



## Review

## Genomic factors associated with substance use disorder relapse: A critical review

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## ABSTRACT

Several genetic and epigenetic factors contribute to the elevated substance use disorder (SUD) relapse vulnerability, yet a comprehensive investigation into these factors is lacking. This review aims to delve into current literature to highlight key genomic factors associated with SUD relapse.

Focusing on genetic predisposition and epigenetic modifications the review synthesized research findings of several genetic polymorphisms, histone modifications and DNA methylation patterns contributing to the initiation of SUD and the elevated relapse susceptibility. Notably, specific gene polymorphisms, such as Dopamine Receptor D2 gene (DRD2), Gamma-Aminobutyric Acid Receptor Alpha gene (GABRA2), Catechol-O-methyltransferase (COMT) gene, Dopamine Transporter (DAT1) gene and others were identified to be connected to various patterns of SUD relapse. Furthermore, SUD initiation and relapse has been shown to be influenced by epigenetics. Specifically, CpG hypermethylation has been associated with severe alcohol use disorder in the 5' untranslated region of the Bladder Cancer Associated Protein gene (BLCAP) and the upstream region of the Active BCR Related gene (ABR). Co-users of cannabis and tobacco showed notable variations in CpG site methylation, especially at the Aryl Hydrocarbon Receptor Repressor (AHRR), and factor II receptor-like 3 gene sites (F2RL3).

In conclusion, there is good evidence of certain associations between genomic factors and relapse to SUD. However, further research is needed to ascertain causality effects of these factors and develop novel interventions for effective treatment and relapse prevention.

## 1. Introduction

Substance Use Disorder (SUD) is a complex, chronic, and often relapsing disorder manifested by compulsive drug-seeking behavior, despite harmful consequences on the individual's health, occupation, and social life (National Institute on Drug Abuse, 2020). While understanding the primary factors that predispose and trigger the onset of SUD is necessary, a comprehensive examination of recovery process is as also

crucial to overcome the high relapse incidence (Aszalos et al., 1999; Pasareanu et al., 2015). Relapse refers to the reoccurrence of two or more of the SUD criteria due to returning to substance use, during the recovery phase, after a period of remission Fig. 1 (Diagnostic and statistical manual of mental disorders : DSM-5™, 2013; Moe et al., 2022). It indicates a setback in the treatment process, hence identifying reliable factors associated with relapse to SUD can guide the development of innovative treatment modalities to improve SUD outcomes and prevent

**Abbreviations:** 5-HTTLPR, Serotonin Transporter Linked Polymorphic Region; AHRR, Aryl Hydrocarbon Receptor Repressor gene; ANKK1, Ankyrin Repeat and Kinase Domain Containing 1 gene; BLCAP, Bladder Cancer Associated Protein gene; COMT, Catechol-O-methyltransferase gene; CUD, Cocaine use disorder; DAT1, Dopamine Transporter gene; DRD2, Dopamine receptor D2 gene; DSM, Diagnostic and statistical manual of mental disorders; EWAS, Epigenome-wide association-studies; F2RL3, Factor II receptor-like 3 gene; GABA, Gamma-Aminobutyric Acid; GABRA2, Gamma-Aminobutyric Acid Receptor Alpha gene; GWAS, Genome-wide association-studies; HAT, Histone acetyl transferase; HDACs, Histone deacetylase; HMTs, Histone methyltransferases; HTR2A, Serotonin receptor; lncRNA, long non-coding RNA; NA, Nucleus accumbens; NMDA, N-methyl-D-aspartate; NR4A2, Nuclear receptor 4A2; OPRM1, Opioid Receptor Mu 1 gene; SNP, Single nucleotide polymorphism; SUD, substance use disorder; uORFs, upstream open reading frames; UPS, Ubiquitin proteasome system; VNTR, Variable Number Tandem Repeat; VTA, Ventral tegmental area.

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relapse.

Biological genetic biomarkers are thought to have a significant role in predicting relapse vulnerability, although research is yet to provide sufficient evidence of specific genetic predictors of relapse. Genome-wide association-studies (GWAS), and Epigenome-wide association-studies (EWAS) have been utilized to detect genetic polymorphisms and epigenetic modifications that are associated with increased relapse rates (Alblooshi et al., 2019; Cozzoli et al., 2021). Genes that regulate reward pathways have been studied to explore the association between specific genetic polymorphism or epigenetic modifications and the susceptibility to substance abuse and potential relapse. These variations and modifications can disrupt crucial biological processes associated with reward process, leading to substance abuse onset or recurrence (Di Chiara, G. & Imperato, 1988; Willuhn et al., 2010). It is important to note that while this study focuses primarily on genomic factors associated with relapse to SUD, initial diagnoses were also taken into consideration, due to the overlap seen among certain genetic polymorphisms contributing to SUD onset and those influencing relapse, such as the GABRA 2 gene (Bauer et al., 2012; Fehr et al., 2006; Sun, X. & Wolf, 2009). This approach allows for a comprehensive understanding of the genetic landscape that impact SUD recurrence, providing the researchers with a valuable foundation for investigating genes associated with SUD initiation in the context of relapse. While genomic factors associated with relapse to SUD may overlap with those involved in the initial onset, it is unclear if they are identical, since psychological, physiological, and environmental triggers may differ at these two disease stages. Understanding genomic relapse-specific factors offers insights into intervention, enabling the development of targeted treatment plans, reducing relapse likelihood and improving treatment outcomes.

Studies on genomic risk factors for SUD relapse reveal significant knowledge gaps, particularly due to the narrow focus on a limited set of genes. A more comprehensive approach utilizing GWAS remains largely underexplored in the context of SUD relapse. Furthermore, existing

research typically focuses on one particular component genetic polymorphisms and epigenetic modifications without comprehensively addressing the complex interplay among these factors. Our review aims to bridge this gap by critically appraising the available evidence and identifying areas where further research is needed to improve our understanding and provide clinically relevant methods to reduce relapse risk.

