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The Genetic Epidemiology of Substance Use Disorder: A Review

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Abstract

Background—Substance use disorder (SUD) remains a significant public health issue. A greater understanding of how genes and environment interact to regulate phenotypes comprising SUD will facilitate directed treatments and prevention.

Methods—The literature studying the neurobiological correlates of SUD with a focus on the genetic and environmental influences underlying these mechanisms was reviewed. Results from twin/family, human genetic association, gene-environment interaction, epigenetic literature, phenome-wide association studies are summarized for alcohol, nicotine, cannabinoids, cocaine, and opioids.

Results—There are substantial genetic influences on SUD that are expected to influence multiple neurotransmission pathways, and these influences are particularly important within the dopaminergic system. Genetic influences involved in other aspects of SUD etiology including drug processing and metabolism are also identified. Studies of gene-environment interaction emphasize the importance of environmental context in SUD. Epigenetic studies indicate drug-specific changes in gene expression as well as differences in gene expression related to the use of multiple substances. Further, gene expression is expected to differ by stage of SUD such as substance initiation versus chronic substance use. While a substantial literature has developed for alcohol and nicotine use disorders, there is comparatively less information for other commonly abused substances.

Conclusions—A better understanding of genetically-mediated mechanisms involved in the neurobiology of SUD provides increased opportunity to develop behavioral and biologically based treatment and prevention of SUD.

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1. Introduction

The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) defines substance use disorder (SUD) as a constellation of behaviors involved in compulsive drug seeking including impaired control of substance use, impaired social interactions with others because of substance use, risky drug use (e.g., substance use in hazardous settings), and pharmacological changes (e.g., experiencing withdrawal symptoms). Further, the DSM-5 defines addiction as the most severe, chronic stage of the SUD diagnosis, which is characterized by subsantial loss of self-control, manifesting in compulsive drug-seeking behavior despite the desire to discontinue use (American Psychiatric Association, 2013; Volkow, Koob, & McLellan, 2016). SUD and addiction remain a significant global public health concern, resulting in substantial socioeconomic burden (Collins et al., 2006; Heslin, Elixhauser, & Steiner, 2015; Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015). Globally, 52.3 million cases of alcohol and drug dependence/problem use were reported in 2004 (World Health Organization, 2008). In 2010, this number increased to 147.5 million cases (Whiteford, et al., 2015), and SUD is expected to become more prevelant over time.

Genetic factors within multiple overlapping neurobiological systems has been consistently implicated in SUD etiology (Nestler, 2001). Here, we summarize the genetic epidemiology of SUD and focus on commonly abused substances including alcohol, nicotine, marijuana, cocaine, and opioids. Although results will be summarized across all substances, genetic epidemiological studies of alcohol and nicotine use currently out number cannabis, cocaine, and opoids. Further, we connect this knowledge with the neurobiology of SUD and provide suggestions for future research in this area

2. Major SUD Neural Substrates

Although different drug classes act on distinct cellular substrates, initial drug reward/saliency appears to be primarily encoded by midbrain dopamine neurons projecting into the prefrontal cortex as well as the dorsal and ventral striatum (Volkow, Fowler, Wang, Baler, & Telang, 2009). Human imaging studies indicate the extent to which a drug increases striatal dopamine is proportional to self-reported euphoria (Drevets et al., 2001; Sharma & Brody, 2009; Volkow, et al., 2009). Nonetheless, it is important to note that responding for rewarding stimuli is also encoded by other ascending monoamine fibers such as norepinephrine (Stein & Himwich, 1962) and other non-dopaminergic systems within the medial forebrain bundle (Crow, 1973).

2.1 Commonly abused substance usurp learning mechanismns

Dopamine also encodes salience or a teaching signal, which may contribute to the learned component of substance abuse. For example, dopamine neurons initially fire with reinforcer delivery, but with time dopamine neuron firing becomes time-locked with predictive

conditioned stimuli that precede an expected reinforcer (the unconditioned stimulus) rather than the reinforcer, itself (Schultz, 1997). Similar findings have also been observed in detoxified cocaine abusers. Specifically, presentation of drug-associated cues increase dopamine levels in brain regions that participate in habit circuitry (Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009; Volkow, Wang, Fowler, Tomasi, & Telang, 2011; Volkow et al., 2006) to a level greater than the drug itself (Volkow, et al., 2011; Volkow, et al., 2006). This dopamine signal is correlated with self-reported craving (Drevets, et al., 2001; Heinz et al., 2014). After repeated or habitual use, previously neutral stimuli become imbued with the drug experience and eventually acquire the ability to increase dopamine in anticipation of reward. This dopamine signal can elicit strong motivation to pursue a drug of abuse (Owesson, White et al., 2009; Salamone, Correa, Farrar, & Mingote, 2007). Thus, dopamine signaling in several brain regions including the nucleus accumbens, dorsal striatum, ventral pallidum, dorsolateral prefrontal cortex, anterior cingulate, and orbitofrontal cortex modulate the motivation to pursue abused substances (Salamone, et al., 2007).

2.2 Compulsive drug-seeking behavior

Once addiction has developed, decreased ability to avoid drug craving and/or inhibit drug-seeking behavior commonly manifests despite decreased hedonic effects of the drug. These inhibitory ‘top-down’ deficits may emerge from a lack of executive control over circuits that parse reward/saliency, aversion avoidance/stress reactivity, interoception, and motivation (Koob & Le Moal, 2001; Volkow, Fowler, & Wang, 2003; Volkow, et al., 2011). Decreased hedonic drug effects may stem from a shift away from phasic and tonic midbrain dopamine firing patterns toward more tonic firing, which results in lower levels of dopamine release (Grace, 2000). Blunted dopamine release and decreased hedonic effects have been observed in cocaine-addicted individuals challenged with either methylphenidate (a cocaine-like compound) or amphetamine (Martinez et al., 2007; Volkow et al., 1997; Volkow, et al., 2011). These and other neural adaptations induced by the drug are thought to usurp normal learning and habit circuitry and increasingly recruit cortical glutamatergic signalling (Bowers, Chen, & Bonci, 2010; Kalivas, 2009; Kalivas & O’Brien, 2008b; Koob & Volkow, 2010; Luscher & Malenka, 2011), which can manifest as compulsive drug-seeking behavior and relapse (Everitt & Wolf, 2002; Hyman, Malenka, & Nestler, 2006).

3. Twin and Family Studies of Substance Use Disorder

3.1 Genetic and Environmental Effects

Family studies report that children of parents with high-risk alcohol dependence, or that are from families where one member is diagnosed with an SUD, are at much greater risk for developing alcohol problems (Chassin, Rogosch, & Barrera, 1991). Consequently, family studies have demonstrated that SUD clusters within families, implicating a role for both genetic and environmental influences. In comparsion to family studies providing estimates of familial clustering, twin studies have estimated specific sources of variance in the etiology of SUD. Twin studies use monozygotic and dizygotic twin pair variances and covariances to estimate the proportion of total phenotypic variance of a trait due to additive genetic (additive genetic effects of alleles at every locus), shared environmental (environmental

influences common to both twins), and unique environmental influences (environmental influences not shared by members of the twin pair; (Cherny, 2009). Twin studies of SUD consistently report that substance initiation is significantly influenced by genetic as well as shared and unique environmental factors. This is consistent across populations that initiate tobacco, alcohol, or cannabis use (Agrawal et al., 2010; Huizink et al., 2010). In contrast, additive genetic influences are greater for substance progression; often defined as regular use as well as dependence. There is no longer a significant influence of shared environmental factors for either regular use or dependence in adulthood, although shared environmental influences remain significant during adolescence (Maes et al., 2017;; Rose et al., 2009; Bergen et al., 2007; Hopfer et al., 2003;). Additive genetic influences remain significant for regular use and dependence even when adjusting for genetic influences specific to substance initiation (Maes et al., 2004; Sullivan et al., 2001). Measurement of progression and dependence varies and can reflect the amount of substance used within a specific time frame or symptoms related to SUD diagnosis.

3.2 Genetic and Environmental Influences on SUD Across Multiple Substances

As a whole, SUD twin studies suggest a common set of genetic and environmental factors that are shared across drugs as well as genetic and environmental influences that are specific to a given substance. Studies of initiation report substantial shared environmental influences common to multiple substances (Fowler et al., 2007; Han, McGue, & Iacono, 1999; Koopmans, Slutske, Heath, Neale, & Boomsma, 1999). In contrast, studies of use and dependence reported significant additive genetic and unique environmental influences shared across SUD as well as genetic and environmental influences specific to a given drug (Agrawal & Lynskey, 2006; Baker, Maes, Larsson, Lichtenstein, & Kendler, 2011; Palmer et al., 2012; Palmer et al., 2009; Xian et al., 2008; Young, Rhee, Stallings, Corley, & Hewitt, 2006). Further, the influence of genetic and environmental factors shared between different forms of substance abuse are likely to remain significant across time (Palmer, et al., 2009).

3.3 Neuroimaging in Twins

Neuroimaging twin studies of SUD have begun to connect knowledge regarding the role of neural networks invovled in SUD with genetic and environmental influences on the disorder. For example, small, widespread negative associations were recently reported between cigarette pack-years and the volume and/or surface area of several cortical as well as subcortical brain structures (Prom-Wormley et al., 2015). Importantly, correlations were the result of shared genetic and unique environmental factors in brain structures involved in the processing of environmental influences related to smoking.

4. Genetic Association Studies

The goal of genetic association studies of SUD is to identify genetic markers that may have a role in the development or progression of addiction. Identifying these markers may aid in the treatment or prevention of SUD. There are two main catagories of genetic association studies. Candidate gene association studies (CGAS) test the association of previously identified markers with SUD phenotypes. Markers are selected for CGAS analysis due to demonstrated functional significance in prior animal, molecular genetic, and/or human SUD

studies (Kwon & Goate, 2000; Rebbeck, Spitz, & Wu, 2004). Together, these studies can develop a strong case for the importance of a genetic variant or biological pathway in SUD etiology. In contrast, genome-wide association studies (GWAS) test for significant associations between a SUD phenotype and hundreds of thousands single nucleotide polymorphisms (SNP) throughout the entire genome without prior knowledge about gene function. Thus, GWAS can identify novel candidate genes contributing to SUD. In addition, the aggregate effect of all SNPs associated with an outcome, whether or not they reach genome-wide significance, can be modeled via a polygenetic risk score (PRS) (Dudbridge, 2013; Ferreira et al., 2009; Purcell et al., 2009).

