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Comorbidity of alcohol use disorder and chronic pain: Genetic influences on brain reward and stress systems

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Abstract

Alcohol use disorder (AUD) is highly comorbid with chronic pain (CP). Evidence has suggested that neuroadaptive processes characterized by *reward deficit and stress surfeit* are involved in the development of AUD and pain chronification. Neurological data suggest that shared genetic architecture associated with the reward and stress systems may contribute to the comorbidity of AUD and CP. This monograph first delineates the prevailing theories of the development of AUD and pain chronification focusing on the reward and stress systems. It then provides a brief summary of relevant neurological findings followed by an evaluation of evidence documented by molecular genetic studies. Candidate gene association studies have provided some initial support for the genetic overlap between AUD and CP, however these results must be interpreted with caution until studies with sufficient statistical power are conducted and replications obtained. Genome-wide association studies have suggested a number of genes (e.g., *TBX19, HTR7, and ADRA1A*) that are either directly or indirectly related to the reward and stress systems in the AUD and CP literature. Evidence reviewed in this monograph suggests that shared genetic liability underlying the comorbidity between AUD and CP, if present, is likely to be complex. As the advancement in molecular genetic methods continues, future studies may show broader central nervous system involvement in AUD-CP comorbidity.

Keywords

alcohol use disorder; chronic pain; comorbidity; candidate association gene studies; genome-wide association studies

1. Introduction

Approximately 15.1 million American adults suffer from alcohol use disorder (AUD) (NIAAA, 2016) and 100 million suffer from chronic pain (CP) (IMNA, 2011). Importantly,

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the co-occurrence of AUD and CP is common though their relation is complex. For example, one epidemiological study reported that 27% of patients with CP used alcohol as a pain-reliever at least “sometimes” (Riley and King, 2009), whereas a prospective study conducted with NESARC data suggested that drinking cessation significantly predicted reduction in bodily pain (Imtiaz et al., 2017). Given this complexity, increasing attention has been paid to the study of AUD-CP comorbidity in recent years due to their considerable public health significance.

Both AUD and CP are multidimensional and heterogeneous conditions involving multiple biopsychosocial systems. A concatenation of genetic, neurophysiological, and behavioral studies has provided evidence supporting the roles of reward and stress systems in understanding AUD and CP. Unfortunately, research on each condition has proceeded independently with little consideration given to their overlap. In a seminal work, Egli, Koob, and Edwards (2012) attempted to bring the two fields together by delineating the overlapping neural substrates implicated in the reward and stress systems and their relevance to both alcohol dependence and pain processing. Moreover, they highlighted the importance of using molecular genetic approaches to further our understanding of the neurophysiological dysregulation of reward and stress systems common to AUD and CP (Egli et al., 2012).

This monograph summarizes the research on the molecular genetic predispositions associated with the dysregulation of the reward and stress systems associated with both AUD and CP; and how shared features of this dysregulation might contribute to the development of AUD-CP comorbidity. We initially describe the prevailing theories regarding the development of AUD and CP. Next, we discuss the substantial overlap in the neurological underpinnings of AUD and CP from the reward deficit and stress surfeit perspective. Third, we review and aggregate results from genetic association studies that have focused on genes implicated in the neurophysiological mechanisms in the reward and stress systems contributing to both AUD and CP. Lastly, we propose directions for future research to elucidate the genetic influences underlying AUD-CP comorbidity.

2. Theories of Development of Alcohol Use Disorder (AUD)

The cycle of alcohol addiction comprises three stages: repeated *intoxication, withdrawal, and craving* (Koob and Volkow, 2010), and the cyclic repetition of these stages, escalating over time results in the development of AUD (Koob, 2016). As AUD develops, this cycle becomes characterized by three major pathological characteristics – *compulsive alcohol seeking*, *uncontrollable alcohol consumption*, and *overwhelming negative affective when alcohol is inaccessible* (Koob and Le Moal, 1997). Research suggests that the development of AUD can be explained, in part, by the *opponent process theory of motivation*, which is characterized by a motivational shift in drinking behaviors from positive to negative reinforcement (Koob, 2003).

According to the opponent process theory of motivation, systems within the central nervous system (CNS) function to maintain equilibrium among affective states. Thus, once a change in affective state is detected, the CNS automatically responds by activating opposing

motivational sub-processes to maintain homeostasis (Solomon and Corbit, 1974). Koob and Le Moal (2008) have used this theory to describe the underlying processes involved with the development and perpetuation of addiction. In this model, acute consumption of a drug (e.g., alcohol) by nondependent users induces a rewarding state called the *a-process*. This rewarding state has a rapid onset and offset, and is thought to positively reinforce early drinking (Koob, 2016). Following the termination of the a-process, an opponent process, the *b-process*, induces a stressful, anti-rewarding state, thus counteracting the rewarding state induced by the a-process. Compared to the a-process, the b-process, has a slow onset and a sluggish decay. Among nondependent users, the intensities of the reward and stress elicited by the a- and b-processes are consistent with the amount of consumption, and this is sufficient to maintain affective homeostasis.

