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Insights into *S*-adenosyl-L-methionine (SAM)-dependent methyltransferase related diseases and genetic polymorphisms

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Abstract

Enzymatic methylation catalyzed by methyltransferases has a significant impact on many human biochemical reactions. As the second most ubiquitous cofactor in humans, S-adenosyl-L-methionine (SAM or AdoMet) serves as a methyl donor for SAM-dependent methyltransferases (MTases), which transfer a methyl group to a nucleophilic acceptor such as O, As, N, S, or C as the byproduct. SAM-dependent methyltransferases can be grouped into different types based on the substrates. Here we systematically reviewed eight types of methyltransferases associated with human diseases. Catechol O-methyltransferase (COMT), As(III) S-adenosylmethionine methyltransferase (AS3MT), indolethylamine *N*-methyltransferase (INMT), phenylethanolamine *N*-methyltransferase (PNMT), histamine *N*-methyltransferase (HNMT), nicotinamide *N*-methyltransferase (NNMT), thiopurine S-methyltransferase (TPMT) and DNA methyltansferase (DNMT) are classic SAM-dependent MTases. Correlations between genotypes and disease susceptibility can be partially explained by genetic polymorphisms. The physiological function, substrate specificity, genetic variants and disease susceptibility associated with these eight SAM-dependent methyltransferases are discussed in this review.

Keywords

Methyltransferases; *S*-adenosyl-L-methionine; Methylation; Phenotypes; Genotypes; Single nucleotide polymorphisms

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Declaration of Competing Interest

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1. Introduction

Methylation reactions catalyzed by methyltransferases are found in many biochemical pathways and are associated with genetic diseases, including cancer and metabolic diseases. The SAM-dependent methyltransferase (MTase) superfamily could be classified either by substrate specificity or based on the nucleophilic atoms targeted for methylation (e.g. O, As, N, S or C,). Based on the properties and functions of the substrates and products, the methylation catalyzed by these enzymes is involved in biosynthesis, signal transduction, protein repair and other physiological processes. Aberrant methylation is closely associated with the occurrence of cancer, genetic disorders or other diseases. Polymorphisms in MTase genes can affect enzyme activity. Single nucleotide polymorphisms (SNPs) are the most common source of protein genetic variation. SNPs are found in promoters, exons or introns. They affect mRNA transcription, splicing, protein expression, structure, enzymatic activity and stability. There are millions of SNPs in the human genome when compared to a reference genome. In the last decade, genetic variations in methyltransferase proteins have been the subject of considerable research. There are now numerous MTase SNPs related to clinical disease. This review aims to systematically summarize eight SAM-dependent methyltransferases, with an emphasis on their substrate specificity, genetic polymorphisms, and crystal structures, as well as the relationships between SNPs and human disease (Table 1). It is not meant to be an exhaustive review, but simply to highlight key disease associations. This information may contribute to a more precise understanding of correlations between genotypes and disease-susceptibility phenotypes or individual risk of toxicity from drug treatment.

To start, we searched the Web of Science database for reports on the eight types of S-adenosyl L-methionine (SAM)-dependent methyltransferases within the past 30 years (Fig. 1). Of a total of 2188 publications recovered, the prevalence of reports on MTase polymorphisms occurred in the order TPMT > COMT > DNMT, with lower numbers of publications for the other enzymes. Each of the SAM MTases was correlated with polymorphisms in the corresponding gene. Studies included in the review were selected using the following criteria: (1) Search for literature types: ‘Review’, ‘Clinical Trial’ or ‘Case Report’ in the Web of Science database; (2) Search synchronously the NCBI web site [chose SNP category, entered specific human MTase, refined by ‘PubMed Cited’ with validation status of ‘by-frequency,’ refined by clinical significance with ‘drug response/ likely benign/risk factor’ to track papers]. Finally, papers from NCBI database were combined with papers from Web of Science database.

2. Catechol-O-methyltransferase (COMT)

Catechol-O-methyltransferases (COMT) catalyze transfer of a methyl group from SAM to the hydroxyl group on a catechol nucleus, resulting in the deactivation of catecholamine neurotransmitters such as dopamine, epinephrine, and norepinephrine [31,32] (Fig. 2). The *COMT* gene is located on the long (q) arm of human chromosome 22 at position 11.21, which codes for both soluble COMT (S-COMT) and membrane-bound COMT (MB-COMT). The differences between these two COMTs are that MB-COMT has 50 additional hydrophobic amino acids [33]. COMT is crucial to the function of the prefrontal

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cortex of the brain, specifically in organizing and coordinating information from other parts of the brain. A U-shaped relationship between hippocampal gray matter volume and presumed COMT activity has been proposed [34]. The COMT Val158Met SNP (rs4680) affects hippocampal grey matter volume and appears to be modified by P2 promoter A > G SNP (rs2097603). Thus, there are four haplotypes: (1) A-Val (P2 promoter carrying base A and rs4680 carrying animo acid Val); (2) A-Met (P2 promoter carrying base A and rs4680 carrying animo acid Met); (3) G-Val (P2 promoter carrying base G and rs4680 carrying animo acid Val); (4) G-Met (P2 promoter carrying base G and rs4680 carrying animo acid Met). When ordered by putative genetic variation of enzymatic activity, A–Val has the highest activity, followed by G–Val, A–Met and finally G–Met, corresponding to high, low, low, and high (U shape) hippocampal gray matter volumes, respectively. The enzymatic activity and hippocampal gray matter volume differences were consistent with a nonlinear effect of extracellular dopamine, extracellular dopamine levels of A-Val<G-Val<A-Vet<G-Vet. Abnormal levels of dopamine neurotransmitters result in psychiatric manifestations, including schizophrenia [35], other psychoses [36], mood disorders, schizophrenia, obsessive-compulsive disorder and substance abuse [37,38].

Microdeletions in COMT are observed in most individuals who present with velocardiofacial syndrome or related clinical syndromes, referred to as 22q11.2 deletion syndrome [41]. People with 22q11.2 deletion have increased risk of schizophrenia, depression, anxiety and bipolar disorder compared with normal individuals [42]. Variations in the *COMT* gene have been identified both in the promotor region and the transcribed sequence. Promoter region variants of MB-COMT (rs2020917, rs737865) are associated with depressive symptomatology among females [43], specifically in the South African Xhosa population [44]. A frequent G > A polymorphism (rs4680) within the coding region of COMT produces a Val to Met substitution at codons 108 and 158 of S-COMT and MB-COMT, respectively [45], which leads to altered activity of both S-COMT and MB-COMT. A meta-analysis determined that the Val158Met polymorphism has a 37 % minor allele frequency (MAF) (Table 2), and Val-carriers show significantly less improvement in positive symptoms relative to Met/Met individuals in schizophrenic and schizo-affective disorder patients [odds ratio (OR) Met/Met = 1.54, 95 % confidence interval (CI): 1.11–2.14, P = 0.0098] [1]. In patients with Parkinson's Disease (PD), a high-COMT activity haplotype (G-C-C-G for rs6269, rs4633, rs4818, and rs4680) is associated with cognitive decline (hazard ratio = 3.24; P = 0.02) [3]. Further studies demonstrated that the COMT rs4680 G/G or G/A genotypes and the COMT rs6267 G/T genotype contribute to pain in PD patients with P = 0.04 and <0.01, respectively [4]. Compared with Met/Val and Val/Val individuals, Met/Met individuals experience a cognitive deficit (n = 107, P = 0.017) [46] and a possible increased risk of bipolar disorder, panic disorder (n = 298, P = 0.0089) [47], obsessive-compulsive disorder and ADHD (n = 230, P = 0.043) [6]. These conditions may be related to inefficient processing of information in the prefrontal cortex and altered levels of muscarinic M1 receptor mRNA in the cortex [48]. It is worth noting that some associations between polymorphisms of COMT and diseases are inconsistent. Results from two meta-analyses do not support an association between COMT SNPs and ADHD [49,50]. Regarding the association between COMT SNP rs4680 and AD, one meta-analysis supported the association between the COMT G/G and G/A genotype and AD in an Asian

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group (OR = 0.702, 95 % CI = 0.517–0.953, $P = 0.023$) [5], but neither COMT genotype proved to be independently associated with AD risk [51,52]. Also, there is research support for a significant association between high alcohol consumption in patients with AD and the COMT polymorphism rs4680 [53].

3. As(III) S-adenosylmethionine methyltransferases (AS3MT)

Arsenic (As) is one of the most common environmental contaminants. It exists in four oxidation states (+V, +III, 0, −III) [54]. In most mammalian species, inorganic As(III) can be methylated primarily to methylarsenite [MAs(III)] and dimethylarsenite [DMAs(III)], and, to a lesser extent, to trimethylarsine [TMAs(III)] by the enzyme As(III) S-adenosylmethionine methyltransferase (AS3MT in animals and ArsM in microbes) [55]. Nearly all ArsM/AS3MT enzymes have four conserved cysteine residues (Cys 32, Cys 61, Cys156 and Cys 206 in the human enzyme) that are required for As(III) binding and catalysis (Fig. 3). Biochemical analyses have focused on the activity of purified human AS3MT. Thomas and co-workers first purified AS3MT from rat liver cytosol, and the rat and human genes were subsequently cloned [56,57]. Styblo and coworkers showed that AS3MT and the most common SNP that encodes the M287 T isoform catalyze arsenic methylation with different activities [58]. We have purified seven additional polymorphic hAS3MT proteins and characterized their enzymatic properties. Each enzyme had low methylation activity due to decreased affinity for substrate [59].

The human *AS3MT* gene, located on chromosome 10q24 has 11 exons and is approximately 32-kb long [57]. Splicing variants of the *AS3MT* gene have been shown to affect the capacity for arsenic methylation. In human AS3MT, there are eight well-studied exonic SNPs with low arsenic methylation activity (Arg173Trp, Met287Thr, Thr306Ile, His51Arg, Cys61Trp, Ile136Thr, Trp203Cys, and Arg251His) (see Fig. 3 and Table 2) [59]. Inefficient arsenic methylation capacity (high MAs% and low DMAs%) is associated with increased disease susceptibility [60], including skin lesions, hypertension [7] or bladder cancer [61]. The SNP rs11191439 (Met287Thr, 860 T > C) occurred with a very high MAF (>5 %) in an arsenic endemic area of Mexico [62]. A case-control study (71 cases with skin lesions and 51 controls) showed individuals carrying the C (T/C and C/C) allele (Thr) were at increased risk of developing skin lesions [OR = 4.28; 95 % CI: 1.0–18.5)] [8].

Individuals with one or more copies of the C allele in rs11191439 (the Mer287Thr polymorphism) may have an elevated risk of bladder cancer (OR = 1.17; 95 % CI = 1.04–1.32) [63]. Moreover, AS3MT rs11191438 (C > G) G/G genotype, AS3MT rs10748835 (A > G) G/G genotype, and AS3MT rs1046778 (C > T) T/T genotype were found to be related to a decreased risk of bladder cancer, where the ORs (95 % CI) were 0.50 (0.31–0.82), 0.49 (0.30–0.79), and 0.54 (0.36–0.80), respectively [61]. Individuals with the AS3MT rs3740392 (intron variant) A/G and G/G genotype genotypes had a lower secondary methylation index, which is related to developmental delay with an OR (95 % CI) of 1.59 (1.08–2.34) [64]. Low level arsenic exposure was reported to be associated with increased cardiovascular disease mortality, and hyperlipidemia was associated with AS3MT polymorphism rs10748835 genotype A/G vs. A/A ($P < 0.05$) (n = 499) [65]. Wood et al. identified 26 SNPs, including 3 non-synonymous coding SNPs (cSNPs) in the

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AS3MT coding regions: Arg173Trp, C > T (rs35232887) in exon 6, Met287Thr, T > C (rs11191439) in exon 9 and T306I, C > T (rs34566438) in exon 10, as well as a variable number of tandem repeats in exon 1 corresponding to the 5′-untranslated region of the gene [57]. The most common exonic SNP is Met287Thr (in exon 9, SNP ID: 1445, rs11191439; T860C; Met287Thr), which is associated with several diseases as discussed previously. A genome-wide association study (GWAS) of 124 women from the Argentinean Andes and a PHIME-CROME study of a Croatian-Slovenian population indicate that arsenic is an environmental stressor that likely has driven an increase in the frequencies of protective alleles of AS3MT [66]. This supports the concept that some SNPs confer a positive selective advantage and represent human adaptation to arsenic-rich environments.

