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# Clinical Implications of Epigenetic Regulation in Pharmacogenes Encoding Metabolic Enzymes for Second-Generation Antipsychotics in Schizophrenia

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## ABSTRACT

Schizophrenia is a multifactorial neuropsychiatric disorder arising from a combination of neurochemical imbalances, genetic and epigenetic influences, environmental exposures, and other non-genetic factors. The field of pharmacoepigenetics examines how epigenetic variations influence an individual's response to medications. This review aimed to provide a descriptive synthesis of current insights into the epigenetic regulation of pharmacogenes encoding metabolizing enzymes involved in the processing of second-generation antipsychotics (SGAs) for schizophrenia and to explore the clinical consequences of these mechanisms. Key pharmacogenes, including CYP2D6, CYP1A2, CYP2C9, CYP2C19, and CYP3A4, were summarized alongside their enzymatic roles in metabolizing SGAs such as clozapine, olanzapine, risperidone, paliperidone, and quetiapine. The review primarily focused on epigenetic processes—DNA methylation, histone methylation, and acetylation—affecting these pharmacogenes, as well as epigenetic modifications triggered by enzyme-inducing drugs and SGAs themselves. Although the literature on epigenetic regulation of pharmacogenes is still limited, current evidence points to DNA methylation and histone trimethylation and acetylation as predominant mechanisms, with certain enzyme-inducing medications potentially promoting additional epigenetic alterations. These findings carry important implications for optimizing the clinical management and pharmacological treatment of patients with schizophrenia.

**Keywords:** Clinical implications, Epigenetics, Antipsychotic drugs, Pharmacogenes, Schizophrenia

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## Introduction

Schizophrenia is a chronic neuropsychiatric disorder that impacts roughly 1% of people worldwide and ranks among the leading causes of disability in developed regions. Alarmingly, suicide rates are high: around 5% of patients die by suicide, over 30% display suicidal tendencies, and the condition is a major contributor to premature death in young adults [1]. These facts highlight the critical importance of exploring how genetic, epigenetic, and environmental factors interact to influence disease progression and treatment outcomes. Epigenetics investigates molecular modifications that alter gene activity without changing the underlying DNA sequence, playing a key role in heritable phenotypic variation, cellular memory of developmental cues, and adaptive responses to external stimuli [2-7]. Well-established epigenetic mechanisms include cytosine methylation in CpG dinucleotides, histone modifications, and the regulatory actions of non-coding RNAs, including both short (sncRNAs) and long (lncRNAs) forms [8].

Pharmacoepigenetics, a subfield of epigenetics, examines how these molecular modifications influence drug response, offering insight into both therapeutic effectiveness and the risk of adverse drug reactions [3, 9]. Understanding the epigenetic and pharmacogenetic underpinnings of schizophrenia is crucial for deciphering the complex interplay between genes, environmental exposures, and medication responses [9]. In particular, variations in pharmacogenes—such as CYP2D6, CYP1A2, CYP2C9, CYP2C19, and CYP3A4—can influence

enzyme activity, resulting in differences in drug metabolism, plasma concentrations, and susceptibility to adverse effects from antipsychotic medications [10, 11]. These insights form the backbone of personalized or precision medicine, which tailors drug choice and dosing according to an individual's genetic and phenotypic profile, taking into account factors such as ethnicity, sex, lifestyle, and ancestry to maximize therapeutic benefits and minimize adverse events [12- 16].

Second-generation antipsychotics (SGAs), also called atypical antipsychotics, are commonly used to manage schizophrenia symptoms. This class includes clozapine, olanzapine, risperidone, paliperidone, quetiapine, amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, sertindole, ziprasidone, and zotepine [17].

A literature search was performed across PubMed, MEDLINE, and Scopus using keywords such as "clozapine," "olanzapine," "risperidone," "pharmacogenes," combined with terms like "epigenetic molecular mechanism," "DNA methylation," "histone methylation," and "histone acetylation." Only studies published between 2000 and April 10, 2025, were considered. The review focused on articles describing epigenetic modifications in pharmacogenes responsible for metabolizing SGAs. Studies unrelated to these criteria were excluded. The aim of this review is to provide a comprehensive summary of current knowledge on epigenetic mechanisms affecting pharmacogenes, their role in drug metabolism, and their clinical significance in schizophrenia, including modifications induced during development or by enzyme-inducing medications.

*Pharmacogenetics*

Pharmacogenetics investigates how genetic variation influences drug metabolism, plasma levels, therapeutic outcomes, and the likelihood of adverse reactions [12, 18, 19]. By understanding the genetic profiles of key pharmacogenes such as CYP2D6, CYP1A2, CYP2C9, CYP2C19, and CYP3A4, clinicians can better predict patient responses to second-generation antipsychotics including clozapine, olanzapine, risperidone, paliperidone, and quetiapine [20, 21].

