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Update of the Methyltransferase Gene Family: Classification, Evolution and Biological Functions

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Abstract

Methylation is a crucial biochemical reaction involved in a wide range of processes including gene regulation, signal transduction, epigenetics, metabolism and detoxification. A number of methyltransferases (MTases) catalyze transfer of methyl groups from S-adenosyl-L-methionine (AdoMet or SAM) to nucleic acids, proteins, and small molecules, affecting chromatin structure, RNA function, and metabolic pathways. MTase dysregulation is associated with maladies such as cancer, neurodevelopmental disorders, and metabolic syndromes. Advancements in bioinformatics and high-throughput genomics have resulted in identification of ~200 human MTase genes, and most of the encoded proteins have now been characterized biochemically. Here, we have classified the human MTases into nine structural homology groups, including a distinct category of methyltransferases with unique structures. Major groups include the versatile seven-β-strand (7BS) MTases, the SET domain MTases which mainly mediate protein lysine methylation, and the SPOUT MTases involved in RNA modification. In addition, we categorized the MTases based on substrate specificity (e.g., nucleic acids, protein, and small-molecule MTases). This article provides a comprehensive classification and structural overview of human MTases, integrating recent nomenclature updates from the HUGO Gene Nomenclature Committee (HGNC). The evolutionary relationships and diversification of methyltransferases are also discussed in the context of structural classification and functional specialization. Emphasis is placed on biological functions, disease associations, and emerging therapeutic potential of the human MTases, particularly in oncology and neurodegenerative research. Despite significant progress, the biological function of many MTases remainselusive, necessitating further research to elucidate their enzymatic mechanisms and potential as drug targets. Understanding the MTase landscape is crucial for advancing biomedical research and developing targeted therapies for methylation-related disorders.

Keywords Classification, Epigenetic regulation, Evolution, Gene families, Methyltransferases, Nomenclature

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Background

Methylation is a fundamental biochemical reaction occurring in all living organisms, playing a crucial role in regulating and optimizing numerous cellular processes, such as gene regulation, signal transduction, metabolism and detoxification [1, 2], and is thus implicated in cancer and a range of genetic, chronicand metabolic diseases. In humans, a number of methyltransferases (MTases) catalyze the transfer of methyl groups (-CH_3) to various substrates, including nucleic acids, proteins and small molecules [3–5]. By acting on these distinct substrate classes, MTases play a central role in maintaining epigenetic regulation, chromatin organization, and coordinating cellular signaling networks, and metabolic pathways. MTases utilize S-adenosyl-L-methionine (AdoMet or SAM) as the primary methyl donor, transferring methyl groups to various target molecules, and whilst converting AdoMet into S-adenosyl homocysteine (SAH) [3, 4, 6] (Fig. 1). Methylation commonly occurs on oxygen (O-) and nitrogen (N-) atoms, with less frequent methylation of sulfur (S-), carbon (C-), and other elements [7].

Advances in mass spectrometry, next-generation sequencing, and bioinformatics have uncovered previously unknown families of MTases, and the intricate regulatory roles of methylation in cellular function. A landmark study from 2011 compiled around 200 human MTases, the "methyltransferasome," encompassing both established and putative MTases identified from sequence similarity and secondary structure prediction [8]. More recently, an evaluation of the largest class of methyltransferases (seven-β-strand MTases) estimated 120 human MTases using reviewed Swiss-Prot entries [9], while the second largest class (SET domain MTases) has been estimated to comprise around 55 MTases [10].

In the 2011 classification of MTases proposed by Petrossian and Clarke [8] (Table 1), there are three major

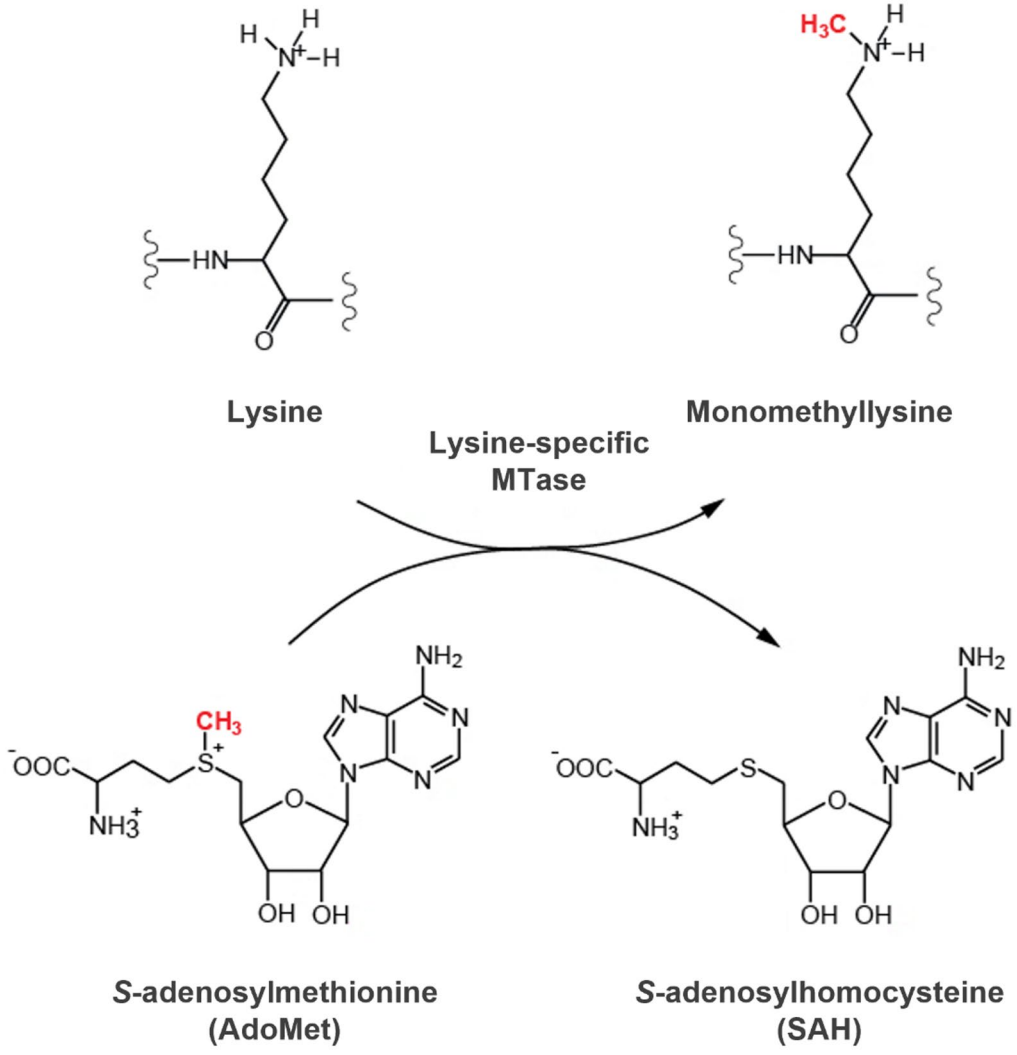

Fig. 1 Catalytic activity of S-adenosylmethionine (AdoMet)–dependent methyltransferases, illustrated using a lysine methyltransferase as an example.

Table 1 Human methyltransferases groups with their structural features.

