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# The Genetics, Neurogenetics and Pharmacogenetics of Addiction

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## Abstract

Addictions are prevalent psychiatric disorders that confer remarkable personal and social burden. Despite substantial evidence for their moderate, yet robust, heritability (approx. 50%), specific genetic mechanisms underlying their development and maintenance remain unclear. The goal of this selective review is to highlight progress in unveiling the genetic underpinnings of addiction. First, we revisit the basis for heritable variation in addiction before reviewing the most replicable candidate gene findings and emerging signals from genomewide association studies for alcohol, nicotine and cannabis addictions. Second, we survey the modest but growing field of neurogenetics examining how genetic variation influences corticostriatal structure, function, and connectivity to identify neural mechanisms that may underlie associations between genetic variation and addiction. Third, we outline how extant genomic findings are being used to develop and refine pharmacotherapies. Finally, as sample sizes for genetically informed studies of addiction approach critical mass, we posit five exciting possibilities that may propel further discovery (improved phenotyping, rare variant discovery, gene-environment interplay, epigenetics, and novel neuroimaging designs).

### Keywords

Addiction; Genetics; GABRA2; rs16969968; ADH1B; CNR1; Pharmacogenetics; Neurogenetics

## Introduction

Excessive use and misuse of psychoactive substances is amongst the leading contributors to morbidity and mortality worldwide [1]. Substance use disorders, as they are referred to in the fifth edition of the Diagnostic and Statistical Manual (DSM) [2], index a highly maladaptive and impairing form of substance use. Previously referred to as abuse and

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dependence, the current definition of substance use disorders requires the endorsement of two or more of 11 diagnostic criteria [3••].

For the purposes of this review, we refer to substance use disorder as *addiction*. This term will encompass diagnostic definitions derived from the DSM as well as other diagnostic schema, such as the International Classification of Diseases (e.g., ICD-10) [4] and the Fagerström measures of nicotine dependence (e.g., FTND, FTQ) [5]. The overwhelming majority of the research presented in this review comes from genetic association studies of alcohol, tobacco, and cannabis, with brief mention of emerging research on cocaine and opioids.

## Heritability of Addiction

Familial aggregation of addiction has been recognized for decades. Rates of alcoholism in male and female siblings of alcoholic probands have been noted to be 50% and 24% respectively, compared with 20% (male) and 6% (female) of participants from the general population [6]. Rates of other addictions (cannabis, cocaine) and habitual smoking are also elevated, not only in alcoholic probands but also their first-degree relatives. Twin studies have revealed that genetic influences are primarily responsible for this familial aggregation of addiction (see [7] for a review). Regardless of substance, 50% of the variance in addictions can be attributed to those segregating genes that are shared by twin pairs [8]. Notably, such estimates are influenced by a variety of factors, including age and exposure. For example, heritability estimates of substance-related problems are as low as 0% during adolescence, and increase during adolescence and adulthood [9]. This has led to the broad consensus that while familial environment is more important for the early stages of experimentation and substance use, genetic factors exert a more pivotal role in later stages of addiction [10, 11]. Twin studies also substantiate the role of common genetic underpinnings to a variety of addictions, including those involving a host of illicit drugs, alcohol, nicotine, and even caffeine (e.g., [12]). This genetic comorbidity extends beyond addictions to other externalizing problem behaviors as well, including general disinhibitory behavior (e.g., [13•]).

## Gene Finding Efforts

Despite this moderate (50%), yet robust, estimate of heritability and evidence for genetic co-aggregation, gene identification for addiction has been extremely challenging. A majority of these gene-finding efforts have relied on candidates with *a priori* biological support. Broadly, these genes can be characterized as those participating in the experience of psychoactive effects of the substance (i.e., genes encoding proteins affecting neurotransmitter signaling) and those regulating their bio-availability and clearance (e.g., metabolizing genes), as shown in Fig. 1.

### Alcohol

**Putative Psychoactive Effects (GABRA2)—**In human association studies, variation in gamma amino butyric acid receptor A ($GABA_A$) genes, particularly the gene encoding the *alpha 2* subunit (*GABRA2*), have been routinely implicated in the etiology of alcohol

addiction [14-18]; however see [19, 20] for examples of non-replications. A recent meta-analysis reports that this association with alcohol dependence is significant for rs279858 (odds-ratio 1.18, $p=5\times10^{-6}$), a synonymous and frequently studied SNP [21•]. As the primary inhibitory neurotransmitter, GABAergic mechanisms putatively mediate many of the behavioral effects of alcohol, including sedation, motor impairment and withdrawal (see [22] for review). However, $GABA_A$ receptors are heteropentameric and receptors containing the α2 subunit are not directly modulated by ethanol [23]. This led investigators to posit that the well-documented associations between *GABRA2* SNPs and alcoholism might be attributed to its comorbidity with other externalizing (e.g., impulsivity) or internalizing (e.g., anxiety) disorders. Consistent with this speculation, studies have noted that the same *GABRA2* SNPs linked to alcoholism also correlate with its earliest developmental precursor, conduct problems [24]. In particular, a recent study found that impulsiveness was a nearly complete mediator of the association between *GABRA2* SNPs and lifetime alcohol problems [25].

