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Review

Genetic variation in alcoholism and opioid addiction susceptibility and treatment: a pharmacogenomic approach

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Abstract: Alcohol and opioid abuse have pervasive and detrimental consequences from the individual to societal level. The extent of genetic contribution to alcoholism has been studied for decades, yielding speculative and often inconsistent results since the previous discovery of two pharmacokinetic variants strongly protective against alcoholism. The neurobiology of addiction involves innumerate genes with combinatorial and epistatic interactions, creating a difficult landscape for concrete conclusions. In contrast, pharmacogenomic variation in the treatment of alcoholism yields more immediate clinical utility, while also emphasizing pathways crucial to the progression of addiction. An improved understanding of genetic predisposition to alcohol abuse has inherent significance for opioid addiction and treatment, as the two drugs induce the same reward pathway. This review outlines current knowledge, treatments, and research regarding genetic predisposition to alcoholism, focusing on pharmacodynamic variation within the dopaminergic system and shared implications for opioid abuse. Multifaceted and highly polygenic, the phenotype of addiction seems to grow more complex as new research extends the scope of its impact on the brain, body, and progeny.

Keywords: pharmacogenomics; alcoholism; opioid; addiction; genetics; alcohol; pharmacodynamics; pharmacokinetics; substance abuse

Abbreviations: ADH1B: alcohol dehydrogenase 1B; ADH1C: alcohol dehydrogenase 1C; ALDH2: aldehyde dehydrogenase 2; AUD: alcohol use disorder; AUDIT-C: Alcohol Use Disorder Identification Test – Consumption; Ca-AOTA: calcium-bis (N-acetylhomotaurinate); CYP2E1: cytochrome P450

family 2, subfamily e, polypeptide 1; DMC: differentially-methylated cytosine; DRD2: dopamine receptor D2; FAM107B: family with sequence similarity 107 member B; FICD: FIC domain protein adenylyltransferase; FTO: fat, mass, and obesity-associated gene; FUT2: fucosyltransferase 2; GABA: gamma aminobutyric acid; GCKR: glucokinase receptor; GPCR: G-protein coupled receptor; GWAS: genome-wide association study; K_{Ca}: calcium-activated potassium channel; KCNB1 ($K_V2.1$): potassium voltage-gated channel subfamily B member 1; KCNMA1 ($K_{Ca}1.1$): potassium calcium-activated channel subfamily M alpha 1; KCNQ5 ($K_V7.5$): potassium voltage-gated channel subfamily Q member 5; K_{IR}: inwardly-rectifying potassium channel; KIF2: kinesin family member 2A; KLB: klotho beta; KOR: kappa opioid receptor; K_V: voltage-dependent potassium channel; LOC257642: rRNA promoter binding protein; MAD2L2: mitotic arrest deficient 2 like 2; NAc: nucleus accumbens; NDMA: N-methyl-D-aspartate; OPRM1: μ opioid receptor 1; ORC4: origin recognition complex subunit 4; PDE4B: cAMP-specific 3',5'-cyclic phosphodiesterase 4B; PFC: prefrontal cortex; PPAP2B: phosphatidate phosphohydrolase type 2b; PTPRM: protein tyrosine phosphatase receptor type M; RDS: Reward Deficiency Syndrome; RNF165: ring finger protein 165; SIX3: SIX homeobox 3; SLC39A8: solute carrier family 39 member 8; SLC39A13: solute carrier family 39 member 13; VTA: ventral tegmental area; WBSCR17: polypeptide N-acetylgalactosaminyltransferase 17

1. Introduction

The disease of addiction is characterized by chronic physiological and psychological need for a substance or behavior [1], often to the extreme detriment of the afflicted. In the United States, an average of 261 people die per day due to excessive alcohol use [2]. Furthermore, total opiate overdoses (including heroin, prescription, and synthetic opioids) increased by 257% from 2007 to 2017, equivalent to an average of 130 overdoses per day [3]. These deaths are preventable and marked by a period of suffering for the addict and family, usually preceding the overdose by several years. Aside from the human suffering and loss of life, alcohol and prescription opioid addiction alone cost approximately $249 billion and $78.5 billion per year, respectively [4].

Although the American Medical Association declared alcoholism a disease in 1956, followed by drug addiction in 1987, treatment has only recently begun to reflect a medical approach [5]. Available pharmacological treatments were and continue to be underutilized. Currently, there are three drugs with FDA-approval to combat alcoholism: disulfiram, naltrexone, and acamprosate [6–8]. While the phenotype of addiction is polygenic and highly complex, the efficacy of pharmacological treatments can be monogenic, or at least partially determined by a single locus [7]. With the advent of pharmacogenomics, or the understanding that a patient's genetic code can dictate treatment response, an avenue has opened to improve the efficacy of treatments for substance abuse, as has been the case for disorders such as depression [9]. Discerning how these variants impact treatment outcomes may shed light on important pathways in addiction, as well.

An enduring juxtaposition surrounding addiction is that of, "nature vs. nurture". As with many phenotypes, both genetics and environment play a significant role. Previously, it was thought that initial patterns of use typically reflected environmental conditions, with genetic factors contributing more to the transition from use to abuse [10]. However, studies within recent years have demonstrated that environmental factors can cause epigenetic changes implicated in the pathology of addiction, bridging the dichotomy of nature and nurture [11]. Twin and family studies have repeatedly asserted

approximately 50% heritability for alcohol and opioid addiction [10,12,14]. Accordingly, children of alcoholics are approximately four times more likely to abuse alcohol or drugs, and over six times more likely to develop anxiety or depression by the time they are young adults [15]. However, these children are also environmentally exposed to alcohol use, which confounds the impact conferred by genetics alone [15]. The heritable component of alcoholism includes variation in genotype and newly discovered epigenetic changes induced by alcohol consumption, passed from one generation to the next [15]. Many of the genetic variants implicated in alcoholism susceptibility are also significant predictors of response to specific medications, which forms the basis of pharmacogenomics.