4. Indolethylamine *N*-methyltransferase (INMT)

In 1961 Julius Axelrod discovered the enzymes indolethylamine *N*-methyltransferase (INMT) and arylamine *N*-methyltransferase, which convert serotonin and tryptamine to the psychotomimetic metabolites bufotenine and *N,N*-dimethyltryptamine, respectively [67]. INMT is widely distributed in mammalian tissues including lung [68], liver and brain [69]. INMT catalyzes metabolism of a group of small molecule acceptors such as tryptamine, serotonin, and other endogenous indole-containing compounds. The human *INMT* gene is located at chromosome 7p15.2–p15.3, has three exons, and is structurally similar to the *NNMT* and *PNMT* genes in other species. INMT utilizes methyl group acceptors as substrates and accommodates a large variety of amines, among which tryptamine is the preferred substrate with the highest apparent K_{cat} [70]. Tryptamine is found in trace amounts in mammal brains and is considered a neuromodulator or neurotransmitter [71] involved in mental illness [72]. INMT produces *N,N*-dimethyltryptamine (DMT) [73], which is a hallucinogen and has high affinity for various serotonergic, adrenergic, histaminergic and dopaminergic receptors (Sig-1R) [74]. DMT is synthesized *via* decarboxylation of tryptophan, followed by double-methylation utilizing AdoMet as a methyl donor (Fig. 4). DMT is found in the brain at an average concentration of 0.56 nM [69] and is considered as a monoamine neurotransmitter. Hallucinogens are psychoactive substances that alter cognition and perception by triggering neurotransmitter receptors in the brain [75]. Consequently DMT, as a product of INMT methyltransferase, is considered to be a neurotransmitter. Differences in the function or levels of INMT variant enzymes can lead to mental behavioral phenotypes generated by exogenous DMT [76].

Contributions to the understanding of the relationships between INMT, its polymorphisms and human health have been made primarily over the last decade. A study involving 187 Hirschsprung's disease (HSCR) patients and 283 controls found a nonsynonymous SNP in the coding region of *INMT* (rs77743549, His46Pro) was associated with significantly increased risk of HSCR (OR = 1.77; corrected $P = 0.002$) [10]. INMT also methylates the essential element selenium (Se), although Se metabolism in humans is not well characterized. A cohort study involving subjects from Bangladesh and Argentina identified 3 SNPs (rs1061644; rs4270015; rs6970396) in the *INMT* gene that are strongly associated with metabolism of Se to the trimethylselenonium ion (TMSe) [78]. Also, samples collected from pregnant women (n = 226) in rural Bangladesh at gestational weeks 8, 14, 19, and 30 showed that urinary concentrations of TMSe were associated with the INMT rs6970396

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A/G and A/A genotypes [79]. Another study demonstrated that the INMT SNP (rs6970396), and AS3MT haplotypes, including Aquaporin 4 and 9 polymorphisms, affected As and Se metabolism in the Croatian-Slovenian population (n = 509) [80]. Although there is some evidence of a relationship between maternal Se and child neurodevelopment, no solid conclusion regarding INMT polymorphism and neuropsychological development could be drawn [81].

5. Phenylethanolamine *N*-methyltransferase (PNMT)

Phenylethanolamine *N*-methyltransferase catalyzes the terminal step of catecholamine biosynthesis with norepinephrine as substrate, forming the product epinephrine, using SAM as the methyl donor (Fig. 2). PNMT plays a key step in regulating epinephrine production [82] (Fig. 1). The *PNMT* gene, located on chromosome 17 (17q21), has been linked to hypertension, which has both genetic and environmental components [83]. PNMT mRNA levels are significantly increased in all four chambers of the heart in hypertensive rats, with the highest expression in the right atrium [84]. Increased PNMT gene expression is a possible mechanism to explain why prenatal exposure to elevated levels of glucocorticoids leads to hypertension later in life [85].

Epinephrine accounts for 5–10 % of the catecholamine content in brain, with the exception of the adrenal medulla. Epinephrine function in the central nervous system has been implicated to control not only blood pressure and respiration, but also neurodegenerate disorders such as AD [86]. AD is a polygenic disorder, with multiple genes contributing to the disease phenotype [12]. PNMT activity is decreased in the brain of AD individuals. The decrease in the hippocampus correlates significantly with the degree of dementia [87]. Transport of the PNMT protein in advanced AD is correspondingly decreased compared with early Alzheimer's cases [88].

Eighteen PNMT SNPs, including four non-synonymous cSNPs (Asn9Ser, Thr98Ala, Arg112Cys and Ala175Thr) were identified in 2005 [100]. The Thr98Ala allozyme displayed significantly lower levels of both activity and immunoreactivity compared to the reference enzyme, indicating that polymorphisms in PNMT could be one explanation for inherited variations in the ability to form epinephrine from norepinephrine [100]. In addition, a case-control study in 2001 reported a significant association ($P \leq 0.007$) between early-onset AD and two polymorphisms, G353A and G148A, in the promoter region of the gene coding for PNMT [12]. Further, there is a connection between PNMT SNPs and hypertension. Two common PNMT promoter SNPs, G367A (rs3764351) and G161A (rs876493), are associated with decreased risk of essential hypertension in Han Chinese [11]. Another case-control study showed that PNMT + 1543 G allele was associated with the development of acute kidney injury (AKI) [OR = 2.19, 95 % CI = 1.04–4.60], and the PNMT −161A (rs876493) allele was associated with lower mortality from AKI [94]. *PNMT* gene polymorphisms rs876493, rs2934965 and rs2941523 have also been associated with crisis pain in sickle cell disease with $P \leq 0.005$. [13]. Finally, rs876493 was shown to increase PNMT promoter activity and reduced risk of asthma [101].

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6. Histamine *N*-methyltransferase (HNMT)

Histamine *N*-methylation is the major process responsible for termination of the neurotransmitter action of histamine in the brain [102]. Histamine-*N*-methyltransferase (HNMT) methylates histamine by transferring a methyl group to the imidazole ring, using SAM as the methyl group donor, yielding methylhistamine and SAH. As a neurotransmitter, histamine affects physiological processes including memory formation, hormonal control, cardiovascular control and thermoregulation [103].

The HNMT gene is located on chromosome 2q22.1, is 50 kb in length, and includes six exons. HNMT mRNA is found in most human tissues, with the highest mRNA levels in kidney and liver cells [104]. HNMT activity was determined in 127 clinical surgery renal biopsy samples. Those samples with the lowest thermal stability also had the lowest levels of enzyme activity [104], similar to what was found with polymorphic COMT [105]. C314 T and A939 G transitions have also been examined. A C314 T transition (rs11558538 s), which corresponds to a Thr105Ile change in the enzyme, led to a significant decrease in HNMT activity [19]. The HNMT 939A > G polymorphism lowers HNMT enzymatic activity by decreasing HNMT mRNA stability in patients with acetylsalicylic acid-intolerant chronic urticaria [106]. The observations that these polymorphisms affect the levels of enzyme activity imply that HNMT polymorphisms might be related to the pathophysiology of diseases that involve variations in histamine metabolism, such as allergy, asthma and neuropsychiatric illness.

The105lle HNMT variant has been proposed to confer a selective advantage. Higher histamine levels might be protective because histamine, IgE and mast cells played defensive roles against nematode infections [107]. In addition, elevated histamine levels in the brain have been associated with PD and schizophrenia [108]. In one case-control study, lower HNMT activity, such as that of the Ile105 allele with 30 %–50 % lower HNMT activity, was associated with the pathogenesis of PD [chi square (χ^2) = 11.65, $P = 0.0006$] [109]. In another case-control cohort of Han Chinese patients with PD, schizophrenia, and healthy controls, the HNMT Thr105Ile polymorphism was suggested to protect against PD (OR = 0.516, $P = 0.007$) and schizophrenia (OR = 0.499, $P = 0.011$) [16]. A meta-analysis that included 4 eligible case-control association studies for the HNMT rs11558538 SNP and the risk for PD (2108 patients, 2158 controls) showed a statistically-significant association with a decreased risk for PD in Caucasian patients (OR = 0.63, 95 % CI = 0.45–0.88) [14]. The C314 T (Thr105Ile) polymorphism was reported as a risk factor for asthma [18,19]. Individuals with HNMT Thr105Ile and His645Asp mutations are more prone to developing symptoms at lower IgE levels [110]. In addition to the non-synonymous C314 T (Thr105Ile) SNP, the A939 G (rs1050891) polymorphism in the 3′-UTR of the *HNMT* gene was also shown to decreased histamine release due to an increased enzyme activity [106]. Histamine participates in immune responses and is involved in autoimmune disorders. The autoimmune disease myasthenia gravis has also been associated with the A939 G HNMT variant, but not the C314 T SNP [111].

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7. Nicotinamide *N*-methyltransferase (NNMT)

Nicotinamide is the active form of vitamin B3, as well as a component of the coenzyme nicotinamide adenine dinucleotide. Nicotinamide has anti-inflammatory actions. Nicotinamide has been considered a beneficial agent for treating inflammatory skin disorders for the past 50 years, as a long-term oral therapy [112]. By enhancing DNA repair and reducing UV-induced suppression of skin immune responses, nicotinamide also acts as a chemoprevention agent [113]. Nicotinamide is methylated by nicotinamide *N*-methyltransferase (NNMT) [114] and yields two products: *S*-adenosyl-L-homocysteine and N1-methylnicotinamide, which are excreted into urine.

NNMT was first identified by cDNA cloning from the liver, where NNMT is predominantly expressed [115]. Interestingly, NNMT was highly-expressed in various cancers, such as papillary thyroid carcinoma [116], liver cancer [117], colorectal cancer (CRC) [118], lung cancer and oral carcinoma [119]. NNMT is a novel serum tumor marker for CRC [118]. Some studies demonstrated that hepatocellular carcinoma patients with higher NNMT mRNA expression levels tended to have a shorter overall survival and significantly shorter disease-free survival [117]. Also, significantly higher NNMT enzyme activities were detected in follicular cell lines [116]. The significant role of NNMT in regulation of metabolic pathways and high levels in several types of cancers indicates that it is a potential molecular target for cancer therapy. Besides being a potential tumor marker, NNMT has been associated with energy metabolism and the body mass index (BMI). NNMT was found to be upregulated in the liver of a mouse model of obesity [120]. A cross-sectional cohort study demonstrated that NNMT knockdown in adipose tissue and liver could prevent diet-induced obesity [121]. A case-control study of obese (n = 289) versus normal BMI individuals (n = 498) was carried out to explore the association between obesity and the NNMT gene polymorphism rs10891644 (intron variant, −129-11693G > T with three genotypes : homozygous dominant G/G, heterozygous G/T, and homozygous recessive T/T). The percentage of body fat difference between individuals with the heterozygous G/T and homozygous (G/G and T/T) genotypes were highly significant ($P < 0.01$). The ORadjusted value of the G/T versus (G/G andT/T) was 1.716, which means that the chance of G/T individuals having high body fat is 1.76 times that of the homozygous (G/G and T/T) individuals, indicating that the heterozygous individuals (G/T carriers) are susceptible to obesity [23]. In addition, a study of hyperlipidemic patients (n = 395) and controls (n = 316) showed that NNMT SNP rs1941404 is significantly associated with hyperlipidemia ($P < 0.0026$) [122]. rs1941404 genotype carriers in the Chinese Han population were also found to be associated with type 2 diabetes ($P < 0.002$, n = 558 T2D patients and 442 healthy controls) [24]. These case-control studies are listed in Table 3, which includes additional epidemiologic studies on MTase polymorphisms.

The human NNMT gene, located at 11q23.1 as determined by fluorescence in situ hybridization [115], is approximately 16.5 kb in length, with 3 exons and 2 introns. Individual differences in xenobiotic and drug toxicity may result from the variation in human hepatic NNMT activity. Human NNMT activity shows a bimodal frequency distribution [123], which was predicted to be a consequence of a genetic polymorphism [124]. We analyzed the NNMT gene mutation data in COSMIC (Catalogue of Somatic

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Mutations in Cancer, https://cancer.sanger.ac.uk/cosmicv), the world's largest and most comprehensive resource for exploring the impact of somatic mutations in human cancer. There are 468 non-synonymous mutations reported in NNMT. NNMT mutations are associated with a variety of cancers, with the largest number of different mutations found in skin cancers and the greatest incidence of mutation found in large intestine cancer [21]. NNMT polymorphisms are also associated with increased incidence of ALL. A study involving 245 pediatric ALL patients (cases) and 500 blood bank donors (controls) found an NNMT SNP (rs694539; C < T, T/T genotype) conferred a 2-fold increased risk of ALL (OR = 2.2; 95 % CI: 1.1–4.6; $P = 0.04$) [91].