In contrast, animal studies assert a more direct pathway between alcohol use and α2 subunit-bearing $GABA_A$ receptors. Deletion of the α2 subunit via systemic gene knock-out increased the sedative (and ataxic) effects of ethanol in one study [26] but decreased sedation [27] in another, while altering self-administration rates in neither. In contrast, selective silencing of the gene in the central amygdala temporarily ameliorated binge drinking in rodents [28]. The effects of *GABRA2* variants on sedation was recently observed in humans, where those carrying a haplotype spanning 5′ GABRG1 to 3′GABRA2 reported decreased sedation upon challenge with alcohol [29].

Despite this evidence, the precise function of *GABRA2* in general, and more specifically, variants studied in humans, remains elusive. The AA genotype of rs279858 is associated with greater *GABRA2* mRNA expression in the prefrontal cortex; however, these mRNA levels did not differ across postmortem brains from alcohol dependent and non-dependent donors [30]. Further, studies imply that the association signal for *GABRA2* may actually arise from the neighboring *GABRG1* gene [31, 32]. Both *GABRA2* and *GABRG1* expression appear to be down-regulated in the hippocampus of alcohol dependent individuals [33]. As $\gamma_1$-subunit containing $GABA_A$ receptors are only expressed in selected brain regions (e.g., central amygdala) that have been implicated in addiction, they have emerged as possible therapeutic targets [34]. However, the extent to which these receptors respond to ethanol remains unknown.

**Metabolism (ADH1B, ALDH2)—**Two polymorphisms in genes encoding alcohol metabolizing enzymes, alcohol dehydrogenase 1B (*ADH1B*) and aldehyde dehydrogenase 2 (*ALDH2*) have been associated with differences in alcohol consumption and dependence [35-37]. The *ADH1B* Arg48His (rs1229984), results in increased oxidation of alcohol to acetaldehyde, while the other variant, *ALDH2* Glu504Lys (rs671), is associated with decreased enzymatic conversion of acetaldehyde to acetate. Consequently both variants, most prevalent among East Asians [38], cause the accumulation of acetaldehyde, which induces aversive reactions to alcohol consumption including flushing, nausea, and palpitations. This aversive response typically decreases alcohol consumption and protects against the development of addiction. Although relatively uncommon in non-Asians, the

protective effects of the *ADH1B* allele on alcohol dependence and consumption were recently supported within a meta-analysis of individuals of European and African American descent [39] and more recently, at genomewide significant levels in a German population [40] and in an independent genomewide association study of European and African-American subjects [41••]. In addition to *ADH1B* and *ALDH2*, other variants in alcohol dehydrogenase encoding genes, such as *ADH1A*, *ADH1C*, *ADH4*, *ADH5*, and *ADH7* have also been sporadically associated with alcohol dependence [36, 37, 42-44].

## Nicotine

**Putative Psychoactive Effect (CHRNA5-A3-B4)—**Among the most replicated associations in addiction are those between polymorphisms in the nicotinic acetylcholine receptor gene cluster encoding the α5, α3, and β4 subunits (*CHRNA5-A3-B4*) with nicotine dependence [45-47], smoking behaviors [48, 49], and treatment response [50]. A majority of studies implicate a non-synonymous SNP, rs16969968, in *CHRNA5* encoding an aspartic acid to asparagine substitution at codon 398 (a highly conserved residue), and a highly correlated proxy SNP, rs1051730, in *CHRNA3*. This variant (rs16969968) was initially identified in a candidate gene association study of nicotine dependent cases [45]. A proliferation of studies followed when multiple genomewide association studies unequivocally identified this variant as a contributor to genetic vulnerability for cigarettes smoked per day (CPD). Aggregating effect sizes across 73,853 subjects, investigators convincingly documented an association on the order of $10^{-73}$ for an association between rs1051730 and CPD [51, 52, 53••].