Multi-investigator research consortia have also been used to study the genetic architechture of SUD. These consortia-based genetic association studies aggregate GWAS data from individual studies in order to address the need to increase sample size and improve power to detect significant associations. Consortia-based genetic association studies often use meta-analyses and report summary data submitted across studies or analyze raw data from multiple GWASs (Panagiotou et al., 2013).

4.1 Alcohol and Nicotine

Significant genetic associations of hundreds of markers with alcohol use disorder have been reported (Li et al., 2011; Manzardo, McGuire, & Butler, 2015) although it has been difficult to consistently replicate these associations across studies (Forero, Lopez-Leon, Shin, Park, & Kim, 2015). In general, genetic association studies of alcohol highlight the importance of genes related to (1) alcohol metabolism (ADH); (2) processing of alcohol intermediates (e.g., *ADH1B, ADH1C*, and *ALDH2*) (Cui et al., 2009; Macgregor et al., 2009) and (3) neurotransmission pathways thought to be involved with stimulus-reward processing in the brain including dopaminergic (e.g., *DRD2*, *MAOA*, *COMT*), serotonergic (*HTR3A*, *HTR1B*, *HTR3B*), GABAergic (*GABRA1*, *GABRA2, GAD1*, *KCNJ9/GIRK3*), and glutamtergic (*GRIN2C*) pathways. Some of these genes have demonstrated functional significance either in animal, human, or molecular genetic studies of SUD (Addolorato et al., 2006; Lobo & Nestler, 2011; Melroy-Greif et al., 2017; Thanos et al., 2001; Vanyukov et al., 2007). SUD is generally characterized as a signalling imbalance through striatal inhibitory D2-like dopamine receptors (DRD2) although this is not necessarily consistent across all drugs. With the execption of cannabinoids, human imaging studies consistently report that affected individuals have lower D2-like dopamine receptor occupancy by a PET imaging ligand compared to controls (Volkow, Fowler, & Wang, 2002). Receptor occupancy is a proxy for the capacity of a receptor to transduce signal that can be influenced by receptor levels as well as intracellular and extracellular factors. Individuals with low D2-like dopamine receptor occupancy are also more likely to describe psychostimulant drugs as pleasurable compared to those with high D2-like receptor occupancy (Volkow et al., 1999; Volkow et al., 2002). Moreover, decreased D2-like dopamine receptor expression is associated with increased disposition to develop alcohol use disorder (Samochowiec et al., 2000). Further, rat alcohol self-administration was decreased by overexpressing D2 dopamine receptors in the nucleus accumbens (Thanos, et al., 2001), rats that are more prone to resume heroin-seeking behavior in response to stress express less striatal D2 dopamine

receptors (Zhou, Leri, Cummins, & Kreek, 2015), and D3 dopamine receptor knockout mice exhibit increased cocaine self-administration (Song et al., 2012).

Recent pathway- and network-based analyses of available candidate gene- and genome-wide- genetic association results of smoking and nicotine dependence indicated the importance of genes related to (1) drug metabolism (e.g., *ADH1B*, *SULT1A1*, *ALDH2*, *CYP17A1*, and *CYP1A1*); (2) synaptic transmission of cholinergic (e.g. *CHRNB4*, *CHRNA1*, *CHRNA*3, *CHRNA5,* and *CHRNA7*), glutaminergic (e.g., *GRM7* and *GRM8*) and dopaminergic (e.g., *DRD1*, *DRD2*, *DRD3*, *DRD4*, and *DRD5*) systems, and (3) reuptake and vesicular packaging of neurotransmitters (e.g., *SLC6A4*, *SLC18A2*, and *SLC9A9*) related to learning and memory (Harari et al., 2012; Liu, Fan, Liu, Cheng, & Wang, 2015; Minica et al., 2017; Yang and Li, 2016; Begum et al., 2016). Consequently, genetic association studies of alcohol as well as nicotine dependence highlight the complex nature of addiction as an outcome with physiological aspects including drug metabolism and availability within the body and brain, as well as neurobiological mechanisms related to the development of addiction.

To date, GWAS of alcohol (Table 2) as well as tobacco use (Table 3) using individual SNPs as well as PRS have reported modest evidence for the role of genetic influences on dependence-related measures. Two recent studies detected significant associations of small effect size (i.e., PRS accounting for less than 1% of the total variance) between polygenic risk scores and alcohol dependence (Kapoor et al., 2016; Salvatore et al., 2014). Further, an association was reported for age of onset for regular drinking that also accounted for less than 1% of the total variance (Vink et al., 2014). GWAS studies using PRS also emphasize the importance of the role of genetic influences in stage of SUD progression. However, results differ across different measures of SUD stages. Two recent studies noted significant associations with measures of dependence rather than initiation in both alcohol as well as tobacco use (Belsky et al., 2013; Kapoor, et al., 2016). Therefore, as identified in twin studies, genetic influences may be more important for maintaining dependence and its related neurobiology rather than early use

4.2 Cannabinoids

Results are inconsistent for *CNR1*, *GABRA2*, *FAAH*, and *ABCB1* (Benyamina et al., 2009; Haughey, Marshall, Schacht, Louis, & Hutchison, 2008a; Lind et al., 2008b; Verweij et al., 2012) and as such require additional investigation. Both *CNR1* and *FAAH* have been associated with phenotypes related to reward sensitivity, impulsivity, and negative affect. Further, additive gene-gene interactions between *FAAH* (C385A; rs324420) and *CNR1* (rs2023239) have been associated with cue reactivity as defined by negative affect during cannabis abstinence (Filbey, Schacht, Myers, Chavez, & Hutchison, 2010; H. M. Haughey, et al., 2008a). *CNR1* encodes a presynaptic cannabinoid 1 receptor with dense expression in regions related to reward, addiction, and cognitive function; i.e., amygdala, cingulate cortex, prefrontal cortex, ventral pallidum, caudate putamen, nucleus accumbens, ventral tegmental area, and lateral hypothalamus, (Glass, Faull, & Dragunow, 1997; Wang, Dow-Edwards, Keller, & Hurd, 2003). *ABCB1* (adenosine triphosphate-binding cassette subfamily B member 1) is responsible for P-glycoprotein production. P-glycoprotein has been studied for

its role in drug pharmacokintetics because it is present in endothelial cells of the blood-brain barrier which limits accumulation of its substates in the central nervous system. For example, P-glycoprotein deficient mice were reported to have significantly higher levels of the psychoactive component of marijuana, delta-9-tetrahydrocannabinol compared to wild-type mice (Bonhomme-Faivre, Benyamina, Reynaud, Farinotti, & Abbara, 2008).

Two single-site GWAS and two multi-site (consortia-based) meta-analysis GWAS studies have been unable to detect genome-wide significant associations with cannabinoid use disorder (Haughey, Marshall, Schacht, Louis, & Hutchison, 2008b; Lind et al., 2008a; Stringer et al., 2016; Verweij, et al., 2012). A recent GWAS meta-analysis using 13 study sites and a sample size of over 32,000 participants identified no significant SNP-level associations, but significant gene-based associations between lifetime cannabis use and *NCAM1*, *CADM2*, *SCOC,* and *KCNT2* were detected. Of these, *NCAM1* has been best characterized and is part of the *NCAM1-TTC12-ANKK1-DRD2* gene cluster, which is related to neurogenesis and dopaminergic neurotransmission (Stringer, et al., 2016). The functional significance of the products of the remaining genes are largely unclear and encourage further investigation (Table 4).

4.3 Cocaine

The primary mechanism of cocaine is blockade of monoamine transporters, and the rewarding properities of cocaine are predomeintly associated with blockade of cell surface dopamine transporters. Thus, cocaine increases dopamine levels in the synaptic cleft by decreasing reuptake (Kiyatkin, 1994; Wise, 1984). Consequently, many genetic association studies of cocaine use disorder focus on genes whose products function in the dopaminergic pathway including genes whose products are responsible for D2 dopamine receptor (*DRD2*) expression, dopamine signalling regulation (ankyrin repeat and kinase domain containing 1, *ANKK1* and tetratricopeptide repeat domain 12, *TTC12*), dopamine metabolism (dopamine beta-hydroxylase*, DBH;* (Kaufman & Friedman, 1965; Weinshilboum, 1978) and degradation (catechol-O-methyltransferase, *COMT*), termination of dopamine transmission across the synapse (solute carrier family 6 member 3, *SLC6A3* and *NCAM1*), and dopamine synthesis (tyrosine hydroxlylase, *TH*; (Bi, Gelernter, Sun, & Kranzler, 2014; Dahl et al., 2006; Farrer et al., 2009; Gelernter et al., 2006; Grucza et al., 2008; Ittiwut et al., 2011; Kalayasiri et al., 2007; Levran et al., 2015; Luo et al., 2004; Malison et al., 2006; Sherva et al., 2010; Zhang et al., 2009; Zuo et al., 2009). Genes whose products function in the monoamine serotonergic signalling pathway have also been implicated; i.e. the gene encoding the 5-HT2C receptor (*5-HT2C*) was associated with two subtypes of cocaine use (Bi, et al., 2014). However, a GWAS of cocaine dependence reported no genome-wide significant associations for dopamine pathway genes, and as such additional replication studies are necessary (Gelernter et al., 2014) (Table 5). Study of additional pathways may also be beneficial since associations have been detected for genes (*CLOCK*, *PER1* and *PER2*) (Malison, et al., 2006; McClung, 2007) whose products function in regulating circadian rhythm which may also regulate dompaminergic activity.