In recent years, SNPs in the human *NNMT* genes have been reported to be significantly associated with neurologic/mental illness, including two noncoding region SNP (rs694539 and rs1941404) [21]. NNMT has been implicated in the pathogenesis of neuropsychiatric diseases. SNP rs694539 is associated with several disorders, including bipolar disorder [125], epilepsy [93], migraine [126], and schizophrenia [22]. First, low NNMT serum levels were found to be significantly associated with bipolar disorder [127]. The rs694539 variant of NNMT was associated with bipolar disorder in a case-control study of 95 bipolar disorder patients and 201 healthy controls ($\chi^2 = 13.382$, P = 0.001). Second, the NNMT rs694539 variant was shown to be involved in the etiology of epilepsy ($\chi^2 = 6.682$, $P = 0.035$, n = 454) [93]; Third, the association of the rs694539 variant with migraine was reported in a case-control study of 433 patients with migraine and 229 healthy controls ($\chi^2 = 6.076$, $P = 0.048$) [126]; Fourth, several NNMT haplotypes were reported to be significantly associated with schizophrenia (global P values <0.05 following permutation test adjustment) [22]. Specifically, a study of a Han Chinese female population (n = 42 schizophrenia patients and 86 healthy controls) found rs694539 has a role in the etiology of schizophrenia ($P = 0.0015$) [92], with rs1941404 also associated with schizophrenia ($P = 0.033$) [22].

8. Thiopurine methyltransferase (TPMT)

In the 1960s, the function of thiopurine S-methyltransferase (TPMT) was found to be the transfer of the methyl group from SAM to the sulfur atom of thiopurines [128]. TNMT, with a molecular mass of 26 kDa is expressed in liver, kidney, intestine, erythrocytes, leukocytes and a number of other tissues [129]. Interest in TPMT emerged initially because of the important role this enzyme plays in metabolic transformation of thiopurine drugs [130]. The thiopurine drugs azathioprine and mercaptopurine are effective in the treatment of disorders of immune regulation, ALL and organ transplant recipients [131]. Thiopurine drugs are converted to toxic compounds, thioguanine nucleotide metabolites (TGNs) that are cytotoxic, immunosuppressive and kill immune system cells in the bone marrow [25]. However, the TPMT enzyme also metabolizes thiopurine drugs into inactive, nontoxic compounds. Thus, the therapeutic window between toxicity and efficacy of thiopurine drugs is narrow. The use of azathioprine in a patient with complete TPMT deficiency resulted in death from neutropenia sepsis [132].

The TPMT gene, located in 6p22.3, is approximately 34 kb in length and consists of 10 exons and 9 introns. TPMT variants are the most well-characterized genetic polymorphisms that affect drug metabolism, and variants have been studied in most populations [133]. More

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than 40 allelic variants of the TPMT gene have been reported to the *TPMT* nomenclature committee and assigned allele names (http://www.imh.liu.se/tpmtalleles) [134]. TPMT has been reported to exhibit genetic polymorphism in Caucasian populations, among which 89 % of individuals have high TPMT activity, 11 % of individuals exhibit intermediate activity, and one in 300 has extremely low or absent activity [135]. A novel TPMT allele, TPMT*45, was identified in a Korean girl whose findings suggested decreased TPMT activity [134]. Currently, approximately 20 variant alleles have been associated with low TPMT enzymatic activity in humans (Table 4). The most prominent TPMT variants include amino acid substitution variants (*TPMT*2*, *3A*, *3B*, *3C*, *3D*, *5*, *6*, *7*, *8*), a premature termination variant (*TPMT*3D*), and a variant that eliminates a splice site (*TPMT*4*). The predominant variant alleles, TPMT*3C, *3A and *2, account for over 95 % of inherited TPMT deficiencies [136]. *TPMT*2,* containing 238 G > C, was the first identified variant with decreased catalytic activity [137]. The second identified and more prevalent variant allele (*TPMT*3A*) contains two nucleotide transition mutations (G460A and A719 G), leading to amino acid substitutions Ala154Thr and Tyr240Cys [138,139]. A single 719A > G polymorphism in the open reading frame (ORF) of the *TPMT*3C* allele also results in reduced protein stability [140]. TPMT*4 is the first reported allele with low TPMT enzymatic activity as the result of a mutation within an intron [141]. TPMT*4, with a G > A transition at the intron 9–exon 10 junction, has the final nucleotide of the intron at the 3′ acceptor splice site sequence deleted, which reduces TPMT activity.

In childhood ALL, the most common cancer in children, the bone marrow produces too many immature lymphocytes [150]. As the number of leukemia cells increases in the blood and bone marrow of ALL patients, healthy white blood cells, red blood cells and platelets are crowded out, leading to infection, anemia and bleeding. The purine analogues mercaptopurine and thioguanine are drugs that have been used as cytotoxic agents in the treatment of leukemias for more than 50 years [151]. Because the therapeutic window between toxicity and efficacy is narrow, thiopurine drugs can potentially have life-threatening toxicity [152]. The impact of the thiopurine methyltransferase genotype on thiopurine dose intensity, myelosuppression and treatment outcome was investigated in the United Kingdom childhood ALL trial, ALL97 [25]. There were 1935 patients on this trial with 1206 patients carrying homozygous wild-type TPMT*1/*1, and 128 patients having low activity variant alleles (99 TPMT*1/*3A; 17 TPMT*1/*3C; 4 TPMT*1/*2; two children with the rare alleles TPMT*1/*9, TPMT*1/*21; three children with novel alleles TPMT*1/*32, TPMT*1/*33, TPMT*1/*34; one compound heterozygote TPMT*2/*3A; one homozygous TPMT*3A/*3A and one TPMT*3C/*3C). The findings from that trial demonstrated that *TPMT* polymorphism affected event-free survival (EFS) of ALL patients [25]: TPMT*1/*3A heterozygotes had a better EFS than TPMT wild-type patients (n = 1206, EFS 80 %, $P = 0{\cdot}05$) or TPMT*1/*3C patients (n = 17, EFS 53 %, $P = 0{\cdot}002$). In addition, the United States Food and Drug Administration states that TPMT genotype testing should be considered if a patient has clinical or laboratory evidence of severe toxicity, particularly myelosuppression. Testing for *TPMT* status is recommended prior to initiation of mercaptopurine therapy, so that the starting dosages can be adjusted accordingly. If the patient is homozygous with two or more functional alleles, the patient should receive the normal starting dose of mercaptopurine. If the patient is heterozygous,

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with one functional allele and one nonfunctional allele, the patient should receive reduced doses of mercaptopurine. If the patient carries only a low or deficient variant (homozygous phenotype), alternative agents for treatment should be considered [153].

9. DNA (cytosine-5)-methyltransferase (DNMT)

Epigenetics is defined as heritable changes in gene activity and expression that occurs without alteration in DNA sequence that guide the genome on" what to express and what not to." DNA methylation catalyzed by DNA methyltransferase enzymes (DNMTs) is a major epigenetic modification in higher eukaryote genomes. In mammals, DNA methylation is essential for embryonic development and plays important roles in gene expression, genomic imprinting, X chromosome inactivation, and maintenance of genome integrity [154–156]. DNA methylation appears to regulate gene expression at different levels. Methylation of CpG sites within the promoters of genes can lead to their silencing, a feature found in a number of human cancers (i.e., the silencing of tumor suppressor genes). DNA methylation has been shown to be involved in silencing of an entire chromosome, as seen in the case of X inactivation [157]. DNA methylation can also affect gene expression by acting on a large chromosome domain containing multiple genes, such as some imprinted loci [158]. Furthermore, DNA methylation can act directly on transcription either by blocking transcription factor binding to the promoter sequences or by interfering with transcription elongation [159].

DNA methylation is predominantly found in cytosine-phosphate-guanine (CpG) dinucleotide sites of the mammalian genome, called CpG Islands (CpGIs), which are 0.4–3 kb in length and relatively rich in guanine and cytosine nucleobases (>55 %) [160]. In mammalian cells, DNA methylation occurs at the 5′ position of the cytosine ring within CpG dinucleotides via addition of a methyl group to create a 5-methyl-cytosine (m5C) [161]. The modification at m5C is catalyzed by DNMTs, including DNMT1, DNMT3a, and DNMT3b in mammals [28]. These enzymes can be further classified as *de novo* methyltransferases (e.g., DNMT3a and DNMT3b) or maintenance methyltransferases (e.g., DNMT1). *De novo* methyltransferases methylate previously unmethylated CpG sequences, but maintenance methyltransferases copy pre-existing methylation marks onto new DNA strands during replication [162]. DNMT1, DNMT3a and DNMT3b map to chromosomes 19p, 2p and 20q, respectively. The DNA methyltransferase homolog DNMT2 maps to 10p and the DNMT3 family member named DNMT3L maps to 21q [163].

DNMT1 is a major maintenance methyltransferase in vivo and ensures replication of DNA methylation patterns after each round of cell division [155]. Global genome demethylation caused by mutation in the *Dnmt1* gene plays an essential role in X-inactivation, genomic imprinting and genome stabilization [164]. The *de novo* establishment of DNA methylation patterns in early mammalian development involves DNMT3 family members, DNMT3A and DNMT3B, and the DNMT3-like non-enzymatic regulatory factor, DNMT3L [155]. Given their function in the *de novo* establishment of DNA methylation, both Dnmt3a and Dnmt3b, in conjunction with their nonenzymatic cofactor DNMT3L, play important roles in normal development and disease [165]. DNMT3A recognizes the unmethylated state of lysine 4 in histone H3 [166], and *de novo* DNA methylation by DNMT3A requires

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alteration of chromatin structure. DNMT3b is specifically required for methylation of centromeric minor satellite repeats. The autosomal recessive disease, Immunodeficiency, Centromeric instability and Facial anomalies syndrome, type I (ICF-1), is associated with hypomorphic mutations in the *DNMT3b* gene, the altered expression of which has also been correlated with the development of tumors [167,168]. The first example of naturally occurring mutations in a mammalian DNA methyltransferase gene related to ICF was reported in 1999 (two missense substitutions and a 3-aa insertion in the *Dnmt3b* gene) [169]. A hydrogen bond in the catalytic loop of DNMT3B causes lower CpG specificity than exhibited by DNMT3A, and site-specific epigenomic alterations seen in ICF syndrome with DNMT3B mutations can be partly explained by a shift in the substrate preference of DNMT3A and DNMT3B [170]. Homozygous missense variants in the DNMT3B gene (NM_ 006892; 2477 G > A, Arg826His) account for ICF-1 cases [27].

DNMT1, DNMT3A and DNMT3B polymorphisms are associated with increased or decreased risk of various tumors. DNMT1 (rs2228612, rs2228611, and rs2114724) and DNMT3B (rs406193 and rs2424932) polymorphisms were examined in 123 melanoma patients. *DNMT1* and *DNMT3B* polymorphisms were shown to affect the clinical course and outcome of melanoma. The DNMT1 rs2228612 genotype was associated with poorer survival ($P = 0.000$), poorer recurrence-free survival, ($P = 0.000$), as well as greater risk of adverse outcome [hazard ratio (HR) = 6.620, 95 % CI: 2.214–19.791, $P = 0.001$]. The *DNMT3B* rs406193 polymorphism correlated significantly with the presence of tumor-infiltrating lymphocytes ($P = 0.012$) [96]. A prospective, longitudinal study (from 2011 to 2017, n = 351) showed a significant association between the *DNMT1* rs2162560 polymorphism and chemotherapy-associated cognitive impairment of breast cancer patients [99]. In 1957 cases, the most frequent DNMT3a mutations (Arg882His and Arg882Cys) occurred at the C-terminal region outside of the MTase domain [30]. At the molecular level, DNMT3A Arg882His confers an 80 % reduction in the methyltransferase activity compared to wild-type [171]. Missense mutations in the *DNMT3A* gene are often observed in hematologic malignances, especially in AML, where the Arg882His mutation is prevalent [172]. A meta-analysis including 2184 cancer cases and 3420 controls concluded that the *DNMT3A* rs1550117 A > G polymorphism may be associated with cancer susceptibility, which was supported by a significant association between *DNMT3A* rs1550117 A > G polymorphism and increased risk of CRC (OR = 3.16; 95 % CI: 1.58–6.29; $P = 0.001$) [98]. Another meta-analysis (3959 cases and 5992 controls) investigated the effect of DNMT1 (rs16999593, rs2228611, rs8101866), DNMT3A (rs1550117, rs13420827) and DNMT3B (rs1569686, rs2424913) polymorphisms on susceptibility to gastric cancer. This meta-analysis demonstrated that rs16999593 (dominant model: OR 1.36, 95 %CI 1.15–1.60) and rs1550117 (dominant model: OR 1.20, 95 %CI 1.01–1.42) could contribute to gastric cancer risk and that rs1569686 (dominant model: OR 0.74, 95 %CI 0.61–0.90) might be a protective factor against gastric carcinogenesis [97].