The burgeoning field of pharmacogenomics considers how an individual's genome and gene products influence response to a given drug treatment; in contrast, the purview of pharmacogenetics is restricted to the impact of a single gene on drug response [9]. Variation in DNA sequences can alter protein formation and activity, which can have critical implications for drug efficacy when the functionality of drug metabolizing enzymes, transporters, or drug receptor targets is altered [9]. For example, a non-synonymous point mutation can abolish metabolic enzyme activity, leading to the accumulation of toxic drug compounds or intermediates, as in the case of the *ALDH2*2* (rs671) mutation (which is expounded on in the next section) [7]. Precision medicine, which encompasses pharmacogenetics and pharmacogenomics, seeks to provide the most effective options for each patient early in treatment, as well as mitigating adverse events resulting from drug-gene interactions [9]. As explained, a single point mutation can alter an individual's response to a specific xenobiotic, potentially also impacting the likelihood of becoming addicted to that substance. A majority of the candidate genes and SNPs relevant to alcohol and opioid addiction affect dopamine transmission.

The common root of all substance-induced reward pathways is the dopaminergic system. Alcohol and opiates affect the mesolimbic reward system (Figure 1A). Alcohol consumption causes the release of β-endorphins and enkephalins, endogenous opioids that bind to μ-opioid receptors (encoded by *OPRM1*) on gamma aminobutyric acid-producing (GABAergic) neurons in the ventral tegmental area (VTA) [16,17]. Exogenous opioids bind directly to inhibitory μ-opioid receptors to depolarize the cell membrane and prevent GABA release. Under typical conditions, GABA transmission provides tonic inhibition of dopamine release. Stimulation of μ-opioid receptors inhibits the release of GABA, thereby enabling dopamine release in the nucleus accumbens (NAc), the brain region responsible for assigning salience to rewards and driving reward-based behavior (Figure 1B) [17,18].

In addition to β-endorphins and enkephalins, the third endogenous opioid, dynorphin, links opioid signaling in the brain to addiction. Dynorphin peptides bind with highest affinity to kappa opioid receptors (KORs), which are distributed throughout the NAc, VTA, and amygdala, among other brain regions [19]. In contrast to the μ opioid receptor, stimulation of the KOR is associated with feelings of stress and conditional place aversion [20]. Numerous, but not all, studies have demonstrated the ability of acute and chronic alcohol exposure to upregulate KOR/DYN signaling in rats – a relationship that requires further delineation [20]. Interestingly, decreased basal DYN/KOR signaling was observed in the NAc and VTA of rat lines bred to voluntarily drink alcohol [21]. As alcohol-induced changes in DYN/KOR signaling are also thought to foster dependence, more research is needed to elucidate these important pathways and mechanisms [20].

Chronic alcohol use also increases dopamine release in the amygdala, responsible for emotional memory, and the prefrontal cortex (PFC) [22,23]. The PFC is responsible for exerting cognitive control over the reward system, ideally making rational choices regarding drug use. In the pathology of

addiction, high concentrations of dopamine in the PFC propagate dopamine receptor D2 (DRD2) downstream signaling, resulting in altered phosphorylation of the GABA receptor and decreased inhibitory GABA signaling within the PFC [24,25]. Concurrently, excitatory glutamate signaling from the PFC to the VTA and NAc grows stronger, significantly contributing to the neuroplastic changes associated with alcoholism [22,26]. In fact, the presence of drug or alcohol cues *alone* can stimulate dopamine-induced reward signaling in addicts, as nicely summarized in a review by Leyton and Vezina [27].

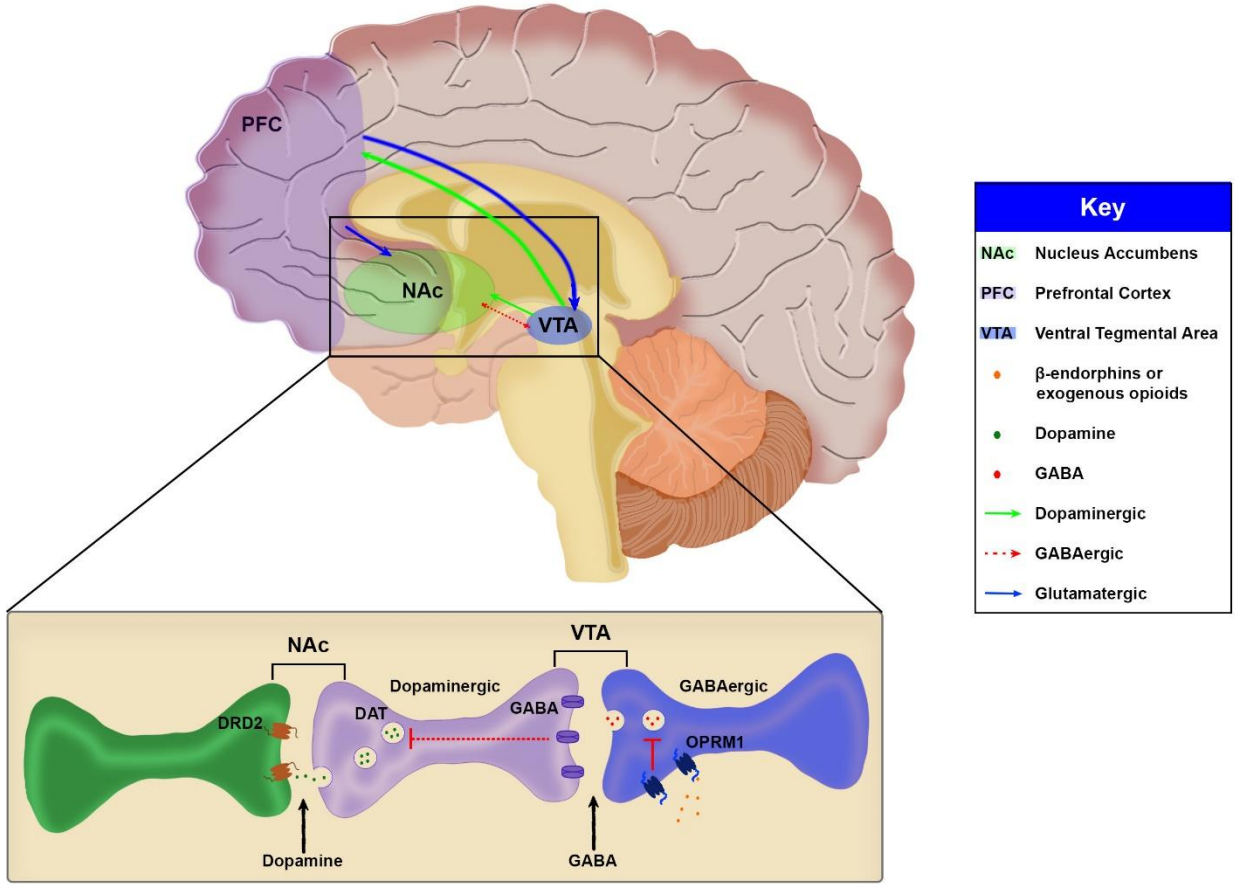

Figure 1. Neurological signaling and brain regions relevant to reward pathway and impulse control. Dopaminergic (green arrows) and glutamatergic (blue arrows) signaling from the pre-frontal cortex (PFC – purple) to the nucleus accumbens (NAc – green) and the ventral tegmental area (VTA – blue). GABAergic (red) and dopaminergic signaling between the NAc and the VTA are also included. The boxed inset highlights opioid-induced dopamine/reward signaling between the VTA and NAc, specifically DRD2 (dopamine receptor D2) and OPRM1 (μ opioid receptor 1).

