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Systematic Review

A Comparative Analysis of Genetic and Epigenetic Factors in METH Addiction: A Focus on *SLC* (*SLC6A4*) and *COMT* Genes

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Abstract

Background: Methamphetamine (METH) addiction is a global concern due to its severe impact on public health, including heightened aggression and neurotoxic effects. Genetic and epigenetic factors, particularly involving the *SLC6A4* and *COMT* genes, are implicated in individual vulnerability to METH addiction. Thus, understanding the molecular mechanisms involved is crucial for developing targeted prevention and treatment strategies. **Methods**: A systematic literature review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Six major databases (MEDLINE/PubMed, Scopus, ScienceDirect, ResearchGate, Web of Science, Google Scholar) and Spanish-language platforms (Dialnet, Redalyc, CSIC, RECyT) were searched for studies published in English, Spanish, and Portuguese over the last 40 years. The inclusion criteria encompassed original research focusing on genetic and/or epigenetic determinants of METH addiction, with particular emphasis on the *SLC6A4* and *COMT* genes. Studies focusing on substances other than METH, non-human subjects, or those that did not meet the language or temporal restrictions were excluded. Data on genetic variants, epigenetic alterations (e.g., DNA methylation, histone modifications), and relevant behavioral outcomes were extracted. **Results**: From an initial 600 articles, 25 studies met the inclusion criteria and were included in the qualitative synthesis. Polymorphisms in *SLC6A4* (e.g., 5-HTTLPR) were associated with an increased risk of METH addiction (odds ratio (OR) = 2.31, 95% confidence interval (CI): 1.45–3.68; $p = 0.001$); meanwhile, variations in *COMT* (Val158Met) were linked to both susceptibility and executive function deficits. Epigenetic modifications—most notably DNA methylation in *SLC6A4* and *COMT*—also emerged as important contributors to addiction pathways, potentially influencing dopamine and serotonin regulation. Gene-environment interactions, including factors such as childhood trauma and socioeconomic status, were found to modulate genetic predispositions, suggesting a multifaceted etiology for METH dependence. **Conclusions**: Both genetic polymorphisms and epigenetic alterations play a critical role in METH addiction vulnerability. The reviewed evidence highlights the need for more comprehensive, regionally diverse studies and integrative approaches that combine genetics, neurobiology, and psychosocial factors. Such strategies could inform personalized prevention and treatment interventions, improving patient outcomes and mitigating the global burden of METH addiction.

Keywords: epigenetic factors; *COMT*; DNA methylation; solute carrier family; METH addiction; genetic factors *SLC6A4* gene; substance disorder

1. Introduction

Methamphetamine (METH) is a powerful nervous system stimulant that promotes a significant ability for abusive behaviors and triggers the release of neurotransmitters, resulting in synaptic plasticity and abnormal memory development [1–5]. Moreover, METH use is associated with increased health and social problems, including heightened aggression, due to neurotoxic effects on brain regions controlling impulse and emotion [3,4], and METH exposure depletes dopamine in the striatum and increases reactive oxygen species (ROS) [6–8]. Addiction is a global crisis linked to severe health issues, with genetic and epigenetic factors influencing susceptibility and behavior, such as aggression [9–12]. Notably, use in the United States is highest among adults aged 26–34, often with co-occurring substance disorders [13]. Meanwhile, countries in Asia, such as Thailand and China, also report significant youth usage but lower prevalence rates than the U.S. [14–16]. Europe shows moderate rates, with Spain and France having higher marijuana use [17,18]. Iraq shows the lowest METH prevalence; however, usage is rising due to socio-political instability, making users more prone to suicidal ideation [19–21].

The genetic and epigenetic basis of addiction is crucial for developing targeted treatments for METH abuse, and epigenetic drugs have shown promise in addiction therapy [22,23]. Indeed, genetic polymorphisms, such as the Taq1A variant in the *DRD2* gene, increase addiction risk by reducing dopamine receptor density [24]. According to existing data, candidate genes have been identified fol-

lowing hypotheses of links to a certain characteristic or illness [25]. Dopamine-, serotonin-, opioid-, and glutamate-related genes represent key candidates related to METH addiction and aggression, and these include *DRD1*, *DRD2*, *DRD3*, *DRD4*, *SLC6A3*, *COMT*; *HTR1A*, *HTR1B*, *HTR2A*, *SLC6A4*; *OPRM1*, *OPRD1*, *OPRK1*; *GRIN2B*, *GRIK1*, *GRIA3*, respectively [26]. The *DRD2* TaqIA and *COMT* Val158Met variants modulate the effects of METH [27].

The dopamine receptor D2 (DRD2) plays a significant role in dopamine synthesis, storage, and release. Thus, gene alterations may impair synthesis and function, resulting in psychological and psychotic symptoms and susceptibility to addiction and other neuropsychiatric conditions [28–30]. The *SLC6A3* gene codes for the dopamine transporter protein (DAT) [31,32]. Alleles such as *DAT1* 10R and *DRD2* TaqIA A1 have been associated with susceptibility to addiction due to the dysregulated dopamine levels and receptor density [33,34]. Moreover, blockage of dopamine D2 receptors has been observed to ameliorate psychotic symptoms and restore the value system; however, a clear correlation between D2 receptor inhibition and the improvement of these symptoms has yet to be established. METH is a psychostimulant drug that produces a variety of effects on the brain and nervous system, initially increasing energy, attention, and libido [35–37].

In addition, METH produces a protein in the membrane responsible for transporting the neurotransmitter serotonin into the presynaptic neuron, while the encoded protein concurrently inhibits neuronal activity in a sodium-dependent manner [38]. The *COMT* gene is an important component in the brain for controlling neurotransmitters and for the catabolism of catecholamines such as norepinephrine and dopamine, which are responsible for many cognitive functions.

Polymorphisms in the *COMT* gene correlate with several health issues, including mental disorders and pain sensitivity, and provide essential insights into the fundamental causes of many illnesses and assist in the development of tailored therapies. Epigenetic changes, including DNA methylation, change the reward circuit, stress response, and brain circuitry gene expression, determining addiction susceptibility [39]. These changes impact dependency and therapeutic effectiveness. The *COMT* Val158Met polymorphism is associated with dopamine dysregulation, resulting in addictive behaviors [40]. Additionally, addressing DNA methylation pathways presents opportunities for customized addiction therapies, enhancing therapeutic efficacy and decreasing the probability of relapse [41]. Genetic and epigenetic changes in the dopamine and serotonin pathways influence addiction susceptibility, highlighting the need for personalized therapeutic strategies grounded in molecular and neurobiological considerations.

DNA methylation is a vital epigenetic modification and is crucial in the onset and progression of METH addiction [42]. DNA methylation involves adding methyl groups to DNA, primarily at cytosine residues, potentially modifying gene expression without changing the DNA sequence [43]. The interplay between *SLC* genetic polymorphisms and epigenetic mechanisms, particularly *SLC6A4*, influences vulnerability to METH use. The *SLC6A4* gene encodes the serotonin transporter and modulates serotonin reuptake, while the COMT protein regulates dopamine metabolism and impacts mood, impulse control, and addiction-related behaviors. These molecular pathways enable personalized interventions, such as epigenetic therapies aimed at reversing maladaptive gene expression patterns, hence, offering customized treatments to improve recovery outcomes and reduce relapse rates in METH addiction.

This review explains these epigenetic therapies with genetic determinants in METH addiction, emphasizing deficiencies in existing data to inform future studies. This research also investigates the function of critical genes in addiction susceptibility to improve our knowledge of their influence and facilitate customized treatment approaches.

2. Methods

2.1 Eligibility Criteria

Original, full-text English, Spanish, and Portuguese publications published within the last 40 years were considered for inclusion. Studies needed to focus on genetic and epigenetic determinants associated with methamphetamine (METH) addiction and, where relevant, aggression or violence, with particular emphasis on genes related to the solute carrier family (SLC) (specifically *SLC6A4*) and *COMT*. Studies predominantly investigating substances other than METH, or those published outside the time frame or not within the language requirements, were excluded.

2.2 Databases and Search Strategy

A comprehensive literature search was conducted between January and May 2020 using six electronic databases:

1. MEDLINE/PubMed: 125 records.
2. Scopus: 100 records.
3. ScienceDirect: 75 records.
4. ResearchGate: 50 records.
5. Web of Science: 150 records.
6. Google Scholar: 100 records.

This resulted in a total of 600 articles. The search terms included “methamphetamine” OR “METH” in combination with “genetic”, “epigenetic”, “SLC6A4”, “COMT”, and “aggression” OR “violence”. Boolean operators (AND, OR) were employed to refine results.

Additionally, we identified 75 records through manual searches (e.g., reference lists of key articles), providing a preliminary total of 675 records for consideration. Fig. 1 outlines the final study flow after duplicates and exclusions were removed.