10. Crystal structure of SAM-dependent MTases

SAM-dependent MTases are widely distributed among almost all organisms and often include conserved Rossmann fold, TIM barrel, and D × G × G×G motifs [173]. X-ray crystal structures of MTase provide insights into substrate recognition and reaction mechanisms.

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From structure-function comparisons of wild-type and variants, it is possible to infer how single amino acid changes produce phenotypic differences. The first reported structure of a SAM-dependent methyltransferase was the DNA C5-cytosine MTase reported by Hhal in 1993 [174]. The crystal structure of SAM-dependent methyltransferases (SAM-MTs) consists of a Rossmann-like fold (domain I) and a substrate-binding domain (domain II). The cofactor molecule (SAM) binds at the interface between adjacent domains, presumably near to the active site(s) of the enzyme [175]. There are five main classes (I-V) of SAM-dependent MTase categorized on the basis of their structural features. The large majority of MTases belong to the Class I or Rossmann-like fold family, catalyzing the majority of methylation reactions across all domains of life.

The crystal structure of human DNMT1, with all the structural domains (hDNMT1, residues 351–1600) in complex with SAH at 2.62 Å (Å) resolution is described in Table 5 and depicted in Fig. 5A. Fig. 5 depicts hDNMT1, composed of CXXC, tandem bromo-adjacent homology (BAH1/2), and methyltransferase domains bound to DNA-containing unmethylated CpG sites [176]. In 2018, a 2.65 Å crystal structure of the DNMT3A-DNMT3L-DNA complex was reported that showed Arg836 of the target recognition domain makes crucial contacts with the CpG dinucleotide, ensuring the DNMT3A enzymatic preference towards CpG sites [177] (Fig. 5B). DNMT3a and DNMT3b preferentially bind to nucleosomes. The structure suggests that nucleosomal DNA must be moved relatively to the nucleosome core for *de novo* methylation to occur. This movement allows the catalytic-like domain of the accessory protein DNMT3B to bind to the acidic patch of the nucleosome core, which orients binding of DNMT3A to the linker DNA [178]. From the structure of the human DNMT3B-3 L complex, human DNMT3b was shown to use two flexible loops to enclose DNA, specifically recognizing CpG sites in the DNA through its Asn779 and Lys777 residues [179].

The structure of human COMT is composed of a seven-stranded β-sheet core sandwiched between two sets of α-helices. The active site of COMT is close to the enzyme surface, which allows a variety of non-native catechol substrates to be methylated [50]. Residue 108 is located in a surface loop with SAM-binding residues at their distal end. Bounding SAM in the COMT protein might restrict the conformational changes caused by the polymorphism at residue 108. For COMT polymorphism rs4689 (Val108/158Met), the methionine variant is less stable than the valine variant, resulting in decreased enzyme activity and protein levels. The slight differences in the structures of 108 Val COMT and 108 Met COMT are attributable to differing interactions of residues Val108 and Met108 within the polymorphic site. Residues in the SAM-binding site were more exposed to the solvent in 108 Met than in the 108 Val COMT protein and the methionine side chain is packed more tightly within the polymorphic site than valine, consequently, interacts more closely with residues A22 (α2) and R78 (α4) than does valine, which may account for enzyme activity differences. [180].

The first X-ray crystallography structure of an As(III) S-adenosylmethionine methyltransferase, the CmArsM from the eukaryotic red alga Cyanidioschyzon merolae, was reported in 2012 [181]. A structural model of the human AS3MT structure was built upon the 1.78 Å ligand-free CmArsM structure [181] (Fig. 5D). From a comparison of residues 136–180 in the human AS3MT model with the rs35232887 Arg173Trp polymorphism, the

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Arg to Trp amino acid substitution is predicted to produce a conformational change due to a shift in the hydrogen bond between Arg173 and Glu170 (3.0 Å) to a longer hydrogen bond between Trp173 and Glu170 (4.5 Å) [181]. This conformation change can explain in part the lower catalytic activity of the Trp173 variant [59]. Trivalent arsenic(III) is methylated up to three times to form methylarsenite [MAs(III)], dimethylarsenite [DMAs(III)] and the volatile trimethylarsine [TMAs(III)] by ArsM (As3MT). Although the human As3MT crystal structure has not been reported, the catalytic mechanism of arsenic (III) SAM MTases in which a disulfide-bond (Cys44 and Cys72) cascade maintains the products in the trivalent state has been proposed based on structure of CmArsM [189] (Fig. 6A). The initial step in the As(III) SAM MTase catalytic cycle [arsenic (III) methylated to Mas(III)] was depicted by a conformational change in the N-terminal domain of CmArsM that moves a loop to allow formation of the 3-coordinate As(III) binding site. And the structure of CmArsM with bound As(III) and SAH [As(lll)/SAH-bound CmArsM, PDB entry 6CX6] has As(III) bound coordinately in three places to Cys44, Cys174, and Cys224, and SAH in the SAM binding site [190] (Fig. 6B). The distance between the sulfur atom of SAH and bound As(III) is approximately 4.9 Å (Fig. 6C1). The distance from the S-methyl group of SAM to the As atom is 2.9 Å, when both are bound, indicating that the methyl group is poised for transfer from SAM to As [190] (Fig. 6C2).

Human HNMT is a 2-domain protein, with the MTase fold in the larger domain that contains a seven-stranded β-sheets flanked on each side by three α-helices [182]. The MTase domain is structurally most similar to COMT (Fig. 5C and E). In the AdoMet binding domain of HNMT, residue 105 is located on the surface. The surface location of residue 105 suggests that this polymorphism is unlikely to affect overall structural stability. However, Ile105 affects the stability of AdoMet binding, with lower Km values for AdoMet and histamine [104]. The HNMT common polymorphism, rs11558538 (Thr105IIe, 314C > T) exhibits high- (Thr) and low- (Ile) activity phenotypes, similar to COMT SNP rs4680 (Met158Val) [182]. In wild-type HNMT, there is a stabilizing hydrogen bond between Thr105 and main chain residue Leu101. In the Ile105 variant, this hydrogen bond is lost, resulting in an increase in the flexibility of the loop between α_B and β3. This slightly destabilizes the carboxyl end of helix α_B, lowering the affinity for SAM, consistent with the effect of COMT SNP rs4680 [182].

NNMT catalyzes the transfer of a methyl group from SAM onto the substrate (nicotinamide) to form 1-methyl-nicotinamide. NNMT possesses a class I SAM-dependent MTases core fold, comprising a central seven-stranded β-sheet, flanked on both sides by α-helices (Fig. 5G). In addition to the MTase core, there are two extra α-helices at the N-terminus with a β-hairpin (Y203-S212) that forms a cap over the active site [191]. Dr. Sven Ruf's research group described their approach to identify potent small molecule inhibitors of NNMT. One kind of inhibitor (a series of imine compounds was tested) makes a hydrogen bond with the hydroxyl group of Tyr20, forming a van der Waals contact (d = 3.3 Å) with the sulfur of SAH. This is the position wherethe methyl group of the co-substrate SAM would be transferred by NNMT to the substrate nicotinamide [191]. Another inhibitor occupies both the nicotinamide and SAM pockets of the catalytic center [191]. There is a large body of crystallography research on NNMT interaction with inhibitors, aimed at identifying selective small molecule inhibitors for treating metabolic disorders [192].

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PNMT uses the methyl donor AdoMet to catalyze the formation of adrenaline from noradrenaline. PNMT and COMT are both part of the catecholamine pathway and they both interact with adrenaline and noradrenaline (Fig. 2). TPMT is a single domain protein with a classic Class-I MTase fold. The crystal structure of human PNMT was solved at a resolution of 2.4 Å in complex with a cofactor product and a sub-micromolar inhibitor. The structure revealed a MTase fold with an active site protected from solvent by an extensive cover formed from several discrete structural motifs [185]. When compared with COMT, PNMT is a much more complicated structure (Fig. 5H). By comparing Fig. 5C and H, it can be seen that COMT is a relatively streamlined structure, with no inserts in the fold. However, there are four insertions in the MTase fold of PNMT, providing the motifs that enclose the active site and contribute a significant number of the ligand binding residues.

TPMT catalyzes thiopurine and thiopyrimidine S-methylation, an important metabolic pathway for thiopurine drugs. Considerable interindividual variation in thiopurine toxicity and therapeutic efficacy occurs, mainly due to genetic polymorphisms. TPMT is a single domain protein with a classic Class-I MTase fold (Fig. 5I). From the structure of TPMT mutant proteins containing variant alleles of TPMT*2, *3A, *3B, and *3C, it appears that forming intra-molecular stabilizing interactions (mainly van der Waals contacts) have the most influence on function [186]. Due to extremely low solubility of thiopurine drugs (6-MP, 6-TG, or 2-thiopurin) in water. No co-crystals of TPMT in complex with drug have been reported to date.

11. Summary and conclusions

MTases are classified based on their methyl-accepting substrates, which include drugs, xenobiotics, neurotransmitters, hormones, proteins, DNA and RNA. SAM-dependent MTases transfer a methyl group from SAM to a nucleophilic acceptor (e.g. O, As, N, S or C). In this review we systematically described eight SAM-MTases and their relationship with human health and disease. COMT is an O-methyl SAM-MTase that uses dopamine as substrate. The physiological role of COMT is to maintain appropriate levels of dopamine and norepinephrine at the front of the brain. Some symptoms in individuals with 22q11.2 deletion syndrome may be related to the deletion of COMT. AS3MT is an As(III)-SAM-MTase that uses the environmental contaminant arsenic as substrate. As(III) SAM-MTases are found in members of every kingdom from bacteria to humans. The most common AS3MT polymorphism, M287 T, is related to susceptibility to diabetes. INMT is an N-methyl SAM-MTase that catalyzes methylation of tryptamine to form the hallucinogen *N,N*-dimethyltryptamine (DMT). *INMT* gene variants are associated with Hirschsprung's disease. Another N-methyl SAM-MTase is PNMT, which catalyzes the final step in catecholamine biosynthesis by N-methylation of norepinephrine to epinephrine. PNMT genetic polymorphisms G (−353)A and G(−148)A, in the 5′-flanking region of the *PNMT* gene are associated with increased risk for sporadic early onset AD, multiple sclerosis and essential hypertension. Another N-methyl MTase, HNMT, uses the neurotransmitter histamine as substrate. The HNMT polymorphism T105 l is associated with PD and schizophrenia. The N-methyl MTase, NNMT is the only enzyme known to utilize nicotinamide, which is used in synthesis of NADH and ATP as a methyl acceptor. NNMT is a potential tumor marker. One physiological function of the S-methyl MTase TPMT is

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metabolism of thiopurine drugs that are used for treatment of ALL, Crohn's disease and rheumatoid arthritis. Variant alleles of TPMT are associated with low TPMT enzyme activity in humans. DNA methyltransferase plays a crucial role in the maintenance of genomic methylation patterns. Mutations in DNMT1, DNMT3A and DNMT3B are associated with cancers. These are some of the most well-characterized genetic polymorphisms of drug metabolism. The various physiological roles of the substrates and products of these eight SAM-MTases (COMT, AS3MT, INMT, DNMT, HNMT, NNMT, TPMT, DNMT) demonstrate their importance to human physiology. Polymorphisms in their genes are related to individual variations in metabolism, disease susceptibility and therapeutic effects of their substrates and products. Although we focused on eight representative SAM MTases, there are many others of considerable importance for human health. Crystal structures of SAM-MTs not only provide important information regarding the catalytic function of the enzymes, but also pave the way for developing more potent and selective inhibitors in the future.