Repeated exposure to a drug (e.g., alcohol) eventually results in the dysregulation of the reward and stress systems seen among dependent users. Over time, the CNS becomes desensitized to the a-process and the rewarding state it once produced is now attenuated, thus increasing the reward threshold for the a-process and increasing tolerance for the drug (George et al., 2012). Simultaneously, the b-process becomes sensitized, protracted, and intensifies, while the stress threshold decreases, thus resulting in withdrawal (George et al., 2012). The changing of the thresholds, or set points, of the reward and stress systems, and their inability to achieve affective and physiological stability, is referred to as allostasis (Sterling and Eyer, 1988). In this model, the repeated exposure to the drug (e.g., alcohol) over time, forces the b-process to become dominant, and as a result, continued alcohol consumption is negatively reinforced through its temporary alleviation of negative affect (Koob, 2016). This reward and stress dysregulation, often referred to as a *reward deficit and stress surfeit disorder* (Koob, 2013), results in a state of allostatic load, and manifests as the pathological state of addiction (Koob et al., 2014).

3. Theories of Pain Chronification

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” by the International Association for the Study of Pain (IASP) (Merskey and Boduk, 1994). Aside from the sensory experience, this definition highlights the significance of the cognitive and affective dimensions associated with the subjective experience of pain by including the higher-order brain structures that receive peripheral pain information from the dorsal root ganglia and spinal cord and integrate this information with various pain-related processes (e.g., cognitive, affective, etc.) (Mitsi and Zachariou, 2016).

Chronic pain has been defined as continuous pain, which persists for at least three months (Merskey and Boduk, 1994). Despite their etiologic heterogeneity, CP conditions share some commonalities: (1) pharmacological options for chronic pain conditions and pain management have limited efficacy (e.g., McNicol et al., 2013), (2) the challenges in finding efficacious pharmacological treatments are partly attributable to the high comorbidities between CP conditions and psychopathologies, such as, depression, anxiety, anhedonia, and/or addiction (e.g., Borsook et al., 2016), and (3) clinical and pharmacological evidence

collectively suggests the involvement of dysregulation in the reward and stress neural circuitries across many CP conditions (e.g., Apkarian et al., 2013).

To elaborate, the transition from an acute to chronic pain state, via self-sustaining and escalating pain-related processes is called pain chronification, and has been hypothesized to share some key features with the development of AUD. For example, Borsook and colleagues (2016) propose a model of pain chronification that they define as culminating in a state of 'reward deficiency' (RD) and 'anti-reward' (AR). More specifically, they propose that, under healthy conditions, activation of an aversion/stress neural circuit by acute pain is followed by activation of the reward system, particularly in response to the alleviation of pain. Prolonged, recurrent acute pain episodes lead to pain chronification in which pain-related cues increase in salience leading to hypersensitivity of the aversion/stress system and hyposensitivity of the reward system. As a consequence, previous levels of experienced pain are insufficient to activate endogenous pain relief pathways in the reward systems and stronger pharmacological pain relievers are required to activate the reward systems for pain alleviation. This leads to what the authors define as a 'feed-forward loop' that produces an escalating disruption of the homeostatic balance between reward and stress/aversion pathways (Borsook et al., 2013). Thus, while these opponent-process models of AUD and CP propose different patterns of progression towards an allostatic load state, the neural mechanisms underlying both models significantly overlap.

4. Dysregulation of Reward System in Development of AUD and Pain Chronification

Dopamine is released in the mesolimbic pathway – nucleus accumbens (NAc) and ventral tegmental area (VTA). The limbic system and medial prefrontal cortex encode and process the reward value of a stimulus through the dynamic interplay between phasic and tonic dopamine levels (Grace, 2000; Knutson and Cooper, 2005). Tonic dopamine levels are characterized by a slow and low-volume of release that is induced by glutamate and degraded by catechol-*O*-methyltransferase (COMT) (Mannisto and Kaakkola, 1999). The tonic level of dopamine is a proxy for the amount of reward one generally expects from any given stimuli (Evers et al., 2017). In contrast, phasic dopamine levels are characterized by an instant high-volume release that is quickly attenuated by D2-autoreceptors that feedback to inhibit further dopamine release and activate the dopamine reuptake transporter to remove excess dopamine from the extracellular space (Ford, 2014). Phasic levels of dopamine are determined by the difference between the received and expected value of a stimulus, and is the proxy for the net value of reward for any particular stimulus. This net value is then processed by the limbic system and medial prefrontal cortex (Knutson and Cooper, 2005), through which the incentive salience of the rewarding stimulus is summarized and attributed (Robinson and Berridge, 1993).

Notably, the balance between phasic and tonic dopamine levels has been related to the stimulating value of alcohol over time (Gilpin and Koob, 2008). More specifically, tonic levels of dopamine are influenced by the amount of dopamine accumulated in the extracellular space. Among nondependent users, acute alcohol consumption results in

increased phasic dopamine release without impacting tonic levels (Weiss et al., 1993). Chronic alcohol exposure, however, results in decreased phasic levels and increased tonic levels due to constant saturation of D2-autoreceptors and an overloaded reuptake process (Ford, 2014). This process has been hypothesized to underlie tolerance observed among dependent users (Melis et al., 2005; Volkow et al., 2007).

In addition to AUD, the phasic-tonic dopamine model has also been implicated in pain chronification given recent studies demonstrating that dopamine is involved in the evaluative processing of aversive stimuli (Taylor et al., 2016). The recent CP literature suggests that a surfeit of glutamate and/or a deficit of COMT may result in excessive tonic dopamine levels that are sufficient to engage the D2-autoreceptors and reduce phasic release (Wood, 2006). Over time, lowering of the phasic/tonic ratio may lead to a reward deficit state that induces pain chronification and its comorbid symptoms relating to lack of interest in approaching naturally rewarding stimuli (Borsook et al., 2016).