4.4 Opioids

There is moderate evidence for the role of genes related to the dopamine and GABA systems. The primary mechanism of opioid action is direct activation of μ-opioid receptors located on GABAergic interneurons, which inhibits GABA release resulting in disinhibition of mesolimbic dopamine neurons. Thus, opioids increase nucleus accumbens dopamine levels (Johnson & North, 1992). In addition to genes centrally related to dopaminergic signaling that have been previously identified (e.g., *ANKK1/DDRD2*, *DRD1*, and *DBH*) (Clarke et al., 2014; de los Cobos et al., 2007; Garrido et al., 2011; Hoenicka et al., 2010), the specific variant encoding the μ-opioid receptor (*OPRM1*, rs1799971, A118G) has frequently been associated with opioid dependence. However, a meta-analysis failed to detect a significant association between this *OPRM1* marker and opioid dependence (Agrawal et al., 2012). Further, these genes have not been significantly represented in GWAS studies.

Genetic association studies of opioid use disorder have also implicated neurotransmission mechanisms in the glutamatergic pathway in addition to the classically identified dopamine and GABA pathways (Table 5). A recent GWAS reported a significant association with *CNIH3,* a gene whose product functions in the glutamtergic pathway and encodes for the production of cornichon family AMPA receptor auxiliary protein 3 (Nelson et al., 2016). This protein increases surface expression of AMPA ionotropic glutamate receptors and mediates channel conductance by slow deactivation and desensitation kinetics (Schwenk et al., 2009). Additionally, a recent study reported significant associations between SNPs in the genes *KCNC1* and *KCNG2* and a symptom count for opiate dependence (N=12,309). The product of these genes produce membrane proteins that mediate voltage-dependent potassium permeability and thus cellular excitability. Variants in the *PITPNM3* locus were also reported to be significantly associated with opiate dependence. The product of this gene is a protein that is involved in phosphatidylinositol transport and is likely to be involved in calcium signalling and long-term potentiation, which is important for metaplasticity and learning (Sanna et al., 2002).

5. Non-Additive Genetic Mechanisms involved in SUD

Although additive genetic influences are important in the etiology of SUD, to date, they have not accounted for a substantial proportion of the total variance in SUD. Further, addiction is thought to result from changes in brain structure and function (Zhou, Enoch, & Goldman, 2014). As summarized in twin/family study results, additive genetic influences, alone, are not expected to contribute to SUD. Therefore, other genetically-mediated mechanisms may influence the regulation of gene expression in the etiology of SUD (Hyman, 2005; Impey, 2007; Jones & Bonci, 2005; Kalivas, 2005; Kalivas & O'Brien, 2008a; Kauer & Malenka, 2007; Koob & Le Moal, 2005; Lu, Koya, Zhai, Hope, & Shaham, 2006; McClung et al., 2004; Moghaddam & Homayoun, 2008; Mulholland & Chandler, 2007).

5.1 Gene-Environment Interplay

Genetic influences may rely on environmental context, and as such gene-environment interplay, including gene-environment interaction (GxE) and gene-environment correlation,

is likely to influence SUD. Gene-environment interaction refers to differences in genetic effects across levels of environmental exposure. A statistical GxE will be detected when there are functional genetic differences in sensitivity to an environment (Mather & Jinks, 1971). Gene-environment correlation occurs because parents and their children share genes and home environments and as such, parental genetic risk may also contribute to environmental risk in their children.

Several twin studies examining the role of GxE in alcohol use suggest that genetic influences on alcohol-related behaviors vary under different circumstances (Young-Wolff, Enoch, & Prescott, 2011). Further, these studies emphasize the importance of many different types of environmental risk factors for drug use in general. Twin and family studies testing the role of GxE in alcohol use have focused on the role of distal and proximal environmental exposures. Distal environmental exposures refer to those for which the individual does not directly engage or influence such as neighborhood-level influences and availability of of alcohol. Proximal environmental influences refers to those where the individual has direct engagement and may possibly influence such as peer use and parental monitoring (Dick & Kendler, 2012a). In general, these studies indicate that genetic influences from late adolescent alcohol use are higher in urban environments, communities with greater migration, and communities with higher proportions of older adolescents and young adults.

GxE studies of specific environments and genetic markers focus on exposure to stress, either as stressful life events or traumatic stress exposure (Dick & Kendler, 2012b). Stressful environmental exposures during childhood increase risk for alcohol dependence. The hypothalamic-pituitary-adrenal (HPA) axis increases glucocorticoid and cortisol production in order to maintain biological homeostasis during exposure to stress, and it is thought that exposure to early stressors has a long-lasting impact on development via the mesolimbic dopamine pathway (Enoch, 2012). Consequently, GxE studies testing the role of specific genetic influences have focused on the evaluation of genes whose products modulate HPA function in response to stressful environments; e.g., *CRHR1* (Blomeyer et al., 2008; Ducci et al., 2008b; Nelson et al., 2010; Ray et al., 2013) or with genes possessing a glucocorticoid response element in their promoter regions, (i.e., *MAOA*, *COMT*, and *SLC6A4;* Ducci et al., 2008a; Enoch, 2013). For example, the short allele of the polymorphic promoter region of the serotonin transporter gene (*5-HTTLPR*) was associated with more frequent drinking as well as heavy drinking and drug use in college students if they had also experienced multiple negative life events in the past year (Covault et al., 2007). The serotonin transporter (*SLC6A4*, also known as 5-HTT or SERT) is responsible for serotonin reuptake from the synaptic cleft (Heils et al., 1996). Alleles in *5-HTTLPR* alter SLC6A4 production, which may influence function of the glucocorticoid receptor as well as HPA axis activity.

In comparison to GxE studies of alcohol use disorder, there are far fewer studies of GxE for nicotine dependence, cannabis use disorder or opioid addiction. Twin smoking studies (Kaprio, 2009) report increased genetic influence on adolescent smoking in the presence of low parental monitoring. Further, a study of nicotine dependence in adults ages 25–44 reported a significant interaction between adolescent parental monitoring and a variant of the alpha 5 neuronal nicotinic acetylcholine receptor subunit (*CHRNA5,* rs16969968); genetic risk was reduced in participants with high levels of parental monitoring (Chen et al., 2009).

This variant was also identified as having a significant interaction with increasing exposure to peer smoking (Johnson et al., 2010). Additionally, the influence of genetic risk variants as measured by a PRS for smoking was increased in individuals who experienced more traumatic events in their lifetime. Further, genetic risk for smoking was reduced in individuals who lived in neighborhoods with high social cohesion (Meyers et al., 2013). Therefore, the magnitude of genetic variance on smoking may increase as the environment is less enriched, either through reduced parental monitoring or through low social cohesion.

5.2 Epigenetic Influences

The study of epigenetic mechanisms refers to investigating how non-genetic influences effect DNA transcription or subsequent gene expression. These influences include: (1) methylation of specific genes, which generally reduce gene expression; (2) changes in microRNA production (miRNA), which are a class of small, noncoding regulatory RNAs that are central to regulating protein translation; and (3) histone modification via acetylation, which changes DNA conformation, altering accessibility for translation (Kenny, 2014; Zhou, et al., 2014).

Human studies of gene expression suggest the importance and diversity of epigenetic influences on SUD. In general, these studies indicate drug-specific changes in gene expression as well as differences in gene expression related to the use of multiple substances (Lehrmann & Freed, 2008; Marie-Claire et al., 2007; Zhou, Yuan, Mash, & Goldman, 2011). For example, cocaine users exhibit significant differences in expression of genes involved in neurotransmitter levels in the nucleus accumbens although these results are not consistent across studies (Bannon, Kapatos, & Albertson, 2005). Additionally, these studies suggest that acute early-stage drug use is associated with expression changes in acute early response genes (Vaccarino, Hayward, Nestler, Duman, & Tallman, 1992). In comparison, chronic substance exposure has been associated with widespread changes in expression of genes related to several diverse and fundamental cellular functions, including ion transport, chromosome remodelling, stress and immune response, cell adhesion, cell cycle, apoptosis, protein and lipid metabolism, and mitochondrial functions (Liu, Chen, Lerner, Brackett, & Matsumoto, 2005; Schroeder et al., 2008; Vilar et al., 2006; J. Wang, Kim, Donovan, Becker, & Li, 2009; Zhao et al., 2006).

Human candidate gene methylation studies have provided some preliminary evidence for the role of epigenetic influences in people affected with SUD. Candidate gene methylation studies of alcohol use have focused on genes whose products function in 5 major systems: (1) well-characterized neurotransmission systems (e.g., monoamine oxidase A- *MAOA,* serotonin transporter- *SERT,* dopamine transporter- *DAT1,* μ opioid receptor- *OPRM1*); (2) additional neurotransmitter systems (e.g., vasopressin and alpha natriuretic peptide- *ANP*); (3) one-carbon metabolism; (4) craving and symptoms of dependence (e.g., proopiomelanocortin- *POMC* and alpha-synuclein- *SNCA*); and (5) neuronal growth and homeostasis (e.g., nerve growth factor- *NGF*)(Andersen, Dogan, Beach, & Philibert, 2015). Generally, these studies reported weak, but significant differential methylation between affected and non-affected groups. Significant results from candidate gene association studies of smoking have reported significant results in genes whose products function in

neurotransmitter metabolism, specifically *MAOA* and *MAOB* as well as catechol-O-methyltransferase – *COMT*). A candidate gene methylation study of the cannabinoid receptor 1 (*CNR1*) promoter region reported significant differences in *CB1* expression when comparing cannabis dependent smokers against non-smokers as well as cigarette smokers (Rotter et al., 2012). Candidate gene studies of opioid use report significant differences in methylation of the promoter region of the gene encoding the μ opioid receptor (*OPRM1*). However, the direction of results is not consistent across studies (Nielsen et al., 2010; Nielsen et al., 2009).

Results from genome-wide methylation studies of SUD generally do not replicate results from candidate gene methylation studies (Andersen, et al., 2015). Studies of chronic smoking using DNA methylation microarrays consistently report decreased DNA methylation in three locations that are involved in mechanisms outside of the CNS including cell signalling and platelet activation (cg05575921 in the the second exon of coagulation factor II receptor-like 3 gene, *F2RL3*), chronic inflammation (cg19859270 in the first exon of the G-protein-coupled receptor 15 gene, *GPR15*), and tumor suppression and cigarette toxin metabolism (cg05575921 in the third intron of the aryl hydrocarbon receptor repressor gene, *AHRR*). Results across genome-wide methylation studies of alcohol have not replicated. One study reported differential methylation at some sites that are involved in pathways related to alcohol metabolism (i.e., alcohol dehydrogenase and aldehyde dehydrogenase) as well as synaptic transmission (gamma-aminobutyric acid type A receptor pi subunit, *GABRP*). To date, there are no genome-wide methylation studies for cannabinoids or opioids (Andersen, et al., 2015).