## 2. Neural pathways in the brain associated with reward activation

The induction of neuroadaptive changes resulting from chronic substance exposure has been the focus of recent studies. It is believed that these changes may subsequently contribute to the development and reinforcement of addictive behavior (Nestler & Lüscher, 2019). Studies of the addictive nature of substances primarily identified two key pathways: the mesocorticolimbic dopaminergic pathway and endogenous opioid pathway (Blum et al., 2012; von Zastrow et al., 2003).

The mesocorticolimbic dopaminergic pathway consists of dopamine neurons projecting from the ventral tegmental area to the limbic system (mesolimbic pathway) and cortical system (mesocortical pathway). These pathways have been shown to be activated by addictive substances at different levels (Camí & Farré, 2003). The mesolimbic dopaminergic pathway is responsible for the pleasurable and rewarding properties in the human brain (Arias-Carrión et al., 2010). It establishes a neural link between VTA and ventral striatum which encompasses the nucleus accumbens (NA) (Hyman & Malenka, 2001; Pezze & Feldon, 2004). By stimulating the dopamine neurons in the VTA area, dopamine release is increased in the NA leading to the activation of the reward system that basically mediates feeling of desire and pleasure due to the wanting and liking, respectively. Therefore, positive reinforcement effect is facilitated (Berridge, 2012; Di Chiara, Gaetano et al., 2004).

The mesolimbic pathway is activated, either directly or indirectly, by



Fig. 1. DSM-5: substance use disorder criteria. Note. The content of the figure is adapted from Diagnostic and Statistical Manual of Mental Disorders: DSM-5™ (2013) and designed using Canva. Own work. (Diagnostic and statistical manual of mental disorders: DSM-5™ 2013).

addictive drugs through the release, inhibition of degradation, or inhibition of reuptake of dopamine neurotransmitter (Engert & Pruessner, 2008). This causes disturbance in the dopamine homeostasis which in turn leads to neuroadaptation and hypodopaminergic state (Febo et al., 2017). For example, it has been shown that alcohol directly stimulates the release of dopamine in the NA (Di Chiara and Imperato, 1988). Psychostimulants consumption affects the reward pathway by directly increasing dopamine concentration in the shell of the NA, blocking dopamine reuptake from the synapse, enhancing the release of Glutamate, the excitatory neurotransmitter, and indirectly activating N-methyl-D-aspartate (NMDA) receptors (Aragona et al., 2008; Febo et al., 2017). Mesolimbic pathway can be influenced by the ventral pallidum and amygdala that also receive dopamine neurons from the VTA. Ventral pallidum enhances the primacy positive reinforcement associated with addictive substances (Volkow, Nora D. et al., 2003), while the amygdala is associated with conditional learning that leads to the formation of discrete stimulus–reward association. This process links the drug-related cues to the rewarding effects of addictive substances, hence the drug-related cues become emotionally salient stimuli, increasing the craving to addictive substances (Mahler & Berridge, 2009; See, 2005).

Along with mesolimbic area, VTA also extends its dopaminergic neurons into the various regions of the mesocortical area, including the prefrontal cortex, orbitofrontal cortex and anterior cingulate, with prefrontal cortex being the key target of the pathway (Belin et al., 2013; Volkow et al., 1993). It has been established that the prefrontal cortex is responsible for regulating executive function, decision making, emotional control, impulsive control, and cognitive function (Belin et al., 2013; Volkow, N. D. et al., 1993). Interestingly, dysregulation of mesocortical pathway has been reported in patients with SUD (Belin et al., 2013; Volkow, Nora D. et al., 2016). This dysregulation manifests as down regulation of dopamine neurotransmitter in the prefrontal cortex, resulting in morphological and functional changes, consequently impairing the decision-making ability, and dysregulating emotional and craving control that leads to an elevated relapse risk (Belin et al., 2013; Volkow, Nora D. et al., 2016).

While the mesocorticolimbic pathway is involved in the cognitive and rewards aspects associated with addictive substances use, the nigrostriatal pathway adds complexity to the pathophysiology of SUD. This is due to its role of movement-related functions (regulated by the nigrostriatal pathway) in enhancing the reward circuit, thereby contributing to the development of addictive behavior (Quik et al., 2011). Both nigrostriatal and mesolimbic systems contain neuronal nicotinic acetylcholine receptors that regulate dopamine release, consequently affecting positive reinforcement to addictive substances and motor behaviors (Quik et al., 2011). Moreover, alterations in the nigrostriatal system in habit formation (related to drug use), resulting in behaviors characterized by stereotypic and rigid addictive-substance use pattern, which may contribute to elevated relapse rate (Spanagel & Heilig, 2005).

The reward property can also be experienced through the endogenous opioid system by direct activation of the dopaminergic rewarding system through interfering with the inhibitory neurotransmitter Gamma-Aminobutyric Acid (GABA) receptors which in turn leads to increased dopamine concentrations in the neuronal synapse of the NA (Le Merrer et al., 2009). Additionally, it can activate the reward property indirectly by creating a sensation of reset, sedation, and blissfulness through stimulating the opioid receptors (Trigo et al., 2010). It has been suggested that the reward, reinforcement, and dependence of some addictive substances are in part mediated by the endogenous opioid system (Le Merrer et al., 2009; Trigo et al., 2010). For example, the reinforcing properties of alcohol and tetrahydrocannabinol have been shown to be blocked by the opioid receptor antagonists naltrexone and naloxone, respectively (Braida et al., 2004; Thorsell, 2013).