Structural group	Core structure	Key examples	Primary substrates
Major MTase families			
Seven-β-strand MTases	Rossmann-like fold	PRMT1, PRMT5, METTL3, DOT1L, DNMT1, DNMT3A, DNMT3B, COMT	Protein (arginine and lysine residues), RNA, DNA, small molecules
SET Domain MTases	SET domain	SUV39H1, EZH2, SETD2	Protein (Lysine residues)
SPOUT MTases	Trefoil knot within beta-sheet	TrmD (bacterial), FTSJ3	tRNA, rRNA
Minor MTase families			
Radical SAM domain containing enzymes*	(β/α) 8 TIM barrel fold	RSAD1, RSAD2	Protein, DNA, RNA, lipids, small molecules
Tetrapyrrole methylase domain containing MTases	Dimeric, active site between two domains	DPH5	Modified histidine
tRNA wybutosine-synthesizing protein domain containing MTases	Novel α/β fold	TYW3	tRNA
Homocysteine domain containing MTases**	Multi-domain structure, with a Rossmann-like fold domain & cobalamin-binding domain	MTR, BHMT, BHMT2	L-homocysteine
Membrane-bound MTases	Six to eight α-helices	ICMT, PEMT, NRM	Protein, lipid
Unique MTases			
	Unique structures	AMT, MGMT, TRMO	DNA, RNA, small molecules

*These enzymes are not MTases, but bind AdoMet and convert it to adenosine radical which is used to mediate difficult chemical transformations

**These enzymes do not use AdoMet but other methyl donors

MTase families and five minor MTase families. To systematically classify the human methyltransferasome the HUGO Gene Nomenclature Committee (HGNC) (https://www.genenames.org/) has expanded and dev eloped a hierarchical system categorizing 208 human genes that encode MTases or MTase-like proteins. Two alternative overarching grouping systems were made, i.e., one based on protein structure (and thus, evolutionary relationships) and another based on the type of substrate that is methylated. In the structure-basedapproach, the MTases were placed in nine structural homology classes, i.e., the eight originally described by Petrossian and Clarke [8], as well as a distinct category for "structurally unique" MTases whose structure is not similar to any other human MTase (Fig. 2). In the substrate-based system, the MTases were subdivided into DNA/RNA MTases, protein MTases, and small molecule MTases (Figs. 2 and 3). This classification facilitates easy retrieval both of MTases that are structurally similar, and of those that target similar substrates. A comprehensive list of the 208 human and 207 mouse MTase genes, as well as their structural and functional groupings, is provided in Supplementary Table S1. This classification was developed partly in conjunction with a review of the human seven-β-strand (7BS) MTase motif-containing family [9]. The HGNC assigns unique symbols and names to human genes and manually curates them into functional groups based on shared characteristics, including sequence similarity, structural homology, common function, and protein complex membership [11, 12]. Some genes in the HGNC classification are included based on homology to known MTases—despite lacking direct experimental validation of enzymatic activity.

The diversity of enzyme structures achieving the same catalytic function suggests a high degree of plasticity in AdoMet-dependent MTases, likely due to the energetic favorability of methylation [4, 13]. Moreover, MTases from different structural classes share no detectable sequence similarity; accordingly, their AdoMet-binding domains also differ in both sequence and structure. Between members of a single class, the overall sequence identity can be very low (≈ 10%), but the residues that interact with AdoMet are typically highly conserved [8, 13].

The MTase gene family encodes a highly diverse group of gene products that regulate cellular methylation across proteins, nucleic acids, and small molecules. In addition to substrate modification, MTases can influence gene accessibility and cellular methylation capacity through consumption of AdoMet, thereby affecting the balance of methylation-dependent regulatory processes [6, 8, 14]. To provide a high-confidence overview of clinically relevant MTases, Fig. 4 summarizes curated associations between human MTase genes and disease phenotypes

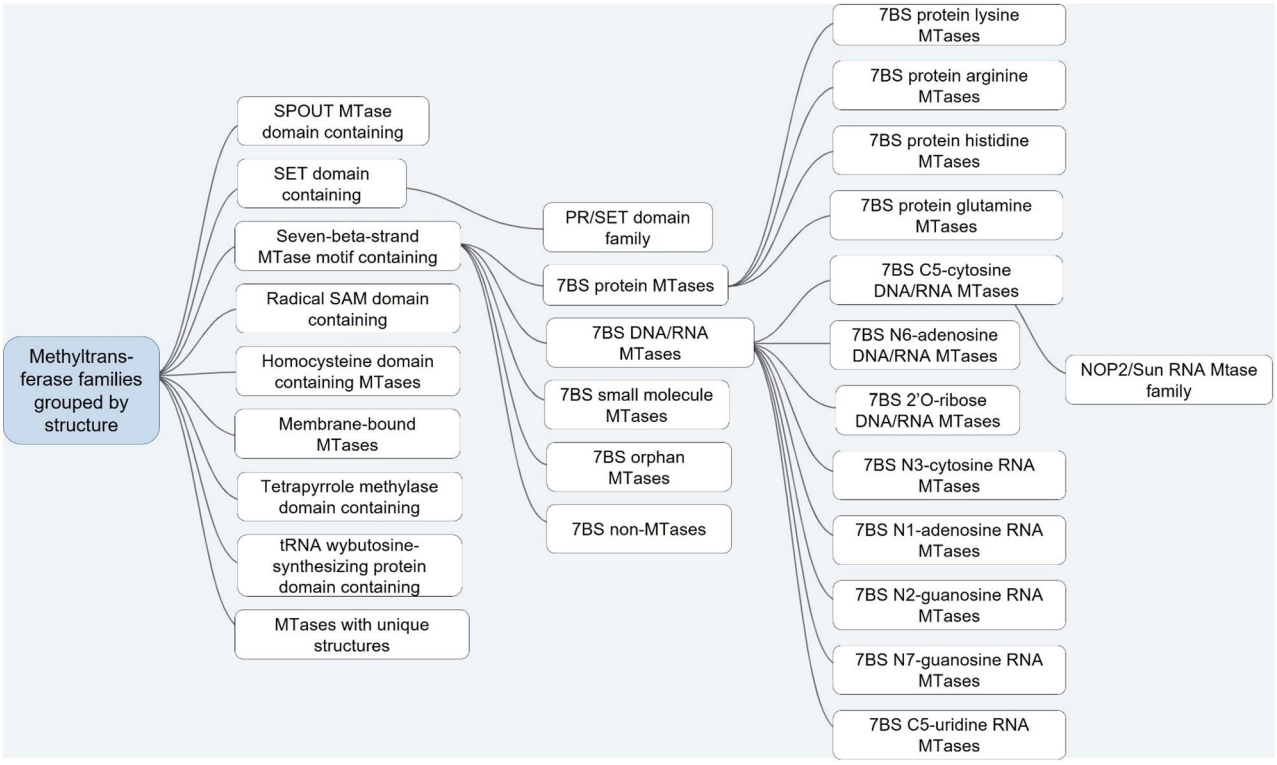

Fig. 2 Human MTase family grouped by structure. Note that at some levels of the HGNC MTase hierarchy,, in addition to the indicated groups, there may be one or more genes (MTases) that have not been assigned to any group [15]. The classification follows the Petrossian and Clarke eight-class framework, with an additional ninth class comprising MTases that do not share structural homology with other MTase families, i.e., i.e., AMT, MGMT and TRMO.

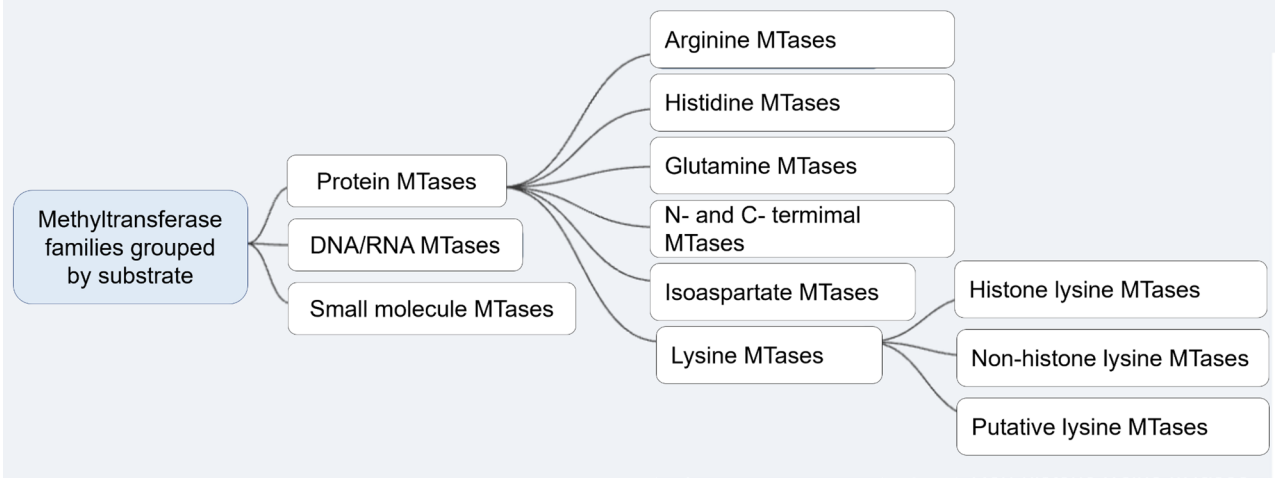

Fig. 3 Human MTase family grouped by substrate. Note that at some levels of the HGNC MTase hierarchy, in addition to the indicated groups, there may be one or more genes (MTases) that have not been assigned to any subgroup [15].

supported by definitive or strong evidence according to ClinGen curation (ClinGen; https://www.clinicalgenome.org). This article is structured around the revised HGNC MTase groupings and is intended to serve as a reference framework for the complete human methyltransferasome, with emphasis on structural organization, functional annotation, and relevance to human disease.