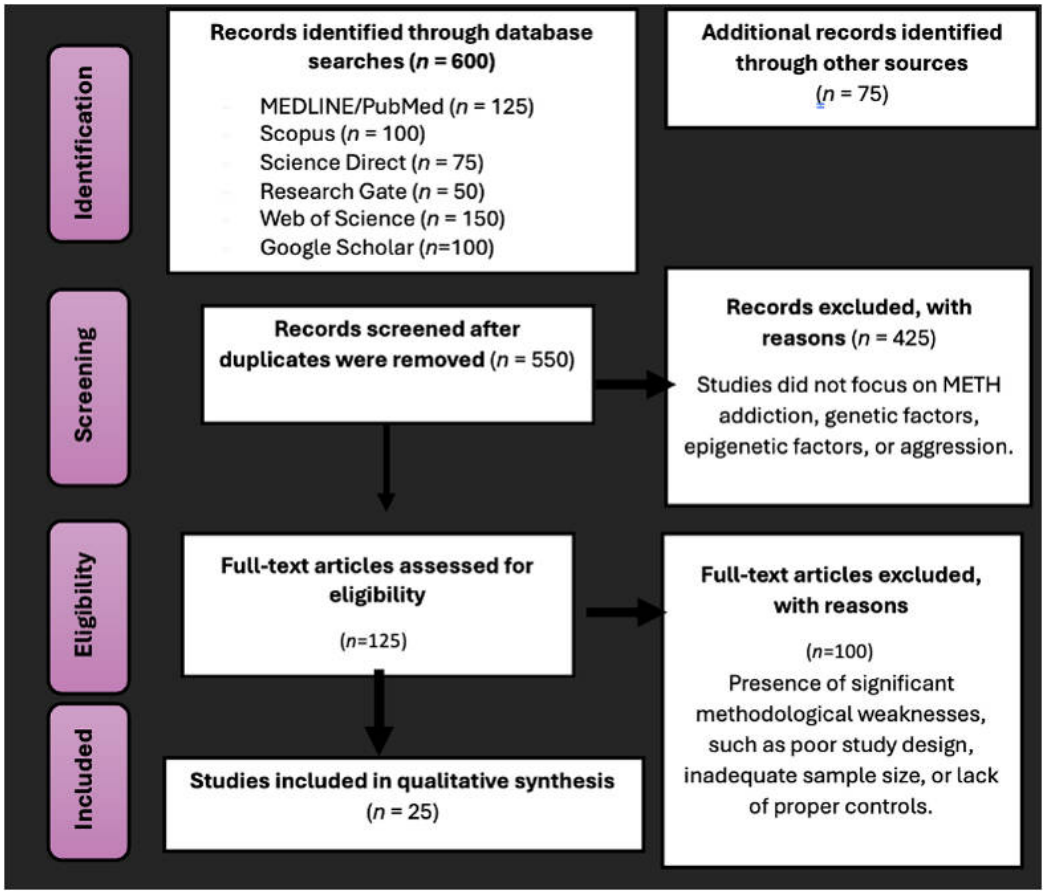

Fig. 1. Flow diagram of article searches and inclusion and exclusion criteria.

Table 1. A summary of the exclusion process during full-text assessment.

Reason for exclusion	Number of articles excluded
Focused on substances other than METH	35
Methodological weaknesses (e.g., no control, n <50)	30
No genetic or epigenetic analysis	15
Language/time frame mismatch	10
Total excluded	100

METH, Methamphetamine.

2.3 Initial Screening and Removal of Duplicates

We removed 50 duplicates, leaving 625 unique records. Titles and abstracts were screened for relevance, and 425 records (e.g., non-METH focus, no genetic or epigenetic data) were excluded. Thus, 200 records remained for full-text review.

2.4 Full-Text Eligibility and Final Inclusion

We retrieved and assessed 200 full-text articles for eligibility; 75 proved to be additional duplicates, commentary pieces, or lacked crucial methodological details, leaving 125 for detailed review. Of these, 100 were excluded for reasons such as insufficient outcome data, a focus on substances other than METH, or failure to meet quality criteria (see Table 1). Consequently, 25 studies met all inclusion criteria and were retained for qualitative synthesis. Please note that the final total (25) is verified and not an approximation.

2.5 Reasons for Exclusion

A summary of the exclusion process during the full-text assessment is provided in Table 1.

2.6 Data Extraction and Quality Assessment

Following the final selection, each of the 25 articles was independently reviewed by two authors, focusing on:

1. Study design: Whether prospective, case–control, cross-sectional, etc.
2. Population demographics: Sample size, age, and geographic origin.

Table 2. Distribution of genetic and epigenetic studies on METH addiction by country.

Country	Percentage of studies (%)	Key findings
United States	28%	Focused on genetic polymorphisms and addiction susceptibility
Japan	28%	Advanced neuroimaging and genetic–epigenetic interactions
Taiwan	12%	Studies on epigenetic modifications
Other countries	32%	Mixed methodologies and emerging research

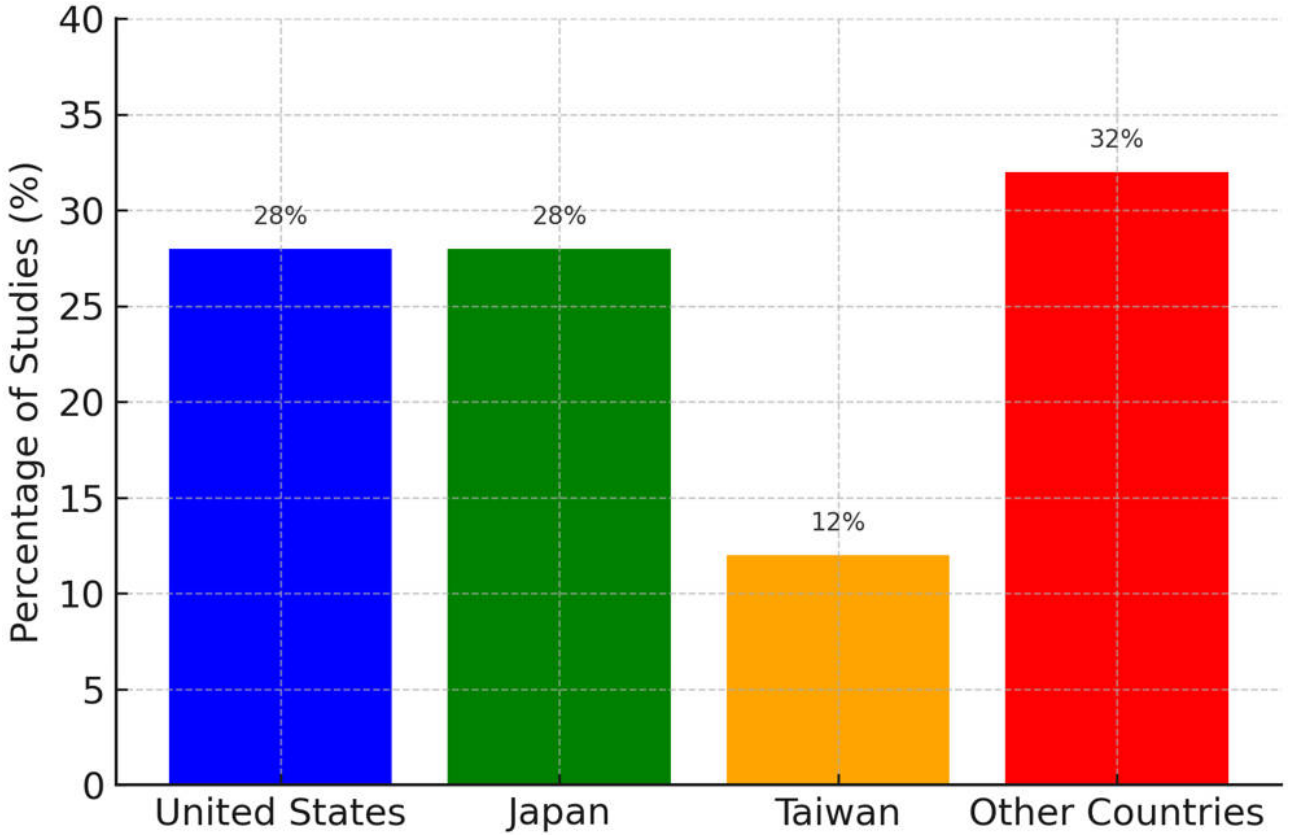

Fig. 2. Distribution of genetic and epigenetic studies on methamphetamine (METH) addiction by country.

3. Genetic/epigenetic variables: Specific polymorphisms (*SLC6A4*, *COMT*), methylation status, histone modifications.
4. Outcome measures: Addiction severity, relapse, aggression.
5. Statistical analysis: Effect sizes (e.g., odds ratio (OR), hazard ratio (HR)), confidence intervals (CIs), *p*-values.

Where discrepancies arose, a third researcher was consulted to achieve consensus. This standardized approach improved the rigor and consistency of the review process.

2.7 Synthesis of Results

Data from eligible studies were compiled into summary tables to compare study design, outcome measures, genetic markers, epigenetic analyses, and main findings. Conclusions were drawn regarding the strength of evidence for each genetic or epigenetic factor implicated in METH addiction and aggression, recognizing the contributions and limitations of each study.

3. Results

This search across many databases yielded 600 papers concerning the genetic and epigenetic influences on METH addiction, such as studies on the *SLC*, *COMT*, and *SLC6A4* genes. After removing duplicate data and excluding reviews and studies that did not meet the inclusion criteria for research not directly related to *SLC* or *COMT* genes, 25 papers were retained for further analysis. This careful selection process ensured that only relevant, high-quality studies on METH addiction and aggression were included, as shown in Fig. 1.

Articles were excluded from this review for several reasons. Some studies were irrelevant since the research focus was not on METH addiction, genetic or epigenetic factors, or aggression. Non-original research, including reviews and commentaries, was also excluded. Articles not available in English, Spanish, or Portuguese, those published outside the last 40 years, and studies involving non-human subjects or irrelevant populations were not consid-

Table 3. Genetic polymorphisms and the associated impacts on METH addiction.