The chronic consumption of addictive substances is associated with dysregulation and impairment of the mesocorticolimbic dopamine reward pathway, known as reward deficiency syndrome. This occurs due

to alterations in the neurotransmission systems in the brain and down-regulation of dopaminergic and opioid receptors (Blum et al., 2018). Moreover, reward deficiency syndrome leads to alteration in the brain's sensitivity towards both natural rewards and addictive substances. This prompts the patient to increase the dose to get the desired effect, which is accompanied by a pattern of compulsive substance use and can lead to abstinence failure during treatment (Christie, 2008; Fraser, 1957; Padmanabhan et al., 2011; World Health Organization, 1994).

Drug-induced changes in the reward system, along with genetic predisposition and epigenetic modifications in genes that regulate reward processes, may collectively induce compulsive drug-seeking, drug-consumption, and relapse to SUD. These genomic factors will be addressed in the following discussion.

### 3. Genetic factors contributing to relapse to SUD

SUD is a polygenic condition that is affected by many physiological systems in the body which are regulated through multitude of genes responsible for the production and regulation of neurotransmitters, receptors, and other elements in those systems (Deak & Johnson, 2021). Ongoing research on the genetics of SUD relapse has mainly aimed to differentiate individuals with addictive and relapse tendencies from healthy subjects by investigating several polymorphisms within genes involved in the reward pathway, stress response, and morphology and functions of the brain. Genome-wide association studies have been primarily employed to understand the molecular bases of individuals with SUD and highlight the most reliable polymorphisms to SUD initiation and relapse (Alblooshi et al., 2019; Cozzoli et al., 2021) Table 1.

#### 3.1. Single nucleotide polymorphism (SNP) meaning and general insights

SNP is a common genetic polymorphism at the single-nucleotide level (point mutation) that conventionally occurs in more than 1 % of the population. SNPs can occur in non-coding regions, or coding (exonic) regions (being either synonymous or nonsynonymous). While most of the SNPs are not biologically significant, others, known as Functional SNPs, have demonstrated varying degrees of effect on the gene function and expression (Albert, 2011; Chorley et al., 2008). These variations can either lead to gain or loss of gene function depending on the location of the polymorphism throughout the different genomic regions and its impact on the encoded protein's structure. In the coding region the Nonsynonymous SNP, where nucleotide change leads to substitution of an amino acid by another amino acid, results in alteration in the protein structure and function, either by stabilizing its structure and enhancing its function or destabilizing the protein's structure and causing a loss of function (due to its degradation) (Albert, 2011; Shastry, 2009). Intronic SNPs used to be considered as non-functional variation, however researchers have revealed that they regulate gene transcription through several mechanisms. They can regulate protein synthesis through influencing the process of mRNA splicing, leading to variation in the gene expression (mRNA sequence), ultimately affecting the quantity and functionality of the synthesized protein (Deng et al., 2017). SNPs within introns may also influence gene expression of imprinted regions due to variations in epigenetic marks (Deng et al., 2017). Moreover, SNPs within introns, which are responsible for transcribing the long non-coding RNA (lncRNA), can impact the structure and function of the resulting lncRNA, thereby influencing its regulatory process (Deng et al., 2017).

#### 3.2. Genetic variants associated with elevated relapse vulnerability

Reward deficiency syndrome, that involves reduction in dopamine or its receptors level (hypodopaminergic state) in synapses within areas of the mesolimbic reward circuit, has been shown to be associated with increased relapse risk, possibly implicating the polymorphisms in genes that affect the brain reward cascade (Blum et al., 2018). A study focusing

**Table 1**  
Gene polymorphisms and their association with SUD initiation and relapse.

Genes Involved	Polymorphism	Association	Reference
Dopamine receptor D2 (DRD2) gene	rs1076560	Higher relapse rates than non-carriers following alcohol-dependence treatment completion	(Dahlgren et al., 2011)
Gamma-Aminobutyric Acid Receptor Alpha (GABRA 2) gene	rs279858	Increased substance positive reinforcement effect in patients with SUD. Increased susceptibility to different substance dependence (such as opioid, alcohol and cocaine) Increased relapse Increased onset of relapse	(Fehr et al., 2006; Sun, Y. et al., 2018) (Fehr et al., 2006; Sun, Y. et al., 2018) (Bauer et al., 2012)
Catechol-O-methyltransferase (COMT) gene	rs4680	Synthesis of enzymes with 3–4 folds lower enzymatic catabolism Increased relapse rate to heroin	(Owusu Obeng et al., 2017) (Su et al., 2015)
Dopamine transporter (DAT1) gene	9-repeat allele of DAT1 VNTR	9-repeat carriers had shown higher dopamine transporter protein production than 10-repeat High relapse vulnerability to addictive substance especially during detoxification 9-repeat variation was not associated with alcohol use disorder overall, but with alcoholic subgroup with alcohol withdrawal seizure or delirium tremens	(Giessen et al., 2009) (Moeller et al., 2013) (YanLei et al., 2011).
Opioid Receptor Mu 1 (OPRM1) gene	Rs1799971	Risk factor for substance abuse among: Jordanian males Asian population Caucasian males Lack of association with drug addiction within the UAE population. Lack of association with opioid addiction in USA population	(Al-Eitan et al., 2021) (Rouvinen-Lagerström et al., 2013) (Woodcock et al., 2015) (Alblooshi et al., 2018) (Crowley et al., 2003)
Serotonin Transporter (SLC6A4) gene	Short allele of Serotonin Transporter Linked-Polymorphic Region (5-HTTLPR) *	Increased susceptibility to alcohol dependence. Associated with relapse to alcohol use disorder	(Sander et al., 1997) (Pinto et al., 2008)
Ankyrin Repeat and Kinase Domain	rs1800497	Associated with alcohol addiction. Failed to exhibit an	(Wang et al., 2013)

**Table 1 (continued)**

Genes Involved	Polymorphism	Association	Reference
Containing 1 (ANKK1) gene		association with alcohol addiction in another study.	(Grzywacz et al., 2019)
CACNB2 GRIN2B PLXDC2 PKNOX2		Associated with the Alcohol use behavior disorder, Nicotine use behavior disorder and Drug use behavior disorder	(Chang et al., 2022)

Note. Data summarized by the author.