MTases classified by structure

The largest group of major MTase families (Table 1) is the seven-β-strand MTases, which are characterized by the presence of a Rossmann-like fold that facilitates the binding of AdoMet (Fig. 5A). Other major groups include the SET domain-containing MTases, which are involved in histone modification and exhibit a distinct structural

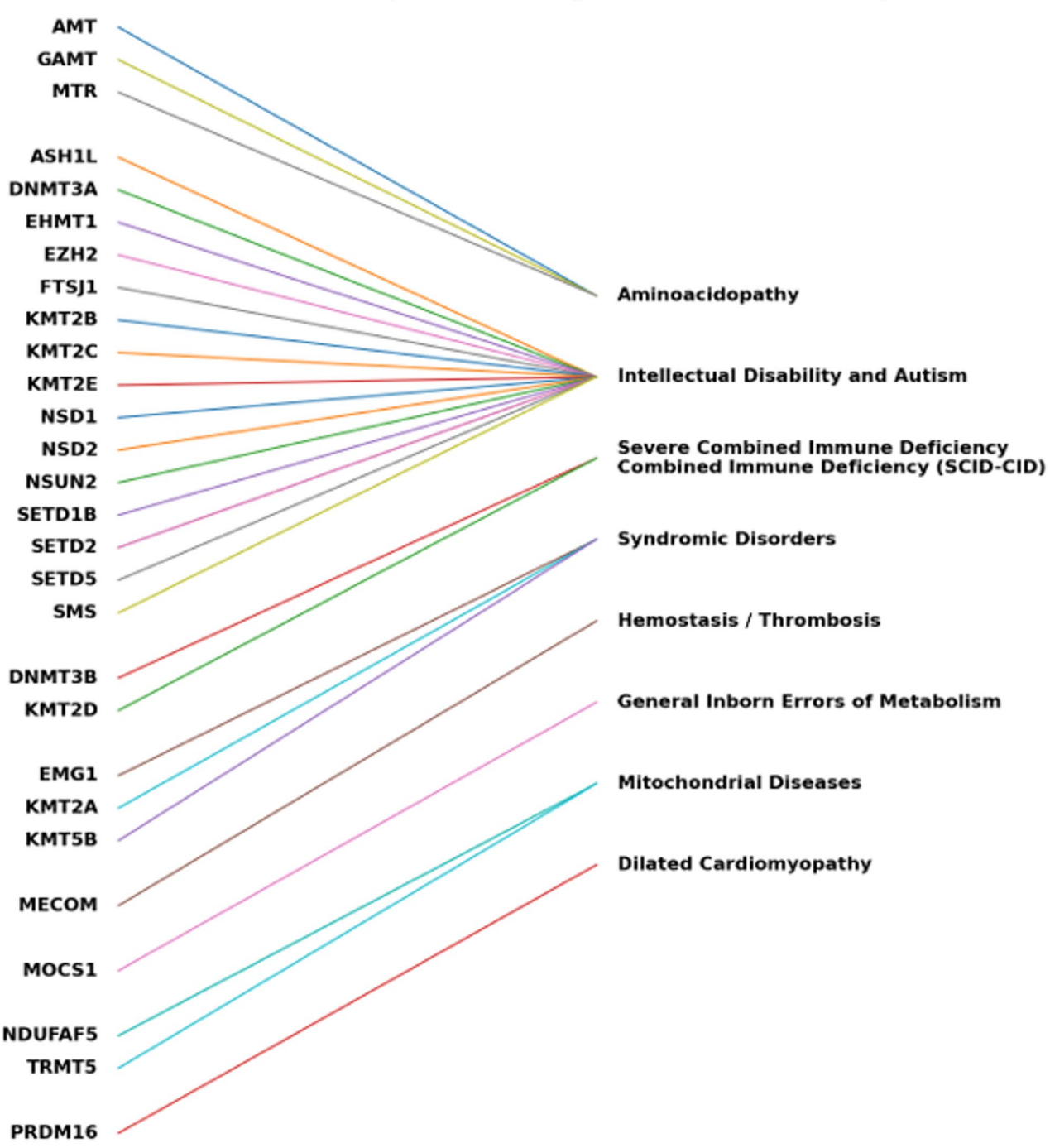

Fig. 4 Associations between MTase genes and ClinGen disease categories. The network shows relationships between human MTase genes and disease categories defined by ClinGen Gene Curation Expert Panels (GCEPs), restricted to phenotypes with strong or definitive gene–disease validity evidence. Gene symbols are displayed on the *left* and corresponding disease categories on the *right*, with connecting lines denoting curated gene–disease associations. Grouping by GCEP-defined disease categories facilitates visualization of shared clinical domains across methyltransferase-associated disorders. Data were derived from the Clinical Genome Resource (ClinGen; https://www.clinicalgenome.org).

architecture (Fig. 5B) and the SPOUT family, distinguished by a unique knot-like structural motif (Fig. 5C) [8, 13]. Furthermore, smaller groups with at least one 3-dimensional structure elucidated (Table 1) include the radical AdoMet MTases, the tetrapyrrole methylase domain-containing MTases, the tRNA wybutosine-synthesizing protein domain containing MTases, the homocysteine domain containing MTases and the membrane-bound MTases [4, 8]. Moreover, a ninth category—which is not mentioned in the original work of Petrossian

