Pharmaceutical Research, Vol. 16, No. 3, 1999

Review

Pharmacogenetics as a Molecular Basis for Individualized Drug Therapy: The Thiopurine S-methyltransferase Paradigm

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Received October 12, 1998; accepted November 27, 1998

Genetic polymorphism of drug metabolizing enzymes can be the major determinant of inter-individual differences in drug disposition and effects. In this mini-review, the evolution of pharmacogenetic studies, from the recognition of phenotypic polymorphisms to the discovery of genetic mutations responsible for these inherited traits, is illustrated by the genetic polymorphism of thiopurine S-methyltransferase (TPMT). TPMT, which exhibits autosomal co-dominant polymorphism, plays an important role in metabolism of the antileukemic and immunosuppressive medications, mercaptopurine, thioguanine, and azathioprine. The genetic polymorphism of TPMT activity in humans was first reported in 1980, and in the last five years the genetic basis for this polymorphism has been elucidated. Isolation and cloning of mutant alleles from humans with TPMT deficiency has identified the major mutant alleles, established the basis for loss of TPMT activity and permitted development of PCR-based genotyping assays to make a molecular diagnosis of TPMT-deficiency and heterozygosity. These studies illustrate the potential clinical benefits of elucidating the molecular basis of inherited differences in drug metabolism and disposition, and future automation of molecular diagnostics will make it feasible to more precisely select the optimal drug and dosage for individual patients.

KEY WORDS: thiopurine S-methyltransferase; genetic polymorphism; mercaptopurine; thioguanine; genotyping.

INTRODUCTION

The discipline of pharmacogenetics has evolved from its beginning in the 1950's, when genetic polymorphisms were defined at the phenotypic level, to the modern era of molecular studies that are elucidating the genetic basis of these inherited traits. At the outset, pharmacogenetic studies focused largely on inherited polymorphisms in drug metabolism enzymes, such as serum cholinesterase (1), N-acetyltransferase (2,3), debrisoquine-hydroxylase (CYP2D6) (3,4), aldehyde dehydrogenase (5), glutathione S-transferase (GST) (6), catechol O-methyltransferase (COMT) (7), thiopurine S-methyltransferase (TPMT) (8,9), mephenytoin-hydroxylase (CYP2C19) (3) and a number of other polymorphic enzymes. While new polymorphisms in constitutive expression and regulatory mechanisms continue to be discovered for drug metabolizing enzymes (10), there is also increasing focus on genetic polymorphisms of drug targets (e.g., receptors). Theoretically, polymorphisms in drug metabolism and disposition (e.g., transporters) will be important in selecting the optimal dosage and schedule of medications for individual patients, while polymorphisms in drug targets will influence the choice of medications for a specific genetic subtype of the disease or receptor.

This mini-review uses the genetic polymorphism of thiopurine S-methyltransferase to illustrate the evolution of pharmacogenetic studies from the recognition of phenotypic polymorphisms to the discovery of genetic mutations responsible for these inherited traits. This review also addresses the advantages and limitations of testing patients at the level of phenotype versus genotype, and discusses new methods that show promise to make molecular diagnosis feasible for the clinical laboratory.

Thiopurine S-methyltransferase (TPMT) as a Paradigm of Clinical and Molecular Studies of Genetic Polymorphisms in Drug Metabolism

We have selected TPMT as the prototype for this review, for three principal reasons: (1) it is now a relatively well characterized polymorphism at both the clinical and molecular level; (2) there are clinically important consequences of this polymorphism, related to both the toxicity and efficacy of thiopurine medications, and (3) it is a genetic polymorphism with which we have first-hand experience.

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ABBREVIATIONS: ALL, acute lymphoblastic leukemia; MP, 6-mercaptopurine; RBC, red blood cells; TG, 6-thioguanine; TGN, 6-thioguanosine nucleotides (mono-, di-, and triphosphates); TPMT, thiopurine S-methyltransferase.

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TPMT was originally discovered by Remy in rodents (11), and subsequently the genetic polymorphism in humans was uncovered in a study of TPMT activity in erythrocytes (RBC) from 298 normal healthy blood donors (12). Family studies established the autosomal co-dominant polymorphism of TPMT in humans, with approximately 90% of Caucasians and African Americans having high activity (10–40 u/ml pRBC), about 10% with intermediate activity (5–10 u/ml pRBC) and 1/300 inheriting TPMT-deficiency (<5 u/ml pRBC) (13,14). It has now been established at the genetic level that these three groups represent individuals with homozygous wild-type, heterozygous and homozygous mutant TPMT genotypes, respectively (Fig. 1) (15).