The level of cue-response in dopamine pathways is frequently implicated in addiction susceptibility. To illustrate, in a study of 49 men, a small taste of beer induced a significantly larger striatal dopamine

response in individuals with a family history of alcohol abuse, compared to individuals without familial alcoholism [28]. Chronic drug use lowers DRD2 availability, increasing an individual's urge to use in order to restore higher dopamine function. Higher dopamine activity makes reward cues more powerful in guiding behavior, often leading to impulsivity. A commonly purported theory is Reward Deficiency Syndrome (RDS), in which genetic variation within the dopamine system produces a hypodopaminergic state in the brain, encouraging compensatory dopamine-seeking behaviors, such as drug use [29]. In addition to receptor function and expression, future research should address how genes controlling dopamine production, transport, and breakdown may also be implicated in cue-response.

While a comprehensive understanding of genetic contribution to addiction remains beyond the reach of current knowledge, genetic variation in addiction *treatment* presents more immediate clinical utility. Investigating how specific genotypes influence treatment response highlights important pathways in the neurobiology of addiction, advancing our understanding of the addictive phenotype as a whole. The following review presents contemporary knowledge and research regarding the genes involved in alcohol pharmacokinetics and pharmacodynamics, with specific attention to variants of high effect and prevalence. Current treatments for alcoholism are summarized and any pharmacogenetic interactions are discussed. Finally, the overlapping pathways of alcohol and opioid addiction are evaluated in terms of genetic implications.

2. Alcohol: pharmacokinetics

Alcohol is metabolized in the liver in a two-step, zero-order process (Figure 2). First, in the rate-limiting step of the reaction, alcohol dehydrogenase (ADH) oxidizes the alcohol group into acetaldehyde [30]. Acetaldehyde, an electrophile, can form adducts with proteins, DNA, and other cellular components; this can result in impaired protein function and DNA damage [31]. Class 1 ADH isoforms (A, B, C) perform 70% of alcohol oxidation in the body [28]. The most important variant is the *ADH1B*2* allele (rs1229984), an Arg > His mutation with a gain-of-function effect [12]. The mutant protein has a maximum reaction velocity approximately 27× faster than wild-type, resulting in accumulation of acetaldehyde in the body [33]. This mutation is common to Asian populations, with the gnomAD genome browser reporting the allele frequency at 73%; hence, the symptoms of alcohol-induced acetaldehyde toxicity are referred to as "Asian flushing syndrome" [8]. These unpleasant symptoms give the SNP a strongly protective effect against alcohol consumption and abuse [12]. Accordingly, the *ADH1B*2* allele has been definitively associated with decreased alcohol consumption for decades [34]. In the brain, a portion of the alcohol-to-acetaldehyde conversion is performed by cytochrome P450 2E1 (CYP2E21). Interestingly, ethanol is a potent inducer of CYP2E1, and increased activity of this enzyme is linked to neurodegeneration in afflicted brain regions, such as the hippocampus and cerebellum [35]. As observed with *ADH1B*2* and CYP2E1 induction, increasing the rate of the first step in alcohol metabolism has pathogenic outcomes.

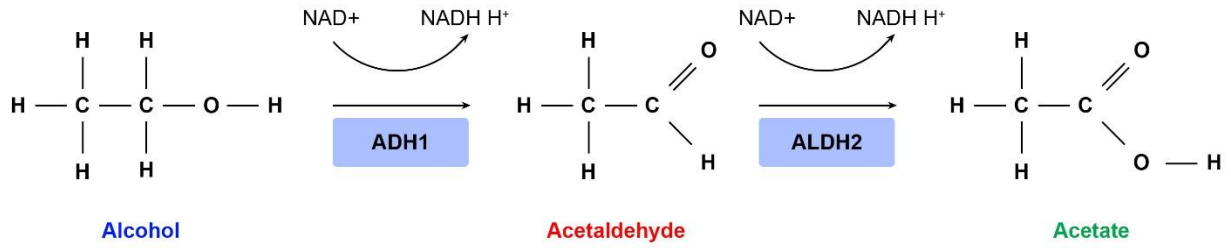

Figure 2. Chemical reactions in the metabolism of alcohol. A simplified illustration demonstrating alcohol being converted to acetaldehyde via ADH1 (alcohol dehydrogenase 1), and this toxic intermediate being converted to acetate by ALDH2 (aldehyde dehydrogenase 2).

The second step in alcohol metabolism, the conversion of acetaldehyde to non-toxic acetate (Figure 2), is performed by mitochondrial aldehyde dehydrogenase 2 (ALDH2) in the liver. The ALDH2 isozyme performs 80% of all aldehyde oxidation in the body [36]. The dominant-negative loss-of-function allele, *ALDH2*2* (rs671), is also prevalent in Asian populations [8]. According to gnomAD, this deleterious allele is present in 26% of East Asians, with older studies citing as high as 35–45% [8]. The Glu > Lys substitution interferes with tetramer formation and damages a co-factor binding site [37]. Carriers (*ALDH2*1/*2*) have less than 50% of enzymatic activity, while homozygous mutant genotypes (*ALDH2*2/*2*) have complete loss of function. The accumulation of acetaldehyde after drinking leads to the same adverse effects previously described for *ADH1B*2* [8]. Genetic deficiency of this enzyme can have severe consequences: alcohol intake aside, simply carrying an *ALDH2*2* allele significantly increases an individual's risk of several types of upper digestive tract cancer, as well as neurological, cardiovascular, and endocrine disorders. Importantly, a carrier who consumes alcohol compounds this risk. Alcohol consumption in Japan is on the rise, with an estimated 26% of heavy drinkers carrying the defective allele [8]. The worsening situation in Japan exemplifies the struggle of alcoholism – continued consumption in spite of adverse effects on health. While these pharmacokinetic variants are well-researched and understood, there are tens to hundreds of genes and variants whose role in alcohol consumption and abuse has yet to be identified and defined.