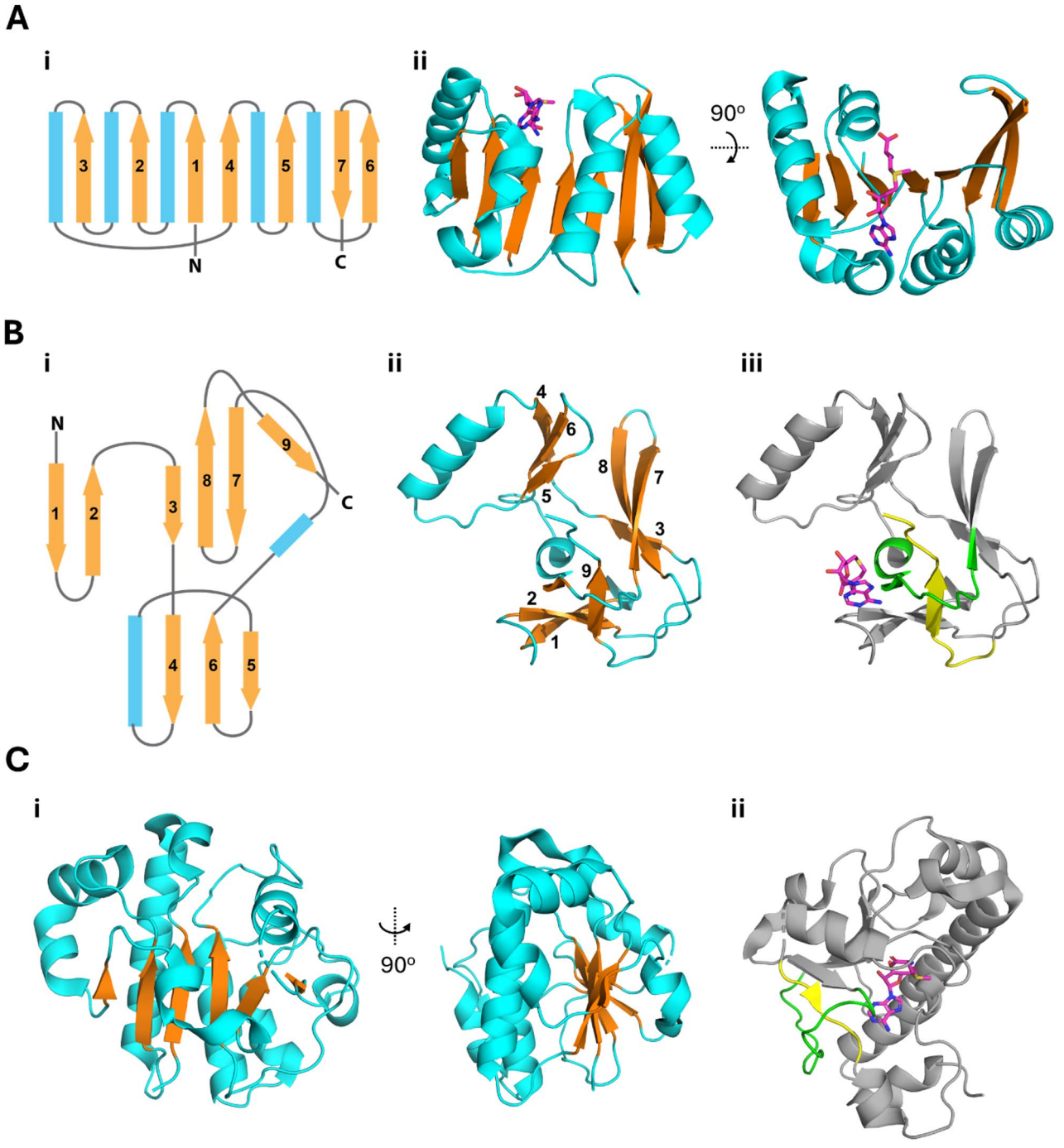

Fig. 5 Structural diversity between the three major MTase classes. When distinguished, β-strands are shown in *orange*, with α-helices and loops in *cyan*. *S*-adenosylhomocysteine (AdoHcy) or *S*-adenosylmethionine (AdoMet) is shown in *magenta*. **A** The seven-β-strand (7BS) MTases. (i) Topology diagram of the canonical 7BS MTase fold. (ii) Cartoon representation of the structure (pdb 3BWM) of the 7BS portion (amino acids 60–215) of COMT (Catecholamine-O-methyltransferase) in complex with AdoMet. **B** The SET-domain MTases. (i) Topology diagram of the canonical SET-domain fold. (ii) Cartoon representation of the structure (pdb 2W5Z) of the core SET-domain portion (residues 3828–3946) of the histone lysine MTase KMT2A (MLL1), with the β-strands numbered. (iii) Illustration of the threading (yellow and green segments) in the characteristic SET-domain pseudoknot, with bound AdoHcy shown. **C** The SPOUT MTases. (i) Cartoon representation of the structure (pdb 5NFJ) of the MTase region (residues 202–379) of the SPOUT MTase TRMT10C, showing the characteristic twisted sheet of parallel β-strands. (ii) Illustration of part of the trefoil knot in TRMT10C, showing threading of the yellow segment through the green loop, with bound AdoMet shown. The cartoon representations of structures were all made using the PyMol Molecular Graphics System (Schrodinger, LCC, ver. 3.1.6.1).

and Clarke—includes three "unique" MTases that have no structural similarity to other human MTases [i.e., aminomethyltransferase (AMT), O-6-methylguanine-DNA methyltransferase (MGMT) and tRNA methyltransferase O (TRMO)] and therefore have been assigned to the subgroup "Methyltransferases with unique structures" [15] (Table S1).

Seven-β-strand MTases

The 7BS MTase family is the most abundant, comprising 126 human genes (Table S1) classified into various subgroups (Fig. 2) [15]. The 7BS group also encompasses five genes that encode non-methyltransferase AdoMet-binding/utilizing proteins (Table S1), which are assigned to the "7BS non-methyltransferases" subgroup. These proteins have the characteristic 7BS structure and the conserved AdoMet-binding motifs but are not MTases. Structurally, the 7BS MTases contain a Rossmann-like fold, consisting of a seven-stranded β-sheet where the individual strands have a characteristic order and direction, with α-helices in between (Fig. 5A). Conserved residues close to the tips of β-strands 1 and 2 coordinate the cofactor AdoMet. The core of these enzymes is composed of about 150 amino acids that show very strong spatial conservation, and the majority of them are relatively small (200–400 residues) e.g., catechol O-methyltransferase (COMT), without any additional annotated domains [9, 13].

However, the substrate-binding and catalytic regions exhibit significant variability, reflecting their broad functional diversity. In some cases, substrate specificity is achieved via additional domains integrated with or appended to the Rossmann-like fold. For example, METTL13 is a human MTase with two 7BS MTase catalytic domains: an N-terminal lysine MTase that mono-/di-methylates Lys55 of eukaryotic translation-elongation factor 1α (eEF1A), and a C-terminal MTase domain that trimethylates the free N-terminus of eEF1A; the third, middle domain is required for high-affinity binding to eEF1A [16–18].

7BS MTases play key roles in biological processes and have significant clinical implications—particularly in developing therapies targeting cancer, infectious and cardiovascular disease, metabolic disorders, and in personalized medicine [8, 9, 16, 19]. In cancer, DNA MTases (DNMTs), for example, can promote tumor growth by silencing tumor suppressor genes through aberrant methylation patterns. This gene silencing facilitates unchecked cellular proliferation and impairs apoptosis mechanisms [20]. Therapeutic agents such as azacitidine and decitabine, which are DNMT inhibitors, have been effective in treating conditions like acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) by reactivating these silenced genes, thereby inhibiting tumor progression.

In neurological disorders, COMT, a small molecule MTase, modulates neurotransmitter levels linked to mood disorders, providing targets for managing schizophrenia, bipolar disorder, and anxiety [21, 22]. COMT also plays a widely recognized role in drug metabolism and inactivation. There are three FDA-approved COMT inhibitors (tolcapone, entacapone, and opicapone) that act not by directly treating the disease, but as adjuncts that prevent rapid metabolism of drugs (carbidopa/levodopa) used to treat Parkinson disease [23].

Cardiovascular disease risk is impacted by glycine N-methyltransferase (GNMT) due to its regulation of homocysteine levels; targeting GNMT may reduce atherosclerosis risk [24]. MTases also regulate immune response and inflammation, making them targets for treating autoimmune diseases such as lupus and rheumatoid arthritis [25]. In infectious disease treatment, MTases in viruses and bacteria aid in immune evasion, with inhibitors potentially offering antiviral and antibacterial benefits for infections like SARS-CoV-2 [26, 27]. Finally, pharmacogenomic applications of 7BS MTases, such as thiopurine S-methyltransferase (TPMT), help tailor drug dosing to individual genetic profiles, optimizing therapy and minimizing side effects, thus, highlighting their potential in treatment and drug development [28, 29].

SET domain-containing MTases

SET domains are well-conserved catalytic domains originally identified as part of a larger conserved region present in the *Drosophila* Trithorax protein, and subsequently identified in the *Drosophila* Su(var)3–9 and 'Enhancer of zeste' proteins, from which the acronym SET is derived [**S**u(var)3–9, **E**nhancer-of-zeste and **T**rithorax] [30, 31]. The human SET domain MTases comprise 54 genes, and a subset of 19 of these encode the divergent PR/SET domain (PRDM) proteins (Table S1, Fig. 2) [15]. SET MTases catalyze the methylation of protein lysine residues mainly within histones (such as histone H3 and histone H4) [31]. In contrast, SETD3 is distinct in that it specifically methylates a histidine residue (His73) in actin [32]. Lysine residues can be mono-, di-, or tri-methylated, depending on the enzyme and the specific context. These different methylation states lead to distinct biological outcomes in terms of gene expression and chromatin regulation [31, 33, 34]. These enzymes organize chromatin into active (euchromatin) or inactive (heterochromatin) states, thereby regulating gene accessibility for transcription [35, 36]. Methylation marks added by SET domain enzymes can persist through cell divisions, enabling the transmission of epigenetic information essential for cell identity and development.