*Pharmacogenes involved in SGA metabolism*

The CYP2D6 gene, located at 22q13.2, encodes the cytochrome P450 2D6 enzyme, which is primarily expressed in the liver (approximately 2% of total CYP450 content) and, to a smaller extent, in the brain, potentially influencing antipsychotic metabolism there as well [22-26]. Individuals carrying the wild-type CYP2D6*1/1 genotype are classified as normal metabolizers (NM). Intermediate metabolizers (IM) typically carry allelic combinations such as CYP2D61/*19, *4/*10, *6/*10, *6/*17, *10/*10, *10/*19, *10/*41, *19/*41, and *49/49, while poor metabolizers (PM) often possess genotypes like CYP2D63/*3, *4/*4, or *5/*5 [19, 27]. CYP2D6 is responsible for metabolizing roughly a quarter of all clinically used medications [19, 22, 28].

CYP1A2, situated at 15q24.1, contributes 8–15% of hepatocyte CYP450 content and mediates hydroxylation and dealkylation of several drugs [29, 30]. The CYP1A2*1A/1A genotype is associated with normal metabolism, whereas CYP1A21C/*1C correlates with reduced enzyme activity and poor metabolism [22, 29, 31].

The CYP2C9 gene is located on the long arm of chromosome 10 (10q24) and encodes the CYP2C9 enzyme, which is mainly expressed in the liver, representing roughly 18% of total CYP450 content. The wild-type CYP2C91 allele forms the CYP2C91/1 genotype, which is associated with normal metabolizer (NM) status [32, 33]. Variants such as CYP2C91/*2, *2/*2, and *1/3 are linked to intermediate metabolizer (IM) phenotypes, whereas CYP2C92/*3, *3/*3, *5/*5, and *6/*6 genotypes confer poor metabolizer (PM) status [34, 35]. CYP2C9 is responsible for metabolizing approximately 15% of clinically utilized drugs [16, 22, 36].

CYP2C19, also situated on chromosome 10 (10q24.1), encodes an enzyme that metabolizes multiple drugs and exhibits substantial interindividual variability. The CYP2C19*1/1 genotype is predictive of NM status, while CYP2C191/2 corresponds to intermediate metabolizers (IM). Poor metabolizer (PM) status is associated with CYP2C192/*2, *2/*3, *3/*3, *4/*4, *5/*5, *6/*6, and *7/*7 genotypes [35, 37-39].

The CYP3A4 gene, located at 7q22.1, encodes one of the most abundant drug-metabolizing enzymes in humans, expressed in both the liver (approximately 60% of total CYP450) and intestine (around 70%). The wild-type allele, CYP3A41.002, produces the CYP3A41/1 genotype, which predicts normal metabolism. Genotypes such as CYP3A42/2 result in intermediate metabolism, whereas CYP3A43/*3, *20/*20, and *22/*22 predict poor metabolizer status [22, 40-42]. CYP3A4 mediates the oxidative metabolism of roughly 30% of all drugs in clinical use, making allelic variations highly relevant to pharmacokinetics, toxicity, and therapeutic outcomes [22, 43, 44].

*Metabolism of major Second-Generation Antipsychotics (SGAs)*

Aripiprazole undergoes phase I metabolism via hydroxylation and dehydrogenation. CYP3A4 and CYP2D6 convert aripiprazole to 4-hydroxy-aripiprazole, which is subsequently glucuronidated, while dehydrogenation generates the active metabolite dehydroaripiprazole. This metabolite undergoes further hydroxylation to 4-hydroxy-dehydroaripiprazole (CYP3A4/CYP2D6) followed by glucuronidation, or N-dealkylation at the piperazinyl nitrogen to form dehydroaripiprazole acid and 1-(2,3-dichlorophenyl)-piperazine (CYP3A4). The latter metabolite is further hydroxylated by CYP2D6 and glucuronidated by UDP-glucuronosyl transferase (UGT) to generate the final O-β-glucuronide derivative [45].

Clozapine, a tricyclic dibenzodiazepine, is primarily metabolized by CYP1A2 and CYP3A4 via N-demethylation to produce norclozapine (N-desmethylclozapine). Hydroxylation occurs through CYP2D6, CYP2C19, and CYP3A4 to form hydroxy-clozapine, while N-oxidation is catalyzed by CYP3A4, CYP3A5, CYP1A2, CYP2C8, and CYP2C19. Phase II metabolism involves N-glucuronidation by UGT1A3, producing clozapine N-glucuronide [18, 46-48].

Olanzapine, a thienobenzodiazepine derivative, undergoes CYP1A2-mediated formation of 4′-N-desmethylolanzapine and 7-hydroxyolanzapine. CYP2D6, CYP3A4, and CYP2C9 convert it into 2-hydroxymethylolanzapine, while CYP2D6 and FMO3 generate olanzapine N-oxide. Phase II metabolism is catalyzed by UGT1A4 and UGT2B10 via N-glucuronidation to produce 10-N-glucuronide olanzapine [27, 49, 50].