A recent (2019) genome-wide association study (GWAS) by Kranzler *et al.* analyzed the electronic health records of 274,424 veterans over an 11-year period to identify loci significant in alcohol use disorder (AUD) and heavy consumption, as screened for by the Alcohol Use Disorder Identification Test – Consumption (AUDIT-C). Five genes were found to be significant in both alcohol-related conditions, with SNPs showing a consistent direction of effect for each gene (Table 1): *ADH1B*, *ADH1C*, *GCKR*, *SLC39A8*, and *FTO*. The *ADH1B*2* (rs1229984) SNP was observed to be the most significant in AUD and AUDIT-C, with p-values of 4.7×10^{-85} and 3.6×10^{-133}, respectively. Another class 1 ADH gene, *ADH1C*, was significantly associated with both conditions, albeit different SNPs (neither of which is well-defined at this point) [12].

Table 1. Significant loci in both AUD and AUDIT-C.

Gene	Function	SNP details[1]	Effect	Relevance to alcohol use	Minor allele frequencies by population	References
ADH1B Alcohol dehydrogenase isoform 1B	Alcohol oxidation	rs1229984 C > T; Arg > His [1]*p-value:4.7×10^{-85}*	Increased function: 27x faster rate of catalysis	Acetaldehyde accumulation causes unpleasant symptoms after consuming	World: 9.6% East Asian: 73.8% Ashkenazi Jewish: 27.0%	[10,22]
ADH1C Alcohol dehydrogenase isoform 1C	Alcohol oxidation	rs1612735 (AUD) T > C *p-value: 7.9×10^{-19}*	Effect unknown	One of three ADH1 isoforms responsible for 70% of alcohol oxidation in body	World: 33.9% European: 47.6% Latino American: 32.58%	[10,21,22,24]
		rs142783062 (rs72119590) (AUDIT-C) *p-value: 9.5×10^{-23}*	Effect unknown		World: 31.5% European: 42.6% American: 29.7%	
GCKR Glucokinase regulator	Inhibits glucokinase in liver	rs1260326 C > T; Pro > Leu [1]*p-value: 2.3×10^{-13}*	Decreased function	Liver metabolism	World: 63.8% African/African-American: 86.7% South Asian: 75.8%	[10,26,27]
SLC39A8 Metal cation symporter ZIP8	Zn influx during inflammation response	rs13107325 C > T; Ala > Thr [1]*p-value: 3.0×10^{-14}*	Predicted to damage protein formation	Better ability to respond to inflammation in WT protein	World: 4.5% Ashkenazi Jewish: 13.3% Latino-American: 3.8%	[10,28,29]
FTO Fat, mass, obesity-associated	RNA demethylase, regulates adipogenesis	rs1421085 (AUD) T > C *p-value: 2.2×10^{-11}*	Elevated fat mass	Other SNPs in the same region are associated with lower EtOH consumption	World: 31.6% Ashkenazi Jewish: 52.1% European: 42.5%	[10,30–32]
		rs62033408 (AUDIT-C) A > G *p-value: 1.1×10^{-19}*	Intronic, putative regulatory region		World: 30.7% Ashkenazi Jewish: 51.0% European: 40.8%	

Notes: List of important genes found in Kranzler et al., 2019 [11] with supporting citations included (far right, 'References') that have been discussed in this review. The gene name ('Gene') and the corresponding molecular role ('Function') are listed next to the SNP and resulting phenotype(s) ('Effect') and the relation to alcohol use. Minor allele frequencies by population were determined with data gathered from both gnomAD (Broad Institute) and dbSNP (NCBI). [1]For genes with the same SNP associated in both conditions, the most conservative p-value is listed.

The functional effects of the remaining three genes associated with both AUD and AUDIT-C are speculative. *GCKR*, encoding the glucokinase regulator, is responsible for the inhibition of glucokinase (a glucose sensor) in the liver [38]. The SNP identified by Kranzler *et al*. in 2019 was rs1260326 – a missense polymorphism previously associated with liver disease and metabolism. As liver metabolism is inherently relevant to alcohol consumption, the significance may result from a common pathway involving alcohol and glucose, or because the metabolism of alcohol affects that of glucose more directly [34]. Next, *SLC39A8* codes for a solute carrier responsible for Zn influx during inflammation. The implicated polymorphism, rs13107325, is a missense mutation predicted to damage protein formation [39]. The immune system responds to the *chronic* presence of alcohol and its metabolites through intestinal inflammation [40]. Therefore, individuals who carry the mutant allele may have a reduced ability to mount this inflammatory response. Finally, different non-synonymous SNPs within *FTO* were found to be significant for AUD vs. AUDIT-C (Table 1). Additional SNPs in the same region of the gene have been associated with lower alcohol consumption [41], and rs1421085 (significant for AUD) has been previously linked to elevated fat mass [42].

Based on the genetic overlap in SNP distribution and evaluation of secondary phenotypes, Kranzler et al. concluded that, while heavy consumption is a requirement for AUD, it is not the sole contributing factor. This GWAS exemplifies how big data can identify novel variants implicated in alcoholism and addiction. Meta-analyses are another powerful tool to arise from big data: a 2020 meta-analysis by Zhou *et al.* affirmed the significance of 10 previously identified variants and discovered 19 novel variants associated with problematic alcohol use. The SNPs rs1229984 (*ADH1B*) and rs1260326 (*GCKR*), highlighted in the Kranzler *et al.* study (Table 1), are among the 10 previously identified variants. The other previously identified variants include SNPs in *DRD2*, *FTO*, *SLC39A8*, *ADH1C*, *KLB*, and *SIX3*; novel variants were discovered in *FUT2*, *SLC39A13*, and *PDE4B*, among others. This meta-analysis also revealed significant genetic correlations between problematic alcohol use and psychiatric disorders, such as major depressive disorder, ADHD, and schizophrenia, as well as the comorbidities of smoking and other substance abuse. SNP-based heritability varied from 6–11% across the five cohorts analyzed [43]. Clearly, large studies are key to advancing the genomic comprehension of disorders as complex as addiction. Future research should focus on understanding how genetic variation, both in the form of SNPs and epigenetic alterations, is implicated in the progression from consumption to addiction – a pharmacodynamic inquiry.