The core SET domain typically comprises around 130–150 amino acids, and adopts a structure that forms the active site responsible for methylating (mainly) lysine residues. The characteristic topology of the core SET domain consists mainly of β-strands, forming three distinct β-sheets (Fig. 5B). Also, the SET-domain contains a so-called pseudoknot structure, which contains conserved residues involved in AdoMet binding [31].

In many SET domain proteins, the target lysine approaches the active site and AdoMet through a narrow channel. In addition to the conserved core SET domain, the SET MTases also contain additional, more variable regions that are important for substrate recruitment, i.e. the N-terminal so-called pre-SET domain, the C-terminal post-SET domain, and the iSET domain, which is inserted within the core SET-domain [37].

As mentioned above, SET domain MTases methylate histones, a key mechanism in epigenetic regulation that influences gene expression, chromatin structure, and cellular memory [36, 38]. Common histone targets are lysine residues H3K4, H3K9, H3K27, H3K36, and H4K20 [39, 40]. For instance, SUV39H1 and SUV39H2 enzymes catalyze H3K9 methylation, associated with gene repression and condensed chromatin. EZH2, as the catalytic subunit of the Polycomb Repressive Complex 2 (PRC2), catalyzes H3K27 trimethylation (H3K27me3), which is also essential for maintaining gene silencing in development and differentiation [41]. In general, the H3K9 and H3K27 MTases facilitate heterochromatin formation and silence repetitive DNA sequences, ensuring transcriptional repression in specific genomic regions [38, 42, 43].

SETD1A and SETD1B methylate H3K4, which is associated with transcriptional activation, particularly at promoters of active genes. Both are part of the 'Complex Proteins Associated with Set1' (COMPASS) complex [44], crucial for sustaining active chromatin states [38]. SETD2, which trimethylates H3K36 (H3K36me3), supports active transcription, RNA splicing, and genome stability, playing a key role in DNA repair [45, 46]. ASH1L, a trithorax group protein, also methylates H3K36, promoting activation of genes involved in developmental regulation, including Hox genes critical for body patterning [35]. EHMT2, which targets H3K9 and non-histone substrates, is associated with transcriptional repression [47, 48]. PRDM proteins, with SET-like domains, methylate specific histone lysines; for instance, PRDM9 marks recombination hotspots by methylating H3K4 during meiosis [49]. However, for most PRDM proteins, MTase activity remains to be demonstrated.

Beyond histones, several SET domain MTases also methylate non-histone proteins. For example, SETD7 targets p53 (TP53), retinoblastoma protein (RB), estrogen receptor α (ERα/ESR1), and STAT3, whereas SMYD2 methylates multiple non-histone substrates including p53, RB, PARP1, HSP90, and GATA4 [50, 51]. These modifications influence protein function, stability, and interactions, playing essential roles in signal transduction, DNA repair, and cellular regulation [52, 53]. These proteins likely evolved through duplication and fusion of an ancestral β-strand structural unit that gave rise to the SET fold, followed by lateral transfer to bacteria [54].

Dysregulation of SET domain MTases is linked to diseases, particularly cancer, where abnormal histone methylation can silence tumor suppressor genes or activate oncogenes [41, 55]. For example, EZH2 overexpression or mutation is associated with lymphomas, and prostate and breast cancers [41]. Additionally, mutations in *SETD2* are common in cancers like renal cell carcinoma, positioning SETD2 as a key target in cancer research [55]. As a result, targeting SET domain enzymes, using EZH2 inhibitors like tazemetostat (approved by the FDA in 2020), shows promise for treating cancers (e.g., follicular lymphoma and epithelioid sarcoma), as well as neurodevelopmental and autoimmune disorders [56].

SPOUT domain-containing MTases

There are 8 SPOUT (SpoU-TrmD) MTase genes found in the human genome (Table S1) [15]. This group is named after the two founding members of the family: the bacterial MTases SpoU (also known as TrmH) and TrmD [57]. SPOUT MTases are RNA-specific MTases involved in post-transcriptional modification of tRNA and rRNA [57–59].

The SPOUT domain (Fig. 5C) consists of a distinct α/β protein fold that forms a deep trefoil knot structure, which is a defining feature that separates SPOUT MTases from other MTase families [57]. This knot is formed by the threading of the protein chain through a loop (Fig. 5C), creating a highly stable structural motif responsible for binding AdoMet [57]. The structural conservation within the SPOUT family is rather low, but a central sheet of 5–6 unidirectional αβ-strands is a common feature. This sheet is flanked by α-helices, yielding a α-β-α sandwich configuration (Fig. 5C). A notable feature of many SPOUT MTases is that homo- or hetero-dimerization is important for the stability and activity of these enzymes. The dimeric structure helps create a functional active site where AdoMet and the RNA substrate can bind.

Human SPOUT MTases catalyze AdoMet-dependent methylation of specific nucleotides within cytosolic and mitochondrial tRNAs [60, 61]. TRMT10A, TRMT10B, and TRMT10C install N^1-methylguanosine or N^1-methyladenosine at defined positions in tRNAs, with substrate recognition determined largely by local tRNA structural elements rather than strict sequence motifs [60, 61]. Collectively, these enzymes contribute to proper tRNA folding, stability, and decoding accuracy.

Associations between tRNA modifications and various diseases, especially metabolic and neurological disorders, as well as cancer have been proposed [62–64]. Interestingly, many tRNA modifications occur at the same positions in both bacteria and eukaryotes, though they are catalyzed by nonhomologous enzymes, making these sites potential targets for antibacterial drugs. A deeper understanding of bacterial SPOUT MTases may therefore be crucial in addressing the growing challenge of antibiotic resistance [59].

Minor MTase groups

Smaller families include the Radical S-adenosylmethionine domain-containing MTases, the Tetrapyrrole methylase domain containing MTases, the tRNA wybutosine-synthesizing protein domain containing MTases, the Homocysteine domain containing MTases and the Membrane-bound MTases. Collectively these families account for less than 10% of the total number of putative and established MTases [8] (Table 1).

Radical S-adenosylmethionine (SAM) domain-containing enzymes

Radical S-adenosylmethionine (SAM) domain-containing enzymes generate a reactive radical through AdoMet cleavage [65, 66] and were first classified as a superfamily in 2001 [67]. Comprising nine genes (Table S1) [15] in the human genome, they play roles in biosynthesis, including the production of cofactors like biotin and lipoic acid, and are involved in bacterial antibiotic resistance, making them targets for drug development [68]. Notably, all these enzymes bind/use AdoMet; however, only *CDKAL1* and *CDK5RAP1* encode active MTases (or specifically–methylthiotransferases) [69, 70].

Radical AdoMet enzymes typically adopt a (β/α) 8 TIM barrel fold, stabilizing a [4Fe–4 S] cluster coordinated by three cysteine residues, which enables AdoMet interaction and radical generation for catalysis [66]. This cluster, receiving electrons from a reductant (e.g., flavodoxin or ferredoxin), facilitates radical formation through a 5'-deoxyadenosyl radical that abstracts a hydrogen from the substrate, facilitating chemically challenging enzymatic reactions - a capability that distinguishes radical AdoMet enzymes from conventional AdoMet-dependent MTases [71].

Although not all members catalyze methyl transfer, radical AdoMet enzymes influence nucleic acid stability, structure, and gene expression; these processes makes these enzymes influential in regulatory processes, including cell response to environmental changes [72, 73]. Dysregulation of radical AdoMet enzymes has been linked to cancer, positioning them as potential therapeutic targets [74].