Risperidone, a benzisoxazole derivative, is converted to its major active metabolite, (+)-9-hydroxyrisperidone (paliperidone), primarily by CYP2D6 and to a lesser extent by CYP3A4. Minor pathways include N-dealkylation by CYP3A4 and CYP3A5, forming inactive metabolites, which are subsequently conjugated via UGT to O-β-glucuronides and excreted in urine. Risperidone has a half-life of ~3 hours, while its active metabolite persists 20–24 hours [27, 50, 51].

Paliperidone, chemically a benzoisoxazole derivative, is primarily a risperidone metabolite, metabolized via CYP3A4 and minimally by CYP2D6. In normal metabolizers, CYP3A4 inducers (e.g., carbamazepine) can reduce plasma levels. Its half-life ranges from 23–30 hours, with 60% excreted unchanged in urine and 10% via bile [47, 52, 53].

Quetiapine, a dibenzothiazepine, is largely metabolized by CYP3A4 (~89%) to norquetiapine, which undergoes CYP2D6-mediated conversion to 7-hydroxy N-alkyl quetiapine and is subsequently inactivated by COMT. Additional minor pathways involve CYP2D6, CYP2C9, CYP2C19, CYP1A2, and CYP3A5, generating inactive metabolites [54, 55].

*General epigenetic molecular mechanisms*

*DNA methylation*

DNA methylation is a fundamental epigenetic process that occurs at cytosine residues within specific genomic regions and plays a critical role in regulating gene expression. It can suppress transcription directly by blocking transcription factor access to promoter sequences or indirectly by recruiting corepressor complexes through methyl-CpG binding proteins (MBPs) [4, 56]. The process is catalyzed by DNA methyltransferases (DNMTs), which transfer a methyl group from S-adenosylmethionine (SAM) to the C-5 position of cytosine within CpG dinucleotides, resulting in the formation of 5-methylcytosine (5mC). During this reaction, SAM is converted into S-adenosylhomocysteine (SAH), which subsequently loses an adenosine molecule to produce homocysteine.

Ten-eleven translocation (TET) enzymes can further oxidize 5mC into 5-hydroxymethylcytosine (5hmC), a modification that occurs in both CpG and CpHpG sequences (where H represents A, T, or C). This conversion generally takes place in the 5′ to 3′ direction during DNA replication, whenever cytosine is immediately followed by a guanine, facilitating the propagation of epigenetic marks to daughter strands [56, 57]. A schematic illustration of this DNA methylation process is presented in **Figure 1.**

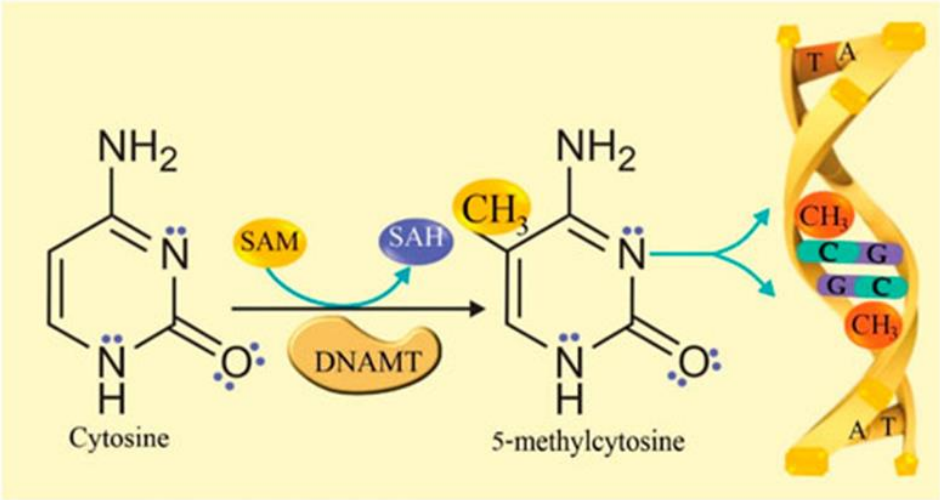



**Figure 1.** DNA methylation reaction mechanism. DNA methyltransferase (DNMT) catalyzes the transfer of a methyl group from S-adenosylmethionine (SAM) to the C-5 position of cytosine, generating 5-methylcytosine (5mC), while SAM is converted into S-adenosylhomocysteine (SAH).

*Histone methylation*

Histones are fundamental proteins that organize DNA into nucleosomes and are integral components of chromosomes, playing a key role in the regulation of gene expression [58, 59]. These proteins can undergo post-translational modifications, such as methylation and acetylation at specific amino acid residues, which can either repress or enhance transcription [58].