TPMT is a cytosolic enzyme that catalyzes the S-methylation of aromatic and heterocyclic sulfhydryl compounds, including the thiopurine medications mercaptopurine (MP), MP from the prodrug azathioprine, and thioguanine (TG), as well as many of their nucleotide metabolites (9).

Comparison of human and murine TPMT amino acid sequences reveals significant similarity (82%, with 72% identical amino acids), making it difficult to positively identify functionally important conserved regions within the amino acid sequence. Recent characterization of a third member of the thiopurine S-methyltransferase family in *Pseudomonas syringae* (45% similarity, with 33% identical aminoacids) clearly demonstrated that this enzyme is substantially conserved throughout evolution. Alignment of the amino acid sequences in these three distant species (primate, rodent and bacteria) helps to highlight conserved sequences which presumably form catalytic/binding centers or maintain the overall protein structure (Fig. 2) (16–18). This conservation also indicates the ancient origin of TPMT and its potential biological importance. Moreover, the common inactivating mutations that result in the loss of TPMT activity in humans, are located in the conserved regions of the polypeptide chain. For instance, gene mutations that alter amino acids at positions 154 and 240 affect amino acid residues that are invariant in all three TPMTs (35). The mutation at codon 80 (Ala → Pro) is located in the longest stretch of identical amino acids and conserved substitutions, located in the first half of the sequence.

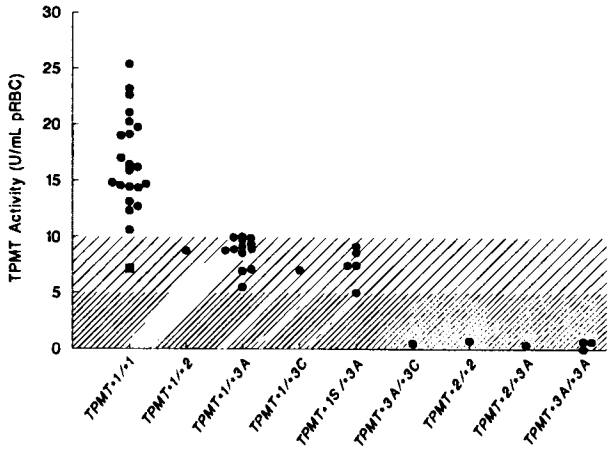

Fig. 1. TPMT activity in patients with different TPMT genotypes, as determined by mutation-specific PCR methods. The heavily shaded area depicts the range of erythrocyte TPMT activity that defines TPMT-deficiency (<5 u/mL packed red blood cells, pRBC) in Caucasians, the lightly shaded area depicts intermediate activity that defines TPMT heterozygous phenotypes (5–10 u/mL pRBC) and the unshaded area depicts the range of TPMT activity in individuals with homozygous wild-type phenotypes. Black circles indicate patients with concordant genotype and phenotype, the black square indicates the one patient with discordant genotype and phenotype. Reproduced with publisher's permission from Yates *et al. Ann. Int. Med.*, (1997) 126:608–614 (15).

Interestingly, no natural substrate is known for TPMT, and its involvement in endogenous metabolic pathways remains obscure. Superexpression of TPMT in bacteria causes resistance to tellurium, a highly toxic but relatively rare element, and TPMT may also be involved in metabolism of selenium (18,19).

TPMT and Thiopurine Toxicity

In humans, TPMT deficiency is associated with severe hematopoietic toxicity when deficient patients are treated with standard doses of MP, TG or azathioprine (20–22). Surprisingly, no known phenotype is associated with TPMT deficiency in humans, until such patients are treated with thiopurine medications. Moreover, this toxicity can be fatal, as exemplified by a TPMT-deficient heart transplant recipient who died of sepsis as a consequence of repeated leukopenia caused by conventional doses of azathioprine, prior to the *post-hoc* diagnosis of TPMT deficiency (23). In contrast, successful cases of thiopurine therapy in TPMT-deficient patients are exemplified by children with ALL who have been successfully treated with 10–15% of the conventional dose of MP (20,21).

Low TGN concentrations in RBC have been associated with a higher risk of relapse in children with ALL treated according to some antimetabolite-based protocols (24,25). Since RBC cellular concentrations of TGN inversely correlate with TPMT activity (Fig. 3), the relation of TPMT activity to relapse was studied in a group of 95 pediatric patients. Among them, a subgroup of children with decreased RBC TGN concentrations had significantly higher TPMT activity, and a higher rate of leukemic relapse, when compared to those having TGN above the population median (25).