The intuitive appeal of the signal coming from *CHRNA3/CHRNA5* arises from the putative effects of rs16969968 on receptor function (but not expression). As α4β2α5 receptors with the asparagine residue show decreased response to a nicotine agonist, carriers may require greater amounts of nicotine and thus, be more vulnerable to dependence [47] (but see also [54]). In addition, α5 knock-out mice appear to be more sensitive to the rewarding effects of nicotine, particularly at higher concentrations, demonstrating profound increases in motivation to seek and consume nicotine [55].

In addition to rs16969968, several other variants in this gene cluster (e.g., rs680244, associated with gene expression) have been associated with smoking as well as alcohol use. Broadly speaking, the linkage disequilibrium (LD) patterns across the genes indicate the presence of 3-4 bins tagged by variants - rs3841324 (*CHRNA5* promoter), rs16969968, and rs578776 (3′-UTR of *CHRNA3*) [56] and there is evidence that these LD bins vary in their relationships with smoking, across populations [57, 58], with each exerting putatively independent effects.

**Metabolism (CYP2A6)—**Nicotine is primarily metabolized by a liver enzyme, cytochrome P450 2A6 (*CYP2A6*), which converts nicotine to cotinine (COT), and further to 3′-hydroxycotinine (3HC) [59, 60]. The ratio of 3HC/COT is a robust and highly heritable (47-67%) marker of nicotine clearance and of metabolic activity [61] and polymorphisms in the *CYP2A6* gene explain 6-19% of this heritable variation [62]. There are numerous polymorphisms in *CYP2A6* and their activities range from fully inactive alleles (e.g.,

*CYP2A6*2)* to those that reduce enzymatic efficiency by varying degrees (e.g., *CYP2A6*9)* [63]. Based on their activity, *CYP2A6* alleles have been used to classify individuals into slow (homozygotes/carriers for no activity allele or carriers for reduced activity allele), intermediate (carriers for reduced activity allele) and normal metabolizers [64]. These correspond, roughly, to <50%, 50-80% and >80% *CYP2A6* activity. Individuals with *CYP2A6* genotypes conferring slower metabolism tend to report smoking fewer CPD, less nicotine dependence, and are more likely to quit by themselves [65, 66] (except see [67]) or with pharmacologic treatment [68] (see also [69]). However, relative to variants in other genes, including *CHRNA5/CHRNA3, CYP2A6* associations less robustly predict nicotine addiction. For example, a genomewide association study (GWAS) meta-analysis found an association between a variant (rs4105144) in linkage disequilibrium with a metabolically deficient *CYP2A6*2* allele (and other reduced activity alleles) and daily cigarette consumption, but not nicotine dependence [52].

### Cannabis

**Putative Psychoactive Effects (CNR1)—***CNR1* encodes the human endocannabinoid receptor 1 (CB1) which is the putative binding site for Δ9-tetrahydrocannabinol. CB1 knock-out mice do not display effects associated with cannabinoids (e.g., antinociception) [70]. Numerous studies have examined the relationship between variants in *CNR1* and cannabis addiction as well as other substance use disorders (for review see [71]). The most frequently studied of these polymorphisms is the $(AAT)_n$ repeat in the 3′ untranslated region of the gene, a variable number of tandem repeats with unknown functional consequence. A recent meta-analysis reported that individuals with greater than 15 repeats may be at increased risk for addiction to illicit drugs [72•]. Other variants (e.g., rs1049353, rs806380) have produced inconsistent results, further complicated by the examination in some studies of addiction to all illicit drugs (even though cannabis is likely to be the most commonly used and misused of these).

**Metabolism (CYP2C9)—**Cannabis is first converted to an active metabolite, 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC), and then to its inactive form, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) by the cytochrome family of enzymes [73, 74]. We are only aware of one study that found that *CYP2C9*3* carriers were more likely to have higher concentrations of THC and, correspondingly, lower concentrations of THC-COOH and show greater sedation upon oral THC administration [75].

## GWAS and Identification of Novel Variants

GWAS, when well powered, can serve as a powerful tool for uncovering common variation associated with addiction phenotypes. For instance, in the largest of the aforementioned meta-analyses of CPD, an aggregate sample size > 140,000 resulted in an association signal for rs1051730 in *CHRNA3* on the order of magnitude of $10^{-73}$ [53••]. Despite the high degree of statistical significance, the effect size was small with each risk allele only associated with one extra CPD. Such weak penetrance likely limits the ability of individual GWAS to produce replication. There have now been nine GWAS on DSM-IV alcohol dependence [76-83] and of these, only three report genomewide significant signals. The first

two report signals in *PECR* (Peroxisomal Trans-2-Enoyl-CoA Reductase) [82] and *ADH1C* (alcohol dehydrogenase 1C) [83], however none of the other studies have replicated these associations. The most recent of these is perhaps the most promising, convincingly demonstrating association between a symptom count of alcohol dependence and SNPs in *ADH1B*, including rs1229984 (p=1.2E-31) in European- and rs2066702 (p=6.3E-17) in African-American subjects [41••]. One meta-analysis has also identified a significant association between daily typical alcohol intake and a variant (rs6943555) within the autism susceptibility candidate 2 (*AUTS2*) gene (*P*=4.1E-9) [84].