Tetrapyrrole methylase domain-containing MTases

The group of precorrin-like MTases was identified using the sequence of cobalt-precorrin-4 C [11]-MTase (CbiF) as a probe [75]. Notably, diphthamide biosynthesis 5, *DPH5* (encoding diphthine methyl ester synthase) is the only human gene classified within this family (Table S1) [15]. Tetrapyrrole methylase domain-containing MTases are structurally dimeric, with active sites located between two domains, each featuring central β-sheets flanked by α-helices, albeit with distinct topologies. The AdoMet molecule binds in a pocket at the domain interface, adopting a folded conformation that exposes the methyl group—a binding mode distinct from those observed in previously described groups [4, 13].

These enzymes primarily target tetrapyrroles, such as cobalt-precorrin-4 MTase, which plays a key role in vitamin B_{12} biosynthesis in microbes. Tetrapyrroles, a class of organic molecules that includes heme and the modified tetrapyrrole vitamin B_{12}, are biologically and clinically significant. They form the core structures of several essential biomolecules involved in critical physiological processes (e.g., heme synthesis) [4, 76].

Dysfunction of *DPH5* can lead to a range of disorders. Defects in heme synthesis may result in conditions such as anemia and porphyrias, where impaired heme production affects oxygen transport [77, 78]. Since heme is also a component of cytochrome P450 enzymes, disruptions can affect drug metabolism in the liver, potentially causing drug toxicity or therapeutic failure [77, 79].

tRNA wybutosine-synthesizing protein domain-containing MTases

The only member of this group in the human genome is the tRNA wybutosine-synthesizing protein 3 (*TYW3*), which encodes a protein that functions within a multienzyme pathway for wybutosine biosynthesis (Table S1) [15]. Wybutosine (yW) is a tricyclic nucleoside classified among hyper-modified nucleosides with a high molecular weight, and it is exclusively found in eukaryotic tRNA-Phe. Its primary role is to enhance codon recognition by stabilizing codon-anticodon interactions during ribosomal decoding, thereby supporting accurate translation [80].

In humans, alterations in *TYW3* have been linked to neurological and metabolic disorders. A genome-wide association study (GWAS) identified the *TYW3/CRYZ* locus as a susceptibility region for amyotrophic lateral sclerosis (ALS), suggesting a potential genetic association [81]. However, the study did not investigate the underlying biological mechanisms through which *TYW3* variants could contribute to ALS pathogenesis.

Similarly, another GWAS discovered that variants near the *TYW3/CRYZ* genes are associated with increased circulating resistin levels, a hormone implicated in insulin

resistance [82]. Despite establishing a genetic correlation, this study did not provide mechanistic insights into how *TYW3* variants might influence resistin levels or insulin resistance.

Homocysteine domain-containing MTases

Human homocysteine MTases are essential enzymes in homocysteine metabolism, an amino acid formed during methionine metabolism. This enzyme family consists of 5-methyltetrahydrofolate-homocysteine MTase (*MTR*, also known as methionine synthase and cobalamin-dependent methionine synthase) and two betaine-homocysteine S-MTases (*BHMT* and *BHMT2*) (Table S1) [15]. The encoded enzymes play critical roles in amino acid biosynthesis, epigenetic regulation, and the methionine cycle, contributing to the synthesis of AdoMet [83].

Methionine synthase is a multi-domain enzyme with a Rossmann-like fold that binds 5-methyltetrahydrofolate (5-MTHF) to facilitate methyl transfer. Notably, this domain comprises five parallel β-strands surrounded by α-helices, differing from the classical six-stranded Rossmann fold and the 7BS MTase fold [84]. It also features a cobalamin-binding domain that uses vitamin B_{12} (cyanocobalamin) as a cofactor, crucial for stabilizing the methyl transfer process and acting as both a donor and acceptor [85, 86]. The enzyme's structure includes a long linker connecting the Rossmann-like fold and cobalamin-binding domains, allowing efficient coordination during the methylation cycle.

Betaine-homocysteine MTases (BHMTs) typically form homotetramers or homodimers. Each subunit contains a Rossmann fold for binding betaine (trimethylglycine), which serves as the methyl donor. Unlike MTR, BHMTs are independent of the folate cycle and use a zinc ion in their active site to stabilize homocysteine and enhance reaction efficiency [87]. The active site coordinates betaine and homocysteine for effective methyl transfer, supporting homocysteine conversion to methionine. These enzymes are predominantly found in the cytoplasm of liver and kidney cells [88, 89].

Both MTR and BHMTs participate in transferring a methyl group to homocysteine, regenerating methionine, or producing other metabolites. MTR is unique among human proteins for possessing a "MetH activation domain," which facilitates the reactivation of oxidized cobalamin during the enzyme cycle. This reactivation involves flavodoxin, which reduces inactive cob(II)alamin to cob(I)alamin, enabling the capture of a methyl group from AdoMet to regenerate methylcobalamin and restart the catalytic process [4]. Structurally, MTR features a horseshoe-like topology with a central β-sheet flanked by helices, where the AdoMet-binding site is located [13].

Dysfunctions in homocysteine MTases, such as methionine synthase (MTR), due to genetic variations or cofactor deficiencies (e.g., vitamin B_{12}), impair the remethylation pathway, leading to the accumulation of homocysteine in the bloodstream (hyperhomocysteinemia) [90, 91]. This hyperhomocysteinemia has been identified as an independent risk factor for cardiovascular diseases—including coronary artery disease and stroke and other health complications [91].

Membrane-bound domain-containing MTases

There are three human members of the membrane-bound MTase family (Table S1): isoprenylcysteine carboxyl methyltransferase (*ICMT*), phosphatidylethanolamine N-methyltransferase (*PEMT*), and nurim (*NRM*) [15].

ICMT completes the final step in prenylcysteine modification of proteins. In eukaryotes, ICMT spans the endoplasmic reticulum membrane with six to eight α-helices, positioning the AdoMet-binding site on the cytoplasmic side. The substrate binds in a cleft extending from the cytoplasm across the membrane surface. Arginine residues in the active-site help position the substrate's carboxyl group for nucleophilic attack on AdoMet's methyl group, while others stabilize the transition state [92].

PEMT is a key hepatic enzyme that catalyzes the sequential methylation of phosphatidylethanolamine to form phosphatidylcholine, a major phospholipid component of cell membranes and lipoproteins. PEMT deficiency is strongly associated with the development and progression of non-alcoholic fatty liver disease although paradoxically, it appears to protect against diet-induced obesity and insulin resistance [93, 94]. Notably, whereas NRM shares significant sequence similarity with ICMT, no MTase activity has been demonstrated for this protein [8].

MTases classified by enzyme substrate

AdoMet-dependent MTases can also be categorized by the different substrates used in methyl transfer reactions as: (a) DNA/RNA MTases, (b) protein MTases and (c) small molecule MTases.

DNA/RNA MTases

DNA and RNA MTases are encoded by 70 genes in the human genome (Table S1) [15], the majority of which belong to the 7BS and SPOUT domain MTase families [95]. DNA MTases (DNMTs) are involved in adding a methyl group to the C5-position of cytosine residues in DNA, typically at CpG dinucleotides. This process is critical for gene silencing, X-chromosome inactivation, genomic imprinting, and the suppression of transposable elements [96]. DNMTs are active during embryonic development but less so in terminally differentiated cells, although they remain active in mature neurons, suggesting a unique role in the brain [97]. The most studied DNMTs include DNMT1, TRDMT1 (DNMT2),

DNMT3A, DNMT3B and DNMT3L — which are classical 7BS MTases [9]. Based on its sequence similarity to the other DNMTs, TRDMT1 was first assumed to be a DNA methyltransferase and named DNMT2, but was later shown to introduce 5-methylcytosine specifically in tRNA and reassigned as TRDMT1.