It is now common to monitor RBC TGN levels in ALL patients treated with protocols containing extensive MP therapy, and it has been suggested that transplant patients be screened for TPMT-deficiency or TGN be monitored during therapy (26). While the greatest risk of toxicity is in patients with TPMT deficiency, there are data emerging that indicate patients with heterozygous phenotypes are also at greater risk of thiopurine toxicity (27,28). It has also been suggested that the wide range of TPMT activity may be an important factor in determining long-term graft survival in azathioprine-treated patients; those with high activity might benefit from doses near the upper limit of those generally recommended (29).

METABOLISM OF THIOPURINES

Metabolism of thiopurines has been extensively studied (for a recent review see (8)). MP and TG are inactive prodrugs, requiring metabolism to TGN via the purine "salvage pathway" to exert cytotoxicity. In cell cultures, resistance to thiopurines is a well-known phenomenon achieved usually through inactivation of the first enzyme of the "salvage pathway"—hypoxanthine phosphoribosyltransferase (HPRT). On the contrary, no clear evidence exists to establish decreased HPRT

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Human TPMT       MDGTRTSLDIEEYSDTEVQKNQVLTLEEWQDKWVNGKTAFHQEQGHQLLKKHLDTFLKGK
Mouse TPMT       -----MSLDMKEHPDAEVQKNQVLTLEDWKEKWVTRHISFHQEQGHQLLKKHLDTFLKGQ
P.syringae TPMT  ----------------------MKADFWLQRWSAGQIGFHQSEVNKDLQQYWSSLN-VV
                                         . . *  .*   .  *** . .. *..   .
                                 80
                                 ↓
Human TPMT       SGLRVFFPLCGKAVEMKWFADRGHSVVGVEISELGIQEFFTEQNLSYSEEPITEIPGTKV
Mouse TPMT       SGLRVFFPLCGKAIEMKWFADRGHTVVGVEISEIGIREFFAEQNLSYTEEPLAEIAGAKV
P.syringae TPMT  PGARVLVPLCGKSQDMSWLSGQGYHVVGAELSEAAVERYFTER----GEQPHITSQGDFK
                  * **  *****. .* * . .*  *** *.**  .  .*.*.     *.*     *
                                                  154                   180
                                                  ↓                     ↓
Human TPMT       FKSSSGNISLYCCSIFDLPRTNIGKFDMIWDRGALVAINPGDRKCYADTMFSLLGKKFQY
Mouse TPMT       FKSSSGSISLYCCSIFDLPRANIGKFDRIWDRGALVAINPGDHDRYADIILSLLRKEFQY
P.syringae TPMT  VYAAPG-IEIWCGDFFALTARDIGHCAAFYDRAAMIALPADMRERYVQHLEALMPQACSG
                   .. * * . *   * *    **.     ** *..*.    .  *   . .*. .
                                                          227
                                                          ↓
Human TPMT       LLCVLSYDPTKHPGPPFYVPHAEIERLFGKICNIRCLEKVDAFEERHK--SWGIDCLFEK
Mouse TPMT       LVAVLSYDPTKHAGPPFYVPSAELKRLFGTKCSMQCLEEVDALEERHK--AWGLDYLFEK
P.syringae TPMT  LLITLEYDQALLEGPPFSVPQTWLHRVMSGNWEVTKVGGQDTLHSSARGLKAGLERMDEH
                 *.  * ** .   **** ** . . *.     .  .   *.    .    *.. . *.
                 240
                 ↓
Human TPMT       LYLLTEK
Mouse TPMT       LYLLTEK
P.syringae TPMT  VYVLERV
                 .*.*
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Fig. 2. Multiple alignment of the amino acid sequences of thiopurine S-methyltransferases (TPMT) from different species. Protein sequences were aligned using the Clustal W program (Clustal W 1.5; gap opening penalty 10.00; gap extension penalty 0.05; gap separation distance 8; hydrophilic residues: GPSNDQEKR). Upper line—human TPMT, middle line—murine TPMT, bottom line—*Pseudomonas syringae* TPMT. Shaded boxes indicate positions of common inactivating mutations in human TPMT, arrows above the unshaded amino acids indicate mutations with currently undefined effects on TPMT activity. Asterisks (*)—identical aminoacids; dots (.)—conservative substitutions.

activity in thiopurine-resistant leukemia cells isolated from patients (30). In addition to HPRT, a second factor determining intracellular concentration of TGN in hematopoietic tissues is TPMT. TPMT-catalyzed methylation of MP and TG yields the corresponding S-methylated thiopurine bases, both of which are inactive metabolites. High TPMT activity shunts more drug down the methylation pathway, leaving less for activation to TGN. TPMT also catalyzes the S-methylation of thioinosine monophosphate and thioguanine nucleotides, nucleotide metabolites of 6MP, thus further shunting drug away from activation to TGN (31).