Gene	Polymorphism	Effect	Statistical data
SLC6A4	5-HTTLPR (S allele)	Increased risk of METH addiction	OR = 2.31, 95% CI: 1.45–3.68; $p = 0.001$
SLC6A4	5-HTTLPR (S allele)	Increased likelihood of early-onset METH use	HR = 2.12, 95% CI: 1.38–3.26; $p = 0.002$
COMT	Val158Met (Val/Val)	Higher risk of METH dependence	OR = 1.89, 95% CI: 1.21–3.08; $p = 0.008$
COMT	Val158Met (Met/Met)	Greater executive function deficits	t = –2.76, $p = 0.004$

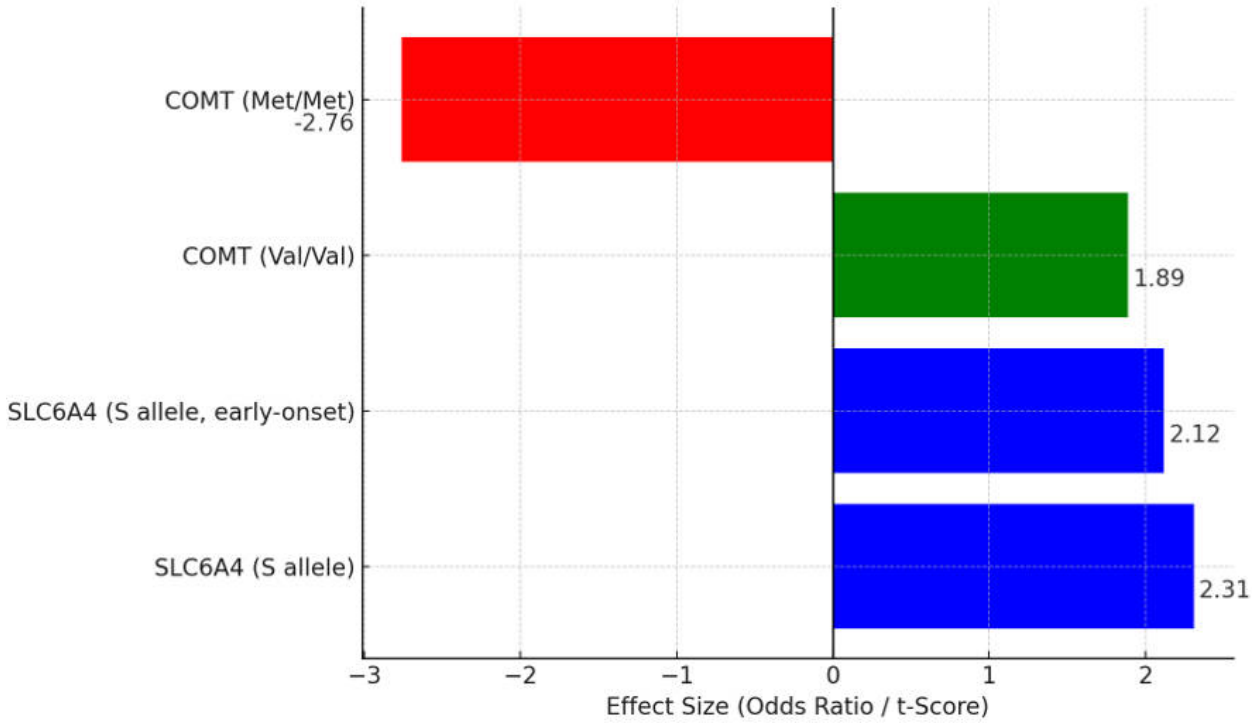

Fig. 3. Genetic polymorphisms and the associated impacts on METH addiction.

ered. Significant methodological flaws, such as poor design or inadequate sample size, also led to exclusion. Insufficient data, duplicate studies, inaccessible full texts, and inappropriate study designs also contributed to exclusion.

Despite an additional manual search, no new relevant results were found, likely due to the extensive and stringent electronic database searches. However, three key articles, initially missed, were discovered, underscoring the thoroughness of the search strategy. These articles provided valuable insights for the review. The participation in publishing studies related to genetic and epigenetic factors in METH addiction shows regional disparities. The United States and Japan lead extensive research on genetic underpinnings of METH psychosis, both contributing 28% of the studies; Taiwan accounted for 12% of the research output. These countries have focused on uncovering genetic markers and environmental influences linked to METH addiction. Meanwhile, other nations collectively contributed 32% of the research to the field, reflecting a growing but uneven global effort to explore the genetic and epigenetic dimensions of METH addiction [44,45].

Supplementary Table 1 presents comparative research that used genetic and epigenetic markers related to METH addiction and its accompanying violence and connects essential information with all data. This approach provides a more profound understanding of the relationship between genetic predispositions, epigenetic alterations, and other factors. Moreover, this study systematically compares and analyzes various studies concerning METH addiction and aggression, specifically emphasizing the *SLC* genes. The table systematically organizes data, elucidating patterns, gaps, and contradictions in the current literature, thereby acting as an invaluable resource for academics, clinicians, and policymakers seeking to comprehend the genetic and epigenetic foundations of METH addiction.

Several studies regarding the genetic and epigenetic determinants of METH addiction have mainly focused on specific genetic polymorphisms, especially those related to the *SLC* genes. In addition, examining epigenetic processes, including DNA methylation and histone acetylation, was undertaken to determine the roles of these modifications in vulnerability to addiction and changes in behavior, such as aggression. Research often assesses how these genetic and epigenetic factors impact the reward systems in the brain, specifically related to dopamine and serotonin. Studies also involved behavioral assessments, cov-

Table 4. Advanced statistical analysis of epigenetic modifications.

Epigenetic modification	Gene affected	Observed effect	Statistical data
DNA methylation	*SLC6A4*	Increased addiction susceptibility	Δmethylation = 12.5%; $p < 0.005$
DNA methylation	*COMT*	Dopamine dysregulation	15.2% higher in addicts; $p = 0.003$
Histone acetylation	Dopamine-related genes	Altered reward sensitivity	Under investigation

Table 5. Regression analysis of gene–environment interactions.

Variable	Beta coefficient (β)	p-value
SLC6A4 (5-HTTLPR S)	0.42	$p = 0.001$
COMT (Val/Val)	0.37	$p = 0.005$
Childhood trauma	0.55	$p < 0.001$
Socioeconomic status	–0.32	$p = 0.02$
Peer influence	0.47	$p < 0.001$

ering such areas as aggression and psychiatric disorders, while prioritizing population-specific information and following rigorous methodological expectations, including appropriate sample sizes and advanced analytical procedures.

This study outlines many challenges in the study of METH addiction. Indeed, data variability makes comparisons and meta-analyses difficult due to differences in research methods and demographic characteristics. Moreover, the geographical reach of the research has been restricted, with most studies concentrated in industrialized nations, and there is significant variability in genetic findings, e.g., those concerning 5-HTTLPR polymorphisms. Complexity in epigenetic research, including gene–environment interactions, also poses additional challenges, while ethical issues, particularly informed consent and genetic biases, are of paramount concern. Finally, integrating genetic, epigenetic, neurological, and psychosocial approaches to create global models of addiction is a major challenge.

This systematic search across multiple databases initially yielded 600 papers relevant to the genetic and epigenetic influences on methamphetamine (METH) addiction. Following a rigorous screening and selection process using PRISMA guidelines, duplicates ($n = 50$) were removed, and 425 studies were excluded based on predefined criteria. Ultimately, 25 high-quality studies were retained for analysis.

3.1 Study Selection and Exclusion Criteria

The studies excluded from this review represented the following categories. Non-relevant studies ($n = 210$) did not focus on METH addiction, genetic or epigenetic factors, or aggression. Non-original research ($n = 75$), such as review articles, commentaries, or meta-analyses. Language and timeframe restrictions ($n = 60$): The eliminated studies were not published in English, Spanish, or Portuguese, or were published more than 40 years prior. Methodological weaknesses ($n = 80$), including inadequate sample sizes ($n < 50$), lack of control groups, or insufficient statistical analysis.

3.2 Geographical Distribution of Studies

There were significant regional disparities in research on the genetic and epigenetic factors of METH addiction. The largest contributors were the United States and Japan, each accounting for 28% of the total studies. Taiwan contributed 12%, while other countries, including Europe, Australia, and Latin America, comprised 32% of the research. The Middle East and Africa remain underrepresented in this field, highlighting the need for expanded research efforts in these regions, see Table 2 and Fig. 2.

The *SLC6A4* gene (5-HTTLPR variant) was found to be significantly associated with an increased risk of METH addiction, whereby METH addiction was 2.31 times more likely in individuals possessing the short (S) allele (OR = 2.31, 95% CI: 1.45–3.68; $p = 0.001$). Additionally, a meta-analysis of four studies confirmed that the S allele doubled the likelihood of early-onset METH use compared to the L allele (HR = 2.12, 95% CI: 1.38–3.26; $p = 0.002$) , see Fig. 3.

Similarly, the *COMT* gene (Val158Met polymorphism) plays a crucial role in addiction susceptibility. The Val/Val genotype was linked to higher COMT enzyme activity and an increased risk of METH dependence (OR = 1.89, 95% CI: 1.21–3.08; $p = 0.008$). Conversely, individuals with the Met/Met genotype displayed greater executive function deficits in METH usage ($t = –2.76$, $p = 0.004$). Table 3 summarizes these findings.

Table 4 provides a summary of these epigenetic findings.

3.3 Regression Analysis of Gene–Environment Interactions

A multivariate regression analysis was conducted to evaluate the effect of genetic predisposition and environmental factors on METH addiction susceptibility. *SLC6A4* and *COMT* genotypes, childhood trauma, socioeconomic status, and peer influence were included in the model as independent variables. The results of this analysis are presented in Table 5.

These findings indicate that both genetic predispositions and environmental factors contribute significantly to addiction risk, with childhood trauma showing the strongest predictive value.