Methyl conjugation is a critical reaction in the metabolism of many drugs (e.g., nicotinamide), thiopurine neurotransmitters (e.g., dopamine, tryptamine, histamine, norepinephrine), and xenobiotic compounds (e.g., arsenic). Individual variation in SAM-dependent MTases are responsible for individual differences in the metabolism of neurotransmitters, therapeutic effects and toxicity of xenobiotics. Most of the SNPs in the eight MTases described in this review lead to lower enzyme activity. Elucidation of the relationship between mutations and the risk of disease is essential for personalized medicine that can provide the correct drug at the appropriate dose for each individual based on the patient's genetic background. Importantly, knowledge about these variants will contribute to a more precise understanding of correlations between genotypes and disease-susceptibility phenotypes or the risk of side effects from drugs.

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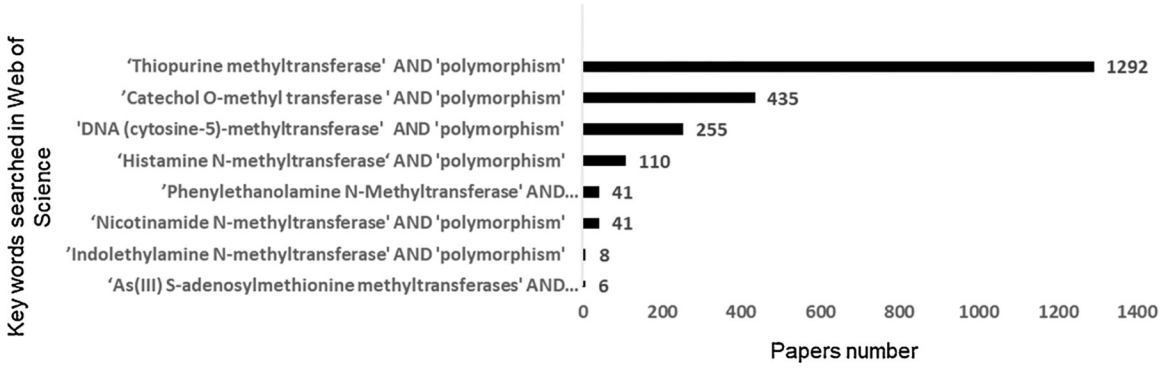

Fig. 1. Publications on S-adenosyl L-methionine (SAM)-dependent methyltransferases in the past 30 years.

A database search (Web of Science, Thomson Reuters) was performed on 20 April 2021. Depicted is the total number of publications using the following search strategies: 'catechol O-methyl transferase' AND 'polymorphism'; 'As(III) S-adenosylmethionine methyltransferases' AND 'polymorphism'; 'Histamine *N*-methyltransferase 'AND 'polymorphism'; 'Indolethylamine *N*-methyltransferase' AND 'polymorphism'; 'Nicotinamide *N*-methyltransferase' AND 'polymorphism'; 'Phenylethanolamine *N*-Methyltransferase' AND 'polymorphism'; 'Thiopurine methyltransferase' AND 'polymorphism'; and 'DNA (cytosine-5)-methyltransferase' AND 'polymorphism'.

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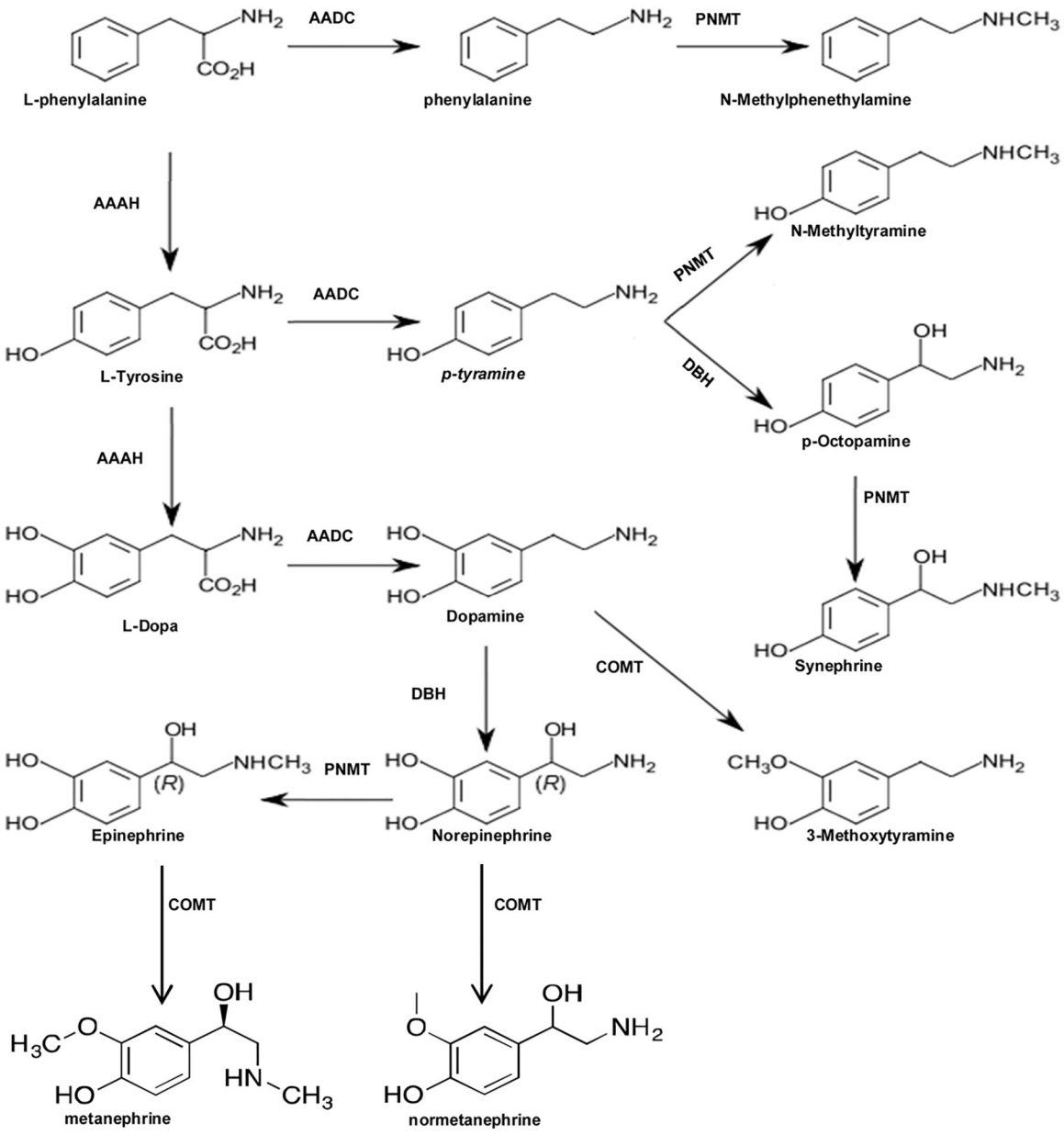

Fig. 2. Human biosynthetic pathway for trace amines and catecholamines.

L-Phenylalanine is converted into L-tyrosine by the enzyme AAAH (aromatic amino acid hydroxylases). L-Tyrosine is converted into L-DOPA (l-dihydroxyphenylalanine) by the enzyme AAAH. L-DOPA is catalyzed to dopamine by the enzyme aromatic L-amino acid decarboxylase (AADC). Dopamine itself is also used as a precursor in the synthesis of the neuro-transmitters, norepinephrine and epinephrine. Dopamine is converted into norepinephrine by the enzyme dopamine β-hydroxylase (DBH) and inactivated by COMT Norepinephrine is converted into epinephrine by the enzyme PNMT with SAM as the cofactor. Epinephrine and norepinephrine are inactivated by COMT. [32,39,40].

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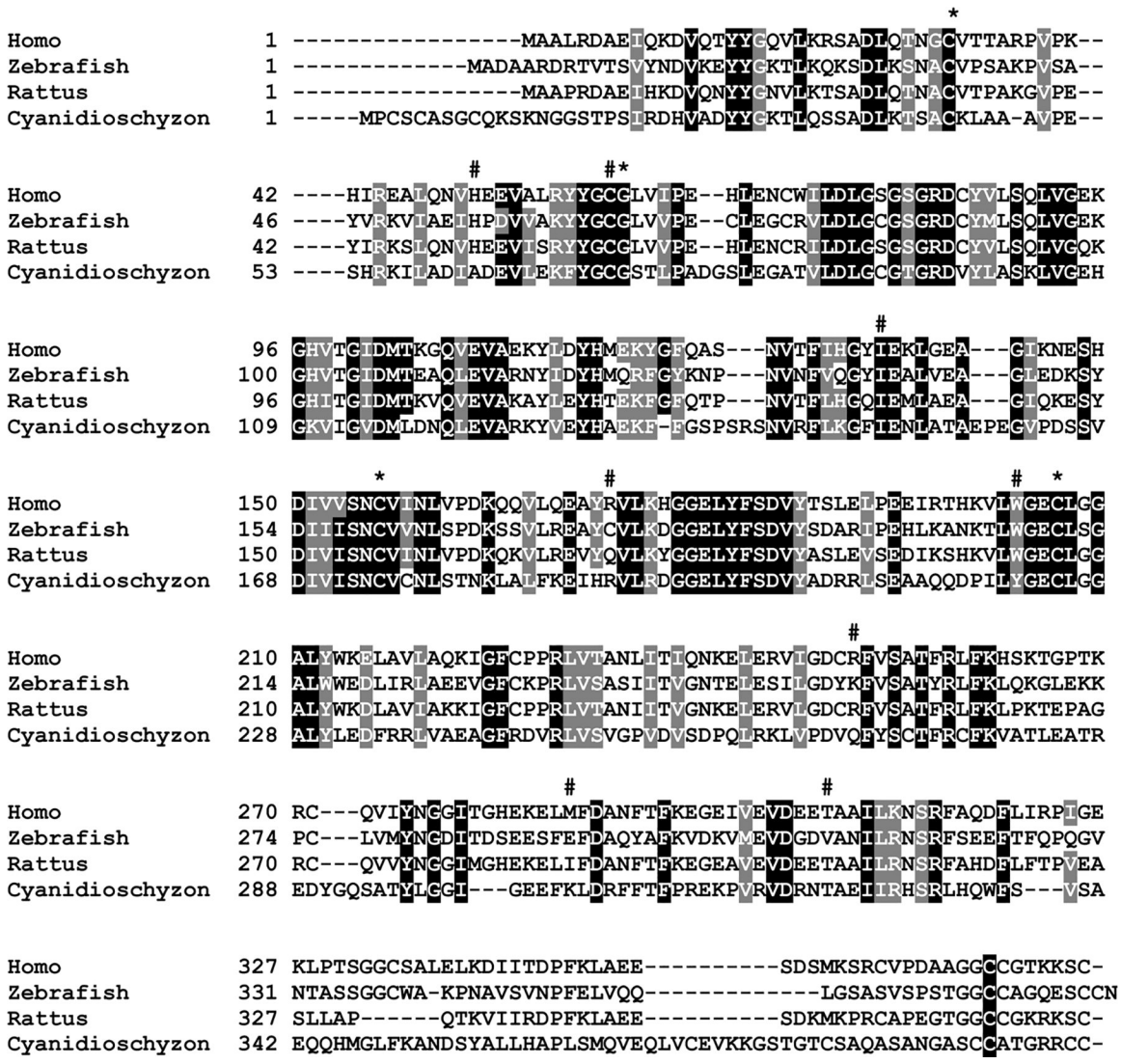

Fig. 3. Multiple sequence alignment of As (III) SAM methyltransferases.

Homo sapiens As(III) *S*-adenosylmethionine methyltransferase (AAI19639) was aligned with eukaryotic orthologues from *Danio rerio* (zAS3MT, NP_001034928), *Rattus norvegicus* (rAS3MT, NP_543166) and *Cyanidioschyzon merolae* (CmArsM, FJ476310). Black shading indicates conserved residues, grey shading indicates conservative replacements, * denotes conserved cysteine residues, # denotes polymorphic residues.