RNA MTases, which add methyl groups either to the terminal RNA cap or internally along the RNA strand [95], play critical roles both in optimizing RNA structure/function, and in regulating its stability, translation, and splicing, underscoring their significance in epitranscriptomics [98]. Nearly half of the human 7BS MTases target RNA, with their methylation activities spanning ribosomal RNA (rRNA), mRNA, tRNA, microRNAs, and other small non-coding RNAs [8, 9].

Protein MTases

Protein MTases represent the largest group of MTases when grouped by substrate, encompassing 94 genes (Table S1) [15]. These enzymes primarily target lysine and arginine residues; however, it has been established that certain protein MTases are also capable of methylating histidine and glutamine residues [99]. Protein MTases modify both histones and non-histone proteins—such as transcription factors, playing a crucial role in the epigenetic regulation of gene expression [2]. Histone MTases specifically methylate lysine and arginine residues on histone tails, with dysregulation of these modifications contributing to cancer and developmental disorders. Structurally, protein MTases belong to the 7BS and SET domain protein families.

Lysine MTases

Lysine MTases (KMTs) are enzymes that catalyze the transfer of methyl groups from a methyl donor, typically AdoMet, to the lysine residues of proteins, particularly histones. To better reflect their substrate preferences and biological functions, they are now classified into three subgroups: "Histone lysine MTases", which act on chromatin-associated histone proteins and are often classified among chromatin-modifying enzymes; "Non-histone lysine MTases", which target other cellular proteins and are not considered chromatin modifiers; and "Putative lysine MTases", which are proteins predicted to have lysine MTase activity based on conserved sequence or domain features but lacking experimental validation [15]. This full KMT group comprises 69 genes (Table S1) [15] and contains representatives from both the 7BS MTases and the SET domain containing structural homology groups.

Most lysine MTases are characterized by the presence of a SET domain, which contains a pseudoknot motif, and is responsible for binding the AdoMet donor and facilitating the methyl transfer to the lysine residue of the target protein [2, 30, 31, 37]. KMTs differ in their product specificity, with some enzymes catalyzing mono- or dimethylation and others capable of trimethylation. This catalytic specificity contributes to the establishment of distinct chromatin states at defined genomic loci [39]. Among KMTs, DOT1L (Disruptor of Telomeric Silencing 1-like, also known as KMT4) specifically targets lysine-79 on histone H3 (H3K79), a modification associated with transcriptional activation. Unlike most KMTs that methylate lysines in the N-terminal tail of histones, DOT1L methylates a lysine within the histone core, a unique feature in histone modification [2, 100, 101].

Due to its distinctive properties, DOT1L has emerged as a promising target for therapeutic interventions. Several small molecule inhibitors have been developed [102–104], with one entering clinical trials for leukemia (i.e., pinometostat), with positive results [104]. Further research is ongoing to explore the efficacy of DOT1L inhibitors in combination with other therapeutic agents, such as venetoclax, to enhance treatment outcomes for leukemia patients [105].

Arginine MTases

Arginine MTases (PRMTs) are encoded by 11 genes in the human genome (Table S1) [15] and they all belong to the 7BS MTase family. The nine canonical enzymes (PRMT1 – PRMT9) share a characteristic three-domain catalytic core: (i) a structurally conserved MTase domain [2, 106], (ii) a PRMT-specific β-barrel, and (iii) a C-terminal dimerization domain. Substrate proteins bind within a pocket located at the interface between the MTase domain and the β-barrel [2, 107].

Based on their reaction products, PRMTs are classified into three catalytic types: Type I (PRMT1, PRMT3, PRMT4/CARM1, PRMT6, PRMT8), which form asymmetric dimethylarginine (ADMA); Type II (PRMT5, PRMT9), which generate symmetric dimethylarginine (SDMA); and Type III (PRMT7), which catalyzes only monomethylation (MMA). These enzymes catalyze the transfer of methyl groups from AdoMet to arginine residues within histone and non-histone proteins, thereby regulating a broad range of cellular processes [108, 109]. Through these modifications, PRMTs influence chromatin structure, transcription, RNA splicing, signal transduction, and DNA repair.

Among canonical members, PRMT1 accounts for most cellular arginine methylation and is essential for viability, whereas PRMT5, the major Type II enzyme, symmetrically dimethylates spliceosomal Sm proteins—core components of small nuclear ribonucleoproteins (snRNPs)—and thereby regulates pre-mRNA splicing and ribosome biogenesis. Other PRMTs, such as CARM1 (PRMT4) and PRMT6, act as transcriptional

co-activators through specific histone H3 arginine methylation events (H3R17me2a and H3R2me2a, respectively).

By contrast, the two atypical family members, METTL23 and NDUFAF7, comprise essentially only the MTase fold and lack the PRMT β-barrel/dimerization module, illustrating the structural diversity that exists within the PRMT group [9]. Notably, METTL23 has been linked to transcriptional regulation through methylation of histone H3R17, whereas NDUFAF7 contributes to mitochondrial complex I assembly via arginine methylation of NDUFS2 [109].

Histidine MTases

The first human protein histidine MTase, SETD3, was identified comparatively recently, although protein histidine methylation was discovered over 50 years ago [110]. The MTase SETD3, with a SET domain structure, introduces 3-methylhistidine (3MH) into actin [99]. Since this discovery, three additional histidine MTases, all belonging to the 7BS family, have been identified (i.e., METTL9, METTL18, CARNMT1) [111–113]. In addition, DPH5, a member of the tetrapyrrole methylase domain containing MTases, does not methylate a free histidine residue but instead trimethylates the diphthine intermediate already formed at His699 of elongation factor 2 (eEF2). This reaction produces diphthine methyl ester, a critical step in diphthamide biosynthesis, which is essential for ribosomal function and translational elongation [114]. This brings the total number of genes in this group to five (Table S1) [15].

Glutamine MTases

Currently this group includes 2 genes, *HEMK1* (HemK methyltransferase 1, mitochondrial release factors N [5]-glutamine) and *HEMK2* (HemK methyltransferase 2, ETF1 glutamine and histone H4 lysine) (Table S1) [15]. HEMK1 catalyzes the N [5]-methylation of a conserved glutamine residue in mitochondrial release factors, a modification that is required for efficient translation termination within mitochondria [115]. Similarly, HEMK2 catalyzes the methylation of the glutamine residue at position 185 in the eukaryotic translation termination factor 1 (eukaryotic release factor 1, ERF1-Q185) [116] and has clinical implications with arsenic-induced toxicity [117].

N- and C-terminal MTases

This subgroup comprises enzymes that methylate the N- or C-termini of protein substrates. This classification includes a total of five genes (Table S1) [15]: *NTMT1*, *NTMT2*, *LCMT1*, *METTL13*, and *ICMT*. The encoded enzymes catalyze terminal-specific methylation reactions that can modulate protein stability, subcellular localization, and molecular interactions [18, 118]. METTL13 is notable as a dual-function MTase—targeting both the N-terminus and a lysine residue on eEF1A [16–18]. ICMT, which methylates the α-carboxyl group of isoprenylated cysteine residues, was previously classified among isoprenylcysteine MTases; however, it is now considered part of the terminal-targeting group owing to its functional specificity for the carboxyl terminus of prenylated proteins [92].

Isoaspartate MTases

Isoaspartate MTases function primarily in protein repair by recognizing and methylating isoaspartate residues that arise from spontaneous deamidation or isomerization. This subgroup comprises PCMT1, PCMTD1, and PCMTD2 (Table S1) [15]. In humans, PCMT1 catalyzes AdoMet-dependent methyl esterification of L-isoaspartyl and D-aspartyl residues in damaged proteins, thereby promoting repair of these abnormal linkages and restoring protein structure and function [119, 120]. The human genome also encodes the putative isoaspartate methyltransferase homologues PCMTD1 and PCMTD2, although their enzymatic repair roles remain to be demonstrated.

Small-Molecule MTases

Small-Molecule MTases (SMMTases) are encoded by 23 genes in the human genome (Table S1) [15], and act on small-molecule substrates such as metabolites, lipids, and natural products, modulating signaling pathways and metabolic flux [5, 121, 122]. One of the most well-known SMMTases is catecholamine *O*-methyltransferase (COMT), which methylates catechol-containing molecules to terminate adrenaline-signaling and metabolize drugs and other xenobiotics [5].