SUD is considered to be a drug-induced disorder of neuroplasticity (Hyman, 2005; Impey, 2007; Jones & Bonci, 2005; Kalivas, 2005; Kalivas & O'Brien, 2008a; Kauer & Malenka, 2007; Koob & Le Moal, 2005; Lu, et al., 2006; McClung, et al., 2004; Moghaddam & Homayoun, 2008; Mulholland & Chandler, 2007; Volman, 2007). There is increasing evidence from the animal and molecular literature suggesting drug use modifies protein translation influencing neurons and neuroplasticity in circuits that parse reinforcement. Hundreds of miRNAs are expressed in the mature mammalian brain, and amongst many other functions, miRNAs are involved in the control of synapse development and neuronal plasticity (Banerjee, Neveu, & Kosik, 2009; Schratt et al., 2006; Siegel, Saba, & Schratt, 2011). Most human studies of the involvement of miRNAs in SUD have focused on cocaine use. These studies indicate widespread changes in dopaminergic, glutamatergic, and peptidergic neurotransmitter systems as well as proteins involved in the control of cytoskeletal organization and transcriptional regulation (Bali & Kenny, 2013; Lehrmann et al., 2003; Mains, Kiraly, Eipper-Mains, Ma, & Eipper, 2011).

Studies of the effects of alcohol on miRNA expression suggest that miRNAs work in coordinated fashion to promote drug adaptation and neuronal plasticity and that this may occur in a relatively rapid fashion. For example, *miR-9* is expected to mediate alcohol-related post-transcriptional regulation of neuronal BK mRNA and can do so rapidly upon exposure (Pietrzykowski et al., 2008; Treistman & Martin, 2009). More specifically, mRNA encoding the voltage-gated potassium channel (BK) is decreased within 15 minutes of exposing rat striatal cultures to alcohol. BK influences the the control of alcohol intake and

tolerance in an individual. This decrease in BK mRNA resulted from increased *miR-9* expression and downstream degredation of BK splice variants containing a *miR-9* binding site in their 3′UTR. The remaining BK variants were those least affected by the presence of alcohol. In addition to changes in BK expression, *miR-9* targets several other genes that influence alcohol use (e.g., neuronal exitability- *GABRB2* and *DRD2*, function of presynaptic terminals- *GABRB2*, and gene expression and lipid metabolism- *PPARA*, peroxisome proliferator-activated receptor alpha). Rat studies suggest that other families of miRNAs may influence additional phenomnea such as the rewarding properties of alcohol via dopamine D1 receptor expression (i.e., *miR-382*) or the motivational effects of alcohol and drugs via regulation of brain-derived neurotrophic factor (*BDNF*) expression (i.e., *miR-206*). Additional research using population-based samples may expand our understanding of the role of miRNAs in development of SUD as well as the possibility of the use of miRNA expression as a biomarker for SUD diagnosis or treatment.

Histone modifications including acetylation and deacetylation play a role in long-lasting changes in brain function associated with SUD. For example, brain region- and cell type-specific histone acteylation modification for gobal/genome-wide and promoter-specific changes have been reported for alcohol use. In particular, dysregulation of gene expression profiles across several brain regions are associated with exposure to alcohol, which is expected to contribute to the development of withdrawal symptoms (Mons & Beracochea, 2016). Similarly, cocaine administration was associated with elevated global histone acetylation levels in reward-related regions (i.e., nucleus accumbens) (Renthal et al., 2009). Consequently, histone modifications are likely to coordinate networks of brain structures to regulate symptoms of drug dependence and withdrawal.

6. Limitations of SUD Genetic Epidemiology Studies

Several significant genetic associations have been detected in candidate gene and genome-wide association studies across several substances. In general, results confirm twin studies and indicate that SUD is polygenic; multiple genes of small effect contribute to SUD risk. Further, many of these genetic variants identified function within neurotransmitter pathways involved in the neurobiology of addicition (Drgon et al., 2010; Hardy & Singleton, 2009; Hirschhorn, 2009; Kraft & Hunter, 2009). Therefore, several genetic variants are expected to influence the neural substrates of addiction. However, genetic epidemiology studies of SUD must be evaluated in light of their limitations. Importantly, there remains an inconsistency in the replication of genetic association results. For example, although several significant genetic associations have been reported, few associations for nicotine dependence have replicated (Lerman & Berrettini, 2003; Quaak, van Schayck, Knaapen, & van Schooten, 2009). This may be due to a variety of reasons including: (1) low effect sizes of variants where each significant variant detected by a genetic association study will have a small influence on an SUD (Marjoram, Zubair, & Nuzhdin, 2014); (2) insufficient power to detect significant associations resulting from low sample sizes particularly in single-site studies (Visscher, Brown, McCarthy, & Yang, 2012); (3) phenotypic heterogeneity due to variance in the measurement of SUDs across samples that may reflect different stages of SUD; (4) genetic heterogeneity characterized by an outcome arising from multiple sets of genes or genetic mechanisms that likely decrease the power to detect a significant genetic association

specific to a substance; (5) racial/ethnic inconsistency between discovery and replication samples (i.e., participants of European ancestry in the discovery sample and African ancestry in the replication sample) that result in a failure to reproduce significant genetic association across samples as a result of differences in ancestry-related local haplotype structures at loci associated with SUD (Enoch, 2013; Melroy-Greif, et al., 2017; Polimanti, Yang, Zhao, & Gelernter, 2015; Verweij, et al., 2012) and (6) phenotypic comorbidity where the SUD diagnosis, itself, may have multiple subtypes (i.e., single-drug versus poly-drug dependence, rate of time from initiation to the development of dependence, or comorbidity between substance dependence and psychiatric conditions) with shared genetic and environmental architecture (Bi, et al., 2014; Palmer et al., 2014). Consequently, there remains discrepancies in the convergence of results from different genetic epidemiology study designs (Vrieze, McGue, Miller, Hicks, & Iacono, 2013).

Studies are beginning to address the aforementioned concerns by: (1) increasing sample sizes; (2) improving the measurement of SUD, particularly; (3) accounting for the genetic and environmental covariances across substances as well as between other comorbid outcomes; (4) increasing data collection of racially/ethnically diverse populations; and (4) accounting for ancestral diversity. The push to increase sample size in order to have appropriate power to detect significant associations for SUD is actively being addressed using consortia-based GWAS (e.g., Psychiatric Genetics Consortium- SUD working group (Agrawal, Edenberg, & Gelernter, 2016) as well as the study of GWAS data from large, nationally representative samples across several outcomes including SUD (e.g., UK Biobank —Littlejohns et al., 2017) and biological markers associated with SUD including neuroimaging (Mackey et al., 2016) may overcome current challenges.

An extension of samples collected for SUD studies is illustrated by a recent GWAS of BMI in alcohol dependent participants that identified a significant variant in *ALDH1A1*, which is responsible for alcohol metabolism and adipocyte plasticity (Polimanti, et al., 2015). Thus, studies of this sort have the capacity to identify genetic and environmental influences that are shared or distinct for SUD and non-SUD outcomes.

An open area of development in the genetic epidemiology of SUD research involves the use of multiple measures. Prior twin studies introduced the idea that multiple measures could be used to understand the characterize SUD. For example, a highly heritable nicotine dependence phenotype was estimated through the use of phenotypic and genetic factor analyses of DSM-IV ND criteria as well as the Heaviness of Smoking Index (Lessov et al., 2004). As GWAS data as well as multiple SUD measures become available, this approach can be adapted for genetic association studies. A recent genetic association study used factor analysis to determine the factor stucture across 42 tobacco use variables (e.g., cigarettes per day, nicotine dependence symptoms). Factor scores reflecting tobacco use were then derived to test for gene-based associations focusing on 231 single nucleotide variants within the CHRN and CYP genes. Suggestive associations were identified for variants in *CYP2B6* near *CYP2A6* (rs45482602) and *CYP4Z2P* (rs10749865; Richmond-Rakerd et al., 2017).

Phenome-wide association studies (PheWAS) are also characterizing SUD by studying genetic variants that influence use of multiple substances as well as those shared between

SUD and non-SUD outcomes. PheWAS refers to a post-GWAS genotype-phenotype association study using datasets which have collected a substantial amount of phenotypic data (phenome; Roden and Denney 2016). PheWAS use a small number of previously identified variants and check their association across the full phenome or with a full completment of traits or measures that are related to the outcome (Bush, Oetjens, & Crawford, 2016). Therefore, PheWAS have the potential to deepen genomic knowledge regarding the range of phenotypic effects associated with GWAS-identified risk alleles. For example, a PheWAS of smoking and alcohol use in 26,394 women replicated prior asosciations between variants in *ADH1B* and alcohol use (e.g., alcohol servings per week, number of medium servings of wine per day, number of drinks of alcohol) as well as between variants in *CHRNA3-CHRNA5* and smoking behaviors (e.g., cigarettes per day, age starte smoking cigarettes regularly; Polimanti, Kranzler & Gelernter, 2016). Further, the combination of PheWAS among affected individuals may also lead to an impoved understanding of SUD as well as other conditions. Recently, a PheWAS of older adult smokers reported a significant associaton between a variant in *CYP2A6* and hearing loss; thus the smoking metabolism pathway may mediate age-related hearing loss (Polimanti, Jensen, & Gelernter, 2017).