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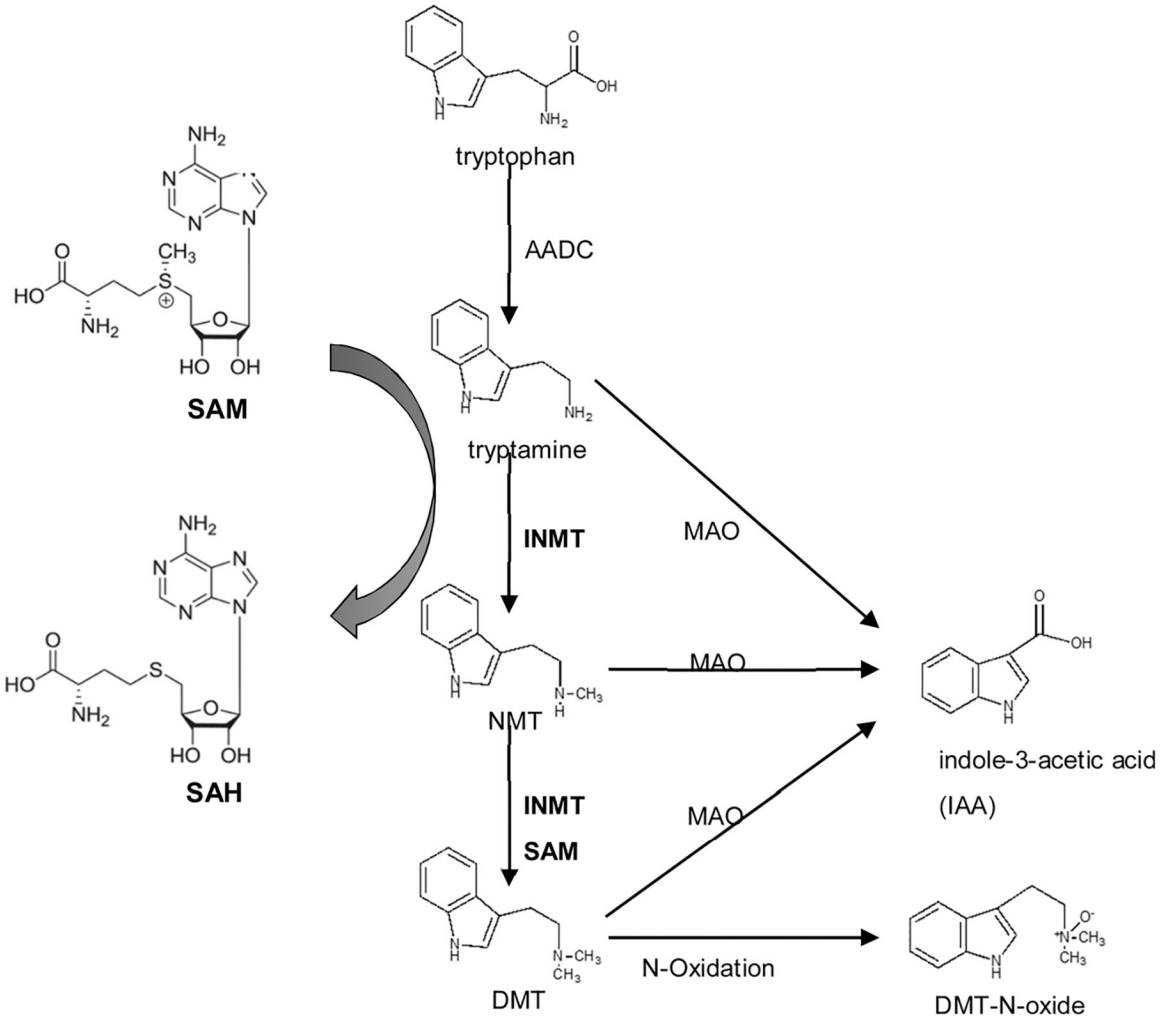

Fig. 4.

Pathways for the biosynthesis and metabolism of DMT. Tryptophan is converted to tryptamine by aromatic amino acid decarboxylase (AADC). Trytamine is dimethylated to first yield N-methyltryptamine (NMT) and then *N,N*-dimethyltryptamine (DMT) by indole-*N*-methyltransferase (INMT), using S-adenosyl-methionine (SAM) as the methyl source. Metabolism: tryptamine, NMT and DMT are all substrates for monoamine oxidase (MAO), yielding indole-3-acetic acid (IAA) as both a common precursor metabolite and the most abundant metabolite of DMT itself. DMT is also converted to DMT-*N*-oxide as the second-most abundant metabolite. Adapted and modified from [77].

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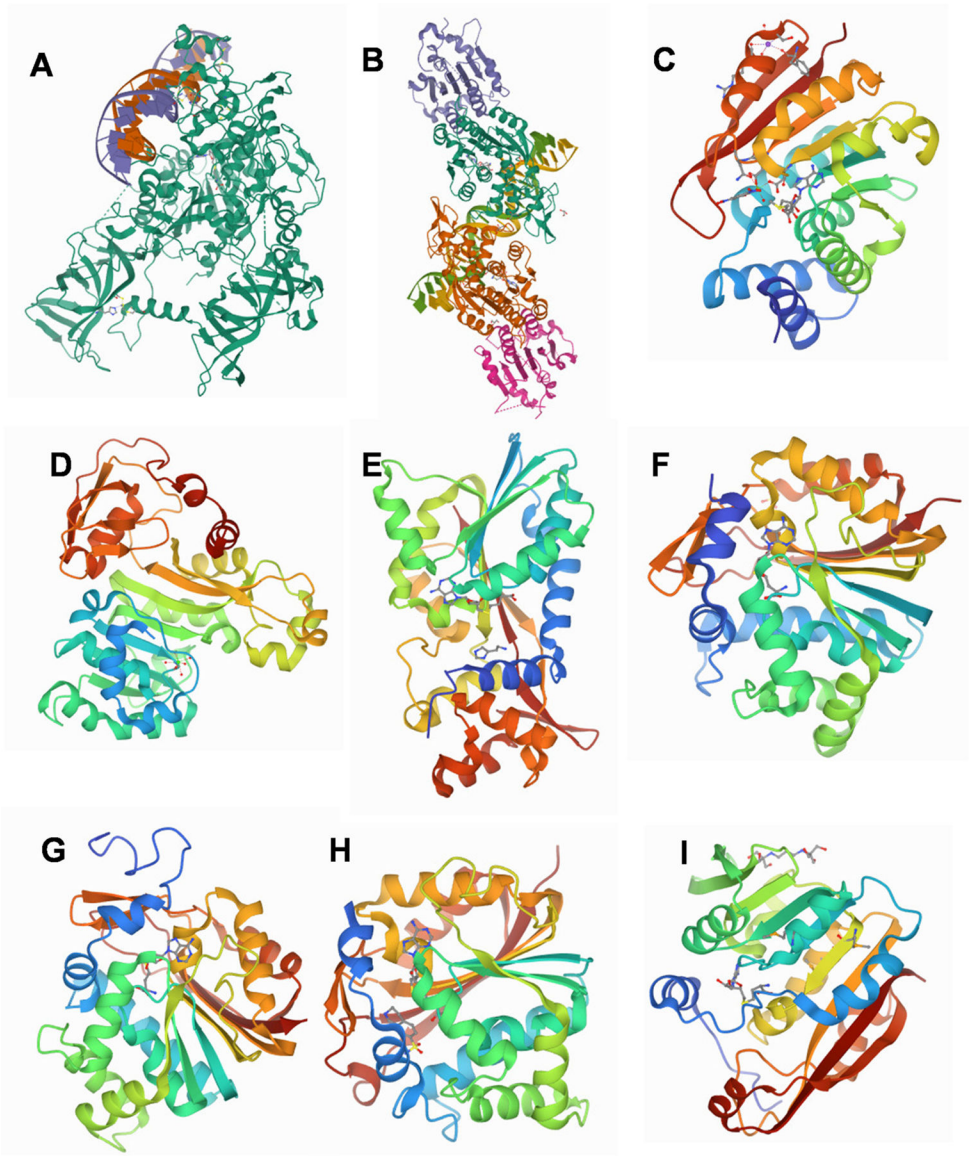

Fig. 5.

Crystal structures of SAM-dependent MTases. (A) human DNMT1(646–1600) in complex with DNA;(B)DNMT3A-DNMT3L in complex with DNA containing two CpG sites;(C) human COMT with bound SAM and DNC;(D) As3MT; (E) human HNMT (Thr105 Polymorphic Variant) complexed with SAH and histamine. DOI: 10.2210/pdb1JQD/pdb; (F) human INMT with SAH. DOI: 10.10.2210/pdb2A14/pdb; (G) human NNMT. DOI: 10.10.2210/pdb2IIP/pdb; (H) Crystal structure of human PNMT complexed with SK&F 29661 and AdoHcy; (I) TPMT. DOI: 10.10.2210/pdb2BZG/pdb.

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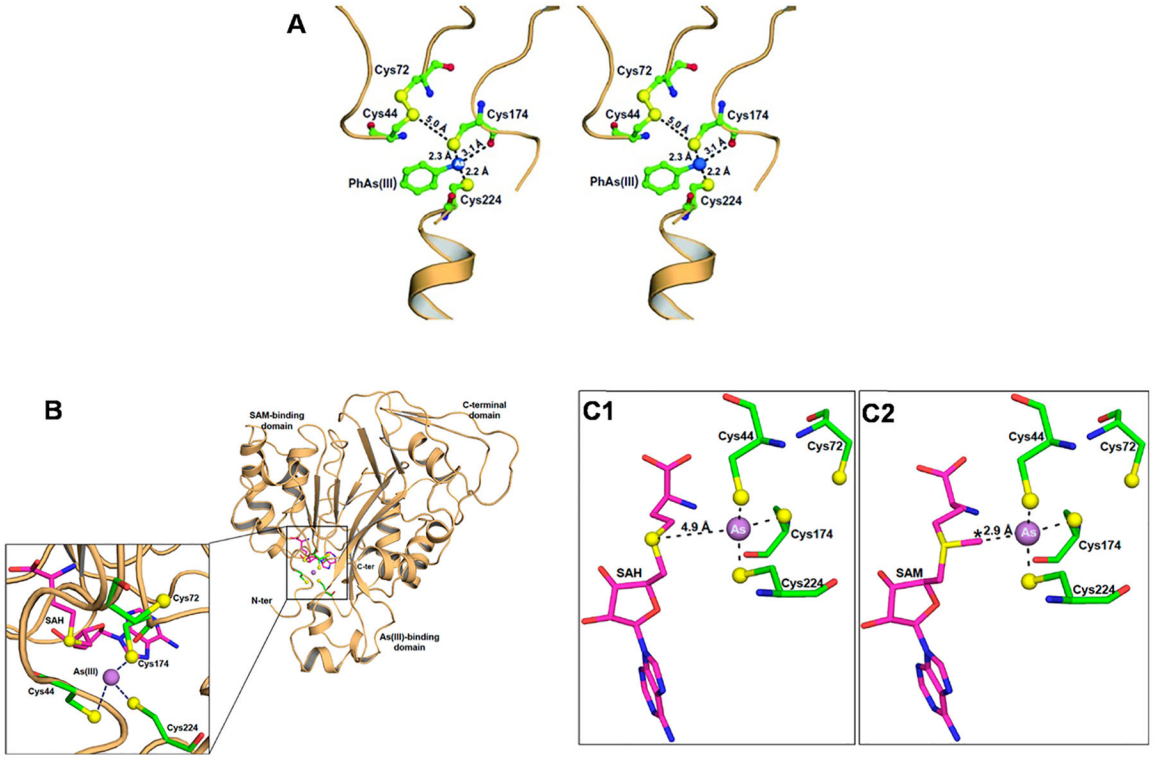

Fig. 6.