\* This polymorphism is characterized by the number of short sequences repeated in tandem. So, no reference SNP identification.

on the initiation of SUD identified the variation A1 (rs1076560) located in the intron 6 of the Dopamine receptor D2 (DRD2) gene (Sasabe et al., 2007). This SNP has been shown to impact the reward process by reducing the dopamine receptor numbers (Noble et al., 1991) hence reducing the normal brain dopaminergic function (Ritchie & Noble, 1996). This leads to diminished sense of reward from typical stimuli in the mesocorticolimbic dopamine reward system (Blum et al., 2018). A study by (Dahlgren et al., 2011), conducted on 375 alcohol-dependent individuals, aimed to investigate whether A1 allele of the DRD2 gene is associated with increased relapse rate in alcohol-dependent individuals. Specifically, this study demonstrated that carrier of the A1 allele variant exhibited higher relapse rates (89 % of carriers) compared to non-carriers (53 % of non-carrier) following alcohol-dependence treatment completion (Dahlgren et al., 2011).

Transitioning to an analysis of genes pertaining to dopamine synaptic concentration, distinct genes have been shown to be associated with inhibiting dopamine production, catabolizing, and clearing from the synapse. Among those genes, Gamma-Aminobutyric Acid Receptor Alpha gene encodes the GABAA α-2 subunit, which, upon activation by GABA, inhibits dopamine release in the NA leading to reward regulation. Several studies have shown that GABRA2 rs279858 SNP (in exon 5, K132K) (Villafuerte et al., 2012) is significantly associated with increased substance positive reinforcement effect in patients with SUD, (Arias et al., 2014; Roh et al., 2011; Uhart et al., 2013) despite some variations the findings and methodologies. (Arias et al., 2014) study, with a cohort of 28 light drinkers and 24 heavy drinkers European-Americans, found that carriers of the rs279858 C allele experienced greater stimulation and euphoria from alcohol after drinking low-dose or high-dose alcohol (Arias et al., 2014). Similarly, (Roh et al., 2011) study, which involved 110 healthy social drinkers undergoing alcohol clamps, demonstrated that the rs279869, rs279858, and rs279837 SNPs in the GABRA2 gene were significantly associated with alcohol subjective effects, mainly the physiologic responses, stimulant and sedative effects, which known to increase the risk to alcohol use disorders (Roh et al., 2011). Moreover, the rs279858 polymorphism was associated with attenuation of negative response, as found by (Uhart et al., 2013) and can further increase the vulnerability to alcohol use disorder as discussed by (Fehr et al., 2006).

Additionally, the rs279858 SNP has been associated with increased susceptibility to other substance dependence such as heroin. According to (Sun, Y. et al., 2018) this SNP increases heroin vulnerability by affecting the reward network. Heroin addiction, in turn, can disrupt the gene expression of the GABRA2 rs279858 variant, leading to disruption in the reward network and impairment of cognitive function. Ultimately, exacerbating heroin addictive behavior.

Moreover, findings from (Bauer et al., 2012) study indicated that GABRA2 and KIBRA genotypes were associated with increased vulnerability to relapse and rapid onset of relapse (Bauer et al., 2012). This study included a reasonable sample size (n = 146), yet an important limitation is related to defining relapse as “any use” rather than the

problematic return to substance use.

Catechol-O-methyltransferase (COMT) gene is another important player in the reward system. It encodes the COMT enzyme that has a notable role in dopamine catabolism and the regulation of dopamine concentration in the synaptic cleft (Owusu Obeng et al., 2017). COMT enzyme has been shown to be influenced by genetic polymorphism. For example, the rs4680 SNP (Val 158 Met) located within exon 4 of the COMT gene (Oberacher et al., 2006) produces an enzyme that exhibits three-to-four-time lower enzymatic activity in dopamine catabolism when contrasted with the wild-type allele (Owusu Obeng et al., 2017). This effect can influence reward processing and impulsivity leading to increased relapse to addictive substance use such as heroin and alcohol (Su et al., 2015; Voisey et al., 2011). In the (Su et al., 2015) study with 564 heroin-dependent patients in the abstinent stage, the rs4680 SNP of the COMT gene was found to be associated with relapse to heroin abuse. However, (Voisey et al., 2011) reported that rs165774 and rs4680 were both associated with alcohol dependence but not nicotine or opiate dependence. In both studies, limitations necessitate further research. In the study the main limitation was incomplete follow-up data leading to missed relapse cases. In (Voisey et al., 2011) P-values were not adjusted for multiple testing and the opiate and nicotine-dependent groups' sample sizes were modest, limiting the generalizability of its findings.