While meta-analyses are pending for other substances, individual GWAS have yielded promising leads for cocaine and opioids. A recent GWAS of cocaine dependence identified rs2629540 in *FAM53B* [85]. The same group of investigators has also recently reported genomewide significant association signals for genes in potassium signalling pathways for opioid dependence [86]. In contrast, results for cannabis use and dependence have been less promising [87, 88]. Despite the lack of statistically significant findings, there is growing evidence that common GWAS variation explains 24-38% of the variation in current smoking [89] and alcoholism [90].

## Neurogenetic Developments

A significant challenge of addiction genetics research involves ascribing function to individual polymorphisms and isolating their role in the addictive process. Evaluating the functional mechanisms of polymorphisms associated with the psychoactive effects of substances is further complicated by the fact that they likely involve neural intermediates. We focus here on neuroimaging outcomes as a promising complement to the association studies discussed above.

The corticostriatal system, which includes the striatum, ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), thalamus, insula, hippocampus, and anterior cingulate cortex (ACC), among other structures, is critical for reward processing (for review see [91•]). Emerging neurogenetics research [92•] suggests that genetic variation associated with addiction risk also predicts individual differences in corticostriatal function, structure, and connectivity, providing putative mediating neural mechanisms through which these polymorphisms promote addictions. While the vast majority of addiction-related neurogenetics research has focused on genetic variation in the dopaminergic system [93, 94], we focus our review on research evaluating variation within *GABRA2*, *CHRNA5-CHRNA3-CHRNB4*, and *CNR1*.

### Alcohol and GABRA2

Two studies have found that genotypes predictive of alcohol addiction (i.e., rs279871 A homozygotes, rs279826 G homozygotes, rs279858 G homozygotes), are also associated with enhanced neural response to reward predictors in brain regions associated with subjective valuation, including the vmPFC [95] and insula [96••]. While these studies suggest that *GABRA2* risk variants may confer vulnerability to alcohol addiction by enhancing the subjective valuation of external cues, there was no evidence that genotype predicted craving [95]. One possibility is that this enhanced reactivity in regions critical for subjective

valuation may drive urgent and impulsive attempts to regulate negative emotional states [96••].

## Nicotine and CHRNA5-A3-B4

Risk-related polymorphisms in *CHRNA5-A3-B4* have been associated with individual differences in corticostriatal circuit reactivity to nicotine cues as well as resting state connectivity. The risk (i.e., A) allele of rs16969968 predicts reduced reactivity in corticostriatal circuit nodes (e.g., dorsal striatum, hippocampus, insula) in response to smoking cues among nicotine-dependent women. Notably, because smoking is associated with enhanced smoking cue reactivity, these results suggest a dissociation between *CHRNA5-A3-B4* genetic risk and neural correlates of smoking. While the reasons for this dissociation are unclear, the authors speculate that risk allele carriers may form relatively poorer drug-cue associations and that stronger cue-related memory may be needed to promote continued smoking in those with relatively lower genetic risk. Another possible interpretation of these data is that because the risk allele at rs16969968 is associated with decreased response to a nicotine agonist [47], independent smoking-related cues may not develop the same predictive value for risk allele carriers, who may need to ingest relatively larger dosages to obtain reward. The risk allele of rs16969968 may confer vulnerability to smoking via blunted corticostriatal response to smoking cues, or via other, not mutually exclusive neural mechanisms, such as neural reactivity to threat [97].

The only other neuroimaging study we are aware of investigating *CHRNA5-A3-B4*, studied resting-state functional connectivity (i.e., the synchronization of intrinsic low-frequency fluctuations between brain regions outside of task performance) within the corticostriatal circuit. Similar to smokers [98], rs16969968 risk allele carriers had reduced functional coupling of the dorsal anterior cingulate cortex (dACC) and striatum/extended amygdala, regardless of smoking status [99]. This study also found that *CHRNA3* rs578776 G (risk) allele carriers had elevated dACC and thalamic resting state connectivity, which was correlated with smoking just prior to the imaging session (measured via expired CO levels). Given these differential associations with lifetime and immediate smoking, and the extant literature demonstrating the independence of their effects, the authors posit that rs16969968 and rs578776 genotypes contribute to trait and state aspects of smoking respectively [99]. In contrast to the study by Janes and colleagues [100], the results of this study suggest that *CHRNA5-A3-B4* genetic risk covaries with corticostriatal correlates of smoking.