3. Alcohol: pharmacodynamics

While genetic variation in alcohol pharmacokinetics involves primarily two genes, an assessment of the pharmacodynamic effects of alcohol is more abstruse because alcohol affects numerous parts of the body. Genes directly involved in dopamine signaling, such as *OPRM1* and *DRD2*, are a logical place to start. To demonstrate, knockdown of *OPRM1* has significantly reduced alcohol self-administration in mice [7]. A non-synonymous mutation in exon 1, A118G (rs1799971), has been repeatedly associated with development of alcohol and opioid addiction. This SNP, resulting in the loss of a glycosylation site within the extracellular N-terminal loop of the protein, is highly prevalent in East and South Asians (36–37%), Europeans (16%), and Latino-Americans (21%). Animal and human laboratory studies have found the G allele to be associated with elevated alcohol reward, which has been replicated in some (but not all) clinical studies. In a 2015 study using knock-in *OPRM1* 118AA (wild-type) and

118GG (mutant) mice, Bilbao *et al.* observed higher alcohol-induced reward properties in GG, but not AA, mice. This conclusion was based on observing a higher alcohol-induced dopamine release, as well as a lowered stimulation threshold, in the brains of GG mice only [7]. Using positron emission topography, Ramchandani *et al.* demonstrated that social drinkers carrying one G allele had enhanced dopamine release in the ventral striatum following alcohol consumption [44]. Correspondingly, the impact of the A118G mutation on alcohol-induced reward has direct clinical implications for naltrexone use [7].

Relatively novel candidates in addiction pathology are potassium channels. Emerging studies show that acute and chronic alcohol consumption targets voltage-dependent (K_V7), GPCR inwardly-rectifying (K_{IR}), and calcium-activated (K_{Ca}) potassium channels. The function and movement of $K_V7.2$ and $K_{Ca}2$ are reduced in the NAc and hippocampus following chronic alcohol exposure. Accordingly, inducing function of these channels has decreased voluntary alcohol consumption in rodents [45]. In 2017, Rinker *et al.* investigated the correlation of ethanol consumption and potassium channel gene expression in the NAc and PFC of ethanol-dependent mice. In the PFC, a set of four potassium channels ($K_V2.1$, $K_V3.1$, $K_{Ca}1.1$, and $K_V7.5$) were found to be upregulated in a subset of mice whose voluntary alcohol intake increased following chronic alcohol exposure. In addition, the same four genes were downregulated in mice whose voluntary drinking did not increase following chronic alcohol exposure. Therefore, the coordinated expression of these four genes may impact voluntary consumption after dependence has been established. To evaluate the effect of altered expression of these four channels, a bioinformatics model compared 1.5× expression (increased drinking) vs. 0.5× expression (no increase in drinking). Increased expression of these channels resulted in an approximate 23% reduction in action potentials, relative to the 0.5× decreased expression, indicating the intrinsic excitability of PFC neurons was reduced [45]. Considering the PFC's role in impulse control, reduced firing of neurons within could weaken its cognitive control over reward-driven regions such as the NAc.

Interestingly, two of the four channels ($K_{Ca}1.1$ and $K_V2.1$) whose expression levels in the PFC correlated *positively* with voluntary drinking had the opposite correlation in the NAc. Following chronic alcohol exposure, transcript levels of *KCNMA1* ($K_{Ca}1.1$) and *KCNB1* ($K_V2.1$) were increased in the brains of mice whose voluntary drinking did not increase, while decreased expression was observed in the brains of mice whose voluntary drinking did increase [45]. If these two channels have a dominant effect on action potential reduction, then brain regions with increased expression could have weakened transmission/excitability, translating more broadly to "weakened power". Considering the opposing positions of the NAc and PFC in directing behavior (reward-driven vs. impulse control, respectively), it is possible that increased expression/weakened power in the PFC would increase drinking, while the same effect in the NAc would *resist* an increase in drinking. The regionally distinct effects of increased expression of these genes illustrate the importance of signal transduction from each region in dictating cognitive control.

Alternatively, in both PFC and NAc, *KCNQ5* ($K_V7.5$, M-current rectifier) transcript levels positively correlated with the change in drinking after chronic alcohol exposure. Alcohol-induced inhibition of M-current channels has been shown to promote excitation of dopaminergic neurons branching out of the VTA, another region critical to the reward pathway [46]. As the inhibition of M-current channels is a critical mechanism of alcohol-induced dopamine release [47], increased expression of *KCNQ5* may yield a greater change in current following alcohol consumption, potentially providing a larger dopamine release than if fewer channels were available for inhibition. This would explain the

positive correlation between *KCNQ5* expression and drinking observed in either brain region of alcohol-dependent mice in Rinker *et al.* [45]. This potassium channel is of particular interest, as the rs3799285 polymorphism in this gene has been associated with the development of alcoholism in African Americans, almost 8% of whom carry the allele [47]. Altogether, potassium channels present a potential pharmacological target for treating alcoholism.

Long-term alcohol use causes neurobiological changes, as demonstrated by the altered expression of potassium channels [47]. Another well-documented example of this is alterations in the brain's epigenetic patterns, particularly in the regions involved in reward circuitry. In rats, oxycodone (a prescription opioid) has been shown to induce the expression of genes associated with synaptic plasticity in the VTA, a feat achieved through demethylation of the DNA itself [11]. Additionally, chronic alcohol or opioid use expands chromatin accessibility in the NAc through increased levels of histone acetylation. Consequently, deletion of the gene encoding a critical histone acetyltransferase has been shown to attenuate sensitivity to substances of abuse [48]. As this vast landscape continues to be mapped, the novel ability for locus-specific epigenetic editing may present a future avenue for treatment [11,48].