Methylation of histone 3 lysine residues has distinct effects depending on the site and degree of methylation. For example, mono-, di-, or trimethylation of lysine 9 (H3K9, H3K9me2, H3K9me3) and di- or trimethylation of lysine 27 (H3K27me2, H3K27me3) within gene promoters or transcription start sites are associated with transcriptional silencing, preventing expression of the encoded proteins or enzymes [60-62]. Conversely, di- or trimethylation of lysine 4 (H3K4me2, H3K4me3) and lysine 36 (H3K36me2, H3K36me3) promotes gene activation, increasing the likelihood that the gene will be expressed and produce functional proteins, though these marks are not solely determinative of activation as other regulatory factors also play a role [58, 63-65].

Histone methylation can also modify chromosome architecture and is primarily mediated by histone methyltransferases (HMTs). Two main classes of HMTs exist: histone lysine methyltransferases (KMTs), which are subdivided into SET and non-SET domain enzymes (including SUV39H1/2, G9a, GLP, SMYD, SETDB1, EZH2), and protein arginine methyltransferases (PRMTs). PRMTs are divided into two types, with PRMT1, PRMT3, PRMT4, PRMT6, and PRMT8 catalyzing monomethylation of arginine residues [66-69].

For illustrative purposes, the N-terminal amino acid sequence of histone 3 is depicted in **Figure 2** (not to scale): alanine (A), arginine (R), threonine (T), lysine 4 (K4), glutamine (Q), threonine (T), alanine (A), arginine (R), lysine 9 (K9), serine (S), threonine (T), glycine (G), glycine (G), lysine (K), alanine (A), proline (P), arginine (R), lysine (K), glutamine (Q), leucine (L), alanine (A), threonine (T), lysine (K), alanine (A), alanine (A), arginine (R), lysine 27 (K27), serine (S), alanine (A), and proline (P). In this sequence, K4 and K27 are prone to methylation, whereas K9 can be acetylated [58]. The proposed mechanism of histone methylation is illustrated in **Figure 2.**

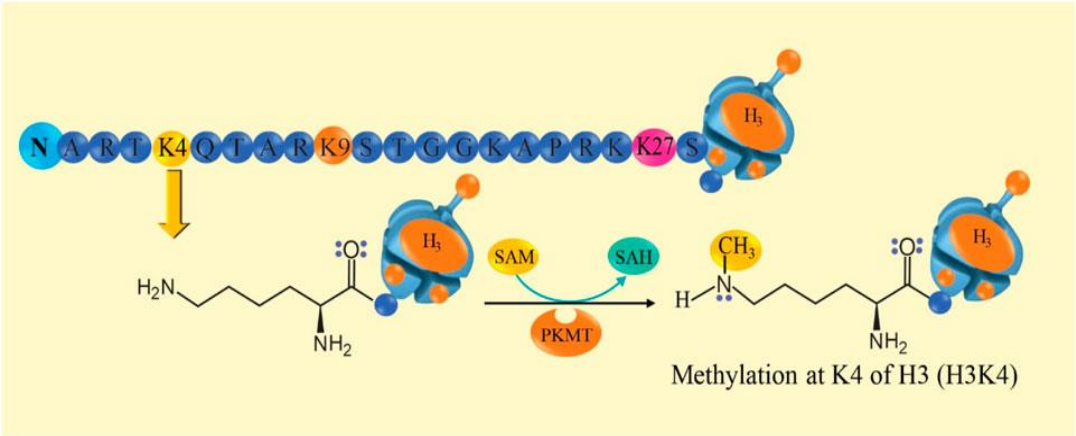



**Figure 2**. Histone methylation reaction mechanism. The amino acid sequence of the N-terminal tail of histone 3 (H3) is shown, highlighting lysine 4 (K4) as a site for methylation. Histone lysine methyltransferase (PKMT) catalyzes the transfer of a methyl group from S-adenosylmethionine (SAM) to the amino group of H3K4, modifying histone-DNA interactions. During this reaction, SAM is converted into S-adenosylhomocysteine (SAH).

*Histone acetylation*

Acetylation of lysine residues on histones is a key epigenetic modification that generally promotes transcriptional activation [56, 62]. This process is mediated by histone acetyltransferases (HATs), which transfer an acetyl group from acetyl-CoA to the ε-amino group of lysine residues in histone tails. Acetylation neutralizes the positive charge of lysine, loosening the interaction between histones and DNA, thereby facilitating transcription. In contrast, histone deacetylases (HDACs) remove acetyl groups, leading to tighter DNA-histone interactions and transcriptional repression, maintaining a dynamic regulatory balance [59, 70, 71].