(A) A disulfide bond between Cys44 and Cys72 in the crystal structure of CmArsM with bound aromatic arsenical, phenylarsenite PhAs (III) (PDB entry 4kw7). The conserved cysteine residues are shown in ball-and-stick representation with atoms colored green (carbon), blue (nitrogen) or yellow (sulfur). The dark blue sphere is the As atom. The length of the disulfide bond is approximately 2.1 Å in the PhAs (III)-bound structure. (B) The overall structure of CmArsM consists of an N-terminal domain, an As(III) binding domain, and a C-terminal domain. The inset shows a close-up of the active site showing the four conserved cysteine residues represented by balls and sticks with atoms colored green (carbon), blue (nitrogen), red (oxygen), and yellow (sulfur). The purple sphere is the arsenic atom, and the SAH in the SAM binding site is represented by balls and sticks and with carbon colored magenta. As(III) is bound among conserved residues Cys44, Cys174, and Cys224. (C1) The As atom in the binding site consisting of Cys44, Cys174, and Cys224 is positioned near SAH in the SAM binding site. The distance between the sulfur atom of SAH and the As atom is 4.9 Å. (C2) Distances between the As atom and the sulfur atoms of SAM is 2.9 Å. The S-methyl group is poised for electron transfer from SAM to As(III).

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Table 1

A brief summary of eight SAM-depended MTases.

SAM-dependent methyltransferases	Gene Localization	Prototypic substrate	Catalysis of the reaction	Related diseases
COMT (Catechol O-methyltransferase)	22q11.21	Catacholamines (dopamine, epinephrine)	SAM + a catechol = SAH + a guaiacol	Schizophrenia [1,2] PD [3,4] AD [5] ADHD [6]
AS3MT (Arsenite methyl transferase)	10q24.32	Arsenic Antimony Tryptamine	SAM + arsenite = SAH + methylarsonate SAM + methylarsonate = SAH + dimethylarsinate SAM + an amine = SAH + a methylated amine.	Hypertension [7] Skin lesions [8] Diabetes [9]
INMT (Indolethylamine *N*-methyltransferase)	7p14.3	Serotonin Thioethers Selenium Tellurium	SAM + dimethyl sulfide = SAH + trimethylsulfonium	Hirschsprung's disease [10]
PNMT (Phenylethanolamine *N*-Methyltransferase)	17q12	Nonrepinephrine	SAM + phenylethanolamine = SAH + N-methylphenylethanolamine	Hypertension [11] AD [12] Sickle cell disease [13] PD [14,15,16,17]
HNMT (Histamine *N*-methyltransferase)	2q22.1	Histamine	SAM + histamine = SAH + N(tau)-methylhistamine	Asthma [18,19] Schizophrenia [16] Migraine [20]
		Nicotinamide		Cancer [21]
NNMT (Nicotinamide *N*-methyltransferase)	11q23.2	Pyridine	SAM + nicotinamide = 1-methylnicotinamide + SAH	Schizophrenia [22] Obesity [23] Diabetes [24]
TPMT (Thiopurine S-methyltransferase)	6p22.3	Azathioprine 6-Mercaptopurine 6-Thioguanine	SAM + a thiopurine = SAH + a thiopurine S-methylether	ALL [25]
DNMT1	19p13.2	Cytosine	SAM + DNA = SAH + DNA containing	ICF syndrome [26,27]
DNMT3A	2p24.1			Cancer [28]
DNMT3B (DNA (cytosine-5)-methyltransferase)	20q11.21	Adenine	5-methylcytosine	Breast cancer [29] Acute myeloid leukemia (AML) [30]

Abbreviations: S-adenosyl L-methionine, SAM; S-adenosyl-L homocysteine, SAH or AdoHcy; Alzheimer disease, AD; Attention-deficit/hyperactivity disorder: ADHD; Parkinson's disease: PD; Acute lymphoblastic leukaemia: ALL; Acute myeloid leukaemia: AML; Immunodeficiency, centromeric instability and facial anomalies syndrome: ICF.

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Table 2

Frequencies of the primary SAM-dependent methyltransferases polymorphisms[1] in the 1000 Genomes Project[2], ExAC[3], and the BUSHMAN Population[4].

MTases	dbSNP rs# [Minor Allele Frequency (MAF)]	Amino Acid change	Base change	Allele frequency (numbers of individuals)[5]	Genotype frequency (numbers of individuals)[6]	Data source
COMT	rs4680 (0.37)	Val158Met Val108 Met	472G > A	G: 0.631 (3159) A: 0.369 (1849)	G|G: 0.413 (1034) A|G: 0.436 (1091) A|A: 0.151 (379)	1000 Genomes Project
COMT	rs4633 (0.37)	His62His Synonymous Variant Leu136Leu	186C > T	C: 0.628 (3147) T: 0.372 (1861) C: 0.703 (3521)	C|C: 0.411 (1028) C|T: 0.436 (1091) T|T: 0.154 (385) C|C: 0.509(1275)	1000 Genomes Project
COMT	rs4818 (0.30)	Synonymous Variant	408C > G/T	G: 0.297 (1487)	C|G: 0.388(971) G|G: 0.103 (258)	1000 Genomes Project
COMT	rs6267 (0.01)	Ala72Thr/Ser	214G > A / T	G: 0.987 (4941) T: 0.013 (67)	G|G: 0.973 (2437) G|T: 0.027 (67)	1000 Genomes Project
COMT	rs2020917 (0.21)	intron variant (Promotor region)	−628C > T	C: 0.787 (3941) T: 0.213 (1067)	C|C: 0.625 (1566) C|T: 0.323 (809) T|T: 0.052 (129)	1000 Genomes Project
COMT	rs737865 (0.23)	intron variant (Promotor region)	92 + 701A > G	A: 0.773 (3873) G: 0.227 (1135)	A|A: 0.602 (1507) A|G: 0.343 (859) G|G: 0.055 (138)	1000 Genomes Project
AS3MT	rs201702937 (0.01)	His51Arg	152A > G	A: 0.9998 (5007) G: 0.000199 (1)	A|A: 0.9996 (2503) A|G: 0.00039 (1)	1000 Genomes Project
AS3MT	rs80317306 (<0.01)	Cys61Trp	183T > G	T: 0.995 (120200) G: 0.005 (646)	T|T 0.991 (60100) T|G 0.009 (646)	Exome Aggregation Consortium (ExAC)
AS3MT	rs112056792 (< 0.01)	Ile136Thr	407T > C	NA 1	NA 1 (Male)	BUSHMAN POP
AS3MT	rs35232887 (0.01)	Arg173Trp	517C > T	C: 0.999 (5003) T: 0.001 (5)	C|C: 0.998 (2499) C|T: 0.002 (5)	1000 Genomes Project
AS3MT	rs370022454 (< 0.01)	Trp203Cys	609G > T	G: 0.999734 (3763) T: 0.000265675 (1)	G|G: 0.999 (1881) G|T: 0.001 (1)	African-American of NHLBI Exome Sequencing Project[7]
AS3MT	rs139656545 (<0.01)	Arg251His	752G > A	G: 0.998 (4997) A: 0.002 (11) T: 0.923 (4622)	G|G: 0.996 (2493) A|G: 0.004 (11) T|T: 0.854 (2138)	1000 Genomes Project
AS3MT	rs11191439 (0.08)	Met287Thr	860 T > C/A	C: 0.077 (386)	C|T: 0.138 (346) C|C: 0.008 (20)	1000 Genomes Project
AS3MT	rs34556438 (<0.01)	Thr306Ile	917C > T	C: 0.99951 (8164) T: 0.000489716 (4) T: 0.765 (3829)	C|C: 0.999 (4080) C|T: 0.001 (4) T|T: 0.589 (1475)	European-American of NHLBI Exome Sequencing Project[7]

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MTases	dbSNP rs# [Minor Allele Frequency (MAF)]	Amino Acid change	Base change	Allele frequency (numbers of individuals)[5]	Genotype frequency (numbers of individuals)[6]	Data source
AS3MT	rs3740392 (0.24)	Intron Variant	610 + 63T > C	C: 0.235 (1179) A: 0.230 (1153)	C|T: 0.351 (879) C|C: 0.060 (150) A|A: 0.082 (205)	1000 Genomes Project
INMT	rs6970396 (0.23)	3 Prime UTR Variant	8797A > G	G: 0.770 (3855)	A|G: 0.297 (743) G|G: 0.621 (1556)	1000 Genomes Project
INMT	rs77743549 (0.01)	His46Pro	137A > C	A: 0.995 (4984) C: 0.005 (24) C: 0.744 (3728)	A|A: 0.990 (2480) A|C: 0.010 (24) C|C: 0.558 (1397)	1000 Genomes Project
NNMT	rs694539 (0.26)	Intron variant	−216–151C > T	T: 0.256 (1280) A: 0.443 (2218)	C|T: 0.373 (934) T|T: 0.069 (173) A|A: 0.204 (510)	1000 Genomes Project
NNMT	rs1941404 (0.44)	Intron variant	−224 + 122A > G	G: 0.557 (2790) G: 0.510 (2555)	A|G: 0.478 (1198) G|G: 0.318 (796) G|G: 0.276 (691)	1000 Genomes Project
NNMT	rs10891644 (0.49)	Intron variant	−129–11693G > T	T: 0.490 (2453) G: 0.587 (2940)	G|T: 0.468 (1173) T|T: 0.256 (640) G|G: 0.368 (921)	1000 Genomes Project
PNMT	rs876493 (0.41)	5 prime UTR variant	93 + 222G > A	A: 0.413 (2068) C: 0.940 (4710)	A|A: 0.194 (485) A|G: 0.438 (1098) C|C: 0.886 (2219)	1000 Genomes Project
HNMT	rs11558538 (0.06) rs1800460	Thr105Ile	314C > T	T: 0.060 (298) C: 0.987 (4944)	C|T: 0.109 (272) T|T: 0.005 (13) C|C: 0.975 (2441)	1000 Genomes Project
TPMT	TPMT*3B (0.01) rs1142345	Ala154Thr	460C > T	T: 0.013 (64) T: 0.961 (4812)	C|T: 0.025 (62) T|T: 0.0004 (1) T|T: 0.925 (2316)	1000 Genomes Project
TPMT	TPMT*3C (0.04)	Tyr240Cys Pro463Pro	719T > C	C: 0.039 (196) T: 0.466 (2334)	C|C: 0.003 (8) C|T: 0.072 (180) T|T: 0.228 (570)	1000 Genomes Project
Dnmt1	rs2228611 (0.47)	Synonymous Variant	1389T > A/C	C: 0.534 (2674) T: 0.802 (4015)	C|T: 0.477 (1194) C|C: 0.296 (740) T|T: 0.653 (1636)	1000 Genomes Project
Dnmt1	rs2228612 (0.20)	Ile327Phe	979T > A/C /G	C: 0.198 (993) G: 0.722 (3615)	C|T: 0.297 (743) C|C: 0.050 (125) G|G: 0.534 (1338)	1000 Genomes Project
DNMT1	rs2162560 (0.28)	Intron Variant	G > A	A: 0.278 (1393) T: 0.955 (4782)	A|G: 0.375 (939) A|A: 0.091 (227) T|T: 0.918 (2299)	1000 Genomes Project
DNMT1	rs16999593 (0.05)	His97Arg	290 T > C	C: 0.045 (226)	C|T: 0.073 (184) C|C: 0.008 (21)	1000 Genomes Project

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MTases	dbSNP rs# [Minor Allele Frequency (MAF)]	Amino Acid change	Base change	Allele frequency (numbers of individuals)[5]	Genotype frequency (numbers of individuals)[6]	Data source
Dnmt3A	rs1550117 (0.11)	Upstream Transcript Variant	A > G/T	A: 0.114 (572) G: 0.886 (4436) C: 0.312 (1562)	A|A: 0.018 (46) A|G: 0.192 (480) G|G: 0.790 (1978) C|C: 0.134 (336)	1000 Genomes Project
Dnmt3B	rs2424913 (0.31)	Intron Variant	C > A/T/G	T: 0.688 (3446) G: 0.276 (1383)	C|T: 0.355 (890) T|T: 0.510 (1278) G|G: 0.125 (312)	1000 Genomes Project
Dnmt3B	rs1569686 (0.28)	Intron Variant	G > T/A/C	T: 0.724 (3625)	G|T: 0.303 (759) T|T: 0.572 (1433)	1000 Genomes Project

[1] Original data were mined from the Ensembl genome browser database (http://useast.ensembl.org/index.html) accessed April 5, 2021. For the 1000 Genomes Project, all donors were over 18 and declared themselves to be healthy at the time of collection. The health conditions for other data source populations are unknown.

[2] **1000 Genomes Project** population: African, American, East Asian, European, South Asian.