## Cannabis and CNR1

Genetic variation in the endocannabinoid system has been implicated in neural response during abstinence-related withdrawal and craving [101]. Specifically, during abstinence, rs2023239 (non-synonymous) heterozygotes have elevated reactivity to marijuana cues in OFC and ACC relative to A allele homozygotes. This elevated reactivity in corticostriatal regions critical for reward processing and the valuation of external stimuli may contribute to increased marijuana craving in rs2023239 heterozygotes following abstinence. Notably, a functional variant (rs324420) in *FAAH*, which codes for the fatty acid amide hydrolase enzyme that catabolizes endocannabinoids, was found to have independent and additive effects along with *CNR1* [103••]. In addition to mediating neural activity in response to cues,

*CNR1* variants have also been linked to altered brain morphology. For example, Schacht et al. [104] found that heavy cannabis users have lower bilateral hippocampal volume than healthy controls, with the smallest volumes found in cannabis users with the rs2023239 G allele. Given that the hippocampus is a region critical in memory processing, these findings provide a putative mechanism underlying the association between heavy cannabis use and deficits in cognitive processes and learning [105].

The few neurogenetic studies of *GABRA2, CHRNA5-CHRNA3-CHRNB4*, and *CNR1* genotypes associated with addiction risk suggest that these polymorphisms may drive addiction risk via their effects on corticostriatal connectivity and reactivity to reward. Notably, while we concentrated on neurogenetic research investigating genetic polymorphisms that are believed to moderate the psychoactive effects of substances, new research suggests that this approach may also afford a remarkable opportunity to examine whether indices of metabolism exert an impact on neural systems. For instance, a revealing new study [106] found that normal metabolizers (defined by *CYP2A6* genotype) have greater smoking cue-induced activation in the right amygdala, striatum, hippocampus, and cingulate cortex relative to reduced metabolizers. Such studies of metabolic-related polymorphisms may be particularly informative in the context of drug-challenge paradigms.

## Putting your Genes to work: Pharmacogenetics

Given the contrast between the modest effect sizes attributable to individual variants and the relatively large impact of environmental control that can be exerted (e.g., increasing taxation, prohibition of use in public places), are genetic studies of addiction worthwhile [107]? Perhaps the most compelling response to this question comes from emerging pharmacogenetic efforts that attempt to tailor pharmacotherapy based on genotype.

### Alcohol

In the broadest sense, disulfuram (*Antabuse*), which inhibits aldehyde dehydrogenase (responsible for conversion of acetaldehyde to acetate) and targets the action of *ALDH2* might be considered a drug with pharmacogenetic underpinnings. Although non-Asians do not carry the protective variant of rs671, disulfuram approximates its effects by inducing aversive reactions upon alcohol intake. A more specific instance in which genotype modulates treatment response for alcoholism comes from well-replicated studies of the Asn40Asp variant (rs1799971) in *OPRM1* which encodes the mu-opioid receptor, and moderates the effectiveness of naltrexone (NTX; a mu-opioid antagonist) treatment [108]. Recent findings show that Asp40 (G) allele carriers have more positive subjective responses [109] and increased mesolimbic dopamine release following alcohol challenge compared to those homozygous for the Asn40 allele [A] [110]. There is evidence that NTX is efficacious in reducing heavy drinking only in Asp40 carriers [111-113]. *GABRA2* variants also have been found to moderate treatment outcomes. Specifically, rs279858 was associated with drinking in individuals assigned to different psychotherapeutic treatments [114]. Although in that study there were no appreciable differences across treatment type (12-step vs. cognitive behavioral vs. motivational enhancement therapy), individuals homozygous for the low-risk A allele, had fewer drinking days when enrolled in 12-step treatment. In another study, carriers of the same risk allele relapsed to drinking earlier than A-allele homozygotes [115].