Histones H3 and H4 possess extended N-terminal tails protruding from the nucleosome core, which are prime sites for acetylation modifications. Specifically, acetylation of lysine 9 on histone 3 (H3K9ac) is associated with transcriptional activation and chromatin relaxation [58]. A schematic of the histone acetylation process is presented in **Figure 3.**

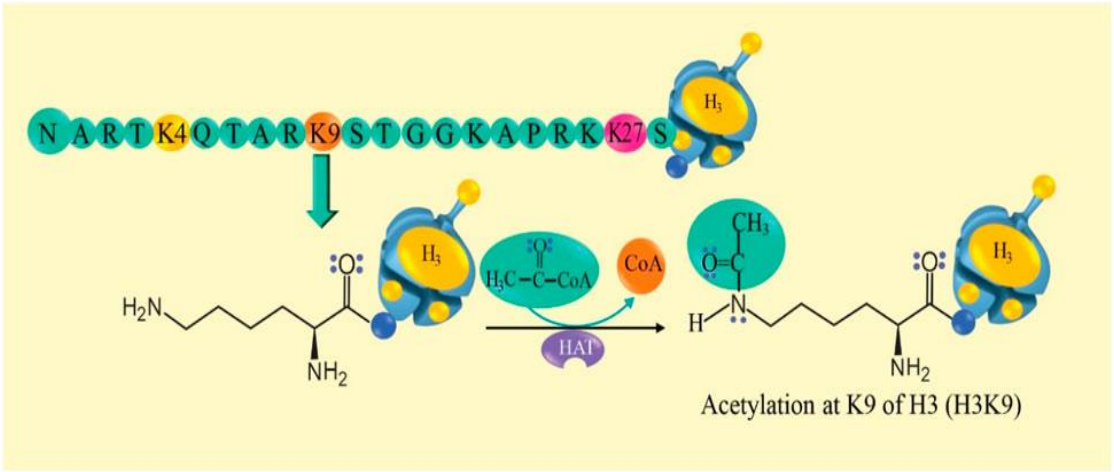



**Figure 3.** Histone acetylation reaction mechanism. The N-terminal tail of histone 3 (H3) is depicted, highlighting lysine 9 (K9) as a site susceptible to acetylation. During this reaction, histone acetyltransferase (HAT) transfers an acetyl group from acetyl-CoA to H3K9 (H3K9ac), which can lead to activation of gene transcription.

*Pharmacoepigenetics*

Pharmacoepigenetics focuses on how epigenetic variations influence drug responses, offering insight for tailoring treatments to individual patients [3].

*Epigenetic modifications in pharmacogenes*

Mechanisms such as DNA methylation, histone post-translational modifications, and microRNA regulation modulate gene expression without altering the underlying DNA sequence, producing heritable phenotypic changes that impact drug metabolism and response [5, 72]. Epigenetic alterations in CYP genes emerge during human development, from neonates to adults [73]. These modifications are shaped by two primary factors: first, liver dysfunction, which reduces enzyme activity and drug metabolism [73-75]; second, exposure to enzyme-inducing medications, which upregulate enzyme expression, lower drug plasma levels, and may lead to therapeutic failure [76, 77].

*DNA methylation in pharmacogenes*

Helsby and Burns (2012) [78] identified two microRNA recognition elements (MREs) in the 3′-untranslated region (3′UTR) of the CYP2C19 gene, which are sensitive to DNA methylation and can suppress gene translation; these findings were observed in HepG2 human hepatoma cells. Additional studies confirmed CYP2C19 methylation following treatment with the methyltransferase inhibitor 5-aza-2′-deoxycytidine (5-aza-dC), though the involvement of other unidentified epigenetic regulators was suggested [79]. Habano *et al*. (2015) [80] reported methylation patterns in CYP2D6, CYP1A2, and CYP2C19, particularly at CpG sites within CYP2C19, across fetal liver tissue, adult small intestine samples, and hepatoma cell lines (HepG2, HuH7, JHH1).

For CYP3A4, promoter region methylation impairs the recruitment of RNA polymerase and transcription factors, thereby modulating gene expression, as shown in studies using pediatric and prenatal liver tissues [81]. Similarly, methylation within CpG dinucleotides was observed in the CYP3A4 promoter and CYP2D6 gene body [82]. Experimentally induced epimutations in CYP2D6, such as a cytosine-to-thymine substitution at position 188 (C>T) in exon 1, result in the CYP2D6*10 allele, which produces reduced-activity enzymes, helping explain individual variability in drug metabolism and guiding precision pharmacotherapy [83].