Several studies have documented that TPMT-deficient patients accumulate very high TGN concentrations in erythrocytes and presumably other hematopoietic tissues, leading to severe hematopoietic toxicity unless the thiopurine dosage is reduced 10–15-fold (20,21,26). The magnitude of TGN accumulation in TPMT-deficient patients is exemplified in Fig. 3, depicting RBC TGN concentrations 5–10 fold higher than the median of other patients (32). For this reason, hematopoietic toxicity following MP and azathioprine is more likely in patients with TPMT-deficiency (22,33), unless these patients are recognized and the MP dose markedly reduced (20).

GENETIC BASIS OF TPMT DEFICIENCY

The initial finding of Weinshilboum and Sladek indicating the inherited nature of TPMT activity in humans has now been established at the molecular level by the identification of inactivating mutations in the human TPMT gene (34–38). The "wild-type" allele is designated *TPMT*1*, and an allele with a T474C silent mutation that does not lead to any amino acid change has been designated *TPMT*1S* (15). Another allele harboring C(-178)T mutation in the untranslated exon 1 was found in an individual with high TPMT activity (38). Currently, nine variant

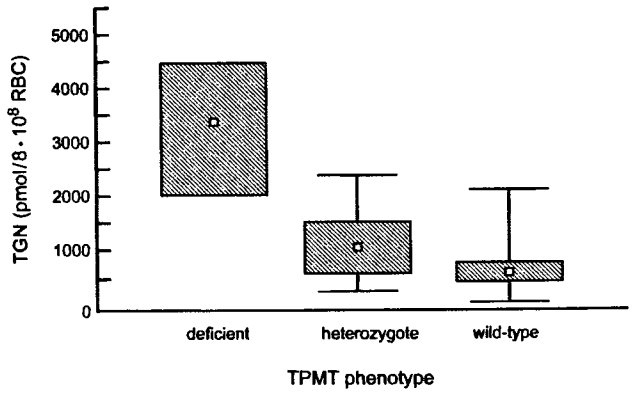

Fig. 3. Relationship between TPMT activity and thioguanine nucleotide accumulation in erythrocytes of children with acute lymphoblastic leukemia receiving uniform mercaptopurine therapy on St. Jude Children's Research Hospital Protocol Total-XII (56).

alleles associated with low TPMT enzymatic activity have been reported (Fig. 4). These alleles contain point mutations leading to amino acid substitutions (*TPMT*2*, **3A*, **3B*, **3C*, **3D*, **5*, **6*, **7*), formation of a premature stop codon (TPMT*3D), or destruction of a splice site (*TPMT*4*). TPMT*3A, *3C and *2 are relatively common mutant alleles, whereas *3B, *3D, *4, *6, and *7 have each been reported in only one or two individuals to date. To date, linkage disequilibrium has not been fully characterized for the TPMT polymorphism, an important area of future investigation, as additional polymorphisms are elucidated. Consequences of amino acid substitutions in the common allelic variants *2, *3A, *3B, and *3C have been extensively characterized in both *in vitro* and *in vivo* experiments (35,39).