Adding to the importance of epigenetic regulation, studies have shown that certain epigenetic changes, in addition to sequential variants, may be transgenerational. In 2017, Asimes *et al.* observed differential methylation patterns in the hypothalami of male offspring of rats exposed to a binge-alcohol protocol during adolescence [15]. The hypothalamus is involved in stress response and has been implicated in vulnerability to binge-drinking [49]. The methylation of DNA, which typically occurs on CpG islands close to transcription promoters, is a heritable epigenetic mark that can be affected by environmental factors. In promoter regions, methylation induces heterochromatin formation, thereby inhibiting the binding of necessary transcription factors. Counterintuitively, 84% of the differentially-methylated cytosines (DMCs) identified were in intronic or intergenic regions, potentially silencing unidentified regulatory elements or non-coding RNAs [15].

Asimes *et al.* observed epigenetic changes in the first-generation offspring of pairs with maternal-only exposure, paternal-only exposure, or dual-parental exposure. Methylation patterns were strikingly distinct depending on which parent was exposed to alcohol. Out of over 200 total hypomethylated DMCs identified, only five were common to all three exposure groups. Similarly, only four of over 200 hypermethylated DMCs were shared by all groups [15]. The nine genes whose hyper- or hypomethylation was consistently observed for all three exposure groups are listed in Table 2. Unexpectedly, the DMCs of single-parent exposure were not found to be additive in the dual exposure group. However, as noted by the authors, recombination events in early conception may mask individual parental contributions [15]. Despite producing different DMC patterns, all alcohol-exposed groups had higher overall hypermethylation relative to control groups, with DMCs distributed across all chromosomes but not within currently defined parental imprinting regions. These DMCs may be induced in the parent and passed to progeny via direct replication of the altered methylation patterns; alternatively, the instructions for epigenetic machinery, such as methyltransferases and histone acetyltransferases, may be explicitly altered. A correlating decrease in mRNA expression was only observed for some differentially methylated genes [15], reinforcing the fact that gene expression is vastly more complicated than the presence or absence of DNA methylation.

While current research on the pharmacodynamic effects of alcohol abuse is unveiling an increasingly complex landscape, the treatment of alcoholism can be more straightforward. Many treatments mimic or manipulate pathways involved in the physiological response to alcohol, capitalizing

on key enzymes and receptors that have previously been defined. Importantly, this relationship is not one-sided: novel associations between genotype and treatment response can highlight genes involved in the manifestation of addiction and its intermediate phenotypes, or endotypes.

Table 2. Summary of discussed genetic variants contributing (either positively or negatively) to the risk of alcoholism and/or opioid abuse.

Risk	Level of association	Gene, SNP	Molecular/proteomic changes	Postulated effect/mechanism of effect
Increasing	****	*OPRM1*, rs1799971-A rs3778150-C	Haplotype rs1799971-A: increased affinity for exogenous opioids rs3778150-C: see below	Decreased receptor expression → increased risk of opioid addiction
	***	*OPRM1*, rs3778150-C	T > C Intronic Decreased receptor expression	Increased heroin use
	***	*OPRM1*, rs1799971	A > G Asn > Asp Decreased receptor expression	Decreased affinity for exogenous opioids → increase in opioid dose required for efficacy
				Treatment with naltrexone and nalmefene is more effective
				Increased affinity for endogenous opioids → increased alcohol-induced dopamine release
	***	*DRD2/ANKK1*, rs1800497 (TaqIA)	G > A Glu > Lys Decreased receptor density	Increased brain reactivity to drug cues → higher heroin consumption
				Increased risk of alcoholism
	*	*KCNQ5*, rs3799285	A > G Intronic	Alcohol intake inhibits M-current K+ channels → excitation of dopaminergic neurons
				Retigabine is a positive modulator of Kv7 channels
	*	*KCNQ5*	Increased expression in PFC	May decrease action potentials in PFC → increased alcohol intake following chronic use
	*	*KCNB1*		
	*	*KCNMA1*		
	*	*KCNC1*		

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Risk	Level of association	Gene, SNP	Molecular/proteomic changes	Postulated effect/mechanism of effect
	*	*FICD*	Hypermethylated in hypothalamus of offspring of parents exposed to alcohol	Parental imprinting as a result of chronic alcohol exposure
	*	*ORC4*		
	*	*KIF2A*		
	*	*PTPRM*		
Unknown	*	*WBSCR17*	Hypomethylated in hypothalamus of offspring of parents exposed to alcohol	Parental imprinting as a result of chronic alcohol exposure
	*	*FAM107B*		
	*	*LOC257642*		
	*	*MAD2L2*		
	*	*RNF165*		
Decreasing ↓	**	*ADH1C*, rs1612735	T > C Intronic	May alter the function of an enzyme responsible for alcohol detoxification
	**	*ADH1C*, rs142783062	Unknown	May reduce the function of an enzyme responsible for alcohol detoxification
	**	*GCKR*, rs1260326	C > T Pro > Leu	May reduce the function of an enzyme involved in liver metabolism
	**	*SLC39A8*, rs13107325	C > T Ala > Thr	May reduce the function of an enzyme that responds to alcohol-induced inflammation
	**	*FTO*, rs1421085	T > C Intronic	SNPs in this region have been associated with lower consumption
	**	*FTO*, rs62033408	A > G Intronic	
	*****	*ADH1B*2*, rs1229984	C > T Arg > His	Faster enzymatic activity → acetaldehyde accumulation → unpleasant symptoms
	*****	*ALDH2*2*, rs671	G > A Glu > Lys	Loss of function → acetaldehyde accumulation → unpleasant symptoms Disulfiram, an ALDH2 inhibitor, mimics this deficiency

Notes: The overall risk assessment increasing (arrow up) or decreasing (arrow down) as inferred by the literature. The level of association corresponds to the strength of supporting data currently available. Gene (and SNP, as necessary) information is included next to the genetic outcome (change in nucleotide and/or amino acid sequence). Last, the discussed effect is listed that briefly explains the phenotype observed.

4. Alcohol: treatments for alcohol abuse

Until relatively recently, alcohol and substance abuse were primarily treated through psychological, rather than pharmacological, means. While the introduction of new therapeutic options over the past 30 years has significantly increased prescription rates, the number of individuals who receive such treatment constitute a small portion of those afflicted with substance abuse disorders. For example, in 2002, a maximum of 9% of those with alcohol use disorders received a single prescription for a drug approved to treat alcoholism [50]. With the goal of attenuating voluntary alcohol consumption, two logical options arise: induce an unpleasant effect, or reduce the perceived reward upon consumption. Two of the three FDA-approved treatments for alcoholism, disulfiram and naltrexone, function in this manner.