**Table 1** summarizes the epigenetic modifications observed in pharmacogenes and their clinical relevance.

**Table 1.** Epigenetic molecular mechanism in pharmacogenes DNA

| Author | Pharmacogenes | Epigenetic Molecular Mechanism | Key Findings and Clinical Relevance |
|---|---|---|---|
| Helsby and Burns (2012) [78] | CYP2C19 | DNA methylation within the promoter region | Leads to silencing of one CYP2C19 allele, reducing hepatic enzyme expression and potentially affecting drug metabolism |
| Habano *et al*. (2015) [80] | CYP2D6, CYP1A2, CYP2C19 | Methylation of exons and 5′ regulatory regions (5′UTR) | Allelic silencing decreases enzyme production, which may contribute to variability in drug response and risk of adverse reactions |
| Vyhlidal *et al*. (2016) [81] | CYP3A4 | Promoter region DNA methylation | Alters mRNA expression levels of CYP3A4, potentially impacting metabolism of drugs processed by this enzyme |
| Shi *et al*. (2017) [82] | CYP2D6, CYP3A4 | CpG methylation in the body of CYP2D6 and promoter region of CYP3A4 | May reduce CYP2D6 enzymatic activity, increasing susceptibility to adverse reactions from drugs like risperidone |

*Histone methylation in pharmacogenes*

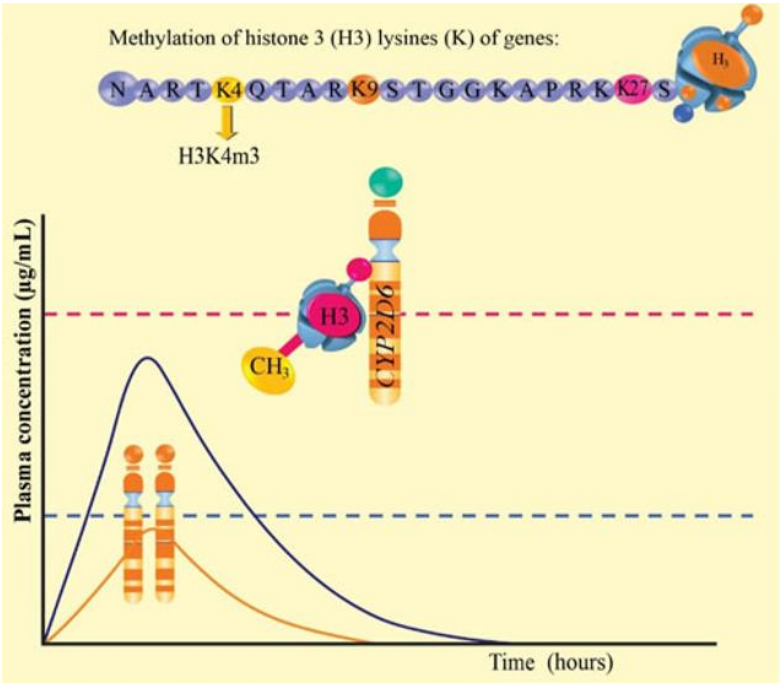
Experimental research has demonstrated that histone methylation occurs in pharmacogenes. He *et al*. (2016) [84] reported methylation along the extended tail of histone H3 associated with the CYP3A4 gene. Similarly, Park *et al*. (2015) [63] observed that the promoter region of CYP2D6 contains 12 CpG dinucleotides that were methylated at a rate of 96.3% in hepatocytes derived from human embryonic stem cells (hESC-Hep), while the gene body, containing 32 CpG sites, showed methylation frequencies of 45.5% in primary human hepatocytes (hPH) and 90.3% in hESC-Hep. For the CYP1A2 gene, the promoter region comprises 10 CpG dinucleotides, fully methylated in both hPH and hESC-Hep; the gene body contains 20 CpG sites, with methylation observed at 40.0% in hPH and 76.7% in hESC-Hep. **Table 2** provides a summary of the histone-associated epigenetic modifications in pharmacogenes, along with their conclusions and clinical significance.