Another important gene in the reward pathway is the Dopamine transporter (DAT1) gene (SLC6A3), since it encodes the dopamine transporter protein that plays a vital role in the reuptake of dopamine from the synaptic cleft (Giessen et al., 2009). The DAT1 VNTR (Variable Number Tandem Repeat) genetic variation affects the dopamine transporter expression and is associated with multiple conditions including the SUD (Giessen et al., 2009). The number of repeats in this gene directly affects the quantity of transporter protein produced. Specifically, the 9-repeat carriers had shown higher dopamine transporter protein production than 10-repeat carriers, resulting in an increased dopamine reuptake from the synaptic cleft subsequently resulting in a decreased dopamine concentration within the synapse (Giessen et al., 2009; Pineau et al., 2019). This phenomenon has been shown to significantly correlate with high relapse vulnerability to cocaine among 9-R carries, especially during detoxification treatment phase, due to increased response to drug-related cues as revealed by (Moeller et al., 2013). In contrast, a meta-analysis across various ethnicities, including Mexican Americans, Caucasian and Asian, did not find significant statistical differences in DAT1 gene polymorphism and its allele distribution between alcoholics and controls indicating that SLC6A3 VNTR A9 variation may not be associated with alcohol use disorder overall, but found an association between the variation and alcoholic subgroup with alcohol withdrawal seizure or delirium tremens (YanLei et al., 2011). However, several limitations should be considered including variations in factors, such as diagnostic criteria and gender ratios, the small sample size of the included studies, limited numbers of overall studies included in the meta-analysis, and the presence of addictive and psychiatric disorders (YanLei et al., 2011). Further research is needed to validate and better understand the association between SLC6A3 VNTR 9-Repeat Allele and SUD initiation and relapse.

In addition to the gene polymorphisms associated with increased relapse vulnerability, other gene polymorphisms were examined for their role in increasing SUD susceptibility that might also contribute to relapse vulnerability. A pivotal reward genetic variant is the exonic A118G SNP (rs1799971) of the OPRM1 gene that encodes for the mu-opioid receptor. This nonsynonymous OPRM1 variant, which eliminates the N-glycosylation site, is associated with decreased OPRM1 receptor expression and level (Haerian & Haerian, 2013; Ray et al., 2011) hence affects the way neurotransmitters, especially endogenous opioids and dopamine, function in people of different ancestry (Peciña et al., 2015). It has been proposed that this variant is considered a risk factor for substance abuse among Jordanian males (Al-Eitan et al., 2021; Peciña et al., 2015), Asian population (Haerian & Haerian, 2013; Rouvinen-Lagerström et al., 2013), and Caucasian males (Woodcock et al.,

2015) and as a risk factor of specifically developing opioid and alcohol use disorders (Clarke et al., 2013; Koller et al., 2012). Yet it was determined that neither the DRD2 rs1076560 SNP nor the OPRM1 rs1799971 SNP demonstrated significant associations with drug addiction within the UAE population (Alblooshi et al., 2018). Of note, this study included subjects who used different types of substances including alcohol, opioids, and non-opioids with no stratification of the disorder phenotype. Older studies have also failed to exhibit an association between the exonic OPRM1 rs1799971 SNP and the opioid addiction (Crowley et al., 2003). However, more recent, large-scale, and well-powered GWAS have confirmed the association with the rs1799971 variant (Deak et al., 2022; Kember et al., 2022; Zhou et al., 2020). The evidence supporting this association is primarily derived from European ancestry samples, possibly due to differences in minor allele frequencies across populations. Overall, the current body of evidence strongly supports a link between opioid use disorder and rs1799971, despite variations among individuals from diverse ancestral backgrounds.

Another important gene polymorphism associated with SUD vulnerability is the Serotonin Transporter Linked Polymorphic Region (5-HTTLPR) genetic variation of the promoter region of the serotonin transporter gene (SLC6A4). The short (S) allele of 5-HTTLPR is associated with reduced serotonin reuptake (Gorwood et al., 2000) and carriers of this allele have been more susceptible to alcohol dependence (Sander et al., 1997). Additionally, findings from (Pinto et al., 2008) study, which included 48 alcohol-dependent male patients in the abstinence phase, indicated that there is a significant association between S allele of the 5-HTTLPR and relapse to alcohol use disorder. However, there is a limitation to the study's generalizability due to its small sample size (Pinto et al., 2008).

A comprehensive meta-analysis demonstrated that the Taq 1A (rs1800497) polymorphism located in exon 8 of ANKK1 gene is associated with alcohol addiction (Palacios et al., 2018; Wang, F. et al., 2013). In contrast, other studies failed to find a significant association between ANKK1 Taq1A genotype and alcohol addiction (Grzywacz et al., 2019). Other comprehensive genetic analysis on 2910 genes associated with SUD from 75 GWAS revealed four genes (CACNB2, GRIN2B, PLXDC2 and PKNOX2) to be associated with the Alcohol use behavior disorder, Nicotine use behavior disorder and Drug use behavior disorder (Chang et al., 2022).

The detection of SNPs related to brain function can be through analyzing DNA samples obtained from brain tissues as well as circulating bodily fluids including saliva and blood. Genetic testing for the analysis of several SNPs, including DRD2 gene rs1076560, GABRA2 rs279858, COMT rs4680 and OPRM1 rs1799971, were performed using blood and saliva samples in several studies. Blood sample is preferred since it has higher DNA concentration, more stable than saliva sample, and less invasive than brain tissue samples (Boyd et al., 2016; Drogou et al., 2020; Suchancka et al., 2020; Wang et al., 2019).

A major concern in the literature on SUD relapse is the reliance on small candidate gene studies. Complex behavioral phenotypes like SUD relapse are polygenic, and findings from such studies may not hold up over time, as seen with other polygenic psychiatric phenotypes like depression (Border et al., 2019) and schizophrenia (Farrell et al., 2015). In these cases, common genetic variants and genes typically have very small effect sizes, requiring large sample sizes for reliable detection. Similarly, many epigenetic studies in this area focus on only a few genes, which limits their scope. The scarcity of GWAS and EWAS on SUD relapse indicates the urgent need for such comprehensive studies. While small candidate gene studies can serve as hypothesis generators (Jorgensen et al., 2009) and provide foundational insights into gene polymorphisms and epigenetic modifications potentially linked to relapse, their limitations remain a concern. Despite offering limited insights, they fall short of capturing the full complexity of the genomic factors associated with SUD relapse.