7. Conclusions and Future Directions

Advances in neurobiology and genetic epidemiology highlight the role of genetic regulation of addiction etiology and provide an opportunity to develop directed behavioral and biologically based treatments. Overall, genes involved in the regulation of the dopaminergic system have been found to be important for SUD. It is known that SUD exerts broad effects that extend to several neurobiological systems including glutamate. Additionally, unique genetic influences involved in the maintenance of addiction for specific substances also appear to be important in addition to those involved in SUD overall. Moreover, examining the role of peripherial systems in SUD; e.g., brain-gut interactions (Kiraly et al., 2016), is an exciting area requiring additional study. For example, the ghrelin signaling system is expected to play a role in SUD because ghrelin activates the cholinergic-dopaminergic reward syste in rodents (Jerlhag et al., 2007). Ghrelin is a circulating orexigenic stomach-derived hormone that regulates energy homeostatsis mainly via hypothalamic growth hormone secretagogue receptor (Cheung & Mao, 2012; Horvath, Diano, Sotonyi, Heiman, & Tschöp, 2001; Kojima et al., 1999; Kojima & Kangawa, 2005; Tschöp, Smiley, & Heiman, 2000). There is some preliminary evidence that single nucleotide polymorphisms located in the pre-proghrelin gene (*GHRL*) and the gene responsible for the production of the ghrelin receptor (*GHSR-1a*) are associated with increased alcohol use and smoking in candidate gene association studies (Landgren et al., 2010; Suchankova et al., 2015). In prior rodent models, ghrelin increases alcohol consumption (Gregory et al., 2012; Jerlhag et al., 2009; Kaur & Ryabinin, 2010), enhances cocaine-induced locomotor stimulation and conditions place preference for cocaine (Davis, Wellman, & Clifford, 2007; Tessari et al., 2007; Wellman, Davis, & Nation, 2005).

The environmental context of SUD also has moderate-to-strong involvement in substance use outcomes. Consequently, genetic regulation of biological changes preceding and as a consequence of SUD require additional clarification as substance use can be a means by

which the individual copes with environmental risk factors. SUD can also be considered to be an environmental exposure when the brain is exposed to commonly abused substances. Future studies of epigenetic mechanisms, such as methylation and the role of miRNAs, could determine the exact role of the environment on patterns of differential gene expression in neurobiological systems of interest that can precipitate a SUD.

While a better understanding of the genetic epidemiology of SUD is expected to reduce its burden on society, prevention has been very successful particularly for reducing rates of population-level drug use. For example, changes in policy and expectations in the social norms related to substance use have reduced the prevalence of smoking initiation in the United States (Do & Maes, 2016). To date, it is unclear how genetic variants influence these outcomes and subsequently translate into successful treatment and prevention of relapse among those with nicotine dependence (Hutchison, 2010). Nonetheless, there are several exciting possibilities for further exploration, as twin studies have reported that additive genetic influences account for 11%–74% of the variance of smoking abstinence (Broms, Silventoinen, Madden, Heath, & Kaprio, 2006; Heath, Madden, & Martin, 1998; Heath & Martin, 1993; Heath, Martin, Lynskey, Todorov, & Madden, 2002; J. Kaprio, Koskenvuo, & Sarna, 1981; Madden et al., 1999; Medlund, Cederlof, Floderus-Myrhed, Friberg, & Sorensen, 1976; True et al., 1997). Moreover, several genetic polymorphisms have also been found to impact therapeutic effectiveness for nicotine use disorders (Colilla et al., 2005; Johnstone et al., 2007; Uhl et al., 2008). Genetic screening may identify individuals who will best respond to naltrexone for the reduction of problem drinking (Anton et al., 2008; Oslin et al., 2003). Therefore, a major challenge for the future rests in translating knowledge regarding the genet ic epidemiology of SUD into effective treatment stratagies for individuals attempting to successfully maintain abstinence. As this challenge is addressed, assisting those affected with SUD to achieve a sustanined abstinence remains an achievable goal.

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Table 1

DSM-5 Diagnostic Criteria for SUD

Criterion	Symptom Description	
Impaired Control	•	Taking substance in larger amounts or over a longer period than intended.
	•	Expressing a persistent desire to cut down or regulate use and may report unsuccessful efforts to do so.
	•	Spending a great deal of time obtaining the substance, using the substance, or recovering from its effects.
	•	Craving manifested by an intense desire or urge for the drug that may occur at any time but is more likely in an environment in which drug use has previously occurred.
Social Impairment	•	Recurrent substance use results in failure to fulfill major role obligations at work, school, or home.
	•	Continuing substance use despite persistent social/interpersonal problems exacerbated by the effects of the substance.
	•	Giving up or reducing important social, occupational, or recreational activities because of substance use.
Risky Use	•	Recurrent substance use in physically hazardous situations.
	•	Continuing use despite knowledge that persistent physical or psychological problems are exacerbated or caused by substance use.
Pharmacology	•	Markedly increased dose of the substance required to achieve desired effect.
	•	Withdrawal symptoms specific to a drug class.

Note: SUD is diagnosed with the occurrence of two or more symptoms. 2 – 3 symptoms = *mild* presentation, 4 – 5 symptoms = *moderate* presentation and 6 or more symptoms = *severe* presentation

Table 2

Summary of GWAS Results for Alcohol Related Phenotypes

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*- value	Effect Size	Effect Allele	Gene	Ancestry	Rep.	Reference
ACT	Community-based Meta-Analysis	784/739/603	rs7031417	1.40e-08	Z=−5.68	C	*LOC100129340*	EA	N	Adkins, D.E. (2015)
ACT	Community-based Meta-Analysis	784/739/603	rs17053864	1.50e-07	Z=−5.25	G	*LOC100129340*	EA	N	Adkins, D.E. (2015)
ACT	Community-based Meta-Analysis	784/739/603	rs11710497	1.20e-07	Z=−5.29	A	*SLC6A1*	EA	N	Adkins, D.E. (2015)
ACT	Community-based Meta-Analysis	784/739/603	rs7019589	2.30e-07	Z=−5.17	T	*LOC100129340*	EA	N	Adkins, D.E. (2015)
ACT	Community-based Meta-Analysis	784/739/603	rs12257178	4.80e-07	Z=−5.04	A	*ADRA2A*	EA	N	Adkins, D.E. (2015)
AD	Case/Control	case=1374 control=6468	rs55768019	7.58e-07	OR=0.80	A	*HPGD*	DA	N	Mbarek, H. (2015)
AD	Case/Control	case=1374 control=6468	rs2253612	8.25e-07	OR=0.70	T	*AOX2P*	DA	N	Mbarek, H. (2015)
AD	Case/Control	case=1374 control=6468	ra62338789	8.81e-07	OR=0.80	C	*HPGD*	DA	N	Mbarek, H. (2015)
AD	Case/Control	case=1374 control=6468	rs56286907	9.20e-07	OR=0.80	C	*HPGD*	DA	N	Mbarek, H. (2015)
AD	Case/Control	case=1374 control=6468	rs5009515	9.63e-07	OR=0.80	C	*HPGD*	DA	N	Mbarek, H. (2015)
AD	Community-based & Publicly available data Meta-Analysis	2752	rs1229984	6.75e-14	Beta=−0.02	T	*ADH1B*	EA	Y	Gelertner, J. (2014)
AD	Community-based & Publicly available data Meta-Analysis	1311	rs2066702	2.18e-09	Beta=−0.02	A	*ADH1B*	AA	Y	Gelertner, J. (2014)
AD	Community-based & Publicly available data Meta-Analysis	1311	rs28864441	6.64e-09	Beta=−0.02	T	*LOC100507053*	AA	Y	Gelertner, J. (2014)
AD	Community-based & Publicly available data Meta-Analysis	2752	rs116203444	8.99e-08	Beta=−0.01	C	*LOC100507053*	EA	Y	Gelertner, J. (2014)
AD	Community-based & Publicly available data Meta-Analysis	1311	rs1614972	1.82e-07	Beta=−0.03	T	*ADH1C*	AA	Y	Gelertner, J. (2014)
AD	Community-based Meta-Analysis	case=1333 control=2168	rs1789891	1.27e-08	OR=1.46	A	*Intronic*	GA	Y	Frank, J. (2012)
AD	Community-based Meta-Analysis	case=1333 control=2168	rs2851300	1.04e-07	OR=1.31	T	*Intergenic*	GA	N	Frank, J. (2012)
AD	Community-based Meta-Analysis	case=1333 control=2168	rs169482	1.24e-07	OR=1.31	T	*Intergenic*	GA	N	Frank, J. (2012)
AD	Community-based Meta-Analysis	case=1333 control=2168	rs1789924	1.92e-07	OR=1.30	T	*ADH1C*	GA	N	Frank, J. (2012)
AD	Community-based Meta-Analysis	case=1333 control=2168	rs4699748	2.51e-07	OR=1.49	A	*LOC102723576*	GA	Y	Frank, J. (2012)