The first pharmacological treatment for alcoholism, disulfiram, was approved in 1949, prior to the recognition of alcoholism as a medical disease [51]. Aptly branded "Antabuse", this compound inhibits ALDH2, causing acetaldehyde accumulation and the corresponding symptoms of facial flushing, headache, nausea, and dizziness. Additional compounds that mimic decreased ALDH2 function, daidzin (from the Chinese Kudzu root) and experimental ALDH2 inhibitors (declinol and CVT-10216), have reduced voluntary alcohol consumption in human and rat models, respectively [52–54]. While lifelong ALDH2 inhibition can be detrimental, a moderate dosing regimen of disulfiram has not been associated with cancer or a higher risk of other long-term health disorders, although patients with cardiac disease are not recommended for this treatment [55].

The second FDA-approved compound for treatment of alcohol abuse is acamprosate [51]. This compound, Ca-AOTA, helps normalize the hyperglutamic state characteristic of alcohol withdrawal [56,57]. In addition to dopaminergic signaling in the mesolimbic brain, glutaminergic projections from the PFC to the NAc and VTA are implicated in the development of drug-seeking behaviors [23]. Accordingly, chronic alcohol consumption upregulates excitatory glutamate signaling, with multiple studies demonstrating elevated extracellular glutamate levels in the NAc following alcohol consumption [57–59]. Abstinence following chronic use of alcohol has also been shown to increase glutamate levels in the NAc, potentially triggering relapsing behaviors. The combination of decreased GABA (inhibitory) and increased glutamate (excitatory) signaling in the NAc makes abstinence difficult in early sobriety [23,59,60]. Acamprosate helps restore the balance between GABA and glutamate transmission originating from the PFC to the NAc. To illustrate, glutamate signaling was reduced in the brains of abstinent alcohol-dependent patients taking acamprosate in a double-blind study. Cerebrospinal glutamate concentrations were also found to strongly correlate with alcohol dependence severity [60]. Therefore, high glutamine levels in a detoxifying alcohol dependent patient may be a biomarker for effective treatment with acamprosate.

The precise molecular mechanism of acamprosate is unknown; however, response to the drug has been linked to the induction of glutamine synthetase, which requires glutamate as a substrate [61]. Initially postulated to be a direct antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, recent studies have attributed the NDMA excitation and anti-relapse activity to the calcium counter ion moiety [56,61]. To illustrate, Na-AOTA was demonstrated to be ineffective in reducing alcohol consumption and relapse behavior in rats, while treatment with calcium salts yielded results similar to treatment with acamprosate (Ca-AOTA) [56]. Due to the role of acamprosate in glutamate activity, it has been shown to be more effective in preventing relapse than reducing cravings – the latter necessitates a more direct effect on dopaminergic reward signaling, as found in naltrexone [62].

The μ-opioid receptor (OPRM1) antagonist, naltrexone, is FDA-approved for the treatment of alcohol and opioid abuse [63]. Inhibition of OPRM1 in the VTA precludes the opioid-induced release of dopamine in the NAc, decreasing reward signaling [7,16]. Due to the heightened dopamine release observed with the A118G (rs1799971) polymorphism, blocking this pathway can have a more pronounced effect on alcohol consumption in variant (G) individuals. For instance, pre-treatment of 118GG mice with naltrexone attenuated alcohol consumption significantly more than it did in 118AA mice [7]. In a free-cage drinking model, treatment with naltrexone significantly decreased alcohol intake in 118GG mice, while no effect was observed in 118AA mice. Both naltrexone and nalmefene (another μ-opioid receptor antagonist) significantly decreased operant self-administration of alcohol in mice of both genotypes, with a greater effect observed in GG mice. Currently approved for treatment of alcoholism in Europe, nalmefene is longer-acting and without the dose-dependent toxicity of naltrexone, demonstrating clear potential as a global alternative to naltrexone [7].

A recent GWAS was performed by Biernacka *et al*. in 2021 to identify pharmacogenomic associations with naltrexone and acamprosate treatment outcomes. In patients treated with naltrexone, rs12749274, an intergenic SNP situated between a long non-coding RNA and *PPAP2B*, was significantly associated with a 2.9 times higher risk of relapsing to heavy drinking. The closest variant to achieving genome-wide significance for both time to relapse and time to heavy relapse during naltrexone treatment was rs62533259, an intronic SNP in protein tyrosine phosphatase receptor D (*PTPRD*), which also increased the risk of heavy relapse by over two-fold. PTPRD has previously been associated with several phenotypes of addiction, as well. The analysis of acamprosate treatment yielded one significant intergenic variant – rs77583603 – that conferred more than a two-fold higher risk of relapse. Finally, meta-analysis of the three included cohorts for both treatments yielded a significant association between a set of 14 SNPs in the brain and reproductive organ-expressed gene (*BRE*) and time to heavy relapse. The most prominent of these, rs56951679, was associated with a 1.5 times greater risk of heavy relapse and has a minor allele frequency of 0.17. While not reaching significance in the meta-analysis, the top SNP associated with time to relapse for either treatment was rs1078110 in *KCNQ4*. Given the emerging role of potassium channels and a minor allele frequency of 0.30, this SNP warrants further investigation for its role in treatment response [64].

Another candidate with pharmacogenomic potential is retigabine, an FDA-approved K_V7 positive modulator. Retigabine has significantly reduced voluntary drinking in mice, with increased efficacy in higher-drinking subjects [45]. Retigabine binds allosterically to potassium channels $K_V7.2–7.5$, stabilizing them in the open state. The most potent action is achieved through the heteromeric $K_V7.2/3$ channel. Normally, *KCNQ*-encoded channels provide continual hyperpolarization of the cell membrane to regulate neuronal excitability. By stabilizing channels in the open state, the cell can respond more rapidly and extremely to depolarization (or neuronal excitement), mitigating the burst firing of neurons [65]. Since the rewarding response of alcohol is dependent on neuronal transmission in the NAc, it is likely that retigabine attenuates the excitability of this pathway [17,45]. Based on this concept of action, the increased efficacy in heavy drinkers is potentially the result of slowing a pathway that holds more importance in heavy drinkers, similar to how *OPRM1* variation affects naltrexone response.