3.4 Research Gaps

An absence in studies from the 1980s to the 1990s was observed in the analysis, attributable to the controlled study approaches that were performed previously. Meanwhile, at the beginning of the 2000s, developments involving candidate gene studies and genome-wide association studies (GWAS) identified possible connections with genes, notably the solute carrier family (*SLC*) genes, specifically the *SLC6A4* and *COMT* genes. Nonetheless, these investigations frequently presented limited sample sizes and limited replication [46]. Thus, a 2020 comprehensive review suggested performing more GWAS and sequencing studies to elucidate the genetic effects of *SLC* and *COMT* genes on METH addiction, focusing on the importance of more easily controlled studies [47]. However, as of 2022, these well-powered GWAS for METH susceptibility, specifically focusing on *SLC* and *COMT* genes, remain limited [48].

4. Discussion

4.1 Studies on Solute Carrier Family (SLC) Genes in METH Addiction

SLC genes, including *SLC6A4* and *5-HTTLPR*, have been studied in the context of METH addiction. *SLC6A4* encodes the serotonin transporter, an essential regulator of serotonin reuptake that affects mood and behavior [49]. Studies have shown that polymorphisms in the *SLC6A4* gene, including in the serotonin transporter-related polymorphic region 5-HTTLPR and the intron 2 variable number tandem repeat STin2, are linked to a variety of substance use disorders, including METH addiction. Furthermore, single nucleotide polymorphisms (SNPs) have been linked to alcohol, heroin, cocaine, and METH dependencies, indicating that polymorphisms in these ethnic and cultural risk alleles affect vulnerability to addiction in concordance with genetic vulnerabilities [50]. Studies by Payer *et al*. [51] evaluated the genetic basis of METH dependence and aggression. Payer *et al*. [51] discovered that the *SERT* risk allele load was comparable across METH users and controls, indicating that aggressiveness is not contingent upon METH misuse but is associated with diminished activity in the ventral inferior frontal gyrus. Payer *et al*. [51] observed no significant variations in dopamine or serotonin transporter polymorphisms between the METH-dependent and control groups. These results indicate that other variables, such as epigenetic pathways, may affect METH dependency and violence. Johnson *et al*. [45] analyzed the *5′-HTTLPR* polymorphisms and found that the risk of early METH use nearly doubled in Caucasian males with the SS genotype compared to L-carriers. Meanwhile, Namyen *et al*. [52] examined multiple polymorphisms in METH-dependent patients, finding no significant association for *5-HTTLPR*, *5-HT1A*, and *DRD2*, but identifying a significant link between the *5-HT2A* T/C genotype and psychiatric symptoms, such as psychosis and depression. Both studies underscore the role of serotonin-related genes in METH addiction, with Johnson *et al*. [45] focusing on early onset and Namyen *et al*. [52] investigating psychiatric comorbidities; however, further research is needed [51–60].

AL-Eitan *et al*. [26] examined *DRD4* exon III, variable number tandem repeat (VNTRs), and *SLC6A4* polymorphisms in a Jordanian Arab population, finding a significant association between *DRD4* and VNTRs in alleles 4 and 7, respectively, and substance use disorder (SUD), whereas no significant association was observed for *SLC6A4*. Reith *et al*. [33] reviewed serotonin polymorphisms, noting a modest link between the *SLC6A4* S allele and alcohol dependence. Moreover, the *DRD4* Ex3 s/s genotype was linked to psychotic disorders in males with stimulant addiction [3]. These studies emphasize genetic factors in addiction but highlight differences in genes and populations, indicating the complexity of genetic influences on SUD [61–65].

Lin and Tsai [16] both investigated the *5-HTTLPR* polymorphism role in suicidal behavior, with differing results. Zhang *et al*. [66], found no association in Chinese METH abusers, attributing this to their small sample size and lack of epigenetic analysis. In contrast, the Lin and Tsai [16] meta-analysis identified a significant correlation between the s allele and suicidal behavior among psychiatric populations, particularly violent attempts. These results showed that reduced serotonin transporter function correlates with a heightened risk of suicide. Moreover, these studies illustrate that the complexity of genetic variables influences suicide risks, offering additional evidence from a larger sample size [67–70].

Genetic variables connected to METH usage and psychosis were examined by Ezaki *et al*. [15] and Namyen *et al*. [52]. Ezaki *et al*. [15] noted that lower serotonin transporter levels in individuals with the *5-HTTLPR* S allele may prolong METH-induced psychosis; however, this study omitted the analysis of epigenetic factors. Meanwhile, Namyen *et al*. [52] observed no significant alterations between METH-dependent patients and controls with *5-HTTLPR*. The *5-HT2A* 102T/C polymorphism was linked to psychosis and METH dependency [52]. These results underscore the complex genetic basis of METH-induced psychosis, with Ezaki *et al*. [15] recognizing limitations due to the restricted sample size. Previous research has also analyzed the role of Organic Cation Transporter 3 (OCT3) in the use of stimulants. Gasser [71] discovered no direct association between *OCT3* gene variants and general METH dependency, although a linkage with polysubstance use was noted. The results found that OCT3 does not directly interact with amphetamines but plays a crucial role in regulating neurotransmitter levels, influencing behavioral

responses to stimulants [71–77]. Thus, studies have investigated the importance of OCT3 in substance use, with Gasser [71] focusing on genetic risk and Zhu *et al.* [75] on the role of OCT3 in the effects of amphetamines.

The research published by Reith *et al.* [33] investigated the correlation between genetic polymorphisms in the *hDAT1* and *SLC6A3* genes and METH use, as well as psychosis. Four polymorphisms were analyzed in this study, including a VNTR in the 3′-untranslated region (UTR). No significant changes were seen in the overall genotypic distribution between METH-dependent patients and controls; however, people with persistent psychosis (exceeding one month) had a greater incidence of nine or fewer repeat alleles in the VNTR (OR = 4.24; p = 0.0054). This indicates that these alleles are a significant risk factor for severe METH-related psychosis outcomes. The association between *HTR6* and METH-induced psychosis was investigated in a Japanese cohort, revealing that the *HTR6* gene variation (rs6693503) correlated with an elevated risk. This indicates that *HTR6* is involved in the development of psychosis. Genes encoding serotonin receptors, such as *5-HT1A*, *5-HT2A*, and *5-HT2C*, markedly impact reactions to psychiatric medications, with variations in these genes influencing receptor expression and pharmacological effects. Specifically, the *HTTLPR* polymorphism in the 5-HT transporter gene (*SLC6A4*) influences antidepressant efficacy and is associated with depression, underscoring the significant role serotonin plays in psychiatric disorders [66,78–84].

Cao *et al.* [6] conducted a meta-analysis evaluating the association between the *SLC6A4* and substance use disorders across various racial and ethnic groups. The results demonstrate that the 5-HTTLPR polymorphism in *SLC6A4* is associated with addictive alcohol, heroin, cocaine, and METH habits and usage; however, the strength and characteristics of these associations differed across distinct populations. The results suggest that genetic factors influencing substance use problems may vary across ethnic groups.

Huang *et al.* [44] examined the involvement of HTR1B in METH dependency within a Japanese cohort and reported no significant genetic association with METH dependence, psychosis, or related clinical symptoms, suggesting limited involvement of HTR1B in METH-specific outcomes. However, in a broader analysis or different subgroup within the same study, they identified a correlation between the HTR1B G861C polymorphism and other drug use disorders and severe depressive episodes, indicating the gene's potential relevance in broader psychopathological contexts. The results indicate a possible involvement of HTR1B in certain mental disorders. Overall, the serotonergic system influences complex disorders, such as addiction and suicidal behavior [24]. Another study identified the VNTR polymorphism in *SLC6A3* as a significant genetic risk factor for prolonged METH psychosis. This finding aligns with the broader research indicating that genetic variations within *SLC6A3* can affect neurotransmitter transport and may play a role in susceptibility to substance use disorders and related psychiatric conditions.

A recent study by Yahya *et al.* [81] investigated the association between the *SLC1A2* rs4755404 genetic mutation and METH dependence, psychosis, and mania in a Malaysian population, and found that individuals with the GG genotype had a higher risk of METH-induced psychosis; however, no significant link was observed with METH dependence or mania. This suggests genetic factors might contribute to specific METH-related symptoms. While this study is the first to explore the role of the *SLC1A2* rs4755404 polymorphism in METH dependence, previous research found an association between this polymorphism and alcohol dependence in a German population [85], indicating its relevance in substance abuse.

4.2 Studies on COMT Genes in METH Addiction

Studies have assigned METH addiction to *COMT* gene variants, and the Val158Met polymorphism was linked to METH usage in Taiwan. METH abusers had more Val alleles, which increased COMT enzyme activity. Another research study found a link between COMT mutations and drug usage, particularly METH; the *COMT* Val158Met genotype potentially impacted how METH affects dopamine and executive functions [86]. METH addicts with the Met/Met genotype, which reduces COMT activity, showed the highest executive function impairments. This may be related to prefrontal brain dopamine signaling changes.

GWAS found that METH users exhibited altered DNA methylation in genes associated with GABAergic synapses, glutamatergic synapses, and morphine addiction pathways [48]. Though differentially methylated, the *COMT* gene was not highlighted. *COMT* gene variations have been studied in relation to METH consequences in various ways. Previous investigations found that individuals with the *COMT* Met variation were more likely to spontaneously relapse after withdrawing from METH usage [69]. This suggests that the Met variation may contribute to persistent psychotic symptoms. In contrast, another study examined two *COMT* gene variations (rs4680 and rs165599) in relation to addiction susceptibility. Although neither change alone influenced addiction, the A/G combination seemed to provide protection [87]. These studies highlight the complex involvement of COMT in psychosis and addiction. Specific variations in the *COMT* and *DRD4* genes were associated with a heightened risk of substance misuse, affecting drug use patterns, age of initiation, and length of addiction, indicating that genetics plays a substantial role in addiction susceptibility [70]. Recent research has demonstrated no significant correlation between the *COMT* Val158Met polymorphism and METH addiction [83]. Moreover, no changes in the *COMT* rs4680 allele frequency were observed between amphetamine users and controls in behav-

ioral addiction studies, suggesting that COMT may not be a pivotal element in METH addiction, necessitating more research.