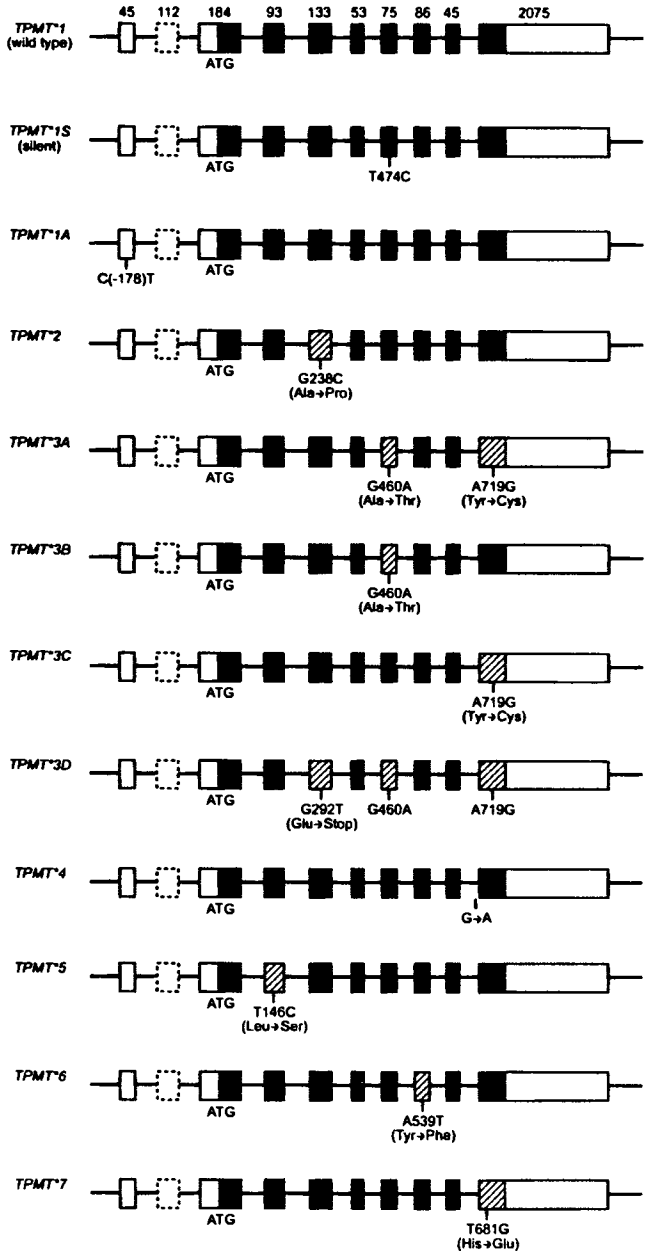

Fig. 4. Allelic variants at the human thiopurine S-methyltransferase (TPMT) locus. Boxes depict exons in the human TPMT gene. White boxes are untranslated regions, and black boxes represent exons in the open reading frame. Hatched boxes represent exons that contain mutations that result in changes of amino acids. The dashed box represents exon 2, which was detected in one of 16 human livers (36).

Although inheritance is the principal determinant of TPMT activity, other factors may also influence its *in vivo* activity in individuals with a wild-type TPMT allele. For example, there are data indicating that patient age (40,41), renal function (42), and thiopurine administration (14,25) alter TPMT activity in erythrocytes. Moreover, tissue-specific expression of TPMT mRNA has also been reported (34,43), with the highest expression of TPMT mRNA in liver and kidney, and relatively low levels in brain and lung (Fig. 5). However, the molecular mechanisms and clinical significance of these observations remain undefined.

MECHANISM OF DEGRADATION OF MUTANT TPMT PROTEINS

Heterologous expression of wild-type and mutant forms of TPMT in yeast and mammalian cells has permitted characterization of catalytic activity and protein stability. Table 1 summarizes results of kinetic experiments performed after heterologous expression of human TPMT in transformed yeast cells. For all cDNAs expressed (including *TPMT*2*, *3A*, *3B*, *3C*) the level of TPMT mRNA was not significantly affected by mutations, indicative of normal synthesis and stability of *TPMT* mRNA (34,39). Similarly, the synthesis rate of the TPMT protein in yeast, as well as *in vitro* translation in rabbit reticulocyte lysate, was not different for mutant *TPMT* cDNAs, compared to wild-type *TPMT* cDNA (39). In contrast, the degradation rates of mutant proteins encoded by *TPMT*2* and *TPMT*3* alleles were markedly enhanced. Table 2 illustrates the differences in half-lives of mutant variants compared to the wild-type protein. TPMT protein levels were 400 fold lower for *TPMT**3A, and 4-fold lower for *TPMT*3B* than for wild-type. Consistent with this finding, there was a dramatic increase in the rate of protein degradation for TPMT*3A (Fig. 6), suggesting that there is a greater effect on the tertiary structure of TPMT when both mutations are present, thus making it more susceptible to proteolysis. A proteasome-mediated, ATP-dependent pathway for degradation of mutant TPMT proteins was demonstrated in experiments using specific inhibitors of proteasome and ATP biosynthesis (39). These data were further corroborated by experiments with the *pre-1* strain of yeast with deficient proteasomal activity (39); both TPMT*2 and TPMT*3A were degraded more slowly in the *pre-1* strain, compared to yeast with wild-type proteasomes.