Endorphins bind with mu-opioid receptors in the pituitary gland and hypothalamus and can produce a hedonic state through facilitation of dopamine release in the VTA and NAc during acute intoxication in animal studies (Oswald and Wand, 2004). Over time, they are involved in the down-regulation of the dopamine system and the development of alcohol tolerance. In the pain literature, acute pain onset has been associated with the release of endogenous opioids (Holden et al., 2005). However, in CP, data have suggested that the activity of endogenous analgesic systems involving mu-opioid receptors is attenuated (Miranda et al., 2015).

G*lutamatergic (excitatory) and GABAergic (inhibitory) mechanisms* within the reward system have also been studied. The immediate consequence of acute alcohol intoxication is a decrease in glutamate and increase in GABA activity resulting in a depression of the CNS (Carboni et al., 1993; Gilpin and Koob, 2008). However, chronic alcohol exposure produces a state of allostasis, and leads to the activation of compensatory processes to achieve homeostasis via an increase in glutamate receptor synthesis to induce hyperexcitability to glutamate (Pulvirenti and Diana, 2001). Together, these compensatory mechanisms lead to: (1) increased tonic presence of dopamine in the extracellular space, which decreases phasic dopamine release, and (2) establishment of context-dependent sensitization that aggravates alcohol cravings and makes sustained sobriety difficult (Tzschentke and Schmidt, 2003). During the transition from non-dependent to dependent alcohol use, compensatory processes also contribute to the desensitization of GABA (esp. $GABA_A$) receptors that leads to alcohol dependence and abuse (Liang and Olsen, 2014). Glutamatergic activity is also increased and sensitized during pain chronification. Additionally, increases in GABA activity inhibit the intercalated cells (ITC) of the amygdala, which block pain signals from reaching the CNS (Neugebauer, 2015). These compensatory mechanisms increase the salience of aversive and noxious stimuli leading to eventual hyperalgesia (Borsook et al., 2016).

5. Dysregulation of Stress System in Development of AUD and Pain Chronification

Having discussed the pathways involved in the reward deficit component, we now discuss how excessive stress contributes to the development of AUD and CP.

Corticotropin-releasing factor receptor 1 (CRF_1 receptor) activated in hypothalamus and amygdala has been associated with stress, anxiety, and hyperalgesia during alcohol withdrawal (Egli et al., 2012; Koob, 2013). Consuming additional alcohol negates these effects further encouraging AUD development *via* negative reinforcement. In pain chronification, CRF_1 released in the amygdala has been related to enhanced nociception (Ji and Neugebauer, 2008), which contributes to the establishment and maintenance of hyperalgesia (Tracey and Dunckley, 2004).

Dynorphins that bind to Kappa-opioid receptors are widely represented in the CNS (Watson et al., 1982) and are released during stress (Knoll and Carlezon, 2010). Activation of Kappa-opioid receptors inhibits dopamine release (Margolis et al., 2003), and increases the expression of CRF (Veer et al., 2012), both of which contribute to the experience of dysphoria, anxiety, agitation, and depression (Knoll and Carlezon, 2010) that characterize alcohol withdrawal. In pain chronification, dynorphins also activate the release of bradykinin, which has been linked to inflammation and hyperalgesia, and thus contribute to the development and maintenance of CP (Lai et al., 2006; Wang et al., 2005).

Neuropeptide Y (NPY) is highly expressed in the ventral striatum and amygdala (de Quidt and Emson, 1986) and has been implicated in an anti-stress system that acts in counter to the effects of CRF_1 by producing an anxiolytic effect (Heilig and Koob, 2007). Suppression of this anti-stress system, and of NPY specifically, is hypothesized to be involved in both AUD development and pain chronification. With respect to AUD, NPY is actively suppressed during alcohol withdrawal, which enhances the stress that characterizes the withdrawal state (Koob and Le Moal, 2001). In pain chronification, NPY is upregulated in the dorsal horn of the spinal cord following inflammation or injuries and inhibits pain signals (Brumovsky et al, 2004; Wakisaka et al., 1991). In animal models, knocking out *NPY* induces hyperalgesia (Solway et al., 2011). While we await evidences from human studies, it is reasonable to hypothesize that genetic variation in the *NPY* gene or any epigenetic changes associated with low NPY expression may play a role in pain chronification.

In sum, the described mechanisms associated with the reward and stress systems indicate that there are overlapping neural mechanisms associated with reward deficit and stress surfeit that contribute to the development and maintenance of AUD and CP. Below, we postulate that shared genetic predispositions may underlie some of this overlap in the neurobiology of AUD and CP.