Another intriguing series of experiments have focused on tailoring medications for alcoholism that act via serotonergic modulation. Two drugs, ondansetron and sertraline, are worth mention for their differential efficacy in the context of individual genotype (short S versus long L) at the promoter polymorphic region (5-HTTLPR) of the serotonin transporter (*SLC6A4; 5-HTT*) gene. Ondansetron is an antagonist of the serotonin (5-HT3) receptors. One study found that the most substantial reduction in drinks/day and days abstinent upon treatment was noted in those who were homozygous for the long (LL) allele of 5HTTLPR and the T allele of a 3′ untranslated region (UTR) variant, rs1042173, putatively due to increased drug-provoked blockade of upregulated post-synaptic serotonin receptors in LL/TT individuals [116, 117]. Sertraline, on the other hand, is a selective serotonin reuptake inhibitor (SSRI) and has been found to be more efficacious, in general, in those with comorbid depression [118]. These observations led to the finding that while sertraline was beneficial in LL individuals who were late-onset alcoholics (typically comorbid with internalizing features [118], it performed worse than placebo in early-onset cases [119], particularly in the context of daily anxiety.

## Nicotine

Both *CHRNA5-CHRNA3-CHRNB4* and *CYP2A6* have been implicated in treatment response. For example, the effectiveness of nicotine replacement therapy (but not bupropion) has been found to be more pronounced in fast versus slow metabolizers [69]. A study has also shown that slow metabolizers tend to require fewer doses of nicotine spray but do not differ in their response to patch usage [120], although there is emerging evidence that slow metabolizers may be at higher risk for patch-related nicotine toxicity [121]. Similarly, one study showed that a high-risk haplotype comprised of variants in *CHRNA5-CHRNA3-CHRNB4* predicted failed abstinence in placebo-treated subjects but not those receiving active pharmacotherapy [122], while another study reported similar findings for the placebo group but greater abstinence in those receiving nicotine replacement therapy [123]. Perhaps the most prominent of therapeutic alternatives for smoking cessation is varenicline, a partial agonist of the α4β2 nicotinic receptor subtype. Variants in *CHRNA4* and *CHRNB2* have been implicated in response to varenicline while variants in *CHRNB4* were associated with nausea, a common side effect of medication use, which typically attenuates adherence [124].

## Opioids

Opioids, particularly heroin, are drugs with extremely high addictive potential [125]. Treatments for opioid dependence can vary from the typical use of methadone (opioid agonist) and buprenorphine (partial agonist) to even naltrexone (opioid antagonist). Response rates vary dramatically and the use of none of these is without risks [126]. One recent study of African-Americans found that for a variant, rs678849, in the gene encoding the delta opioid receptor (*OPRD1*), CC individuals had more positive urine tests (24 weeks post-treatment) if treated with buprenorphine but less positive tests when treated with methadone [127]. Another recent study implicates a functional variant (rs2760118) in the gene encoding the succinic semialdehyde dehydrogenase enzyme (*ALDH5A1*) in response to methadone maintenance with T allele carriers more likely to be non-responders [128].

## Where do we go from here?

*"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness…"* [129]. These are exciting times for the genetic study of addictions. What is next in this "age of wisdom"? We propose the following as promising avenues for future research:

1. **We are what we measure**: Early addiction studies relied heavily on diagnostic entities (e.g., alcohol dependence), assuming homogeneity within the construct. Evidence from rodent models (e.g., [130]) substantiated by human genetic studies (e.g., [131•, 132]) imply that such an assumption of homogeneity, particularly for alcohol and nicotine addictions, may be inaccurate. Aspects of addiction that may appear non-diagnostic are also worth study. For instance, cocaine-induced paranoia, a dangerous consequence of excessive cocaine use has been successfully investigated with particular attention to variants in dopamine beta-hydroxylase (*DBH*; associated with dopamine metabolism) (e.g., [133]). This research complements findings from a recent pharmacogenetic trial that implicated rs1611115 in *DBH* in predicting efficacy of a novel vaccine for cocaine misuse [134], such that vaccinated carriers of the T allele (putatively associated with lower DβH activity) showed a more dramatic decrease (77 to 51% versus 83 to 72% in CC individuals) in positive urines across a 16-week study period [135]. Sample size restrictions remain an essential barrier to the study of individual components or sequelae of addictions, and may require institutional support for data collection efforts targeted at phenotypic refinement. To this end, another possibility is to investigate those features that underpin a variety of addictions, for instance impulsivity and compulsivity. Such behaviors are frequently assessed across a variety of studies as they integrate not only across substance use behaviors but also likely underpin behavioral addictions (e.g., disordered gambling [136]), including the more recent and controversial notion of food addictions [137].