**Table 2**. Epigenetic molecular mechanism in pharmacogene histones and its clinical importance

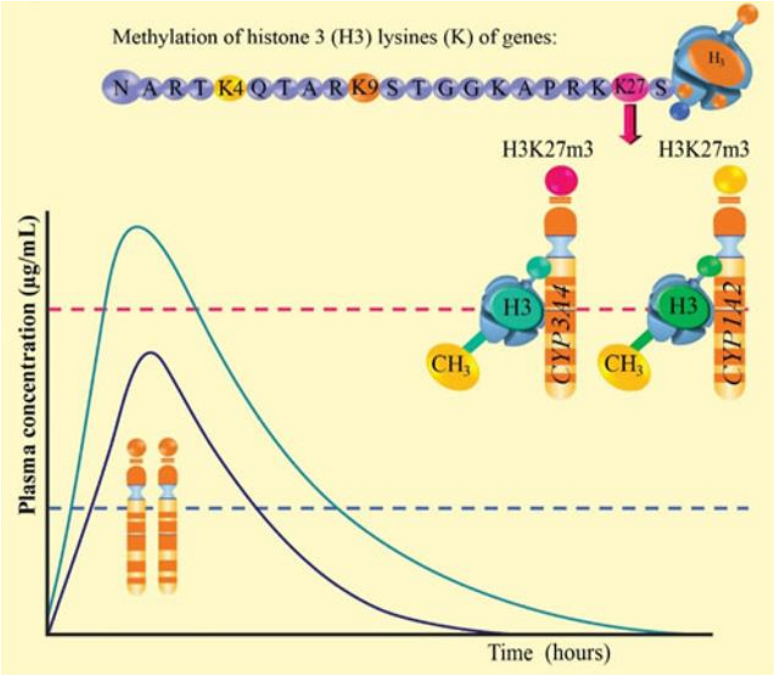
| Author | Pharmacogenes | Epigenetic Molecular Mechanism | Key Findings and Clinical Relevance |
|---|---|---|---|
| Kacevska *et al*. (2012) [85] | CYP3A4 | Hypermethylation at CpG sites in the regulatory region | Leads to suppression of CYP3A4 transcription, reducing enzyme expression and helping explain interindividual variability in drug metabolism |
| He *et al*. (2016) [84] | CYP3A4 | H3K4 di-methylation (H3K4me2) enhances transcription; H3K27 tri-methylation (H3K27me3) represses transcription | These modifications influence CYP3A4 mRNA levels in adult liver, with H3K27me3 and H3K4me2 patterns changing during development from conception to adulthood |
| Park *et al*. (2015) [64] | CYP2D6, CYP1A2 | H3K4 tri-methylation (H3K4me3) in the CYP2D6 promoter in hPH activates transcription; H3K27 tri-methylation (H3K27me3) in hESC-Hep suppresses CYP1A2 transcription; H3K4me3 in the CYP1A2 gene body in hPH promotes transcription | Epigenetic regulators, including DNA methyltransferases, modulate limited expression of CYP2D6 and CYP1A2 in human embryonic stem cell-derived hepatocytes and primary hepatocytes |

**Abbreviations:** H3K27me3: tri-methylation at lysine 27 of histone 3; H3K4me2: di-methylation at lysine 4 of histone 3; hESC-Hep: human embryonic stem cell-derived hepatocytes; hPH: human primary hepatocytes; CpG: cytosine-phosphate-guanine dinucleotides.

**Figures 4a and 4b** depict the extended tail sequences of histone 3 for the CYP2D6, CYP3A4, and CYP1A2 genes. In **Figure 4a**, trimethylation at lysine 4 (K4) of histone 3 on the CYP2D6 gene (H3K4me3) enhances transcriptional activity, resulting in higher levels of active CYP2D6 enzyme. This increased enzyme expression can accelerate drug metabolism, potentially reducing plasma drug concentrations below the minimum effective level (illustrated beneath the dashed blue line and orange curve), while individuals with standard genotype and phenotype maintain therapeutic drug levels (purple curve). In **Figure 4b**, trimethylation at lysine 27 (K27) of histone 3 on the CYP3A4 and CYP1A2 genes (H3K27me3) suppresses gene transcription, producing minimal or absent enzymatic activity, which may elevate drug plasma levels above the toxic threshold (shown above the dashed red line and green curve), compared to normal metabolism levels represented by the purple curve within the therapeutic range.




a)




b)

**Figure 4.** Schematic showing histone 3 lysine 4 trimethylation (H3K4me3) on the CYP2D6 gene (a) and lysine 27 trimethylation (H3K27me3) on CYP3A4 and CYP1A2 genes (b).

*Epigenetic modulation by enzyme-inducing drugs*

Certain medications, including carbamazepine, phenytoin, and rifampicin, can upregulate CYP3A4 expression, increasing enzyme levels and accelerating drug metabolism [76]. This can result in lower plasma concentrations of medications such as aripiprazole, potentially necessitating higher doses to achieve therapeutic effects [86]. Rifampicin has been shown to enhance histone H3 acetylation, stimulate H3K4 trimethylation (H3K4me3), and reduce H3K27 trimethylation (H3K27me3) in promoter regions, collectively boosting CYP3A4 mRNA levels [87]. Long non-coding RNAs (lncRNAs) are also implicated in this induction of CYP450 enzymes during exposure to enzyme-inducing drugs such as rifampicin and phenobarbital [88]. For instance, HNF4A-AS1 has been reported to promote histone tri-methylation, generating both H3K4me3 and H3K27me3 modifications [89].

*Epigenetic effects triggered by antipsychotic drugs*

Some second-generation antipsychotics—including clozapine, risperidone, olanzapine, and quetiapine—can alter DNA methylation patterns and induce demethylation events [90]. **Table 3** provides a detailed overview of studies examining how these drugs modulate epigenetic mechanisms in the context of schizophrenia.