As illustrated, drug-gene interactions relevant to substance abuse treatment hold immediate clinical utility, with the potential to increase the proportion of individuals who respond to treatment and prescription rates. Meanwhile, new advances in treating alcoholism and addiction are the subject of vast

research and literature. For example, neuroepigenetic editing and alteration of miRNA expression are being investigated for potential therapeutic utility in combatting addiction [11]. Hopefully, the era of genomic medicine will yield significant progress in understanding and targeting addiction through precision medicine and biologics.

5. Alcohol and opioids: shared genetic implications

As illustrated by the dual use of naltrexone, alcohol- and opioid-induced rewards stem from the same neurological pathway. Accordingly, there are genes implicated in both addictions, such as the dopamine receptor D2 (*DRD2*) and *OPRM1*. A frequently studied polymorphism pertaining to *DRD2* is the TaqIA SNP (rs1800497, G > A) in the ankyrin repeat and kinase domain containing one gene (*ANKK1*), located 10 kb downstream of *DRD2* [66]. This SNP results in loss of an N-glycosylation site that is necessary for proper membrane presentation [67]. Carriers of TaqIA (A1+) have 30% decreased DRD2 density in the striatum, reducing basal reward sensation [68]. This can lead to drug-seeking behavior in order to achieve increased stimulation; in support of the Reward Deficiency Syndrome, the A1 allele has been associated with higher heroin consumption [29,66]. In a 2019 study by Li *et al.*, heroin-addicted carriers of the A1 allele showed increased brain reactivity to heroin-related cues in the prefrontal, mesolimbic, and visuospatial attention regions. This may indicate that heroin has a greater influence on the executive function and reward system of A1 carriers [66].

The *ANKK1*/*DRD2* TaqIA allele has demonstrated the same direction of effect in susceptibility to alcoholism as in opioid addiction. Over 50 studies regarding this SNP and alcohol use disorder have been done over the past three decades, with a large portion having validated this association, while several have not [69–71]. The heterogeneity of alcoholic patients is a potential explaining factor for the discrepancy in results [72]. A 2013 meta-analysis by Wang *et al.* confirmed the significant association between alcoholism and carrying the TaqIA allele using both allelic and genotypic methodologies [71]. In addition, a pilot study found alcohol-dependent carriers of the TaqIA allele were seven times more likely to relapse than non-carriers, although the sample size was small [73]. Given the importance of dopamine signaling in the pathology of addiction, there are likely additional *DRD2* variants that influence substance abuse. As an example, the GWAS by Kranzler *et al.* in 2019 identified two novel SNPs within *DRD2*, rs61902812 and rs4936277, with opposing effects on alcohol consumption [12].

The *OPRM1* receptor is the point of initiation for both alcohol- and opioid-induced reward sensations. The A118G Asn40Asp variant isoform has a three-fold higher affinity for *endogenous* opioid ligands, such as β-endorphins, which explains the higher alcohol-induced dopamine release in G (variant) carriers observed by Bilbao *et al.* in 2015 [7,74]. In stark contrast, the *exogenous* opioids morphine and methadone have demonstrated decreased potency at the variant receptor [67]. For instance, in a humanized mouse model, morphine was found to be five times less potent in 118GG than 118AA neurons [75]. Correspondingly, in 118G carriers, decreased OPRM1 receptor signaling was observed in the secondary somatosensory cortex, a region of the brain that processes the perception of pain, which reduced the clinical efficacy of prescription opioids [76].

Despite the higher affinity of the OPRM1 wild-type isoform for exogenous opioids, numerous studies evaluating the OPRM1 118-A (wild-type) allele with increased susceptibility to opioid addiction have yielded conflicting results [13,77]. However, in 2015, Hancock *et al.* discovered a potential explanation for the inconsistency: the haplotype nature of rs1799971-A and a second SNP in *OPRM1*,

rs3778150 (T > C). Individually, the variant (C) allele of rs3778150 was significantly associated with decreased OPRM1 expression and increased risk of heroin addiction. In contrast, rs1799971-A was only significantly associated with heroin addiction when in haplotype configuration with rs3778150-C. Initially discovered using cases from the Urban Health Study, this association was significantly replicated via meta-analysis with two additional independent cohorts, for a total sample pool of 16,729 European, Australian, and African American drug users. The haplotype nature of rs3778150-C and rs1799971-A may resolve the inconsistency observed between the rs1799971-A allele and increased susceptibility to opioid addiction, especially considering the relatively high haplotype frequency (16–19%) observed across the independent cohorts [13]. In general, this haplotype exemplifies genetic contribution to opioid and alcohol addiction: SNPs may be equivocal in isolation, while contributing significantly to susceptibility when combined with other variants of the same effect. Moving forward, high-frequency haplotype studies can provide valuable insight into the impact of multiple SNPs on addiction and its intermediate phenotypes.

6. Conclusions

While numerous family and pedigree studies demonstrate approximately 50% heritability for alcoholism and opioid addiction, current GWAS and meta-analyses are only able to account for 6–11% in SNP-based heritability [10–13,43]. The difference between the predictive power of causative variants and population-based heritability is termed, "missing heritability", and is common to complex phenotypes [78]. One of the greatest challenges is polygenicity: tens to hundreds of genes in multiple brain regions and signaling pathways are involved in the pathology and treatment of addiction. In addition, epistatic interactions between genes could also contribute to the missing heritability [78]. To this day, the well-defined pharmacokinetic variants *ADH1B*2* and *ALDH2*2* represent the most concrete predictors of alcohol consumption (Table 2) [12,34]. The identification of more pharmacodynamic genes implicated in dopaminergic response, such as *DRD2*, *OPRM1*, and potassium channels, should help account for a larger portion of the inherited susceptibility to alcoholism (Table 2). Reflective of an overlapping reward pathway, many of these variants are also implicated in opioid addiction. At present, notable SNPs have the highest clinical utility in predicting treatment response [7,45,79]. Applying pharmacogenomic insight to the treatment of alcoholism and opioid addiction may result in increased effectiveness of medications and increased prescription rates. Yet, the identification of genes influencing treatment outcomes has clear potential to advance the biochemical and molecular understanding of addiction. Ultimately, through delineating the effects of implicated variants and their resulting influence on the intermediate phenotypes of addiction, a complex "praddictive" model for additive risk based on genotyping may one day be possible.

Conflict of interest

The authors declare no conflict of interest in this paper.

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