Experiments with transgenic yeast reflect the situation in human cells: lower TPMT protein was observed in erythrocytes from patients inheriting *TPMT*2*, *TPMT*3A* and *TPMT*3C* (39,44), indicating that the mechanism for loss of function results in lower TPMT protein levels in both yeast and humans. The one discordance was TPMT*3C, which was not rapidly degraded when heterologously expressed in yeast (39), but is present in low levels in erythrocytes of those who inherit this allele (44). However, more recent studies have established that TPMT*3C undergoes enhanced proteolysis in mammalian cells, consistent with low cellular levels in those who inherit the TPMT*3C allele (45). As depicted in Fig. 7, there was a strong correlation between RBC TPMT protein levels on Western blots and RBC TPMT activity in patients with different TPMT phenotypes.

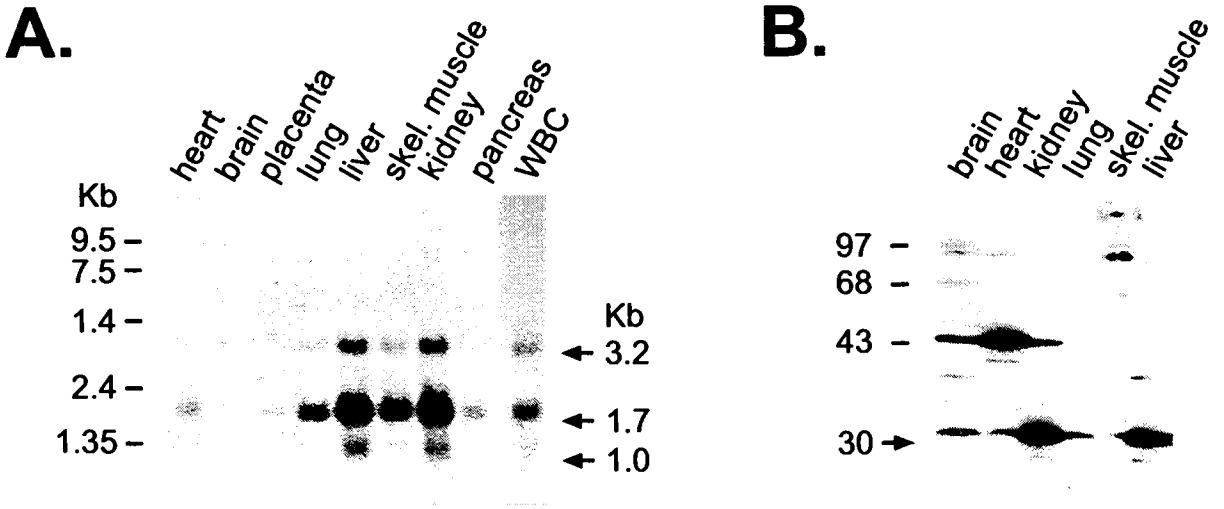

Fig. 5. Panel A: Northern blot analysis of poly (A^+) RNA isolated from various tissues and hybridized with wild-type TPMT cDNA, demonstrating the presence of multiple TPMT mRNA transcripts. Reproduced with publisher's permission from Krynetski et al. Proc. Natl. Acad. Sci. (USA) (1995): 92, 949–953. Panel B: Western blot analysis of human tissues probed with polyclonal antibody raised against GST-TPMT fusion protein. Arrow indicates TPMT protein band. Reproduced with publisher's permission from Krynetski and Evans in "Anticancer Drug Toxicity" (H.-P.Lipp, ed.) Marcel Dekker (in press) 1999.

It should be recognized that the natural substrate for TPMT has not been identified, and it is not known whether mutations leading to loss of function for S-methylation of thiopurines will also affect catalytic activity for its endogenous or environmental substrate(s). However, it is clear that enhanced protein degradation is a primary mechanism for loss of TPMT activity with TPMT*2 and TPMT*3 alleles, which represent the great majority of mutant TPMT alleles in Caucasians (15), African-Americans (46) and Asians (47). Therefore, the absence of TPMT protein in individuals inheriting these mutant alleles means these individuals will have deficient metabolism of thiopurines and the as yet unknown endogenous substrates.

DETECTION OF TPMT DEFICIENCY

The conventional method for monitoring TPMT activity in patients is based on a biochemical assay that measures the methylation of 6-mercaptopurine with [^{14}C-methyl]-S-adenosylmethionine (SAM) as the methyl donor (48). With this assay, erythrocytes are typically used as surrogate cells for drug metabolizing tissues, and a strong correlation between TPMT activity in erythrocytes and other tissues has been confirmed (13,49–51). It should be noted that in patients who have received an RBC transfusion within 30–60 days, TPMT activity can be significantly changed if a deficient or heterozygous patient is transfused with blood from a homozygous wild-type individual.