6. Genetic Studies of AUD and CP

Both AUD and CP have a strong genetic component. Reviews of twin studies have reported that 43% - 53% and 25% - 50% of the variability in AUD and CP, respectively, are

attributable to genetic factors (Nielsen et al., 2012; Verhulst et al., 2015). Quantitative genetic studies estimating the genetic correlation between AUD and CP have not yet been conducted. Nonetheless, it is reasonable to theorize that AUD and CP would share some genetic variants that contribute to their risk, based on the substantial heritability estimates reported for each condition and their substantial overlap at the neurobiological level. When discussing genetic contributions to AUD and CPCs, three classes of genetic involvement should be considered: genes that influence (1) both AUD and CPCs (e.g., *COMT* gene variation associated with the reward pathway, Stallings et al., 2016; Zorina-Lichtenwalter, et al., 2016), (2) AUD independent of CPCs (e.g., *ALDH2* gene variation associated with alcohol metabolism, Stallings et al., 2016), and (3) CPCs independent of AUD (e.g., *ACAN* gene variation associated with damage of structural protein in pain, Zorina-Lichtenwalter et al., 2016). Figure 1 provides a conceptual overview of how genetic variation might influence AUD, CP, and their comorbidity. Though prototypical examples of each class are offered in the figure, oftentimes the boundaries across classes may be fuzzy due to the intricate effects of mediation and modulation among genes on phenotypes.

Association designs have been widely employed to study phenotype-genotype relations in molecular genetic studies in recent decades. These studies typically rely on a case-control design to examine whether a specific allele is more likely to be found among “cases” than “controls” at the population level (Gizer et al., 2015). Currently, the two primary types of association studies are the candidate gene and genome-wide association studies. Through such studies, significant insights have been gained in understanding the genetic contributions to AUD and CP individually. Yet, to our knowledge, no studies have been published examining genetic variants that might contribute to their comorbidity. Thus, we review published findings of genetic variants associated with AUD and CP individually to shed light on the possibility of genetic overlap associated with neurotransmitter systems involved in reward and stress dysregulation.

6. A. Candidate gene association studies (CGAS)

Early endeavors in genetic association research were dominated by CGAS due to constraints in genotyping technologies prohibiting the interrogation of large sets of genetic variants (Gizer et al., 2015). CGAS rely on a theory-driven perspective using *a priori* knowledge regarding the function of a specific gene and its relation to the phenotype of interest to restrict the search to a single or small set of gene(s). A substantial number of CGAS have been conducted to identify genetic variants associated with AUD and CP (e.g., reviews by Buhler et al., 2015; Stallings et al., 2016; Zorina-Lichtenwalter et al., 2016). This monograph does not aim to provide an exhaustive list of findings from both literatures, but rather, to offer the most commonly studied examples highlighting the possible overlap in genetic influences underlying AUD and CP as they relate to the reward and stress systems (Table 1). It should be noted, however, that almost all published CGAS have been statistically underpowered, and there is evidence to suggest that a substantial proportion of findings from these studies represent false positives (Siontis et al., 2010).

Polymorphisms located in genes encoding for proteins involved in *dopaminergic mechanisms* have shown the strongest overlap with respect to AUD and CP. One of the most

widely studied polymorphisms in relation to AUD and CP is the Taq1A polymorphism (rs1800497) located in the Ankyrin repeats and kinase domain containing 1 (*ANKK1*) gene. Although this polymorphism is a nonsynonymous polymorphism located in exon 8 of *ANKK1*, it was originally thought to be located in the dopamine D2 receptor gene (*DRD2*). Functional studies have suggested that this variant results in reduced dopamine synthesis via its impact on *ANKK1* function (Mrazek, 2010), and has also been related to altered dopamine D2 receptor density in the striatum (Jonsson et al., 1999). CGAS have related the minor A1 allele (*vs*. A2 major allele) to risk for both AUD and migraine (e.g., Le Foll et al., 2009 and Ghosh et al., 2013, respectively). While robust support for the association with AUD was demonstrated in a recent meta-analysis (Wang et al., 2013), a similar meta-analysis has yet to be conducted for CP phenotypes. Additionally, the potential influence of the Taq1A polymorphism on the ANKK1 and DRD2 proteins has made it difficult to determine which gene is likely to exhibit a causal relation with each disorder. Nonetheless, a second variant in *DRD2*, an NcoI polymorphism (rs6275) located in the 7th exon of *DRD2* has been associated with a reduction in dopamine-activated upregulation of D2 receptor expression (Duan et al., 2003). The minor T allele (*vs*. the C major allele) has been associated with *increased* risk for AUD (Meyers et al., 2013), but *reduced* risk for migraine (Peroutka et al., 1998). The opposite directions of effect for this variant on risk for AUD and migraine requires further study. It could be a reflection of meaningful differences in how this genetic variant contributes to the etiology of each condition, or it could be that the relation with one or both of these conditions represents a false positive.

The *COMT* gene, and the functional rs4680 polymorphism in exon 4 of this gene, has also received substantial attention with respect to AUD and CP. The minor A allele (*vs*. G major allele) of rs4680 causes an amino acid change from valine (Val) to methionine (Met) (Buhler et al., 2015), with the Val allele associated with higher rates of dopamine degradation. CGAS of AUD have yielded conflicting results, however, as some have related the Val allele to increased risk for AUD (e.g., Sery et al., 2006), while other studies have reported that the low degradation activity Met allele was associated with increased risk for AUD (e.g., Tiihonen et al., 1999). Association studies of rs4680 and CP have been somewhat more consistent. The low activity Met allele has been implicated in many CP conditions, such as low back pain (e.g., Jacobsen et al., 2012) and fibromyalgia (e.g., Finan et al., 2011), with recent meta-analyses suggesting robust associations with migraine (Chen et al., 2015) as well as fibromyalgia and chronic widespread pain (Tammimaki and Mannisto, 2012). Nonetheless, the conflicting pattern of results for AUD make it difficult to speculate how this variant and *COMT* might relate to a shared genetic component underlying AUD and CP.