**Table 3.** Epigenetic molecular mechanisms induced by second-generation antipsychotic drugs and their clinical relevance

| Author | Study Type | Drug | Epigenetic Molecular Mechanism | Key Findings and Significance |
|---|---|---|---|---|
| Dong *et al*. (2008) [91] | Mouse experimental study | Clozapine | Promoter-associated acetylation of H3K9 and H3K14; demethylation of RELN and GAD67 promoters in striatal GABAergic neurons | DNA demethylation enhances expression of GABAergic genes, potentially correcting GABA deficits implicated in schizophrenia and bipolar disorder |
| Guidotti *et al*. (2011) [92] | Mouse experimental study | Clozapine and Olanzapine | Demethylation of the GAD67 promoter in GABAergic neurons; effect enhanced with VPA (HDAC inhibitor) | Targeted DNA demethylation may restore normal GABAergic gene expression, offering a potential therapeutic approach for |

| | | | | |
|---|---|---|---|---|
| | | | | schizophrenia and bipolar disorder |
| Melka *et al*. (2014) [93] | Rat experimental study | Olanzapine | DNA methylation of genes related to dopaminergic signaling, transporter proteins, receptors, neural development, and hippocampal functions | Epigenetic modifications could underlie both symptom improvement and certain adverse effects of olanzapine |
| Li *et al*. (2004) [94] | Mouse experimental study | Risperidone | Histone H3 phosphoacetylation (H3pS10-acK14) via DR2 blockade, mediated by cAMP-dependent PKA and postsynaptic NMDA receptor signaling; overexpression in striatal neurons | Histone modifications dynamically regulate chromatin structure in response to dopaminergic and glutamatergic signals |
| Rami *et al*. (2022) [95] | Mouse experimental study | Risperidone | CpG2 site methylation of DRD2 in prefrontal cortex (PFC) and amygdala (AMY) | Reduced methylation at DRD2 enhances receptor expression, potentially improving dopaminergic signaling in these brain regions |

**Abbreviations:** AMY, amygdala; PFC, prefrontal cortex; DRD2, dopamine receptor type 2; H3K9, histone 3 lysine 9; H3K14, histone 3 lysine 14; RELN, reelin gene; GAD67, glutamate decarboxylase 67; PKA, protein kinase A; cAMP, cyclic adenosine monophosphate; NMDA, N-methyl-D-aspartate; HDAC, histone deacetylase; VPA, valproic acid.

*Clinical implications of epigenetic mechanisms*

Epigenetic modifications, including histone trimethylation and DNA methylation in the CYP3A4, CYP2D6, CYP1A2, and CYP2C9 genes, can lead to silencing of one allele. This phenomenon helps explain the existence of genotypes that predict metabolic phenotypes associated with increased risk of adverse drug reactions and therapeutic failure in patients treated with second-generation antipsychotics. Consequently, a potential clinical strategy to reverse DNA methylation in GABAergic promoters and the dopaminergic receptor type 2 (DRD2) involves administering clozapine, olanzapine, or risperidone in combination with valproic acid (a histone deacetylase inhibitor), thereby improving drug efficacy in individuals with schizophrenia and bipolar disorder. These insights provide psychiatrists with scientific evidence to guide treatment decisions and optimize pharmacological therapy.

This review has some limitations that could introduce bias. Key constraints include the limited availability of published pharmacoepigenetic research in schizophrenia, the scarcity of studies specifically examining epigenetic modifications in genes encoding enzymes that metabolize second-generation antipsychotics, and the use of studies with methodological limitations such as small sample sizes, in vitro models using various tissue types, and animal experiments. Nevertheless, this review contributes by consolidating current pharmacoepigenetic knowledge and provides a foundation for future research, including prospective longitudinal cohort studies, human observational studies, standardized clinical epigenetic trials, and integrative pharmacoepigenetic-pharmacokinetic investigations.

## Conclusion

Based on the evidence reviewed, DNA methylation, histone methylation, and histone acetylation emerge as the most common epigenetic mechanisms affecting the CYP3A4, CYP2D6, CYP1A2, and CYP2C19 pharmacogenes, while enzyme-inducing drugs can also trigger epigenetic modifications. These changes may account for both intra- and interindividual variability in allele expression, thereby influencing the safety and effectiveness of second-generation antipsychotics in patients with schizophrenia.

Further studies are necessary to explore epigenetic regulation in pharmacogenes using larger cohorts of biological samples from schizophrenia patients, to validate and expand upon the findings summarized in this review. Such research is particularly valuable for clinicians, providing an additional tool to consider epigenetic mechanisms as a factor in drug response. Moreover, these insights support the inclusion of epigenetic data in Pharmacogenomic Guidelines and the advancement of personalized or precision medicine, ultimately aiming to enhance treatment outcomes and quality of life for patients with schizophrenia.

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**Conflict of Interest:** None

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**Ethics Statement:** None

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