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*- value	Effect Size	Effect Allele	Gene	Ancestry	Rep.	Reference
AD	Meta-Analysis of Publicly Available Data (SAGE/COGA)	case=1409 control=1518	rs1057239	2.80e-07	OR=1.32	T	*KIAA0040*	EA	Y	Zuo, L. (2012)
AD	Meta-Analysis of Publicly Available Data (SAGE/COGA)	case=1409 control=1518	rs4949400	2.30e-07	OR=1.32	?	*SERINC2*	EA	N	Zuo, L. (2012)
AD	Meta-Analysis of Publicly Available Data (SAGE/COGA)	case=1409 control=1518	rs7445832	2.80e-07	OR=1.38	?	*HTRIA*	EA	N	Zuo, L. (2012)
AD	Meta-Analysis of Publicly Available Data (SAGE/COGA)	case=1409 control=1518	rs11583322	4.00e-07	OR=0.76	?	*STK40*	EA	N	Zuo, L. (2012)
AD	Meta-Analysis of Publicly Available Data (SAGE/COGA)	case=1409 control=1518	rs257906	5.00e-07	OR=1.43	?	*SLC27A6*	EA	N	Zuo, L. (2012)
AD	Meta-Analysis of Publicly Available Data (COGA/SAGE/ OZALC)	case=1283 control=1416	rs6701037	1.86e-07	OR=1.36	C	*KIAA0040*	EA	N	Wang, K. (2011)
AD	Meta-Analysis of Publicly Available Data (COGA/SAGE/ OZALC)	case=1283 control=1416	rs6425323	3.13e-07	OR=1.35	T	*KIAA0040*	EA	N	Wang, K. (2011)
AD	Meta-Analysis of Publicly Available Data (COGA/SAGE/ OZALC)	case=1283 control=1416	rs1869324	4.71e-07	OR=1.54	A	*THSD7B*	EA	N	Wang, K. (2011)
AD	Meta-Analysis of Publicly Available Data (COGA/SAGE/ OZALC)	case=1283 control=1416	rs1057302	5.12e-07	OR=1.34	C	*KIAA0040*	EA	N	Wang, K. (2011)
AD	Meta-Analysis of Publicly Available Data(COGA/SAGE/ OZALC)	case=1283 control=1416	rs750338	1.47e-06	OR=1.48	C	*PKNOX2*	EA	N	Wang, K. (2011)
AD	Meta-Analysis of Publicly Available Data(COGA/SAGE/ OZALC)	case=681 control=508	rs11922615	1.90e-07	NR	?	*LOC440944*	AA	N	Zuo, L. (2011)
AD	Meta-Analysis of Publicly Available Data (COGA/SAGE/ OZALC)	case=681 control=508	rs6643238	4.4e-07	NR	?	*LOC440944*	AA	N	Zuo, L. (2011)
AD	Meta-Analysis of Publicly Available Data (COGA/SAGE/ OZALC)	case=681 control=508	rs7777391	7.00e-07	NR	?	*CTTNBP2*	AA	N	Zuo, L. (2011)
AD	Meta-Analysis of Publicly Available Data (COGA/SAGE/ OZALC)	case=681 control=508	rs3792686	1.70e-06	NR	?	*D4S234E*	AA	N	Zuo, L. (2011)
AD	Meta-Analysis of Publicly Available Data (COGA/SAGE/ OZALC)	case=681 control=508	rs17028719	4.2e-06	NR	?	*NPHP4*	AA	N	Zuo, L. (2011)
AD	Case/Control	case=1897 control=1932	rs10893366	1.93e-07	OR=1.39	T	*PKNOX2*	AA/EA	N	Beirut, L.J. (2010)

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*- value	Effect Size	Effect Allele	Gene	Ancestry	Rep.	Reference
AD	Case/Control	case=1897 control=1932	rs2039617	5.95e-07	OR=0.69	T	*CC2D2B*	AA/EA	N	Beirut, L.J. (2010)
AD	Case/Control	case=1897 control=1932	rs9302534	2.73e-06	OR=0.78	C	*Intergenic*	AA/EA	N	Beirut, L.J. (2010)
AD	Case/Control	case=1897 control=1932	rs1318937	3.54e-06	OR=1.35	G	*SH3BP5*	AA/EA	N	Beirut, L.J. (2010)
AD	Case/Control	case=1897 control=1932	rs2700648	3.99e-06	OR=1.29	A	*Intergenic*	AA/EA	N	Beirut, L.J. (2010)
AD	Case/Control	case=847 control=552	rs4758533	4.80e-05	OR=0.70	?	*OSBPL5*	EA	N	Edenberg, H.J. (2010)
AD	Case/Control	case=1299 control=1560	rs2247219	6.23e-06	NR	?	*SEMA3E*	EA/DA	N	Lind, P.A. (2010)
AD	Case/Control	case=1460 control=2332	rs7590720	9.72e-09	OR=0.74	A	*Intergenic*	GA	Y	Treutlein, J. (2009)
AD	Case/Control	case=1460 control=2332	rs1344694	1.68e-08	OR=0.76	G	*Intergenic*	GA	Y	Treutlein, J. (2009)
AD	Case/Control	case=1460 control=2332	rs705648	1.78e-08	OR=1.29	C	*PECR*	GA	Y	Treutlein, J. (2009)
AD	Case/Control	case=1460 control=2332	rs1864982	3.46e-08	OR=1.36	A	*PPP2R2B*	GA	Y	Treutlein, J. (2009)
AD	Case/Control	case=1460 control=2332	rs12388359	3.57e-08	OR=0.62	G	*CDH13*	GA	Y	Treutlein, J. (2009)
ADF	Community-Based Association	812	rs6777876	4.00e-07	NR	G	*Intergenic*	AA	N	Kendler, K.S. (2011)
ADF	Community-Based Association	812	rs3738843	4.00e-06	NR	A	*Intergenic*	AA	N	Kendler, K.S. (2011)
ADF	Community-Based Association	812	rs12020569	5.00e-06	NR	C		AA	N	Kendler, K.S. (2011)
ADS	Community-Based Association	2010	rs12903120	1.09e-06	Beta=−0.18	?	*C15orf53*	EA	Y	Wang, J. (2013)
ADS	Community-Based Association	2010	rs7168475	2.00e-06	Beta=−0.18	?	*C15orf53*	EA	N	Wang, J. (2013)
ADS	Community-Based Association	2010	rs12916379	2.79e-06	Beta=−0.17	?	*C15orf53*	EA	N	Wang, J. (2013)
ADS	Community-Based Association	2010	rs2132157	3.02e-06	Beta=−0.17	?	*C15orf53*	EA	N	Wang, J. (2013)
HDF	Community-based Meta-Analysis	8766	rs9512637	1.20e-07	Beta=−0.10	C	*Intergenic*	EA	N	Heath, A.C. (2011)
HDF	Community-based Meta-Analysis	8766	rs8040009	3.10e-07	Beta=−0.12	T	*C15orf32*	EA	N	Heath, A.C. (2011)
HDF	Community-based Meta-Analysis	8766	rs2369955	1.60e-06	Beta=−0.14	A	*TMEM108*	EA	N	Heath, A.C. (2011)
HDF	Community-based Meta-Analysis	8766	rs10935045	1.70e-06	Beta=−0.13	C	*TMEM108*	EA	N	Heath, A.C. (2011)
HDF	Community-based Meta-Analysis	8766	rs195204	9.10e-06	Beta=0.10	T	*TNFSF4*	EA	N	Heath, A.C. (2011)
MD	Community-Based Association	6325	rs11201929	4.11e-08	Z=5.88	A	*GRID1*	AA/IA/EA/EAA/SAA	N	Webb, B.T. (2017)
MD	Community-Based Association	6325	rs73317758	1.10e-08	Z=−5.71	A	*COL14A1*	AA/IA/EA/EAA/SAA	N	Webb, B.T. (2017)

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*- value	Effect Size	Effect Allele	Gene	Ancestry	Rep.	Reference
MD	Community-Based Association	6325	rs11201928	6.46e-08	Z=5.41	A	*GRID1*	AA/IA/EA/EAA/SAA	N	Webb, B.T. (2017)
MD	Community-Based Association	6325	rs4891087	8.60e-08	Z=−5.35	T	*Intergenic*	AA/IA/EA/EAA/SAA	N	Webb, B.T. (2017)
MD	Community-Based Association	6325	rs79514906	1.11e-07	Z=−5.31	T	*Intergenic*	AA/IA/EA/EAA/SAA	N	Webb, B.T. (2017)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs1229984	5.96e-15	Beta=−0.26	A	*ADH1B*	EA	Y	Xu, K. (2015)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs2066702	2.50e-15	Beta=−0.16	A	*ADH1B*	AA	Y	Xu, K. (2015)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs1789882	2.10e-09	Beta=−0.13	A	*ADH1B*	AA	Y	Xu, K. (2015)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs28864441	3.68e-09	Beta=−0.15	T	*LOC100507053*	AA	Y	Xu, K. (2015)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs1693457	4.20e-09	Beta=−0.14	C	*ADH1B*	AA	Y	Xu, K. (2015)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs28600890	5.22e-09	Beta=−0.16	C	*LOC100507053*	AA	N	Xu, K. (2015)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs33948359	1.04e-08	Beta=−0.15	CT	*LOC100507053*	AA	N	Xu, K. (2015)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs904092	1.45e-08	Beta=−0.13	A	*LOC100507053*	AA	N	Xu, K. (2015)
MD	Community-based & Publicly available data Meta-Analysis	YalePenn=5543 SAGE=4012	rs28470942	4.23e-08	Beta=−0.15	T	*LOC100507053*	AA	Y	Xu, K. (2015)
MD	Community-Based Association	595	rs1858881	1.74e-09	Beta=−0.51	?	*ALDH2*	HA	N	Quillen, E.E. (2014)
MD	Community-Based Association	595	rs671	4.73e-08	Beta=0.88	?	*ALDH2*	HA	Y	Quillen, E.E. (2014)
MD	Community-Based Association	595	rs3782886	2.02e-16	Beta=−0.73	?	*ALDH2*	HA	N	Quillen, E.E. (2014)
MD	Community-Based Association	595	rs4766566	8.70e-12	Beta=−0.55	?	*ALDH2*	HA	N	Quillen, E.E. (2014)
MD	Community-Based Association	595	rs6490029	7.11e-10	Beta=−0.49	?	*ALDH2*	HA	N	Quillen, E.E. (2014)
MD	Community-Based Association	595	rs10774610	1.74e-09	Beta=−0.51	?	*ALDH2*	HA	Y	Quillen, E.E. (2014)
MD	Community-Based Association	595	rs11065750	3.08e-10	Beta=−0.53	?	*ALDH2*	HA	N	Quillen, E.E. (2014)
MD	Community-Based Association	595	rs925368	5.52e-08	Beta=−0.64	?	*ALDH2*	HA	N	Quillen, E.E. (2014)
MD	Community-Based Association	595	rs16960688	5.02e-08	Beta=−0.64	?	*ALDH2*	HA	N	Quillen, E.E. (2014)
MD	Meta-Analysis of Publicly Available Data	COGA=2322 SAGE=2593	rs1229984	2.04e-08	NR	T	*ADH1B*	EA	N	Kapoor, M. (2013)
MD	Meta-Analysis of Publicly Available Data	COGA=2322 SAGE=2593	rs4758317	7.20e-07	NR	C	*LMO1*	EA	Y	Kapoor, M. (2013)
MD	Meta-Analysis of Publicly Available Data	COGA=2322 SAGE=2593	rs59677118	1.16e-06	NR	A	*Intergenic*	EA	N	Kapoor, M. (2013)