In addition to dopaminergic genes, genes related to the *endogenous opioid system* have also been widely studied in the AUD and CP literatures. The most widely studied gene is the opioid receptor mu 1 (*OPRM1*) gene. The polymorphism, rs1799971 (A major *vs*. G minor allele), is located within exon 1 of *OPRM1*, and involves an A to G substitution causing an amino acid change from asparagine (Asn) to aspartic acid (Asp) that enhances beta-endorphin binding (Bond et al., 1998). This polymorphism has been consistently implicated in AUD with a recent meta-analysis that included more than 28,000 participants suggesting that the G (Asp) allele is associated with reduced risk for substance use disorders, including AUD (Schwantes-An et al., 2016). In the CP literature, some studies have also found a link

between rs1799971 and pain. For example, Janicki and colleagues (2006) found that the frequency of the G allele was significantly lower in a group of CP patients relative to a comparison group of postoperative patients with acute pain, suggesting that the G allele may be associated with reduced risk for CP. Thus, the G allele of rs1799971 appears to be associated with protection against the development of both AUD and CP.

Thus far, to our knowledge, genetic overlap between AUD and CP has not been found among other reward and stress mechanisms in CGAS using human samples. A few studies using animal models of these conditions have suggested overlapping genetic signals between AUD and CP. For example, in the stress system, variants in *OPRK1* have been implicated in AUD in human samples (Gerra et al., 2007; Xuei et al., 2006), while animal studies have suggested variation in this gene is related to pain sensitivity in mice (Fukagawa et al., 2014). Similarly, variation in *NPY* has been implicated in AUD in human studies (Kovanen et al., 2010), and has been related to pain sensitivity in mice (Solway et al., 2011). These data have led to speculations that genetic overlap in the stress system is plausible, thus meriting a closer examination of *OPRK1* and *NPY* variation in human research.

In sum, CGAS provide some indication that there is overlap in the genes that contribute to the development of AUD and CP, though whether these genes contribute to their comorbidity has yet to be addressed. Additionally, the pitfalls of CGAS, such as poor replication rates and inflated false positive rates suggest researchers need to interpret the reviewed findings with caution and employ other methods, such as meta-analysis, to buttress the findings from CGAS. It is also important to note that while these studies highlight potential areas of genetic overlap, they also serve to highlight the current dearth of knowledge regarding the genetic etiology of these traits. Specifically, genes involved in dopamine and opioid systems represent obvious targets for both, but are likely to represent a very restricted view of their overlap.

6. B. Genome-wide association studies (GWAS)

In contrast to CGAS, GWAS use a data driven approach to individually test for associations with millions of SNPs across the genome. P-values are corrected for multiple testing such that associations below 5e-8 threshold are considered significant. For small-effect, common variants to reach this threshold a minimum of 30,000 participants are required to achieve sufficient statistical power (PGC, 2009). Consequently, it is important to note that many of the current GWAS of AUD and CP are underpowered, leading to the development of large-scale consortia to achieve the required sample sizes. Currently, however, consortia studying these conditions are in their infancy. As a result, we provide a brief review of published findings to date, with a focus on describing how future GWAS efforts might help us better understand those facets of the reward and stress systems that influence AUD, CP and their comorbidity. Studies published between 2000–2016 were identified using search strategies adapted from two recent, comprehensive reviews of molecular genetic studies of AUD (Buhler et al., 2015) and CP (Zorina-Lichtenwalter et al., 2016). The top association signals from these studies as well as lists of suggestive results, as defined by the authors of the individual studies, when available were reviewed. Genes and variants that showed suggestive or significant associations with both AUD and CP are presented in Table 2. Nonetheless, it

should be noted that the goal of this monograph is not to provide a comprehensive review of genetic overlap between AUD and CP, but rather to provide examples that afford insights for studying comorbidity of AUD and CP. Thus, only a small number of findings are described in detail.

As noted, GWAS of AUD and CP conducted to date have been relatively underpowered. Thus, there are few significant results and no overlap among them. Nonetheless, there has been overlap in the suggestive findings reported for each group of disorders. Looking at individual SNPs, thirteen have yielded suggestive associations with both AUD and CP. The SNPs are located in or near the *PRPF3* (rs1260401, rs1776276, rs519126), *RPRD2* (rs1260419, rs1776270), *MRPS21* (rs12747669, rs1694374, rs494041, rs573351), and *ONECUT2* (rs4940804, rs4940805, rs4940806) genes and one in an intergenic region (rs2263190 - 6q16.1) (Gelernter et al., 2014; Gormley et al., 2016; Wang et al., 2013). None of these common genes or regions has shown a genome-wide significant relation with AUD or CP and do not fall into the reward or stress systems, suggesting that any substantive interpretation of these results would be premature and require further replication.

In contrast, after annotating each SNP associated with AUD or CP to its nearest gene, there is overlap among the implicated genes, including genes that are hypothesized to play a role in the reward or stress systems (Table 2). These genes can be broken down into three broad categories, namely those hypothesized to be directly involved in either the reward or stress systems, those that may be involved in mechanisms that play a modulatory role or interact with the reward and/or stress systems, and those critical for central nervous system organization and activity in general but whose specific relations to the reward or stress system have yet to be delineated. We provide a brief discussion of genes from each of these categories in the following paragraphs.