[3] **Exome Aggregation Consortium (ExAC)** population: African/African American, Latino, East Asian, Finnish, Non-Finnish European, South Asian and others.

[4] **BUSHMAN Population**: Northern Kalahari of Africa.

[5] Presented in order as Ancestral; Variants.

[6] Presented in order as Homozygous dominant; Heterozygous; Homozygous recessive.

[7] African-American (AA), European-American (EA) of NHLBI Exome Sequencing Project are AA or EA population from National Heart Lung and Blood Institute (NHLBI) Exome Sequencing Project using deep whole exome resequencing of >7000 individuals to study genetic contributions to the risk of several heart, lung and blood phenotypes.

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Table 3

Case-control and prospective cohort studies relating SAM-dependent MTases polymorphisms to disease.

Polymorphisms	Diseases(symptom)	Study sample	Statistical analysis	Notable observations
COMT rs4680	Schizophrenia (SCZ)	meta-analysis (n = 1416); atypical antipsychotics (n = 1207)	P = .0098, OR Met/Met = 1.54, 95% CI: 1.11–2.14	COMT Val158Met polymorphism is associated with response to antipsychotics in schizophrenia and schizo-affective disorder patients [1]
COMT rs6269, rs4633, rs4818, rs4680	Parkinson's disease (PD)	409 PD patients	Hazard ratio = 3.24; P = 0.02	high-COMT activity haplotype (G-C-C-G for rs6269, rs4633, rs4818, and rs4680) showed a high risk of cognitive decline in PD [3]
COMT rs740603	Surgery acute pain	241 children of African American and 277 of European Caucasian ancestry	A allele, OR: 0.69, 95 % CI: 0.48–0.99, P = 0.046	COMT rs740603 was related to high pain in European Caucasian subjects [89]
COMT rs6267	Pain in PD patient	418 PD patients for evaluating pain severity	P < 0.01	COMT rs4680 and COMT rs6267 contribute to pain in PD patients [4]
COMT rs4680	Stress mindset on affect and cognition	Participants (n = 107) were exposed to a stress mindset manipulation	($F_{4,32}$ = 3.52, p = .017, η^2 = .306	Genetic variation at rs4680 modified the effects of stress mindset on affective and cognitive responses to stress [90]
COMT rs4680	Alzheimer disease (AD)	345 AD and 253 healthy controls	OR = 6.71, 95 %CI 3.36–13.41, P < 0.001	OMT Val158 Met polymorphism as an associated risk factor for Alzheimer disease [52]
AS3MT rs11191438 rs10748835 rs1046778	Bladder cancer	216 bladder cancer patient and 648 healthy controls	(OR) (95 % CI) was 0.50 (0.31–0.82), 0.49 (0.30–0.79), and 0.54 (0.36–0.80),	rs1119438 C/C, rs10748835 A/A and rs1046778 C/C, were associated with bladder cancer risk; AS3MT rs1046778 C/C + C/T genotype increase the risk of BC [61]
AS3MT rs3740392	Developmental delay	179 children with developmental delay and 88 controls	OR and 95 %o CI, 1.59 (1.08–2.34)	AS3MT rs3740392 A/G + G/G genotype had a significantly higher OR than those with AS3MT low-risk haplotypes [64]
AS3MT rs11191439	Diabetes	N = 255	OR = 11.4 (95 % CI 2.2–58.8)	Individuals with M287 T polymorphisms were more frequently diabetic than the respective wild-type carrier [9]
AS3MT rs11191439	Skin lesions	71 cases with skin lesions and 51 controls	OR = 4.28; 95 % CI (1.0–18.5)	Met287Thr influences the susceptibility to premalignant As skin lesions [8]
INMT rs77743549	Hirschsprung's disease (HSCR)	187 HSCR patients and 283 controls	OR = 1.77; corrected P = 0.002	rs77743549 of INMT may be associated with the risk for HSCR [10]
NNMT rs694539	ALL	245 pediatric ALL patients (cases) and from 500 blood bank donors (controls)	OR = 2.2; 95 % CI, 1.1–4.6; P = 0.04	the NNMT IVS —151 TT genotype showed a 2.2-fold increased ALL risk [91]
NNMT rs694539	SCZ	cohort of 42 SZ patients and 86 healthy controls	P = 0.0015	NNMT rs694539 contribute to etiology of SCZ in a Han Chinese female population [92]
NNMT rs694539	Epilepsy	215 patients with epilepsy and 239 healthy controls	χ (2) = 6.682, P = 0.035	NNMT gene rs694539 variant involve in the etiology of epilepsy in male patients [93]
NNMT rs1941404	SCZ	202 unrelated families including a schizophrenia patient and her/his parents	P = 0.033	NNMT rs1941404 were significantly associated with schizophrenia [22]
NNMT rs10891644	Obesity	289 of high body fat group, 494 of low body fat group	$P_{adjusted}$ = 0.002, 95% CI = 1.240–2.235	the variation of the tagSNP, rs10891644 is significantly associated with obesity [23]

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Polymorphisms	Diseases(symptom)	Study sample	Statistical analysis	Notable observations
PNMT rs5638	Acute kidney injury (AKI)	194 AKI patients and 767 controls	OR = 2.19, 95 % CI = 1.04–4.60	The PNMT + 1543 G allele was associated with AKI [94]
PNMT G-353A and G-148A	AD	131 necropsy confirmed AD cases, and 947 adult nondemented controls	$P \leq 0.007$	genetic variation in the promoter of the PNMT gene is associated with increased susceptibility to Early-Onset AD [12]
PNMT rs3764351 rs876493	Hypertension	316 hypertension patients and 316 controls	$P = 0.01$; adjusted OR 0.17; 95% CI 0.05–0.58	The 2-SNP AA haplotype in the PNMT promoter is associated with decreased risk of essential hypertension in Han Chinese [11]
HNMT rs11558538	PD	2108 patients with PD, 2158 controls	OR = 0.63; 95 % CI = 0.45–0.88 for Caucasian patients	HNMT rs11558538 minor allele reduced risk of developing PD [14].
HNMT rs11558538	Asthma	192 asthma patients and 237 controls	OR = 1.9, $P < 0.01$	Variants with low HNMT activity were associated with asthmatics [19]
HNMT rs11558538	PD	913 patients with PD and 958 controls	$\chi(2) = 11.65$; $P = 0.0006$	Lower HNMT activity plays a role in the pathogenesis of PD [15]
HNMT rs11558538	PD and SCZ	564 PD patients and 496 controls; 423 SCZ patients and 457 healthy controls	PD (OR = 0.516, p = 0.007); SCZ (OR = 0.499, $P = 0.011$)	Ile allele was associated with reduced risk of PD and SCZ [16]
DNMT1 rs2228611 rs2228612	Primary osteoarthritis (OA).	244 OA patients and 244 controls	OR (95 % CI) 0.71 (0.51–0.97)	Haplotype C-T exhibited a lower risk with significant differences [OR (95% CI) 0.71 (0.51–0.97)] [95]
DNMT3b rs2424913	Primary osteoarthritis (OA).	244 patients and 244 controls	OR (95 % CI) 1.6 (1.1–2.4)	The C/C genotype of rs2424913 of DNMT3B was associated with an increased risk [95]
Dnmt1 rs2228612	Outcome of melanoma patients	123 melanoma patients	Hazard ratio = 6.620, 95 % confidence interval (CI): 2.214–19.791, $P = 0.001$ [15]	DNMT1 rs2228612 carriers had an increased risk for adverse outcome of nemanoma [96]
DNMT3B rs406193	Outcome of melanoma patients	123 melanoma patients	$P = 0.012$	DNMT3B rs406193 polymorphism correlated significantly with the presence of tumor-infiltrating lymphocytes [96]
DNMT3B rs1569686	Gastric Cancer	3959 cases and 5992 controls	OR 0.74, 95 %CI 0.61–0.90	rs1569686 might be a protective factor against gastric carcinogenesis [97]
DNMT3A rs1550117	Colorectal cancer	2184 cancer cases and 3420 controls	AA vs. GG (OR, 3.16; 95 % CI, 1.58–6.29; $P = 0.001$)	DNMT3A rs1550117 A > G polymorphism increased risk of colorectal cancer [98]
Dnmt1 rs2162560	Chemotherapy-Associated Cognitive Impairment (CACI)	Prospective cohort study with 351 early-stage breast cancer patients	OR = 0.45, 95 % CI: 0.25–0.82, $P = 0.01$	The allele carriers were associated with lower odds of self-reported cognitive decline [99]

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Table 4

List of allele variants at the human *TPMT* locus.

Locus	SNP	Location	Enzyme activity
TPMT 1*			Wild type: high activity
TPMT 1A*	C178T	Exon 1	Higher enzymatic activity [142]
TPMT 2* (the 1st identified variant allele)	G238C (Ala80Pro)	Exon 5	This mutation led to a 100-fold reduction in TPMT activity and very low levels of immunodetectable protein [137]
TPMT 3A* (contains two transition mutations, *3B and *3C)	G460A (Ala154Thr) and A719 G (Tyr240Cys)	Exon 7 and 10	The most common variant allele responsible for low TPMT activity in Caucasians; 400-fold decrease in protein levels and no detectable enzyme activity [139]
TPMT 3B*	G460A (Ala154Thr)	Exon 7	Four-fold decrease in protein levels
TPMT 3C*	A719 G (Tyr240Cys)	Exon 10	More frequently identified in African and Southeast Asian populations; 1.4-fold reduction in protein level and associated with lower immunodetectable TPMT protein and catalytic activity [140]
TPMT 3D*	G292 T/G460A (Glu-Stop)	Exon 5 and 7	Formation of a premature stop codon [143,144]
TPMT 4*	G to A transition	Intron 9–exon 10 junction	Destruction of a splice site [141], with reduced TPMT activity
TPMT 5*	T146C (Leu49Ser)	Exon	Intermediate TPMT activity [145]
TPMT 6*	A539 T (Tyr180Phe)	Exon 8	Korean subject with intermediate activity [145]
PMT 7*	T681 G (His227Glu)	Exon 10	European subject with intermediate TPMT activity
TPMT 8*	G644A (Arg215His)	Exon 10	African American subject with intermediate activity [146]
TPMT 9*	A356C (Lys119Thr)	Exon	No function [147]
TPMT 10*	G430C (Gly144Arg)	Exon	Deficient activity
TPMT 11*	G395A (Cys132Tyr)	Exon	No function
TPMT 12*	C374 T (Ser125Leu)	Exon	No function
TPMT 13*	A83 T (Glu28Val)	Exon	No function
TPMT 14*	A1G (Met1Val),-G1A,	Exon 3	Splicing defect [148]
TPMT 15*	G488A (Arg163His),	Intron 7	
TPMT 16*	C124 G (Gln42Glu),	Exon	
TPMT 17*	G211A (Gly71Arg)	Exon	
TPMT 18*		Exon	
TPMT 1S*	T474C	Exon	Silent mutation that does not lead to any change in enzymatic activity [149]
TPMT 45*	C676 T (Pro226*)	Exon	nonsense mutation that decreased TPMT activity [134]

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Table 5

Crystal structure information of SAM-dependent MTases extracted from the Protein Data Bank (PDB).[1].

SAM-dependent methyltransferase	PDB ID	Resolution (ångström /Å)	Amino acid sequence length	Organism(s)	Reference
COMT	3BWM	1.98	214	Homo sapiens	[180]
COMT 108 Met mutant	3BWY	1.30	214	Homo sapiens	[180]
ArsM (AS3MT)	4FS8	1.60	383	Cyanidioschyzon sp. 5508	[181]
HNMT	1JQD	2.28	292	Homo sapiens	[182]
INMT	2A14	1.70	263	Homo sapiens	[183]
NNMT	2IIP	2.05	283	Homo sapiens	[184]
PNMT	1HNN	2.40	282	Homo sapiens	[185]
TPMT	2BZG	1.58	232	Homo sapiens	[186]
DNMT1	4WXX	2.62	1256	Homo sapiens	[187]
DNMT1-DNA	3PTA	3.60	956	Homo sapiens	[176]
DNMT3A	5YX2	2.65	285	Homo sapiens	[177]
DNMT3B	6KDL	3.27	286	Homo sapiens	[188]

[1]RCSB PDB: Homepage, https://www.rcsb.org/.