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*- value	Effect Size	Effect Allele	Gene	Ancestry	Rep.	Reference
MD	Meta-Analysis of Publicly Available Data	COGA=2322 SAGE=2593	rs55731057	3.31e-06	NR	T	*Intergenic*	EA	N	Kapoor, M. (2013)
MD	Meta-Analysis of Publicly Available Data	COGA=2322 SAGE=2593	rs67031482	4.07e-06	NR	C	*PLCL1*	EA	N	Kapoor, M. (2013)
MD	Meta-Analysis of Publicly Available Data	COGA=1059 SAGE=1628 OZALC=3137	rs11128951	4.27e-08	NR	G	*Intergenic*	EA	N	Pan, Y. (2013)
MD	Meta-Analysis of Publicly Available Data	COGA=1059 SAGE=1628 OZALC=3137	rs17144687	9.27e-08	NR	C	*Intergenic*	EA	N	Pan, Y. (2013)
MD	Meta-Analysis of Publicly Available Data	COGA=1059 SAGE=1628 OZALC=3137	rs12108602	1.50e-07	NR	G	*Intergenic*	EA	N	Pan, Y. (2013)
MD	Meta-Analysis of Publicly Available Data	COGA=1059 SAGE=1628 OZALC=3137	rs2128158	2.28e-07	NR	A	*KCNB2*	EA	N	Pan, Y. (2013)
MD	Meta-Analysis of Publicly Available Data	COGA=1059 SAGE=1628 OZALC=3137	rs2929576	2.71e-07	NR	T	*KCNB2*	EA	N	Pan, Y. (2013)

Note: Replication (Rep.) is defined as an additional confirmation of SNP significance at p <.05 within each study. All significant SNPs are included for each study, or the five most significant SNPs if they are non-significanct and p ≤ 5.00e-06. Only one SNP is listed per study if p > 5.00e-06. MD = Maximum Drinks taken in 24 hours ever; AD = Alcohol Dependence; ACT = Alcohol Consumption Trajectory; ADS = Alcohol Dependence Symptom Count; HDF = Heavy Drinking Factor Score; ADF = Alcohol Dependence Factor Score; NR = Not Reported. AA=African Ancestry; EA=European Ancestry; EAA=East Asian Ancestry; SAA=South Asian Ancestry; EA=European Ancestry; DA = Dutch Ancestry; HA = Han Chinese Ancestry; GA = German Ancest

Table 3

Summary of GWAS Results for Nicotine Use Phenotypes

Trai t	Study Design/Sample	*N*	Best SNP	SNP *p*-value	Effect Size	Affect Allele	Gene	Ancestry	Rep.	Reference
CPD	Population-Based Association	11,696	rs8102683	3.80e-43	Beta=−4.00	0 copy	*CYP2A6*	JA	Y	Kumasaka N. (2012)
CPD	Population-Based Association	11,696	rs11878604	9.40e-30	Beta=−2.69	C	NR	JA	Y	Kumasaka N. (2012)
CPD	Consortium Based Meta-Analysis	32,389	rs2036527	2.00e-08	Beta=0.04	A	*CHRNA5*	AA	N	David S.P. (2012)
CPD	Consortium Based Meta-Analysis	32,390	rs3101457	3.00e-07	Beta=0.041	A	*C1orf100*	AA	N	David S.P. (2012)
CPD	Consortium Based Meta-Analysis	32,391	rs547843	6.00e-07	Beta=0.035	C	*LOC503519*	AA	N	David S.P. (2012)
CPD	Consortium Based Meta-Analysis	32,392	rs667282	2.00e-07	Beta=0.033	C	*CHRNA5*	AA	N	David S.P. (2012)
CPD	Consortium Based Meta-Analysis	32,393	rs938682	3.75e-07	Beta=0.033	A	*CHRNA3*	AA	N	David S.P. (2012)
CPD	Consortium Based Meta-Analysis	32,394	rs3813570	9.85e-07	Beta=0.034	C	*PSMA4*	AA	N	David S.P. (2012)
CPD	Consortium Based Meta-Analysis	Up to 74,035	rs1051730	3.00e-73	1.02	G	*CHRNA3*	EA	Y	The Tobacco and Genetics Consortium (2010)
CPD	Consortium Based Meta-Analysis	Up to 74,036	rs1329650	6.00e-10	0.37	T	*LOC100188947*	EA	Y	The Tobacco and Genetics Consortium (2010)
CPD	Consortium Based Meta-Analysis	Up to 74,037	rs3733829	1.00e-08	0.33	G	*EGLN2, CYP2A6*	EA	Y	The Tobacco and Genetics Consortium (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs1051730	2.00e-69	Beta=0.8	A	*CHRNA3*	EA	Y	Thorgeirsson T.E. (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs6474412	1.00e-08	Beta=0.29	T	*CHRNB3*	EA	Y	Thorgeirsson T.E. (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs215614	2.00e-07	Beta=0.22	G	*PDE1C*	EA	Y	Thorgeirsson T.E. (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs4105144	2.00e-12	Beta=0.39	C	*CYP2B6*	EA	Y	Thorgeirsson T.E. (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs7260329	6.00e-06	Beta=0.2	G	*CYP2B6*	EA	Y	Thorgeirsson T.E. (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs13280604	1.30e-08	Beta=0.31	A	*CHRNB3*	EA	Y	Thorgeirsson T.E. (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs215605	5.40e-09	Beta=0.26	G	NR	EA	Y	Thorgeirsson T.E. (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs7937	2.40e-09	Beta=0.24	T	*RAB4B*	EA	Y	Thorgeirsson T.E. (2010)
CPD	Consortium Based Meta-Analysis	31,266	rs1801272	1.10e-04	Beta=0.68	A	NR	EA	Y	Thorgeirsson T.E. (2010)
CPD	Community-based association	Female=2282 Male=2060	rs6437740	f=3.70e-05 m=1.30e-03	Beta(f)=−0.14 Beta(m)=−0.10	?	*BBX*	EA	N	Caporaso N. (2009)
CPD	Community-based association	Female=2282 Male=2062	rs7050529	f=2.80e-06 m=7.30e-02	Beta(f)=−0.28 Beta(m)=−0.06	?	*TRPC5*	EA	N	Caporaso N. (2009)
CPD	Community-based association	842 (417 m)	rs17354547	2.54e-03	Beta(m)=0.41	C	Upstream from *IL-5*	EA1/AA2	Y	Liu Y.Z. (2009)
CPD	Community-based association	842 (417 m)	rs1402812	5.36e-03	Beta(m)=0.42	G	Upstream from *IL-5*	EA1/AA2	Y	Liu Y.Z. (2009)

Trai t	Study Design/Sample	*N*	Best SNP	SNP *p*-value	Effect Size	Affect Allele	Gene	Ancestry	Rep.	Reference
CPD	Community-based association	842 (417 m)	rs4956396	3.86e-03	Beta(m)=0.43	A	Upstream from *IL-5*	EA1/AA2	Y	Liu Y.Z. (2009)
CPD	Community-based association	842 (417 m)	rs4956302	1.97e-03	Beta(m)=0.34	C	Upstream from *IL-5*	EA1/AA2	Y	Liu Y.Z. (2009)
CS	Community-based association	3497	rs6570989	7.73e-05	OR=0.74	A	*GRIK2*	EA	Y	Vink J. (2009)
CS	Community-based association	3497	rs4423615	6.78e-05	OR=0.81	G	*GRB14*	EA	Y	Vink J. (2009)
CS	Community-based association	3497	rs10868236	9.64e-05	OR=0.75	G	*NTRK2*	EA	Y	Vink J. (2009)
HS	Community-based association	12,471	rs16969968	2.20e-07	1.32	A	*CHRNA5*	EA/AA/IA	N	Saccone N.L. (2017)
ND	Community-Based Association	21,298	rs56175056	1.20e-04	Beta=0.85	A/G	*CHRNA4*	EA	N	Thorgeirsson T.E. (2016)
ND	Consortium Based Meta-Analysis	9,137 mild 4,881 mod 3,056 sev	rs2273500	8.00e-09	Beta=0.058	C	*CHRNA4*	EA	Y	Hancock D.B. (2015)
ND	Meta-Analysis of Publicly Available Data	case= 1079 control = 1341	rs7163369	3.27e-06	NR	?	*SLCO3A1*	EA	Y	Wang K.S. (2012)
ND	Meta-Analysis of Publicly Available Data	case = 1079 control = 1341	rs9308631	9.06e-06	NR	?	Near *ANAPC1*	EA	Y	Wang K.S. (2012)
ND	Community-based association	2267	rs1451240	2.44e-08	OR=0.65	A	*CHRNB3*	EA/HA/AA	Y	Rice J.P. (2012)
ND	Community-based association	8847	rs848353	5.40e-06	OR=1.37	?	*PNPLA8, THAP5, DNAJB9, C7orf66, LOC154907*	KA1/AA2/EA 2	Y	Yoon D. (2011)
ND	Community-Based Association and Patients	10,995	rs1051730	6.00e-20	Beta=0.1	T	*CHRNA3*	EA	Y	Thorgeirsson T.E. (2008)
ND	Case/Control	case=1050 control=879	rs2836823	1.53e-06	OR(f)=1.46 OR(m)=1.35	T	NR	EA	Y	Bierut L. J. (2007)
ND	Case/Control	case=1050 control=879	rs4142041	5.64e-06	OR=1.14	G	*CTNNA3*		Y	Bierut L.J. (2007)
TOL	Community-based association	1962	rs11031684	1.29e-08	HR=1.46	G	Near *WT1* & *RCN1*	EA	Y	He L. (2016)
TOL	Community-based association	1962	rs2304808	3.81e-08	HR=1.31	C	*FBUP3*	EA	Y	He L. (2016)

Note: Replication (Rep.) is defined as an additional confirmation of SNP significance at p <.05 within each study. All significant SNPs are included for each study, or the five most significant SNPs if they are non-significanct and p ≤ 5.00e-06. Only one SNP is listed per study if p > 5.00e-06. CPD = Cigarettes per Day, CS = Current Smoking, ND = Nicotine Dependence, TOL = Tolerance, HS = Heavy Smoking. AA = African Ancestry, EA = European Ancestry, HA = Hispanic Ancestry, IA = American Indigenous Ancestry, JA = Japanese Ancestry, KA = Korean Ancestry. HR = Hazard Ratio; OR = Odds-Ratio YSM=Yale University School of Medicine; UCHC=University of Connecticut Health Centre; UPSM=University of Pennsylvania School of Medicine; MUSC=The Medical University of South Carolina; MH=McLean Hospital Harvard Medical School; CATS=The Comorbidity and Trauma Study; WCH=Sample collected by West China Hospital.