Although none of the identified genes in Table 2 were related directly to the reward system, one belonging to the stress system is of particular interest – T-Box 19 (*TBX19*). A SNP in *TBX19* (rs1003502) was identified in an early GWAS of alcohol dependence (Yu et al., 2008), while a different SNP (rs2268550) was identified in a GWAS of postoperative pain (Cook-Sather et al., 2014). Although acute postoperative pain does not belong to the classic CP conditions, it provides insight on pain sensitivity among individuals who may be more susceptible to developing CP in the future (an endophenotype that will be defined below) and has been frequently studied in the CP literature. Of relevance to the present review, *TBX19* has been shown to regulate the expression of the adrenocorticotropic hormone (ACTH) precursor, pro-opiomelanocortin (POMC), in the pituitary gland (Liu et al., 2001), and functional mutations in *TBX19* result in Isolated Adrenocorticotropin Deficiency (Vallette-Kasic et al., 2005). Thus, it appears to play a critical regulatory role in the HPA system and stress regulation, suggesting a possible shared mechanism through which variation in this gene could contribute to the development of AUD and CP.

Examples of genes showing suggestive associations with AUD and CP and hypothesized to play a modulatory role and interact with the reward and stress systems, as can be seen in Table 2, cover many physiological systems. They included serotonin receptors (e.g. *HTR7*), adrenergic receptors (e.g. *ADRA1A*), calcium channel regulators (e.g. *CACNA1A*),

interleukin receptors (e.g. *IL-1RN*), hormonal receptors (e.g. *ESR1*), and so on. It is beyond the scope of this monograph to describe them all in detail. Thus, we use two examples, *HTR7* and *ADRA1A*, to illustrate the involvement of these genes in AUD and pain. Two variants, rs7916403 and rs2800143, in the 5-hydroxytryptamine (serotonin) 7 receptor (5-HT_7) gene (*HTR7*) have been respectively associated with susceptibility to alcohol dependence (Zlojutro et al., 2011; Zuo et al., 2014) and increased risk of migraine (Cox et al, 2012). The interaction of serotoninergic and dopaminergic neurons plays a major role in reinforcement learning and memory that subsequently determine incentive salience and motivation (Cools et al., 2011). Moreover, 5-HT_7 receptors modulate the stress-related activity of the HPA system (Garcia-Iglesias et al., 2013; Terron, 2014) and are involved in the endogenous pain inhibitory system *via* mediating the effect of opioid and endocannabinoid-induced analgesia in response to acute stress in animal models (Yesilyurt et al., 2015). SNPs in the *ADRA1A* gene that interact with the stress system have also been implicated in GWA studies of AUD (Kapoor et al., 2013; chr8: 26608070, rs10101664, rs10105967, rs17088266, and rs61670721) and CP (Peters et al., 2013; rs1048101). These receptors bind with catecholamines mediating the sympathetic nervous system's response to acute stress, including stress that occurs during alcohol withdrawal and pain (Piascik and Perez, 2001). Thus, there is strong evidence supporting the regulatory role of *HTR7* and *ADRA1A* in the reward and stress systems, supporting a certain degree of etiological overlap between AUD and CP.

Finally, there are also overlapping genes described in Table 2 with broad expression across the central nervous system, though their roles in the neural structures critical to the reward and stress systems have yet to be fully described. For example, a SNP in cadherin 13 (*CDH13*), rs11640875 has been implicated in a GWAS of AUD (Biernacka et al., 2013; Treutlein et al., 2009), and another SNP in the same gene, rs1559437 has been associated with migraine in a GWA study (Gormley et al., 2016). *CDH13* is highly expressed in the central nervous system (Takeuchi et al., 2000) where it encodes for a protein, T-cadherin, that is involved in cell adhesion (Cho et al., 2015). Animal studies have suggested that T-cadherin regulates GABAergic inhibitory interneurons in hippocampus (Rivero et al., 2015). Additional work has shown that adiponectin binds with T-cadherin in order to regulate oxidative stress (Kasahara et al., 2013). Alcohol consumption and migraine have been linked to increases in oxidative stress (Albano, 2006; Borkum, 2016), and thus, dysregulation in oxidative stress may further exacerbate the development of AUD and migraine, providing another potential mechanism through which *CDH13* might influence AUD and CP. This evidence suggests further genetic influences that may be shared between AUD and CP and that this shared etiology may involve neurological systems beyond the reward and stress pathways, which are the primary focus of the present review.

7. Commentary and Future Directions

This monograph provides an extensive look at the genetic overlap between AUD and CP. CGAS of human samples have documented several potentially important overlapping genetic signals in the dopaminergic and opioidergic neurotransmitter systems, including the *ANKK1-DRD2* gene region, *COMT*, and *OPRM1*, but given the small sample sizes involved in these studies, these findings require further replication. An additional limitation

of these CGAS is that they are restricted to a small set of genes and variants that have been studied across many phenotypes, and thus provide a very limited examination of the potential genetic influences contributing to these conditions. Though still in the early stages, the findings obtained from GWAS of AUD have begun to yield suggestive results identifying novel genes that may be contribute to the etiology of AUD and CP (e.g., AUD: Gelernter et al., 2014, Pain: Anttila et al., 2013). However, GWAS are not without limitations either. Most of the studies conducted for AUD and CP have been underpowered. Thus, while the present review identified some variants and genes with suggestive relations with AUD and CP, it is plausible that many additional variants that exert a significant effect on the disorders and their comorbidity have yet to be identified. As additional studies are conducted and data are contributed to large-scale meta-analytic efforts, statistical power of these studies will increase, allowing for the discovery of additional variants and the genes that they impact. As discussed earlier, evidence from studies using animal models also suggests that genetic overlap exists between AUD and CP outside this small number of genes. Notably, as more robust evidence implicating specific genes in the etiology of AUD and CP accumulates, animal models in which a specific gene or variant can be altered will provide additional insights into how these genes contribute to the development of AUD and CP.