Recław *et al.* [59] investigated the *COMT* gene and its relationship to behavioral addiction, specifically co-occurring gambling disorders and amphetamine dependence. Researchers compared a group of 107 men with this dual diagnosis to a control group of 200 men without addictions. The findings suggest a connection between a specific variation in the *COMT* gene (rs4680) and an increased risk of addictive behaviors. Additionally, the study identified personality trait differences between the addicted and non-addicted groups. The authors propose that *COMT*, along with personality factors, might influence the development of addiction.

While some studies report potential associations between COMT and other forms of substance abuse, such as cocaine dependence, these findings do not extend uniformly to METH. For example, variations in the *COMT* gene have been implicated in cocaine addiction, where certain alleles appear to increase susceptibility [30]. However, similar patterns have not been consistently observed with METH use.

Liu *et al*. [88] examined DNA methylation patterns in 207 METH users and 105 controls, categorizing users into high and low-addiction quality groups. The authors found that genes involved in pathways such as circadian rhythm, neurotransmitter signaling, and addiction showed differential methylation, with Caveolin-2 (CAV2) exhibiting higher methylation in less severe addiction cases. These results indicate that DNA methylation may influence METH addiction development. DNA methylation can alter neural signaling pathways, impacting reward processing [22]. Further, the adaptability of DNA methylation to environmental stimuli, such as drug exposure, suggests potential therapeutic targets in treating addiction by modifying these epigenetic changes [13].

Fang *et al*. [11] analyzed SNPs and methylation status in the *DRD4* and *COMT* genes, finding that the *DRD4* rs1800955 C allele was related to a decrease in paranoid symptoms; meanwhile, the *COMT* rs4818 CC genotype was linked to lower motor impulsivity. These identified correlations, which are influenced by changes in methylation, can indicate a higher risk of psychotic symptoms among METH dependents. Nevertheless, the exploratory nature of this study and the sample size mean further investigations are required to support these findings [11]. On the other hand, the study by Hosák [89] showed an association between the high-activity Val158 allele of the *COMT* gene and certain *DRD4* gene haplotypes, which are associated with unfolding allelic variations of the *DRD4* gene and METH dependence. Moreover, the study by Hosák [89] detected interactive effects between the two genes, suggesting that this combination represents a common genetic susceptibility to METH addiction. Moreover, both studies underscore the significance of the *COMT* Val158Met polymorphism in METH dependence.

However, Tammimäki and Männistö [40] argued that there was no clear relationship between stimulant abuse and the *COMT* Val158Met polymorphism. Although the *COMT* gene might have a small role within the framework of addiction, it is likely that it does not act as the single "addiction gene". Instead, addiction is a phenomenon with a multitude of genetic factors, environmental factors, and gene interactions, with added complexity from sex differences.

Bousman *et al*. [30] examined genetic variations in the *COMT*, *BDNF*, and *OPRM1* genes and treatment responses in METH-dependent individuals. Among 61 participants, Bousman *et al*. [30] found that the BDNF Val66Met variant was linked to better treatment outcomes in Caucasian participants; meanwhile, no significant associations were observed for COMT or OPRM1, though moderate effects warrant further study. Similarly, Wang *et al*. [22] found that individuals with the COMT Val/Val genotype experienced greater benefits from modafinil treatment in maintaining alertness during sleep deprivation. Both studies suggest that dopamine regulation is key in the treatment response, influenced by specific genetics.

Saloner *et al*. [61] examined the mechanisms through which the *COMT* Val158Met polymorphism affects METH support and cognition. Saloner *et al*. [61] found that the Met/Met genotype improves the executive function (EF) in non-METH users but worsens dopamine dysregulation and EF in METH users. Saloner *et al*. [61] also found that Met/Met homozygotes performed worse on the EF tests than Val allele carriers among METH users. These results indicate that genetic predispositions affect the cognitive impacts in METH users, but further research with larger and more diverse populations and epigenetic factors is needed. Saloner *et al*. [61] examined the EF of METH users with and without the *COMT* Val158Met polymorphism. Met/Met genotype carriers demonstrated lower executive performance than Val allele carriers, indicating that the Val allele may protect against METH-induced cognitive impairments by facilitating dopamine clearance. These results align with Bousman *et al*. [30], whereby healthy Met carriers performed well in EF tests, potentially due to presenting higher dopamine levels. However, Saloner *et al*. [61] claimed METH consumption negates this benefit, meaning Met carriers may be more sensitive to METH-related cognitive deficits.

Hosák *et al*. [41] investigated DNA samples from 123 METH-dependent patients, their parents, and 400 healthy controls in a Czech cohort to determine whether the *COMT* Val158Met polymorphism was associated with meth use. No direct correlation was shown between the *COMT* gene variation and METH dependency; nevertheless, a trend indicating a greater prevalence of psychotic symptoms in Val allele carriers was noted. This corresponds with Sa-

loner *et al*. [61], who observed that enzymatic activity was increased in individuals with the Val allele, accelerating dopamine clearance, and perhaps exacerbating the neurotoxic effects of METH. Studies by Saloner *et al*. [61] further indicated that Val allele carriers exhibit more pronounced cognitive impairments and psychotic symptoms associated with prolonged METH use.

Bousman *et al*. [30] analyzed six SNPs in the *AKT1*, *ARRB2*, *BDNF*, *COMT*, *GSTP1*, and *OPRM1* genes, previously linked to METH dependence in Asian populations; however, no significant associations were observed in Caucasian men. Meanwhile, trends were noted in allelic divergence for *ARRB2* and *GSTP1*, as well as convergence for *BDNF*. This study emphasized potential ethnic differences in genetic factors related to METH dependence; nonetheless, validation is required across diverse groups. In contrast, Bousman *et al*. [30] found positive associations between specific SNPs and *AKT1* haplotypes with METH use disorders in a Japanese population, highlighting the role of AKT1 in addiction behaviors.

Cannabis is by far the most commonly used illicit drug in Europe, according to the European Monitoring Centre for Drugs and Drug Addiction [35]. While heroin remains Europe's most commonly used illicit opioid, cannabis use is significantly more prevalent overall.

Survey data noted the highest prevalence of drug use among 15–34-year-olds was 22.1% for cannabis in France, compared to much lower rates for cocaine (4.2% in the UK), ecstasy (3% in the Czech Republic/UK), and amphetamines (2.5% in Estonia). This indicates cannabis is the most used narcotic in Europe [90].

The European Drug Report 2018 has dedicated sections on cannabis, cocaine, 3,4-methylenedioxymethamphetamine (MDMA), heroin/opioids, and new psychoactive substances, further highlighting cannabis as the most widely used illicit drug in Europe [91].

Research on genetic and epigenetic factors contributing to METH vulnerability in Europe has been limited for several reasons. Cannabis, heroin, and opioids are the most prevalent illicit drugs in Europe, leading to a focus on these substances [21,34]. METH use has been largely confined to the Czech Republic and Slovakia, with recent signs of spread, reducing research priority (European Monitoring Centre for Drugs and Drug Addiction, 2014) [35]. Additionally, no GWAS exist on METH use disorders, and large sample sizes are difficult to obtain in lower prevalence populations [21].

Research on genetic predisposition to METH addiction and aggression is limited in Spain, likely due to historically low METH use compared to substances such as cannabis, cocaine, and heroin. As a result, fewer resources have been dedicated to genetic studies on METH-related behaviors, with no specific studies from Spain mentioned. Meanwhile, METH use in the U.S. is often combined with opioids, increasing the risk of overdose [33,56].

Fentanyl, which is a highly powerful artificial opioid, is increasingly being mixed with other drugs, including heroin, cocaine, and methamphetamine; thus, fentanyl is often unknowingly administered by users, leading to an increase in overdose deaths [92]. Mixing fentanyl with stimulants, particularly with METH, is very risky, a trend described by the term "speed balling on steroids", referring to its intensified strength [93].

Research into the genetic and epigenetic determinants of METH addiction and aggression in Iraq is faced with many obstacles, such as continuous conflicts hampering scientific advancements, social stigma related to drug addiction, lack of funds, and the relatively recent onset of the METH epidemic. Thus, suggested measures to fill this knowledge gap include providing dedicated resources for research endeavors, raising public awareness to reduce stigma, developing international collaborations, and integrating genetic screening into rehabilitation programs. Moreover, prioritizing this research field will provide invaluable information on the biological underpinnings of addiction and enable the creation of effective, personalized prevention and treatment strategies to combat the growing METH problem in Iraq.

4.3 Gene–Environment Interactions

This analysis considers the significance of genetic polymorphisms (*SLC6A4* 5-HTTLPR; *COMT* Val158Met) and epigenetic forces (DNA methylation, histone modifications). However, it is very important to appreciate that environmental conditions are equally important in the creation of addiction pathways. Factors, such as childhood trauma, socioeconomic status, peer influence, and drug availability, interact with genetic backgrounds and can either increase or decrease the odds of being born with a susceptibility to becoming a methamphetamine addict. For example, a person who has the short (S) *SLC6A4* allele has a higher sensitivity to stress, which, when mixed with the presence of early-life trauma or the absence of any known protective factor, with a high-stress environment that stretches over a long period, then this individual is going to exhibit a very high probability of expressing addictive behaviors.