Table 4

Summary of GWAS Results for Cannabis Related Phenotypes

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*-value	Effect Size	Affect Allele	Gene	Ancestry	Rep.	Reference
CDS	Meta-Analysis of Publicly Available Data (Yale-Penn/SAGE/ICGHD)	6000	rs143244591	4.32e-10	?	G	*LOC107986140 - TM4SF18*	AA	N	Sherva, R. (2016)
CDS	Meta-Analysis of Publicly Available Data (Yale-Penn/SAGE/ICGHD)	6000	rs146091982	1.33e-09	?	A	*SLC35G1*	AA	N	Sherva, R. (2016)
CDS	Meta-Analysis of Publicly Available Data (Yale-Penn/SAGE/ICGHD)	6000	rs77378271	2.13e-08	?	A	*CSMD1*	AA	N	Sherva, R. (2016)
CDS	Meta-Analysis of Publicly Available Data (Yale-Penn/SAGE/ICGHD)	8754	rs77378271	5.16e-08	?	A	*CSMD1*	EA	N	Sherva, R. (2016)
CDS	Meta-Analysis of Publicly Available Data (Yale-Penn/SAGE/ICGHD)	8754	rs73252553	5.57e-08	?	A	*LOC105374535*	EA	N	Sherva, R. (2016)
AFU	Population-Based Association	6744	rs35487050	1.60e-07	?	?	*ZNF181*	DA	N	Minica, C. (2015)
AFU	Population-Based Association	6744	rs2434422	3.70e-06	?	?	*MIR643*	DA	N	Minica, C. (2015)
AFU	Population-Based Association	6744	rs321908	8.50e-06	?	?	*MIR643*	DA	N	Minica, C. (2015)
AFU	Population-Based Association	6744	rs57523152	3.30e-05	?	?	*ZNF766*	DA	N	Minica, C. (2015)
AFU	Population-Based Association	6744	rs139570481	2.30e-04	?	?	*ZNF766*	DA	N	Minica, C. (2015)
EU	Community-Based Meta-Analysis	ever=4075 never=6015	rs1417205	8.41e-07	Beta=−0.06	A	GNG5P5	EA	N	Verweij, K. (2013)
EU	Community-Based Meta-Analysis	ever=4075 never=6015	rs10507554	8.41e-07	Beta=0.06	T	ELAC2	EA	N	Verweij, K. (2013)
EU	Community-Based Meta-Analysis	ever=4075 never=6015	rs1417202	1.03e-06	Beta=0.06	C	NELL1	EA	N	Verweij, K. (2013)
EU	Community-Based Meta-Analysis	ever=4075 never=6015	rs1538803	1.03e-06	Beta=0.06	T	LOC105371899	EA	N	Verweij, K. (2013)
EU	Community-Based Meta-Analysis	ever=4075 never=6015	rs9316288	1.31e-06	Beta=−0.06	*A*	*LOC101928280*	EA	N	Verweij, K. (2013)
CD	Case/Control	case=708 control=2346	rs1019238	6.12e-07	OR=1.45	?	*ANKFN1*	AA	Y	Agrawal, A. (2011)
CD	Case/Control	case=708 control=2346	rs1431318	9.14e-07	OR=0.71	?	*ANKFN1*	AA	N	Agrawal, A. (2011)
CD	Case/Control	case=708 control=2346	rs12491921	1.03e-06	OR=1.39	?	*LOC101929485*	AA	Y	Agrawal, A. (2011)
CD	Case/Control	case=708 control=2346	rs8065311	2.10e-06	OR=1.43	?	*ANKFN1*	AA	Y	Agrawal, A. (2011)
CD	Case/Control	case=708 control=2346	rs11007350	2.68e-06	OR=0.73	?	*RPL21P93*	AA	N	Agrawal, A. (2011)

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*-value	Effect Size	Affect Allele	Gene	Ancestry	Rep.	Reference
LU	Consortium-Based Meta-Analysis	32330	rs2099149	5.10e-07	Beta=−0.17	T	*Intergenic*	EA	N	Stringer, S. (2016)
LU	Consortium-Based Meta-Analysis	32330	rs4471463	9.00e-07	Beta=0.10	T	*NCAM1*	EA	N	Stringer, S. (2016)
LU	Consortium-Based Meta-Analysis	32330	rs4984460	2.20e-06	Beta=−0.11	T	*LOC107984800*	EA	N	Stringer, S. (2016)
LU	Consortium-Based Meta-Analysis	32330	rs58691539	2.20e-06	Beta=−0.29	T	*Intergenic*	EA	N	Stringer, S. (2016)
LU	Consortium-Based Meta-Analysis	32330	rs2033867	4.20e-06	Beta=0.23	A	*Intergenic*	EA	N	Stringer, S. (2016)

Note:

[a]The effect in the sample represents the direction for this SNP within each sample included in analyses. Replication is defined as an additional confirmation of SNP significance at p <.05 within each study. All significant SNPs are included for each study, or the five most significant SNPs if they are non-significanct and p ≤ 5.00e-06. Only one SNP is listed per study if p > 5.00e-06. LU = Lifetime Cannabis Use scored as yes/no; CDS = Cannabis Dependence Symptom Count; AFU = Age at First Experimental Use; EU = Ever Versus Never used Cannabis. EA = European Ancestry; AA = African Ancestry; DA = Dutch Ancestr

Table 5

Summary of GWAS Results for Cocaine and Opioid Use Phenotypes

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*-value	Effect Size	Effect Allele	Gene	Ancestry	Rep.	Authors
CODS	Community-Based Meta-Analysis	5697	rs2629540	7.64e-08	?	?	*FAM53B*	AA/EA	N	Gelernter, J. (2014)
COD	Case/Control Meta-Analysis	case=4291 control=1406	rs2005290	2.86e-07	?	?	*OR3A2*	AA/EA	N	Gelernter, J. (2014)
CODS	Community-Based Meta-Analysis	5697	rs4782559	7.54e-07	?	?	*CDH13*	AA/EA	N	Gelernter, J. (2014)
COD	Case/Control Meta-Analysis	case=4291 control=1406	rs6912117	2.51e-06	?	?	*PXT1*	AA/EA	N	Gelernter, J. (2014)
COD	Case/Control Meta-Analysis	case=4291 control=1406	rs59955083	2.62e-06	?	?	*PXT1*	AA/EA	N	Gelernter, J. (2014)
ODb	Case/Control Meta-Analysis	case=1167 control=161	rs10799590	4.30e-09	OR=0.64	A	*CNH13*	EA	Y	Nelson, E.C. (2016)
ODb	Case/Control Meta-Analysis	case=1167 control=161	rs12130499	4.31e-09	OR=0.64	T	*CNH13*	EA	Y	Nelson, E.C. (2016)
ODb	Case/Control Meta-Analysis	case=1167 control=161	rs298733	1.25e-08	OR=0.65	A	*CNH13*	EA	Y	Nelson, E.C. (2016)
ODb	Case/Control Meta-Analysis	case=1167 control=161	rs1436171	2.17e-08	OR=0.66	A	*CNH13*	EA	Y	Nelson, E.C. (2016)
ODb	Case/Control Meta-Analysis	case=1167 control=161	rs1369846	2.60e-08	OR=0.66	C	*CNH13*	EA	Y	Nelson, E.C. (2016)
OD	Case/Control	case=370 control=134	rs4791746	2.230e-07	OR=0.46	T	Unmapped	HA	N	Kalsi, G. (2016)
OD	Case/Control	case=370 control=134	rs2288156	2.82e-07	OR=0.39	T	CCDC42	HA	N	Kalsi, G. (2016)
OD	Case/Control	case=370 control=134	17:8631468	3.79e-07	OR=0.47	C	Unmapped	HA	N	Kalsi, G. (2016)
OD	Case/Control	case=370 control=134	rs4739179	3.62e-06	OR=0.50	G	Unmapped	HA	N	Kalsi, G. (2016)
OD	Case/Control	case=370 control=134	rs1881509	4.15e-06	OR=0.49	G	BRSK2	HA	N	Kalsi, G. (2016)
ODS	Community-Based and Publicly Available Data Meta-Analysis	5390	rs62103177	6.68e-10	?	?	*KCNG2*	AA	N	Gelernter, J. (2014)
ODS	Community-Based and Publicly Available Data Meta-Analysis	5390	rs114070671	2.26e-09	?	?	*APBB2*	AA	Y	Gelernter, J. (2014)
ODS	Community-Based and Publicly Available Data Meta-Analysis	5390	rs60349741	9.26e-09	?	?	*KCNC1*	AA	Y	Gelernter, J. (2014)
ODS	Community-Based and Publicly Available Data Meta-Analysis	5390	rs73411566	1.75e-08	?	?	*PARVA*	AA	Y	Gelernter, J. (2014)

Trait	Study Design/Sample	*N*	Best SNP	SNP *p*-value	Effect Size	Effect Allele	Gene	Ancestry	Rep.	Authors
ODS	Community-Based and Publicly Available Data Meta-Analysis	5390	rs115368721	1.92e-08	?	?	*APBB2*	AA	Y	Gelernter, J. (2014)

[a]This sample included controls who were opiate users who over time had not progressed to dependent users.

[b]Cases are defined as daily injectors, controls are defined as non-dependent misusers.

Note: Replicationm (Rep.) is defined as an additional confirmation of SNP significance at p <.05 within each study. All significant SNPs are included for each study, or the five most significant SNPs if they are non-significanct and p ≤ 5.00e-06. Only one SNP is listed per study if p > 5.00e-06. CODS = Cocaine Dependence Symptom Count; COD = Cocaine Dependence; OD = Opiod Dependence; ODS = Opiod Dependence Symptom Count. EA = European Ancestry; AA = African Ancestry; HA = Han Chinese AncestrY