2. **Rare variants for commonly occurring disorders**: GWAS capitalize on the common disorder-common variant hypothesis, and as such, this is proving to be fruitful for even rarer psychiatric disorders (e.g., schizophrenia). Nonetheless, existing exome arrays and emerging sequencing strategies present opportunities for the study of rare variants for these commonly occurring addictions [138]. For instance, Vrieze et al. [139] recently reported that even though individual rare variants were not statistically significant, when combined with common (GWAS) variation, these polymorphisms explained up to 84% of the heritable variation in illicit drug use [139]. Another study conducted targeted deep sequencing of 17 ionotropic glutamate (N-methyl-D-aspartate) receptors and identified rare variants in the disrupted in schizophrenia (*DISC1*; rs139667828) and glutamate receptor, ionotropic, N-methyl D-aspartate 2B (*GRIN2B*; rs146792012) gene for opioid dependence in African-Americans [140]. The study of rare variants is not without challenges, in particular, the requirement for large samples. Family data is also exceptionally valuable in their study but methodologies for the study of general

enrichment or the specific transmission of individual variants are still being honed, particularly for whole genome data.

3. **Genes and environment**: Even in this era of skepticism [141, 142], there is little doubt that the etiology of addictions involves gene-environment interplay. Even for variants impacting metabolism, such as rs671 in *ALDH2*, there is evidence that increasing social pressures to drink have contributed to cohort-related increases in alcohol consumption in heterozygous carriers, who drink despite flushing [143]. There is also evidence that childhood adversity intensifies the risk posed by absence of the protective allele of rs1229984 (*ADH1B*;[144]). Such environmental moderation is likely to be even more pronounced for genes that regulate the psychoactive effects of these substances (e.g., *GABRA2* genotypes and parental monitoring,[24]; *CHRNA5* SNPs and peer smoking [145], parental monitoring [146], childhood adversity [147], and early age of onset [148]). Thus, if statistical challenges can be surmounted, this is an exceedingly promising avenue for future enquiry.

4. **Epigenetic (dys)regulation**: The impact of environmental adversity, particularly during childhood, may extend well beyond moderation of changes in DNA sequence to expression differences that are epigenetic in nature (i.e., changes in gene expression unrelated to sequence) [149]. For instance, hypermethylation of CpG sites of genes such as *ALDH1A1* and *CHRNA5* have been noted in peripheral tissue from alcoholic patients with a history of childhood adversity [150]. Relative to controls, early studies also reported increased global methylation in leukocytes from alcoholic subjects [151], in particular in the promoter regions of genes implicated in alcohol addictions, such as *OPRM1* [152] and the dopamine transporter *(SLC6A3*), with the latter predicting craving severity [153]. The principal challenge with epigenetic studies is the use of peripheral tissue and their uncertain association with regionally specific differences within the brain [154]. Although relatively few studies have investigated epigenetic mechanisms within the post-mortem brain, one study [155] found increased methylation levels in 3 prodynorphin *(PDYN)* CpG-SNPs in the dorsolateral prefrontal cortex of alcohol dependent subjects.

5. **Drugs and the developing brain**: A majority of neurogenetics, and in fact, neuroimaging studies have relied on samples of addicted individuals responding to cues. Such cross-sectional studies pose the quintessential dilemma of whether differences noted can be attributed to predisposing characteristics that preceded drug exposure (e.g., family history) or whether they are a consequence of prolonged drug use. Twin pairs discordant for addiction status offer an elegant control for genetic liability. Utilizing this paradigm, one study found that relative to their exposed but non-regular smoking identical co-twin, the genetically identical twin who smoked regularly showed no differences in corticostriatal response to reward when whole brain analyses were conducted, although regions associated with cognitive control were differentially activated [156]. This suggests that extant findings implicating structures in the corticostriatal system in the etiology of addiction relate to inherited differences, rather than variations that evolve as a

function of drug exposure. Likewise, prospective neurogenetic studies of addiction are of immediate importance.

## Conclusions

Table 1 provides an overview of key accomplishments in addiction genetics. We detail there a handful of key genes in relation to their role in the psychoactive effects and metabolism of alcohol, nicotine, or cannabis. However, there has not been consistent replication of these findings. GWAS are beginning to reveal intriguing findings and meta-analyses that will aggregate data across these individual GWAS have begun to be formulated. However, unlike schizophrenia [157], such efforts lag considerably in accruing sample sizes large enough to detect variants of the expected modest effect size. Neurogenetic studies continue to inform the functional relevance of polymorphisms uncovered using genetic association methods, however they are limited by the phenotypes they investigate (e.g., how does craving relate to general addiction?), how these phenotypes relate to addiction (e.g., how do genes that affect corticostriatal response relate to alcoholism?) and low statistical power. In response to these challenges, it is likely that advances in addictions research over the next decade will stem from collaborative and translational science. There are other exciting avenues for translational research that are beyond the scope of this review, such as the utility of animal models (e.g., rodent [158], and drosophila models [159] of drinking) or the remarkable potential of using skin biopsies from addicted individuals to induce pluripotent stem cells that differentiate into neuronal tissue and examining the effect of ethanol exposure to live tissue [160]. Such modest efforts at examining the many facets of the biological processes underlying addictions will eventually culminate in great strides, both in scientific discovery and in our considerably enhanced ability to treat addictions - common, yet personally and societally burdensome mental disorders.