SMMTases are a heterogeneous group that do not share a single catalytic fold or methyl-donor system. Many are AdoMet-dependent 7BS (Rossmann-like) enzymes with a broadly conserved AdoMet-binding site and methyl-transfer geometry, whereas substrate specificity is dictated by variations in the substrate pocket [9]. In contrast, several human SMMTases, including BHMT, MTR, and PEMT, do not belong to the 7BS family and/or use non-AdoMet methyl donors, and therefore follow distinct catalytic mechanisms [85, 87].

Aside from therapeutic uses of SMMTases for Parkinson disease [23], important applications in toxicology include detoxification of xenobiotics through drug metabolism by thiopurine S-methyltransferase (TPMT) [123] and regulation of AdoMet levels by glycine N-methyltransferase (GNMT) [124].

MTase evolution

The human methyltransferasome has evolved through molecular adaptation, diversification, and functional specialization, transforming from simple ancestral MTases into a vast network of highly specialized enzymes that regulate critical biological functions [125, 126]. Their origin traces back to very early life forms, where they initially facilitated basic metabolic processes before diversifying into more specialized regulatory functions [127]. The emergence of AdoMet as a universal methyl donor was a defining event, enabling MTases to modify a range of chemical substrates across different evolutionary lineages [128]. In bacteria and archaea, MTases were initially involved in fundamental metabolic functions, such as cofactor biosynthesis and ribosomal RNA modification, ensuring efficient protein synthesis [129, 130]. One of the earliest roles of DNA MTases (DNMTs) in bacteria was in restriction-modification systems, where they distinguished host from foreign DNA, together with corresponding restriction endonucleases—providing a defense mechanism against bacteriophages [131]. These early MTases laid the foundation for regulatory functions, with some archaea developing DNA methylation as a means to regulate gene expression in response to environmental changes [132]. Radical AdoMet enzymes, found in both bacteria and archaea, emerged as a key group catalyzing challenging biochemical reactions [128].

As eukaryotic life emerged, MTases diversified significantly, acquiring roles in epigenetic regulation and chromatin remodeling. In invertebrates, MTases underwent lineage-specific expansions and losses, reflecting adaptations to different genomic and environmental pressures [133]. A comparative analysis of 580 animal species by Klughammer et al. [134] revealed that DNA methylation patterns in invertebrates are highly variable, with some lineages such as *Drosophila melanogaster* and *Caenorhabditis elegans* lacking DNA methylation entirely [135]. The absence of functional DNMTs in these species suggests that alternative regulatory mechanisms—including histone post-translational modifications and small RNA-mediated pathways—can compensate for the loss of DNA methylation [135]. In other invertebrates, such as mollusks and annelids, DNA methylation remains prevalent, contributing to gene silencing and developmental regulation [136, 137]. Eusocial insects, including ants and bees, exhibit reduced DNA methylation levels, hinting at a possible link between methylation and caste differentiation [138]. In plants, O-MTases modify phenolic compounds and alkaloids; thus, they are essential for plant secondary metabolism, aiding in defense mechanisms and structural integrity [139, 140].

The transition to vertebrates marked a major shift in MTase evolution, with an increased complexity in DNA and histone methylation systems [141]. Vertebrate genomes are characterized by highly conserved methylation landscapes, where DNA methylation is tightly associated with gene regulatory elements [134]. In vertebrates, the DNA MTases DNMT1 and DNMT3A/3B acquired distinct but complementary roles that are conserved across fish, amphibians, reptiles, and mammals, underscoring their central importance for development, genome stability, and cell identity. Histone MTases, particularly the SET domain enzymes, became critical for regulating chromatin state and gene expression, with conserved regulatory functions across fish, amphibians, reptiles, and mammals [31, 134]. The 7BS MTases also expanded during vertebrate evolution, acquiring functions in gene expression and cellular signaling [9, 16].

Despite their deep conservation, MTases exhibit significant sequence divergence, making phylogenetic classification challenging [9]. A comparison of human and mouse methyltransferase repertoires shows that both species (which diverged from one another ~ 80 million years ago) encode a similar number of MTase genes, with humans possessing 208 curated protein coding MTases and *Mus musculus* approximately 207 (Tables S1) [15]. Although the total gene counts are comparable, notable lineage-specific differences within the DNA MTase family illustrate ongoing evolutionary adaptation during these last ~ 80 million years. For example, rodents possess the germline-specific *Dnmt3c*, a *de novo* DNA methyltransferase that originated from a rodent-specific duplication of *Dnmt3b* and is absent in humans [142].*Mus musculus* also shows lineage-specific expansions including two annotated *Tmt1a* paralogs (*Tmt1a2* and *Tmt1a3*) [15], and a duplication of *Bhmt1* (*Bhmt1b*) [83]. Mouse lacks direct orthologs of certain human methyltransferase paralogs such as *METTL2B* [143] and *TYW1B*, and the primate-specific *PRDM7* which arose from a recent duplication during primate evolution [144, 145], and also lack coding copies of the *CSKMT* [146], *ASMTL*, *SETD9* and *TRMT61B* genes. Mouse has, however, retained a functional *Mettl21e* gene that corresponds to a unitary pseudogene (*METTL21EP*) in human [147]. Additionally, mice encode a conserved but previously unnamed putative methyltransferase, *Mettl28*, that is present in multiple vertebrates but absent from apes [148]. These examples illustrate how a conserved core methylation machinery, centered on DNMT1 and DNMT3A/3B, can be selectively modified to meet lineage-specific regulatory demands.

Collectively, convergent evolution has led to multiple independent enzyme families performing similar catalytic functions, particularly in lysine methylation [16]. In the context of DNA methylation, comparative genomic analyses highlight DNMT1 and DNMT3A/3B as a conserved core epigenetic module whose evolutionary maintenance across vertebrates underscores their central

importance for development, genome stability, and disease susceptibility. Advances in comparative genomics continue to provide insights into MTase evolution, emphasizing their role in genome stability and cellular complexity [134]. As research progresses, the functional diversity of these enzymes will be further elucidated, also shedding light on their broader impact across the Darwinian tree of life.

Conclusion

The human MTase gene family encodes a diverse set of enzymes essential for life. These enzymes can be classified by structural homology, including 7BS, SET domain, and SPOUT MTases, or by substrate specificity, such as DNA, RNA, protein, and small molecule MTases. Currently, 208 human and 207 mouse protein coding MTase genes have been identified and curated by HGNC, refining their classification and nomenclature. Dysregulation of these enzymes has been associated with cancer, neurological disorders, and metabolic syndromes, making them promising therapeutic targets. Insights into the evolution of key DNA MTases, particularly DNMT1 and DNMT3A/3B, underscore how evolutionary conservation and lineage-specific diversification of DNA methylation machinery contribute to epigenetic regulation and human disease. However, the functions of many MTases remain uncharacterized, sharing homology with known MTase-encoding genes but lacking confirmed catalytic activity, thereby highlighting the need for further research to validate their function. Ongoing structural and functional studies will be essential for elucidating their precise roles and clinical significance. HGNC will continue to update the classification and nomenclature as new insights emerge from the literature.

Supplementary Information

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Supplementary Material 1.

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Author contributions
VV, DWN, AIK conceived this project. AIK drafted the manuscript. PØF, EB, BB, QMH, and MDH contributed to portions of the manuscript. All authors reviewed the manuscript and provided edits. All authors have read and approved the final manuscript.

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Data availability
All data supporting the findings of this study are available within the article and its supplementary files. Gene information and classification were obtained from the HUGO Gene Nomenclature Committee (HGNC) database (https://www.genenames.org/). All gene symbols and names conform to the official HGNC updates, and previous aliases are listed in Supplementary Table S1 for reference.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
VV serves as the Editor-in-Chief, EB serves as an Executive Associate Editor and DWN as a Section Editor of the Human Genomics journal. AIK, BB, PØF, QMH, MDH and DCT declare no competing interests.

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