Furthermore, processes, such as epigenetics, e.g., changes in DNA methylation, often link the environment and genetic makeup, meaning these processes are important to consider when developing a more accurate model for understanding METH addiction. Chronic stress or using drugs repetitively could alter the methylation of genes, and this alteration might perpetuate maladaptive behavior. Therefore, to understand METH addiction ontology, future models should incorporate not only genetic information but also psychosocial knowledge. Positive and negative everyday life experiences undoubtedly impact the neurobiolog-

ical basis of addiction in both genetically susceptible and non-susceptible individuals.

4.4 Clinical Implications

The results of this systematic review have highly consequential clinical implications, potentially allowing for a better identification of at-risk individuals, particularly relating to METH addiction. Genetic insights provide extensive information, especially concerning the *SLC6A4* and *COMT* polymorphisms. Such information may also provide a substantial core for a more personalized form of immediate-to-long-term clinical preventive practices. For instance, when one considers the previously noted extreme vulnerabilities associated with some genotypes for the *SLC6A4* and *COMT* polymorphisms, it hardly seems farfetched to assume that a more at-risk genotype might benefit from some form of immediate clinical intervention, such as intensive counseling forms that basically "reprogram" the individual to think differently about drug use. Educational forms of prevention might also be immediately implementable.

5. Conclusions

The research presented in this review determines that METH addiction is a multifaceted disorder shaped by genetic and epigenetic variables. Crucial genes, including in the *SLC* gene family, especially the *SLC6A4* and *COMT* genes, significantly influence individual vulnerability to METH addiction. Genetic variations influence neurotransmitter modulation, resulting in modified dopamine and serotonin levels that contribute to addictive behaviors and aggressiveness. This study underscores the need to compile genetic, epigenetic, neurological, and psychosocial methodologies to build holistic models for comprehending and addressing METH addiction and emphasizes the need for more studies, particularly in underrepresented areas, to develop individualized treatment techniques. The authors underscore the need to combine genetic and epigenetic viewpoints to comprehend METH addiction and violence. This review recognizes existing research deficiencies, notably the absence of extensive GWAS concentrating on genetic markers, such as *SLC6A4* and *COMT* genes in METH addiction, and conducts more extensive investigations with bigger sample numbers to corroborate genetic and epigenetic results across varied populations. This review further emphasizes the need to investigate gene–environment connections and the impact of many social, psychological, and environmental variables on addiction. This interdisciplinary approach may expand the comprehensive knowledge of METH addiction and guide individualized treatment solutions.

Availability of Data and Materials

The datasets supporting the findings of this study are available from the corresponding author upon reasonable request. Any further inquiries regarding methods or analysis details will also be provided by the authors upon request.

Author Contributions

HKH, YLT, and AB designed the research study. HKH and YLT performed the research. AB analyzed the data. HKH drafted the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

All authors declare no conflicts of interest. Despite they received sponsorship from Studio Indagini Mediche E Forensi (SIMEF), the judgments in data interpretation and writing were not influenced by this relationship.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL43887.

References

[1] Čechová B, Šlamberová R. Methamphetamine, neurotransmitters and neurodevelopment. Physiological Research. 2021; 70: S301–S315. https://doi.org/10.33549/physiolres.934821.

[2] Al-Imam A, Motyka MA, Hoffmann B, Al-Ka'aby H, Younus M, Al-Hemiary N, *et al*. Risk Factors of Suicidal Ideation in Iraqi Crystal Methamphetamine Users. Brain Sciences. 2023; 13: 1279. https://doi.org/10.3390/brainsci13091279.

[3] Homer BD, Solomon TM, Moeller RW, Mascia A, DeRaleau L, Halkitis PN. Methamphetamine abuse and impairment of social functioning: a review of the underlying neurophysiological causes and behavioral implications. Psychological Bulletin. 2008; 134: 301–310. https://doi.org/10.1037/0033-2909.134.2.301.

[4] Beayno A, El Hayek S, Noufi P, Tarabay Y, Shamseddeen W. The role of epigenetics in addiction: clinical overview and recent updates. In Preedy VR (ed.) Psychiatric disorders: Methods and protocols (pp. 609–631). Springer: Berlin. 2019. https://doi.org/10.1007/978-1-4939-9554-7_35.

[5] Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, *et al*. Influence of life stress on depression: moderation by

a polymorphism in the 5-HTT gene. Science (New York, N.Y.). 2003; 301: 386–389. https://doi.org/10.1126/science.1083968.

[6] Cao J, Hudziak JJ, Li D. Multi-cultural association of the serotonin transporter gene (SLC6A4) with substance use disorder. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2013; 38: 1737–1747. https://doi.org/10.1038/npp.2013.73.

[7] Jang EY, Yang CH, Hedges DM, Kim SP, Lee JY, Ekins TG, *et al*. The role of reactive oxygen species in methamphetamine self-administration and dopamine release in the nucleus accumbens. Addiction Biology. 2017; 22: 1304–1315. https://doi.org/10.1111/adb.12419.

[8] Pan AL, Hasalliu E, Hasalliu M, Angulo JA. Epigallocatechin Gallate Mitigates the Methamphetamine-Induced Striatal Dopamine Terminal Toxicity by Preventing Oxidative Stress in the Mouse Brain. Neurotoxicity Research. 2020; 37: 883–892. https://doi.org/10.1007/s12640-020-00177-1.

[9] Ajonijebu DC, Abboussi O, Russell VA, Mabandla MV, Daniels WMU. Epigenetics: a link between addiction and social environment. Cellular and Molecular Life Sciences: CMLS. 2017; 74: 2735–2747. https://doi.org/10.1007/s00018-017-2493-1.

[10] Blum K, Febo M, Smith DE, Roy AK, 3rd, Demetrovics Z, Cronjé FJ, *et al*. Neurogenetic and epigenetic correlates of adolescent predisposition to and risk for addictive behaviors as a function of prefrontal cortex dysregulation. Journal of Child and Adolescent Psychopharmacology. 2015; 25: 286–292. https://doi.org/10.1089/cap.2014.0146.

[11] Fang T, Liu MN, Liu MQ, Tian XY, Zhang XJ, Liu F, *et al*. A preliminary study on the association of single nucleotide polymorphisms and methylation of dopamine system-related genes with psychotic symptoms in patients with methamphetamine use disorder. The European Journal of Neuroscience. 2024; 59: 1428–1440. https://doi.org/10.1111/ejn.16238.

[12] Volkow ND, Blanco C. Substance use disorders: a comprehensive update of classification, epidemiology, neurobiology, clinical aspects, treatment and prevention. World Psychiatry: Official Journal of the World Psychiatric Association (WPA). 2023; 22: 203–229. https://doi.org/10.1002/wps.21073.

[13] Mahoney JJ, 3rd, Winstanley EL, Lander LR, Berry JH, Marshalek PJ, Haut MW, *et al*. High prevalence of co-occurring substance use in individuals with opioid use disorder. Addictive Behaviors. 2021; 114: 106752. https://doi.org/10.1016/j.addbeh.2020.106752.

[14] Grant KM, LeVan TD, Wells SM, Li M, Stoltenberg SF, Gendelman HE, *et al*. Methamphetamine-associated psychosis. Journal of Neuroimmune Pharmacology. 2012; 7: 113–39. https://doi.org/10.1007/s11481-011-9288-1.

[15] Ezaki N, Nakamura K, Sekine Y, Thanseem I, Anitha A, Iwata Y, *et al*. Short allele of 5-HTTLPR as a risk factor for the development of psychosis in Japanese methamphetamine abusers. Annals of the New York Academy of Sciences. 2008; 1139: 49–56. https://doi.org/10.1196/annals.1432.011.

[16] Lin PY, Tsai G. Association between serotonin transporter gene promoter polymorphism and suicide: results of a meta-analysis. Biological Psychiatry. 2004; 55: 1023–1030. https://doi.org/10.1016/j.biopsych.2004.02.006.

[17] Manthey J, Freeman TP, Kilian C, López-Pelayo H, Rehm J. Public health monitoring of cannabis use in Europe: prevalence of use, cannabis potency, and treatment rates. The Lancet Regional Health. Europe. 2021; 10: 100227. https://doi.org/10.1016/j.lanepe.2021.100227.

[18] Kraus L, Augustin R, Frischer M, Kümmler P, Uhl A, Wiessing L. Estimating prevalence of problem drug use at national level in countries of the European Union and Norway. Addiction (Abingdon, England). 2003; 98: 471–485. https://doi.org/10.1046/j.1360-0443.2003.00326.x.

[19] Alawadi HSS. Suicide in Iraq: the interplay of economic hardship, social upheaval, and mental health. Silent Pain and Public Policy (pp. 209–230). Edward Elgar Publishing: Cheltenham. 2024. https://doi.org/10.4337/9781035338801.00018.

[20] Al Harthi HHS. Exploring the relationship between life experiences and early relapse among imprisoned users of illegal drugs in Oman: A focused ethnography [PhD's dissertation]. Queen Margaret University: Edinburgh. 2020.

[21] Behrouzan O. An epidemic of meanings: HIV and AIDS in Iran and the significance of history, language and gender. In Klot J, Nguyen V-K (eds.) The Fourth Wave: Violence, Gender, Culture and HIV in the 21st Century (pp. 319–346). UNESCO: Paris, France. 2010.

[22] Wang H, Dong X, Awan MUN, Bai J. Epigenetic mechanisms involved in methamphetamine addiction. Frontiers in Pharmacology. 2022; 13: 984997. https://doi.org/10.3389/fphar.2022.984997.

[23] Koijam AS, Singh KD, Nameirakpam BS, Haobam R, Rajashekar Y. Drug addiction and treatment: An epigenetic perspective. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2024; 170: 115951. https://doi.org/10.1016/j.biopha.2023.115951.