In addition to single variant association analysis, pathway- and network-based approaches have the potential to further our understanding of the genetic factors involved in the etiologies of AUD, CP, and possibly their comorbidity. Pathway analyses focus on the joint analysis of variants within gene sets that are created based on the known function of gene products (e.g., G-protein-coupled receptor activity, cell adhesion) or demonstrated interactions between gene products in the case of protein-protein interaction (PPI) networks (Lin et al., 2016). Additionally, data mining approaches that incorporate data from multiple sources (e.g., association studies, PPI studies, transcriptomics and other omics-level studies) can be used to develop disease/disorder-specific networks, which then can be compared across phenotypes to identify areas of overlap (Kontou et al., 2016). As these types of data accumulate, both approaches will likely expand our understanding of the genetic influences that contribute to the reward and stress systems and how individual differences in these systems contribute to the development of AUD and CP.

Notably, GWAS data also have the potential to inform our understanding of the overlap between these conditions beyond gene discovery. For example, several recently developed approaches allow researchers to aggregate the effects of variants and genes on disorders in ways that allow for the estimation of genetic correlations between traits, and in some cases, test hypotheses regarding the causal pathways underlying them. For example, LD Hub is a centralized database containing an extensive amount of GWAS summary-level data associated with mental and physical disorders (Zheng et al., 2017). It contains a web interface for conducting LD score regression, which allows the estimation of genetic correlations between different complex disorders from GWAS summary-level results (Bulik-Sullivan et al., 2015). Similarly, polygenic risk score approaches have been developed to investigate the relations between complex phenotypes and have been used in some instances to test causal relations among psychiatric phenotypes using Mendelian Randomization designs (e.g., Richmond et al., 2014).

While the described approaches have the potential to significantly expand our understanding of the etiology of AUD and CP, there are some issues that will require special consideration. First, due to the heterogeneity of AUD and CP, endophenotypes or sets of endophenotypes that index one or more transdiagnostic mechanisms that undergird both disorders may be more powerful than using manifest diagnoses as phenotypes for gene identification. Endophenotypes of a disorder are heritable traits associated with the disorder of interest, manifested in preclinical individuals, and co-segregate with the disorder in pedigree analysis (Gottesman and Gould, 2003). Examples of endophenotypes for comorbidity of AUD and CP may include hyperkatifeia or hyperalgesia; however, the selection of such endophenotypes may be limited to our current knowledge regarding the biological underpinnings of each disorder. Thus, the application of phenome-wide association study (PheWAS) methods to genes and variants robustly associated with both AUD and CP may be considered to identify novel phenotypes or endophenotypes that may be used in future studies to identify genetic variants that predispose to the comorbidity of AUD and CP (Polimanti et al, 2016).

Additionally, it is important to mention that genetic influences do not act in isolation. Thus, it is crucial to consider the joint effect of genetic and environmental factors in studying the comorbidity of AUD and CP. As mentioned above, oftentimes, inconsistent findings across studies are attributable to the interaction between genetic and environmental factors. For example, gene-environment interactions (GxE) can be tested at the candidate gene or genome-wide level (GxE GWAS) to investigate whether specific environmental factors, such as social stress (e.g., Singh et al., 2015), moderate the influence of individual variants on AUD and CP. Further, network-based approaches using machine-learning algorithms have been developed to not only identify gene-networks as described above, but also to identify networks that incorporate the moderating effects of environmental variables as well. Notably, one recent example developed such a network to quantify GxE effects on AUD (e.g., Zollanvari et al., 2017), and could be extended to the study of CP and potentially AUD-CP comorbidity. Finally, it will also be important to study the mechanisms through which environmental influences exert their force on genetic influences. For example, through DNA methylation, environmental influences can impact DNA expression by modifying the activity of a DNA sequence without changing the sequence itself. Thus, the transactional nature of gene-environment relations will need to be incorporated into the molecular genetic study of these conditions in order to fully understand their etiology.

8. Conclusion

Neurobiological evidence has suggested that similar dysregulation of reward and stress pathways contribute to AUD and CP, and there is some suggestion that genetic influences on these pathways may contribute to both conditions. CGAS have provided initial evidence to support this premise, but should be evaluated with caution. A number of SNPs suggestively associated with AUD and CP have been identified from GWAS that studied AUD and CP independently, and several of these SNPs have been located in or near a common set of genes. These common genes are either directly or indirectly related to the reward and stress systems, as well as from genes that are more broadly involved with the CNS, whose links to reward and stress systems have yet to be studied. This monograph points to the fact that, if a

shared genetic architecture underlies AUD-CP comorbidity, it is likely to implicate systems beyond reward and stress mechanisms and involve instances of mediation and modulation among these systems. Advancement in research designs and methods should help further elucidate the potential genetic overlap between AUD and CP. If shared genetic contributions to AUD and CP can be identified, such knowledge can be used to inform our understanding of the underlying mechanisms that contribute to the etiologies of each disorder and their co-occurrence, and thus has the potential to refine and improve the diagnosis and treatment of AUD and CP.