Given the importance of MP for curative therapy of acute lymphoblastic leukemia and the role of azathioprine immunosuppression in organ transplant recipients (52), a DNA-based method to prospectively diagnose TPMT-deficiency offers a clinically important strategy to minimize the risk of potentially life-threatening hematopoietic toxicity in patients treated with these medications. To date, it has become

Table 1. Kinetic Parameters of Substrate (MP) and Cosubstrate (SAM) for S-Methylation of MP Catalyzed by Human TPMT cDNAs Expressed in Yeast

cDNA expressed	K_m (μM)	V_{max} (nmol/min/mg TPMT)	V_{max}/K_m (ml/min/mg TPMT)
Mercaptopurine (MP)			
Wild-type	95.3 ± 5.5	260.6 ± 9.8	2.7
*TPMT*3B*	4396 ± 1367[a]	958.5 ± 187.9[a]	.2
*TPMT*3C*	182.5 ± 10.1	338.8 ± 13.5	1.9
*TPMT*3A*	ND	ND	—
S-Adenosyl Methionine (SAM)			
Wild-type	6.6 ± 1.1	173.1 ± 14.1	26.2
TPMT*3B	1375 ± 211[a]	704.9 ± 69.7[a]	.51
TPMT*3C	9.5 ± 1.4	226.9 ± 19.1	23.9
TPMT*3A	ND	ND	—

Note. Kinetic parameters for 6MP were estimated using 1 mM SAM; and parameters for SAM were estimated at 2 mM 6MP. All values are expressed as mean ± SE. ND = activity not detectable.
[a] Significantly different from wild-type and TPMT*3C ($P < 0.01$).

Table 2. Half-Lives and Synthesis Rates of Wild-Type and Mutant TPMT Proteins in Yeast

Parameter	TPMT*1	TPMT*2	TPMT*3A	TPMT*3B	TPMT*3C
Degradation half-life $t_{1/2}$, hr	18	0.2α 14.8β	0.25	6.1	18
Formation rate fmol/mg/hr	335	409	268	349	220

* $p < 0.05$ when compared to TPMT*1.

possible to detect the presence of TPMT inactivating mutations with more than 95% concordance between genotype and phenotype in American white subjects (15). This good level of concordance demonstrates the feasibility of these genotyping methods for making a molecular diagnosis of TPMT-deficiency or heterozygosity. However, a word of caution is in order, since there are clearly several (>5) new mutant alleles, most of which have been detected in only a single individual to date (i.e., *4, *5, *6, and *7), including individuals of unreported ethnic origin (37,38). Ethnic differences in the nature and frequency of mutant TPMT alleles is to be expected, as exemplified by similar studies of CYP2D6 (53) and other polymorphic enzymes. Furthermore, the number of mutant alleles for CYP2D6 has increased from the original two reported in 1988 (54) to >50 mutant alleles recognized today (55). While the number of allelic variants for TPMT may be markedly lower than for CYP2D6, the reliability of genotyping methods will be enhanced as these more rare mutations are discovered. Ultimately, DNA-chip based genotyping methods will make it possible to rapidly screen for all known mutations in polymorphic genes such as TPMT or CYP2D6, providing a rapid, sensitive and automated method for making the molecular diagnosis of these inherited enzyme deficiencies. With more broad screening of TPMT-deficient individuals from various ethnic groups, the reliabilty of TPMT genotyping methods will continue to improve.

INDIVIDUALIZING CHEMOTHERAPY

TPMT exemplifies an inherited trait that can profoundly influence the pharmacologic effects of medications; in this case, thiopurine therapy for leukemia and immunosuppression. Characterization of the molecular mechanisms of this genetic polymorphism makes it possible to accurately identify patients who are at high risk of toxicity, thereby providing a rational basis for individualizing the dosage of these important antileukemic and immunosuppressive medications. Furthermore, adjusting the dose of MP (i.e., 10–15-fold decrease as compared to conventional doses) makes thiopurine therapy as tolerable and effective in TPMT-deficient patients as it is in those with normal