Understanding the genomic factors associated with SUD relapse rates can lead to the development of personalized treatment approaches. The

identification of genetic and epigenetic risk factors can help in the development of diagnostic kits that can detect individuals with increased susceptibility to relapse and treat them accordingly (Alchakee et al., 2022). Moreover, an individual's genomic profile can guide the behavioral intervention, for example, carriers of the short allele of the 5-HTTLPR genetic variation showed altered mood regulation, therefore the behavioral intervention could focus on this area (Sander et al., 1997). Additionally, identifying genomic risk factors can significantly contribute to the development of novel therapeutic interventions; for example, developing a treatment that targets the OPRM1 gene, which encodes for the mu-opioid receptor, can reduce the risk of opioid addiction, potentially by restoring opioid's normal binding to their receptors hence improve the treatment outcomes (Haerian & Haerian, 2013; Ray et al., 2011).

Furthermore, regarding epigenetic modifications, studies suggest that HDAC inhibitors could significantly reverse these changes and restore the normal gene function. If confirmed, this and similar agents could be promising treatment approaches (Nestler, 2014).

In summary, by identifying the genomic risk factors of relapse to SUD, determining the patient's genomic profile, and integrating them with other clinical data, we can develop a precise treatment plan for each patient hence improve treatment outcomes.

#### 4. Epigenetic factors contributing to relapse to SUD

Epigenetic modifications serve as a mechanism through which most of the risk factors interact with the individual's DNA. Hence, they either activate or suppress the expression of key genes associated with substance addiction and relapse without altering the underlying DNA sequence. Furthermore, epigenetic changes occurring in several brain regions, particularly those associated with dopamine reward system and opioid system, oppose the drug's effect due to alteration in cellular dynamics, neuroadaptation, and changes in the brain's reward areas (Nestler & Lüscher, 2019). Additionally, they manifest in various neurocognitive and behavioral consequences, ultimately leading to tolerance, withdrawal effects and impairment in hedonic function (Gipson & Beckmann, 2023; Sinha, 2008). The altered cellular dynamics and neuroadaptation persist while dopaminergic neuron continue to be stimulated by addictive drugs, and even for weeks after complete drug abstinence (Nestler, 2016). Hence, neuroadaptation may contribute to long lasting craving and relapse to drug seeking, especially to psychostimulants, opioids, nicotine, and alcohol (Werner et al., 2021).

Epigenetic changes primarily include histone modifications, DNA methylation, non-coding RNA activity modification and chromatin remodeler-associated modifications (Nestler & Lüscher, 2019). Among these, DNA methylation and histone modifications have probably received the most extensive focus in research (Cadet, 2016). These modifications influence the activity of genes, which are specialized stretches of DNA determining specific phenotypes within an organism. Each gene carries a genetic code that is transcribed into an mRNA and then translated into a protein. The complex structure of the gene plays an important role in regulating its expression. The promoter region is a DNA sequence located upstream of the gene and provides binding sites for transcription factors that, upon binding to the promoter region, recruits RNA polymerase to start transcribing that specific gene (Polyak & Meyerson, 2003). Promoters often encompass CpG islands that help in regulating gene expression. These islands are rich in cytosine: Guanine dinucleotides. They are typically not methylated during cellular differentiation, with exceptions such as in gene silencing during the inactivation of x chromosome in female. However, some CpG sites become susceptible to methylation when influenced by several environmental factors, such as the chronic consumption of specific addictive substances, where methyl group is added to the cytosine residues preventing gene transcription. The methylation of CpG site leads to gene silencing by both inhibiting the recruitment of factors associated with opening chromatin structure (ZF-CxxC domain proteins) and facilitating

the recruitment of complexes that repress gene transcription (Histone deacetylase (HDACs) complexes). This epigenetic modification is highly stable; hence reactivation of the impacted gene becomes extremely challenging (Blackledge & Klose, 2011).

Epigenetic modifications cannot be directly detected by GWAS, but through several other methods that can then be integrated with GWAS to better understanding the genetic base of the epigenetic modification and their role in SUD initiation and relapse. Methods, including Quantitative Trait Loci (QTL) Mapping and EWAS, generate Epigenetic modifications data that can be overlapped with GWAS data to identify genetic basis of the variant that may contribute to the disease or trait studies (Gibbs et al., 2010; Relton & Davey Smith, 2010).

##### 4.1. DNA methylation

DNA methylation is a frequently studied epigenetic modification in the context of SUD, it may occur following the chronic drug abuse influencing gene expression by either increasing or decreasing gene transcription to mRNA, hence affecting cellular functions. Measuring the methylation level of promoter CpG sites indicates the affected-gene's expression level: hypermethylation is associated with gene silencing, while hypomethylation is with increased gene activity (Blackledge & Klose, 2011; Lea et al., 2018).

Chronic alcohol use has been shown to trigger epigenetic modifications in various genes, and these changes were associated with the severity of the alcohol use disorder, where severe cases led to CpG hypermethylation involving methylation of multiple regions. This included upstream of ABR gene, 5' untranslated region of BLCAP gene (Philibert et al., 2012) and various CpG sites of the Monoamine oxidase A gene in women (Philibert et al., 2008). Moreover, cannabis with tobacco users have shown significant difference in numerous CPG sites methylation compared to control, with notable emphasis on three sites: AHRR, Alpha-2-Lipoprotein (ALPG) and F2RL3 (Osborne et al., 2020). AHRR methylation was also associated with marijuana use in a diverse population (Nannini et al., 2023). Moreover, (Nielsen et al., 2010) demonstrated that former heroin addicts showed significantly higher methylation level than controls. Specifically, this study showed that opioid use triggered differential hypermethylation in promoter region of the OPRM1 gene, blocking the binding of several transcription factors, ultimately resulting in reduced the gene expression and Mu opioid receptor levels (Nielsen et al., 2010). While understanding the influence of epigenetic modification on the SUD relapse vulnerability has valuable insights, the human study in this area is limited. (Land et al., 2020) conducted a noteworthy study in this area examining how methylation pattern contributes to relapse behaviors in cocaine use disorder (CUD). This study, which involved 48 controls and 53 patients with CUD recruited from two major centers in Texas and Virginia, USA, revealed the significant association between DNA methylation pattern in different sites in the promoter region of the serotonin receptor (HTR2A) gene and personality traits related to relapse in individuals with cocaine use disorder (CUD). Percent methylation at sites -1224 and -253 of HTR2A gene were positively correlated with impulsivity traits and increased attentional bias toward cocaine-related cues in individuals with CUD, respectively. While percent methylation at site -1420 was negatively correlated with the tendency to prefer smaller immediate rewards over larger delayed reward (delay discounting) in control group but not individuals with CUD. These findings indicate that methylation influences relapse-related behaviors, hence impacts the vulnerability to relapse to CUD (Land et al., 2020).

