publication, the webmaster can usually provide him or her with an allelic designation but not release the information on the website until the manuscript has been accepted or published
 - (8) Any novel SNPs should be submitted to dbSNP (NCBI) after *TPMT* allele designation to obtain a unique rsID for marker mapping – this rsID should then be submitted to the website to be added to the table
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dbSNP, single nucleotide polymorphism database; TPMT, thiopurine methyltransferase.

^a<http://www.imh.liu.se/tpmtpalleles>