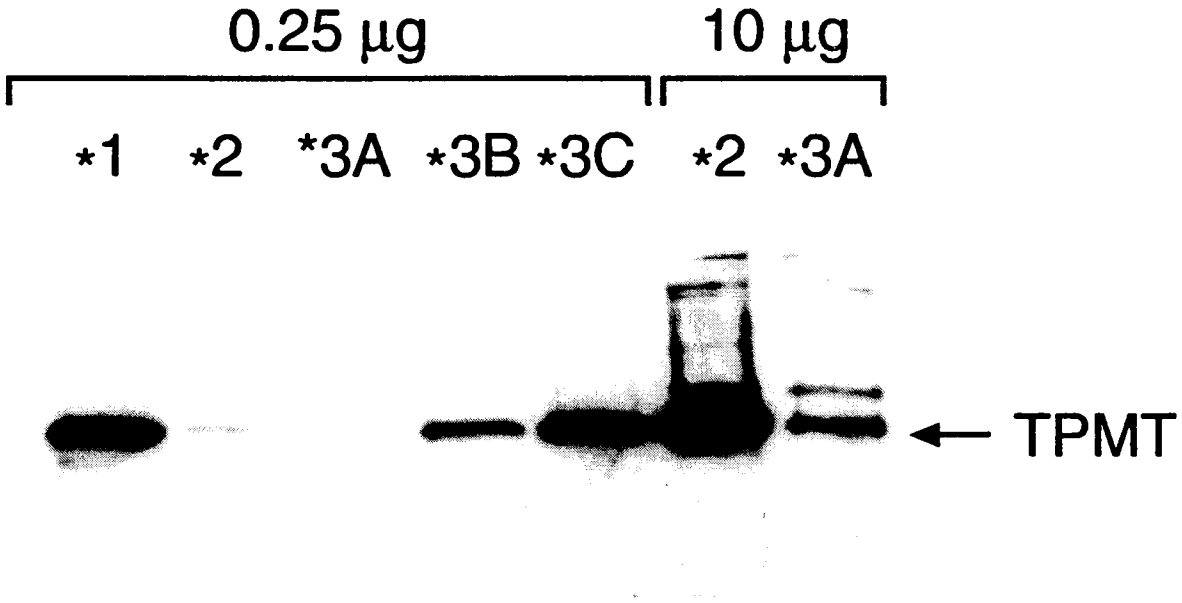

Fig. 6. Western blot of recombinant human TPMT protein in yeast cytosol expressing wild-type (*1) and mutant TPMT cDNAs (*2, *3A, *3B, and *3C) after a 24-hour culture in galactose-containing medium. The amount of total protein loaded in each lane is indicated at the top. Reproduced with publisher's permission from Tai *et al., Proc. Natl. Acad. Sci.* (USA) (1997) 94: 6444–6449.

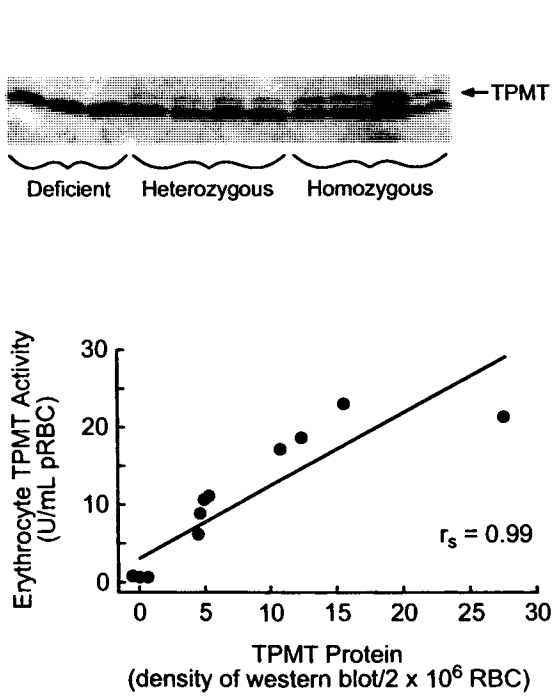

Fig. 7. (A) Western blot of TPMT protein in RBC lysates, and (B) correlation of erythrocyte TPMT activity and protein in 11 individuals with different TPMT phenotypes. The Spearman rank order coefficient (r_S) was 0.99 ($p < 0.001$). Reproduced with publisher's permission, from Tai *et al. Proc. Natl. Acad. Sci.* USA 1997: 94, 6444–6449.

TPMT activity. Collectively, the TPMT polymorphism exemplifies the potential impact of genetic polymorphisms on drug disposition and effects, and illustrates the potential utility of elucidating the genetic basis for such traits and developing molecular diagnostics that can be used to prospectively optimize drug therapy for individual patients (56). One can anticipate that during the next decade, as the human genome becomes more fully characterized, such molecular individualization of drug therapy will be extended to a broad range of medications.

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