##### 4.2. Histone modifications

Histones, proteins that compress the DNA into nucleosomes, undergo epigenetic modifications that further regulate gene expression by either activating or suppressing gene transcription to mRNA. Histone H3 and H4 types of the core histone possess an N-terminal that is susceptible to

several chemical modifications. This is due to the abundant availability of the easily modified Lysine and Arginine amino acids in the N terminal of these subtypes (Shepard & Nugent, 2020).

While histone is susceptible to various chemical modifications, acetylation and methylation are most extensively studied in SUD. Histone acetylation by histone acetyl transferase (HAT) leads to unwrapping the DNA including the gene resulting in the activation of its transcription to mRNA. Conversely, histone methylation by histone methyltransferases can lead to either unwrapping or rewrapping the DNA depending on the methylation site leading to activation or repression of gene transcription to mRNA, respectively (Browne et al., 2020).

Histone acetylation and DNA methylation interact to control gene expression. Promoter CpG hypermethylation was associated with deacetylation of adjacent histone hence leading to gene silencing (Vaissière et al., 2008). Moreover, histone methylation at promoter region can contribute to gene silencing by repressing chromatin structure and restricting transcription factors access to the gene, ultimately inhibiting gene expression (Miller & Grant, 2013).

Evidence from human studies has shown significant correlations between histone modification and SUD. A study has revealed that regulators of histone acetylation, including both HAT and HDACs, are affected by chronic cocaine consumption, that induces the disengagement of HDAC3 from Nuclear receptor 4A2 (NR4A2) resulting in prolonged acetylation of the gene and upregulation of its function. Remarkably, individuals experiencing NR4A2 gene dysfunction in the medial habenula have shown significant association with decreased relapse behavior (López et al., 2019). Moreover, the chronic use of cocaine has also been found to elevate acetylation of H3Ac/H4Ac in 1651 gene promoters and decrease acetylation to 206 gene promoters within the NA (Renthal et al., 2009). This dual impact on acetylation has affected the reward circuit. For instance, chronic and acute cocaine use has been linked to a reduction in CBP, a type of HAT enzyme, consequently decreasing the H3K14Ac and H2BK12Ac in the NA, and may lead to an attenuation of cocaine rewarding effect (Malvaez et al., 2011).

In addition to cocaine, substances like methamphetamine, and opioids, among others, have been shown to induce histone acetylation changes in different brain regions, contributing to the subsequent addictive behavior and potential relapse of SUD (Cheng et al., 2023).

Histone methylation in relation to SUD relapse has been studied in animal models, yet to the best of our knowledge, no studies have been conducted in human subjects. Alongside acetylation and methylation, phosphorylation and ubiquitination have detrimental role in drug addiction and behavior.

Neuroplasticity involving the brain's ability to change and reorganize synapses has been implicated in SUD (Weerasinghe-Mudiyanselage et al., 2022). It is thought that the ubiquitin proteasome system plays a critical role in the protein degradation, which affects synaptic plasticity and memory (Fioravante & Byrne, 2011). Drug addiction appears to share common mechanisms with memory formation processes hence studying the overlap pathway is detrimental (Hyman et al., 2006; Milton & Everitt, 2012). The NA is key in the reinforcing effects of drugs (Cardinal & Everitt, 2004), and changes in NA plasticity are thought to contribute to escalation in drug use (i.e., from recreational, temporary to long term compulsive) (Belin et al., 2009).

The UPS has been linked to synaptic plasticity in cultured NA neurons (Sun, X. & Wolf, 2009), and studies show that drug exposure triggers the degradation of specific proteins in the NA, crucial for synaptic plasticity in addiction development. Targets of the UPS, including proteins like Shank, GKAP, CREB, and deltaFosB, are likely regulated by this process (Carle et al., 2007; Dong et al., 2008; Lee et al., 2008).

On the molecular level, there are 3 steps in the protein synthesis pathway which are initiation, elongation, and termination. Initiation is a rate limiting step and there are several mechanisms involved in controlling this phase (Buffington et al., 2014; Sonenberg & Hinnebusch, 2009). One of the mechanisms is by controlling the compilation of

ternary complexes by phosphorylating the translation initiation factor eIF2 $\alpha$ . The phosphorylation of eIF2 $\alpha$  inhibits overall translation, yet it leads to an increase in translation for a specific group of mRNAs that carry upstream open reading frames in their 5' untranslated region. (Buffington et al., 2014; Sonenberg & Hinnebusch, 2009). According to (Huang et al., 2016) upon injecting small amount of cocaine to adolescent mice, a reduction in the IF2 $\alpha$  phosphorylation was observed in the VTA, along with enhancement in the synaptic inputs to dopaminergic neurons in the VTA leading to drug-related behavior induction. Hence, manipulating eIF2 $\alpha$  phosphorylation-mediated translational control in brain reward areas could be a promising approach for treating a wide range of addictive behaviors influenced by various substances.