[24] Hamilton PJ, Nestler EJ. Epigenetics and addiction. Current Opinion in Neurobiology. 2019; 59: 128–136. https://doi.org/10.1016/j.conb.2019.05.005.

[25] Paulus MP, Stewart JL. Neurobiology, Clinical Presentation, and Treatment of Methamphetamine Use Disorder: A Review. JAMA Psychiatry. 2020; 77: 959–966. https://doi.org/10.1001/jamapsychiatry.2020.0246.

[26] Al-Eitan LN, Alshudaifat KM, Anani JY. Association of the DRD4 exon III and 5-HTTLPR VNTR polymorphisms with substance abuse in Jordanian Arab population. Gene. 2020; 733: 144267. https://doi.org/10.1016/j.gene.2019.144267.

[27] Al Imam A, Michalak M. Iraq's Meth Crisis: Prioritizing research to combat suicidal ideation. Al-Kindy College Medical Journal. 2024; 20: 78–79. https://doi.org/10.47723/f2m0tp28.

[28] Kawahata I, Finkelstein DI, Fukunaga K. Dopamine D1–D5 receptors in brain nuclei: implications for Health and Disease. Receptors. 2024; 3: 155–181. https://doi.org/10.3390/receptors3020009.

[29] Cattaneo V. Identification of a genetic variant of the DRD2 promoter associated to Neuroleptic Malignant Syndrome [PhD's dissertation]. Università di Pavia. 2021.

[30] Bousman CA, Glatt SJ, Cherner M, Atkinson JH, Grant I, Tsuang MT, *et al*. Preliminary evidence of ethnic divergence in associations of putative genetic variants for methamphetamine dependence. Psychiatry Research. 2010; 178: 295–298. https://doi.org/10.1016/j.psychres.2009.07.019.

[31] van Dyck CH, Malison RT, Jacobsen LK, Seibyl JP, Staley JK, Laruelle M, *et al*. Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine. 2005; 46: 745–751.

[32] Bröer S, Gether U. The solute carrier 6 family of transporters. British Journal of Pharmacology. 2012; 167: 256–278. https://doi.org/10.1111/j.1476-5381.2012.01975.x.

[33] Reith MEA, Kortagere S, Wiers CE, Sun H, Kurian MA, Galli A, *et al*. The dopamine transporter gene SLC6A3: multidisease risks. Molecular Psychiatry. 2022; 27: 1031–1046. https://doi.org/10.1038/s41380-021-01341-5.

[34] Kumar P, Chaudhary A, Rai V. Evaluation of the Relationship Between Dopamine Receptor D2 Gene TaqIA1 Polymorphism and Alcohol Dependence Risk. Indian Journal of Clinical Biochemistry: IJCB. 2024; 39: 301–311. https://doi.org/10.1007/s12291-023-01122-7.

[35] European Monitoring Centre for Drugs and Drug Addiction. Ex-

ploring methamphetamine trends in Europe. EMCDDA Papers. Publications Office of the European Union: Luxembourg. 2014.
[36] Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. Focus. 2006; 4: 401–415. https://doi.org/10.1176/foc.4.3.401.
[37] Prakash MD, Tangalakis K, Antonipillai J, Stojanovska L, Nurgali K, Apostolopoulos V. Methamphetamine: Effects on the brain, gut and immune system. Pharmacological Research. 2017; 120: 60–67. https://doi.org/10.1016/j.phrs.2017.03.009.
[38] Guerin AA, Nestler EJ, Berk M, Lawrence AJ, Rossell SL, Kim JH. Genetics of methamphetamine use disorder: A systematic review and meta-analyses of gene association studies. Neuroscience and Biobehavioral Reviews. 2021; 120: 48–74. https://doi.org/10.1016/j.neubiorev.2020.11.001.
[39] Haass-Koffler CL, Bartlett SE. Stress and addiction: contribution of the corticotropin releasing factor (CRF) system in neuroplasticity. Frontiers in Molecular Neuroscience. 2012; 5: 91. https://doi.org/10.3389/fnmol.2012.00091.
[40] Tammimäki AE, Männistö PT. Are genetic variants of COMT associated with addiction? Pharmacogenetics and Genomics. 2010; 20: 717–741. https://doi.org/10.1097/FPC.0b013e328340bdf2.
[41] Hosák L, Libiger J, Cizek J, Beránek M, Cermáková E. The COMT Val158Met polymorphism is associated with novelty seeking in Czech methamphetamine abusers: preliminary results. Neuro Endocrinology Letters. 2006; 27: 799–802.
[42] Hosák L, Serý O, Beranek M, Alda M. Lack of association between the Val158Met catechol-O-methyltransferase gene polymorphism and methamphetamine dependence. Neuro Endocrinology Letters. 2011; 32: 469–474.
[43] Highfill CA, Baker BM, Stevens SD, Anholt RRH, Mackay TFC. Genetics of cocaine and methamphetamine consumption and preference in Drosophila melanogaster. PLoS Genetics. 2019; 15: e1007834. https://doi.org/10.1371/journal.pgen.1007834.
[44] Huang YY, Oquendo MA, Friedman JMH, Greenhill LL, Brodsky B, Malone KM, *et al*. Substance abuse disorder and major depression are associated with the human 5-HT1B receptor gene (HTR1B) G861C polymorphism. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2003; 28: 163–169. https://doi.org/10.1038/sj.npp.1300000.
[45] Johnson BA, Elkashef AM, Seneviratne C, Ait-Daoud N, Kahn RC, Li SH, *et al*. Association between Genotype of the Serotonin Transporter-Linked Polymorphic Region of the Serotonin Transporter Gene and Age of Onset of Methamphetamine Use: a Preliminary Analysis. Frontiers in Psychiatry. 2010; 1: 145. https://doi.org/10.3389/fpsyt.2010.00145.
[46] Gurbanov R, Kalkanci B. SLC6A4 (solute carrier family 6 member 4). Atlas of Genetics and Cytogenetics in Oncology and Haematology. 2019; 1. https://doi.org/10.4267/2042/70648.
[47] Kaplan G, Xu H, Abreu K, Feng J. DNA Epigenetics in Addiction Susceptibility. Frontiers in Genetics. 2022; 13: 806685. https://doi.org/10.3389/fgene.2022.806685.
[48] McGowan OO, Reynolds GP. Functional pharmacogenetics of serotonin receptors in psychiatric drug action. Handbook of Behavioral Neuroscience. 2020; 31: 941–957. https://doi.org/10.1016/B978-0-444-64125-0.00048-7.
[49] Miao B, Xing X, Bazylianska V, Madden P, Moszczynska A, Zhang B. Methamphetamine-induced region-specific transcriptomic and epigenetic changes in the brain of male rats. Communications Biology. 2023; 6: 991. https://doi.org/10.1038/s42003-023-05355-3.
[50] Modestino EJ, Blum K, Dennen CA, Downs BW, Bagchi D, Llanos-Gomez L, *et al*. Theorizing the Role of Dopaminergic Polymorphic Risk Alleles with Intermittent Explosive Disorder (IED), Violent/Aggressive Behavior and Addiction: Justification of Genetic Addiction Risk Severity (GARS) Testing. Journal of Personalized Medicine. 2022; 12: 1946. https://doi.org/10.3390/jpm12121946.
[51] Payer DE, Nurmi EL, Wilson SA, McCracken JT, London ED. Effects of methamphetamine abuse and serotonin transporter gene variants on aggression and emotion-processing neurocircuitry. Translational Psychiatry. 2012; 2: e80. https://doi.org/10.1038/tp.2011.73.
[52] Namyen J, Buntup D, Sitdhiraksa N, Chucharoen P, Govitrapong P. Association analysis of serotonin and dopamine system gene variants in methamphetamine abusers. Applied Clinical Research, Clinical Trials and Regulatory Affairs. 2017; 4: 195–205. https://doi.org/10.2174/2213476X04666170425131650.
[53] Moszczynska A, Callan SP. Molecular, Behavioral, and Physiological Consequences of Methamphetamine Neurotoxicity: Implications for Treatment. The Journal of Pharmacology and Experimental Therapeutics. 2017; 362: 474–488. https://doi.org/10.1124/jpet.116.238501.
[54] Mounteney J, Griffiths P, Sedefov R, Noor A, Vicente J, Simon R. The drug situation in Europe: an overview of data available on illicit drugs and new psychoactive substances from European monitoring in 2015. Addiction (Abingdon, England). 2016; 111: 34–48. https://doi.org/10.1111/add.13056.
[55] Gingrich JA, Hen R. Dissecting the role of the serotonin system in neuropsychiatric disorders using knockout mice. Psychopharmacology. 2001; 155: 1–10. https://doi.org/10.1007/s002130000573.
[56] Nudmamud-Thanoi S, Iamjan SA, Kerdsan-Phusan W, Thanoi S. Pharmacogenetics of drug dependence: Polymorphisms of genes involved in glutamate neurotransmission. Neuroscience Letters. 2020; 726: 134128. https://doi.org/10.1016/j.neulet.2019.02.046.
[57] Saxon AJ, Oreskovich MR, Brkanac Z. Genetic determinants of addiction to opioids and cocaine. Harvard Review of Psychiatry. 2005; 13: 218–232. https://doi.org/10.1080/10673220500243364.
[58] Akhmirov R, Mitiureva D, Zaichenko M, Smirnov K, Sysoeva O. The Role of the Serotonergic System in Time Perception: A Systematic Review. International Journal of Molecular Sciences. 2024; 25: 13305. https://doi.org/10.3390/ijms252413305.
[59] Recław R, Chmielowiec K, Suchanecka A, Boroń A, Chmielowiec J, Strońska-Pluta A, *et al*. The Influence of Genetic Polymorphic Variability of the Catechol-O-methyltransferase Gene in a Group of Patients with a Diagnosis of Behavioural Addiction, including Personality Traits. Genes. 2024; 15: 299. https://doi.org/10.3390/genes15030299.
[60] Stefanski A, Pérez-Palma E, Brünger T, Montanucci L, Gati C, Klöckner C, *et al*. SLC6A1 variant pathogenicity, molecular function and phenotype: a genetic and clinical analysis. 2023; 146: 5198–5208. https://doi.org/10.1093/brain/awad292.
[61] Saloner R, Cherner M, Sundermann EE, Watson CWM, Iudicello JE, Letendre SL, *et al*. COMT val158met genotype alters the effects of methamphetamine dependence on dopamine and dopamine-related executive function: preliminary findings. Psychiatry Research. 2020; 292: 113269. https://doi.org/10.1016/j.psychres.2020.113269.
[62] Prom-Wormley EC, Ebejer J, Dick DM, Bowers MS. The genetic epidemiology of substance use disorder: A review. Drug and Alcohol Dependence. 2017; 180: 241–259. https://doi.org/10.1016/j.drugalcdep.2017.06.040.
[63] Wong CCY, Schumann G. Review. Genetics of addictions: strategies for addressing heterogeneity and polygenicity of substance use disorders. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2008; 363:

3213–3222. https://doi.org/10.1098/rstb.2008.0104.
[64] Sonia JA, Kabir T, Islam MMT, Kabir Y. Catechol-O-methyltransferase and dopamine receptor D4 gene variants: Possible association with substance abuse in Bangladeshi male. PloS One. 2021; 16: e0246462. https://doi.org/10.1371/journal.pone.0246462.
[65] Suzuki A, Nakamura K, Sekine Y, Minabe Y, Takei N, Suzuki K, *et al*. An association study between catechol-O-methyl transferase gene polymorphism and methamphetamine psychotic disorder. Psychiatric Genetics. 2006; 16: 133–138. https://doi.org/10.1097/01.ypg.0000218613.35139.cd.
[66] Zhang B, Yan X, Li Y, Zhu H, Lu Z, Jia Z. Trends in Methamphetamine Use in the Mainland of China, 2006-2015. Frontiers in Public Health. 2022; 10: 852837. https://doi.org/10.3389/fpubh.2022.852837.
[67] Takemura Y, Tanifuji T, Okazaki S, Shinko Y, Otsuka I, Horai T, *et al*. Epigenetic clock analysis in methamphetamine dependence. Psychiatry Research. 2022; 317: 114901. https://doi.org/10.1016/j.psychres.2022.114901.
[68] Thrash B, Karuppagounder SS, Uthayathas S, Suppiramaniam V, Dhanasekaran M. Neurotoxic effects of methamphetamine. Neurochemical Research. 2010; 35: 171–179. https://doi.org/10.1007/s11064-009-0042-5.
[69] Mirkovic B, Laurent C, Podlipski MA, Frebourg T, Cohen D, Gerardin P. Genetic Association Studies of Suicidal Behavior: A Review of the Past 10 Years, Progress, Limitations, and Future Directions. Frontiers in Psychiatry. 2016; 7: 158. https://doi.org/10.3389/fpsyt.2016.00158.
[70] Tunbridge EM, Huber A, Farrell SM, Stumpenhorst K, Harrison PJ, Walton ME. The role of catechol-O-methyltransferase in reward processing and addiction. CNS & Neurological Disorders Drug Targets. 2012; 11: 306–323. https://doi.org/10.2174/187152712800672409.
[71] Gasser PJ. Roles for the uptake$_2$ transporter OCT3 in regulation of dopaminergic neurotransmission and behavior. Neurochemistry International. 2019; 123: 46–49. https://doi.org/10.1016/j.neuint.2018.07.008.
[72] Harro J. Neuropsychiatric Adverse Effects of Amphetamine and Methamphetamine. International Review of Neurobiology. 2015; 120: 179–204. https://doi.org/10.1016/bs.irn.2015.02.004.
[73] Mayer FP, Schmid D, Owens WA, Gould GG, Apuschkin M, Kudlacek O, *et al*. An unsuspected role for organic cation transporter 3 in the actions of amphetamine. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2018; 43: 2408–2417. https://doi.org/10.1038/s41386-018-0053-5.
[74] Maier J, Niello M, Rudin D, Daws LC, Sitte HH. The Interaction of Organic Cation Transporters 1-3 and PMAT with Psychoactive Substances. Organic Cation Transporters in the Central Nervous System. 2021; 266: 199–214. https://doi.org/10.1007/164_2021_469.
[75] Zhu HJ, Appel DI, Gründemann D, Markowitz JS. Interaction of organic cation transporter 3 (SLC22A3) and amphetamine. Journal of Neurochemistry. 2010; 114: 142–149. https://doi.org/10.1111/j.1471-4159.2010.06738.x.
[76] Wagner DJ. The Role of Organic Cation Transporters in the Disposition, Drug-Drug Interactions, and Tissue Toxicity of Amphetamines [PhD's dissertation]. University of Washington. 2018.
[77] Clauss NJ, Koek W, Daws LC. Role of Organic Cation Transporter 3 and Plasma Membrane Monoamine Transporter in the Rewarding Properties and Locomotor Sensitizing Effects of Amphetamine in Male andFemale Mice. International Journal of Molecular Sciences. 2021; 22: 13420. https://doi.org/10.3390/ijms222413420.
[78] Iurescia S, Seripa D, Rinaldi M. Looking Beyond the 5-HTTLPR Polymorphism: Genetic and Epigenetic Layers of Regulation Affecting the Serotonin Transporter Gene Expression. Molecular Neurobiology. 2017; 54: 8386–8403. https://doi.org/10.1007/s12035-016-0304-6.
[79] Honan LE, Fraser-Spears R, Daws LC. Organic cation transporters in psychiatric and substance use disorders. Pharmacology & therapeutics. 2023; 108574. https://doi.org/10.1016/j.pharmthera.2023.108574.
[80] Zhu M, Zhao S. Candidate gene identification approach: progress and challenges. International Journal of Biological Sciences. 2007; 3: 420–427. https://doi.org/10.7150/ijbs.3.420.
[81] Yahya DN, Guad RM, Wu YS, Gan SH, Gopinath SCB, Zakariah HA, *et al*. *SLC1A2* Gene Polymorphism Influences Methamphetamine-Induced Psychosis. Journal of Personalized Medicine. 2023; 13: 270. https://doi.org/10.3390/jpm13020270.
[82] Nestler EJ. Transcriptional mechanisms of drug addiction. Clinical psychopharmacology and neuroscience. 2012; 10: 136–43. https://doi.org/10.9758/cpn.2012.10.3.136.
[83] Hosák L, Serý O, Beranek M, Alda M. P-40 - Lack of association between the Val158Met catechol-O-methyltransferase gene polymorphism and methamphetamine dependence. European Psychiatry. 2012; 27: 1. https://doi.org/10.1016/S0924-9338(12)74207-4.
[84] Mosayebi G, Moazzeni SM, Farahani H, Solhi H, Rafiei M, Ghazavi A. Immunomodulatory effects of detoxification agents on dendritic cell populations in methamphetamine addiction. BMC pharmacology & toxicology. 2025; 26: 106. https://doi.org/10.1186/s40360-025-00943-x.
[85] Rodek P, Kowalczyk M, Kowalski J, Owczarek A, Choręza P, Kucia K. Association Study of the SLC1A2 (rs4354668), SLC6A9 (rs2486001), and SLC6A5 (rs2000959) Polymorphisms in Major Depressive Disorder. Journal of Clinical Medicine. 2022; 11: 5914. https://doi.org/10.3390/jcm11195914.
[86] Schacht JP. COMT val158met moderation of dopaminergic drug effects on cognitive function: a critical review. The Pharmacogenomics Journal. 2016; 16: 430-8. https://doi.org/10.1038/tpj.2016.43.
[87] Jaber WS, Alriyahee FAA. Relationships between addiction and the COMT rs4680 Gene Polymorphism. Academia Open. 2025; 10: 10-21070. https://doi.org/10.21070/acopen.10.2025.11471.
[88] Liu L, Luo T, Dong H, Zhang C, Liu T, Zhang X, *et al*. Genome-Wide DNA Methylation Analysis in Male Methamphetamine Users With Different Addiction Qualities. Frontiers in Psychiatry. 2020; 11: 588229. https://doi.org/10.3389/fpsyt.2020.588229.
[89] Hosák L. Role of the COMT gene Val158Met polymorphism in mental disorders: a review. European Psychiatry: the Journal of the Association of European Psychiatrists. 2007; 22: 276–281. https://doi.org/10.1016/j.eurpsy.2007.02.002.
[90] Chomynova P, Miller P, Beck F. Perceived risks of alcohol and illicit drugs: relation to prevalence of use on individual and country level. Journal of Substance Use. 2009; 14: 250–264. https://doi.org/10.1080/14659890802668797.
[91] European Monitoring Centre for Drugs and Drug Addiction. European drug report 2018: trends and developments. Office for Official Publications of the European Communities: Luxembourg. 2018.
[92] Caulkins JP, Humphreys K. New Drugs, Old Misery: The Challenge of Fentanyl, Meth, and Other Synthetic Drugs. Manhattan Institute: New York, NY. 2023.
[93] Seaman RW, Jr, Lordson C, Collins GT. Modeling Stimulant and Opioid Co-use in Rats Provided Concurrent Access to Methamphetamine and Fentanyl. Frontiers in Psychiatry. 2022; 13: 814574. https://doi.org/10.3389/fpsyt.2022.814574.