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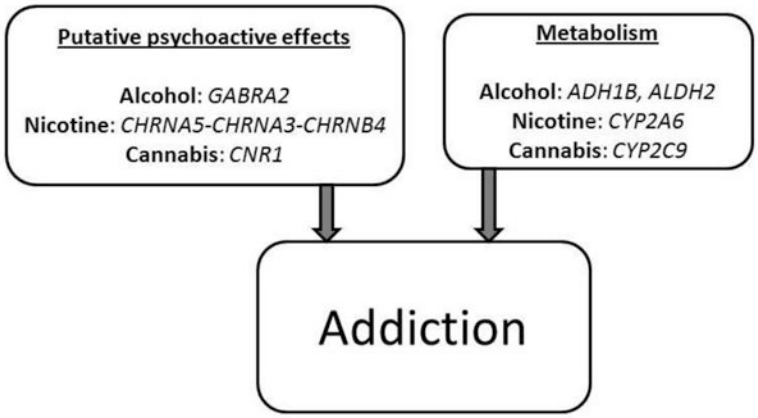


**Fig. 1. Broad groups of genetic factors influencing addiction and genes that influences this process for alcohol, nicotine and cannabis addiction**

**Table 1**

**Overview of key genetic findings for addictions**

| Substance | Gene | SNPs | Phenotypic association evidence | Neurogenetics evidence | Pharmacogenetic role |
|---|---|---|---|---|---|
| Alcohol | *GABRA2* | rs279858 (s); rs279871; rs279826 | Alcohol & illicit drug addiction; impulsivity & externalizing problems. | Greater activation in regions of internal and external subjective valuation in risk allele homozygotes. | Linked to time to relapsed drinking and fewer drinking days during treatment. |
| | *OPRM1* | rs1799971 (ns) | - | - | Greater reduction of heavy drinking in Asp40 carriers prescribed Naltrexone. |
| | *ADH1B* | rs1229984 (ns) | GWS; protective effects on alcohol addiction due to flushing (rs671 in Asians only). | - | - |
| | *ALDH2* | rs671 (ns) | | - | Disulfuram targets this enzymatic function. |
| | *ADH1C* | rs1789891 (p) | GWS; correlated with Arg272Gln that modifies enzymatic efficiency of alcohol conversion to acetaldehyde. | - | - |
| | *AUTS2* | rs6943555 | GWS for drinks/day; mRNA differences in human prefrontal cortex. | - | - |
| Nicotine | *CHRNA5*<br>*CHRNA3*<br>*CHRNB4* | rs16969968 (ns)<br>rs1051730 (p)<br>rs578776 (utr) | GWS for cigarettes per day; multiple independent signals associated with nicotine dependence. | Reduced corticostriatal activity; reduced coupling of dorsal ACC and striatum and extended amygdala. | Haplotype predicts cessation and cessation success in those receiving placebo. Increased abstinence in treatment group. |
| | *CYP2A6* | Several | GWS; classifies individuals as slow, normal and fast metabolizers; associated with smoking. | Greater activation in ACC, amygdala, striatum, hippocampus in fast and normal relative to slow metabolizers. | Slow metabolizers at risk for patch-related toxicity; nicotine replacement therapy more effective in fast metabolizers but no effect on bupropion. |
| Cannabis | *CNR1* | (AAT)n repeats | Associated with illicit drug addiction in meta-analysis. | - | - |
| | | rs2023239 (ns) | Withdrawal & craving to cues. | Striatal activation to marijuana cues. | - |
| | *FAAH* | rs324420 (ns) | Some evidence*. | | |
| | *CYP2C9* | CYP2C9*3 | Lower enzymatic conversion of THC to THC-COOH; greater sedation. | - | - |

s=synonymous; ns=non-synonymous; p=proxy to nonsynonymous; utr=in untranslated region; GWS=genomewide significant at $p < 5\times10^{-8}$; ACC=anterior cingulate cortex.

**FAAH* has been sporadically studied in the context of addictions, however we do not cover that modest literature in this review