In exploring the epigenetic modifications occurring due to chronic drug consumption, it becomes clear that these molecular changes lead to dysregulation in the neural gene transcription by modifying the genetic information accessibility. One important example is the histone deacetylation process by HDACs that results in condensed chromatin structure and transcriptional repression (Romieu et al., 2011). HDACs have also been associated with DNA methylation and gene silencing (Kennedy et al., 2013). The inhibition of this chromatin remodeling enzyme by HDAC inhibitors has shown promising results in the context of SUD. HDAC inhibitors have been shown to induce the reactivation of genes that had been silenced due to DNA methylation (Ng & Bird, 1999). Additionally, Kennedy and colleagues (2013) findings showed that extended HDAC enzyme inhibition in the NA by HDAC inhibitor led to heightened histone acetylation and reduced DNA methylation. These modifications resulted in decreasing the NA neuron inhibitory level, ultimately opposing the behavioral effects induced by cocaine (Kennedy et al., 2013). Another study investigating HDAC inhibitor's impact on cocaine users showed that pretreatment with HDAC inhibitor was associated with diminished cocaine reinforcement and motivation for its use in rats (Romieu et al., 2008). A related study further supported these observations, where it demonstrated that HDAC inhibitors had substantially decreased the recurrence of cocaine seeking behavior in rats (Romieu et al., 2011). Collectively, the data suggest that HDAC inhibitor is a promising candidate in the field of SUD, exhibiting the potential to improve treatment outcome and decrease the relapse rate.

Taken together, the findings from studies of epigenetic modifications offer insights into understanding the neurobiological mechanisms beyond the persistent seeking of the addictive substance, heightened sensitivity to environmental trigger, substance craving, and most importantly relapse even after prolonged period of abstinence (Cozzoli et al., 2021).

## 5. Conclusion and gap of knowledge

Relapse prevention is an important and challenging goal in the treatment of SUD since patients remain at high risk for many years. Genomic factors are thought to play an important role in the dynamic of relapse to SUD. In the brain, specific gene polymorphisms affect the reward system by influencing the respond to addictive substances through increasing sensitivity to their effect and vulnerability to their craving. Additionally, gene polymorphism can influence the regulation of coping mechanism. Moreover, the reward system can be significantly affected by the chronic use of addictive substances leading to dysregulation in many reward pathways. The dysregulation is primarily caused by epigenetic modifications that may be detected through EWAS. These studies, conducted to identify both genetic polymorphisms and epigenetic modifications, are critical for guiding our understanding of the genomic factors associated with increased relapse rates.

The cumulative evidence presented in this review highlights the significance of understanding the genomic factors that contribute to an elevated SUD relapse rate. However, research is yet to provide sufficient evidence of specific predictors of relapse and validate their viability to reduce relapse rate in patients with SUD. Literature also lacks information regarding the dynamic and plastic nature of epigenetic

modification throughout the treatment journey, during abuse, withdrawal, and long-term abstinence, and whether these modifications are reversible with time of abstinence and/or biopsychosocial interventions. Moreover, most GWAS studies have focused on the genetic variants contributing to the development of SUD but not to its relapse. An increased understanding regarding these risk factors will empower organizations and institutes to develop effective, and science-based programs that can help in reducing relapse rates.

Studies on genomic risk factors associated with relapse to SUD revealed notable gaps in knowledge, with several points needing further clarification. Current studies focus on a limited number of genes contributing to SUD relapse, a broader genome-wide analysis is needed to map the genetic architecture of relapse to SUD and potential interaction between candidate genes involved in relapse. Moreover, most GWAS studies have focused on the genetic variants contributing to the development of SUD not to its relapse. In general, the genetic landscape influencing relapse has not been thoroughly explored.

The exact epigenetic modifications and mechanisms by which they influence relapse is not understood yet and worth further exploration. EWAS are necessary to identify these modifications and integrating them with GWAS will help in identifying genetic basis of the variant that may contribute to relapse to SUD. The current literature lacks information regarding the dynamic and plastic nature of epigenetic modification throughout the treatment journey, during abuse, withdrawal, and long-term abstinence, and whether these modifications are reversible with time of abstinence and/or biopsychosocial interventions.

The interplay between various genetic and epigenetic factors needs in-depth exploration to obtain a comprehensive understanding of how they influence each other and various biological systems, ultimately increasing the relapse rate. Also integrating genomic data with other omics data can help in developing biomarkers for relapse to SUD. There is also a lack of population diversity in literature, which limits the generalizability of the findings. This field needs a large-scale and diverse population sample size to ensure that research findings are representative and applicable to various ethnicities. Longitudinal studies are also needed to elucidate the dynamic nature of relapse and its interaction with genomic factors over extended duration.

To gain a more comprehensive understanding of relapse risk, future research should examine the relation between biological, psychological, sociodemographic, and genetic and epigenetic factors. This information can be used to develop personalized interventions for SUD patients to reduce their relapse risk and improve their treatment outcomes.

#### Author Contributions

**NAM:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – Review & Editing. **HAA:** Conceptualization, Methodology, Data Curation, Supervision, validation, Writing – Review & Editing. **HAS:** Resources, Writing – Review & Editing, Visualization. **MOA:** Resources, Writing – Review & Editing, Visualization.

Declaration of AI-assisted technologies in the writing process.

During the preparation of this work the authors used ChatGPT in order to improve the language of certain paragraphs. After using this tool, the authors reviewed and further edited the content as needed and take full responsibility for the content of the publication.

#### CRediT authorship contribution statement

**Noora Al-Marzooqi:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Hanan Al-Suhail:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Mohammad O. AlRefai:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Hamid A Alhaj:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

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#### Data availability

Data will be made available on request.

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