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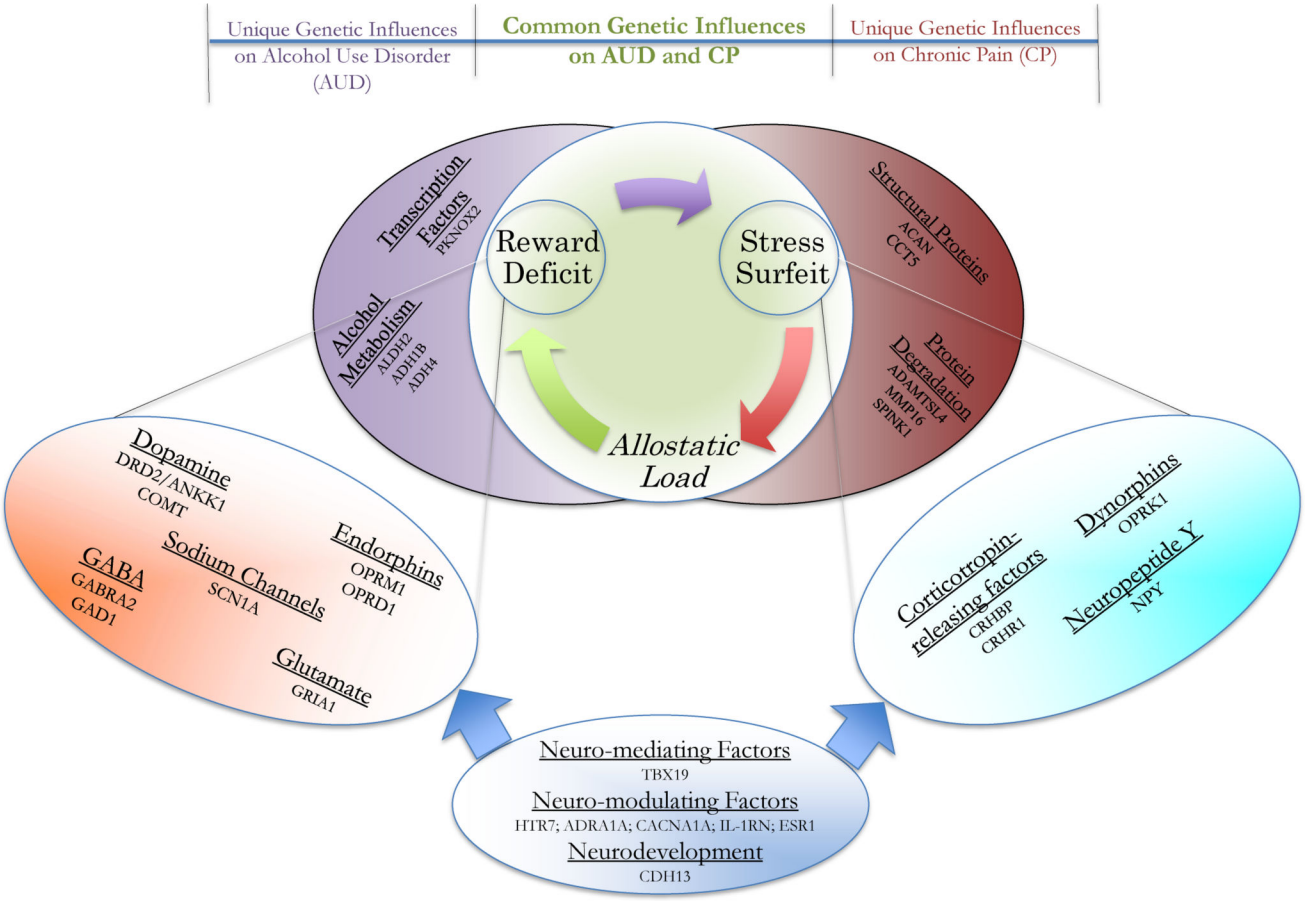

Figure 1. Unique and common genetic influences to AUD and CP

Three classes of genetic involvement should be considered: possible genes that influence (1) both AUD and CP (genes in tangerine ellipse are associated with the reward pathways & genes in turquoise ellipse are associated with the stress pathways), (2) AUD independent of CP (in purple ellipse), and (3) CP independent of AUD (in red ellipse). Furthermore, there are genes that mediate or modulate the reward and stress systems, or broadly affect the central nervous system (in blue ellipse). The gene groups and corresponding genes in each group in this figure serve as examples and do not represent an exhaustive list. Among them, some have been supported by existing empirical findings, whilst others await further investigations.

Table 1

Genes Implicated in Alcohol Use Disorder, Chronic Pain, or Both

Gene	Study Citation(s) for Alcohol Use Disorder	Study Citation(s) for Chronic Pain
	Dysregulation of Brain Reward System	
	Dopaminergic Mechanisms	
ANKK1 (ankyrin repeat and kinase domain containing 1)	Gelernter et al., 1993; Goldman, 1993; Le Foll et al., 2009; Munafo et al., 2007; Smith et al., 2008	Migraine: Del Zompo et al., 1998; Ghosh et al., 2013; Peroutka et al., 1998
COMT (catechol-o-methyltransferase)	Enoch et al., 2006; Sery et al., 2006; Tiihonen et al., 1999; Voisey et al., 2011	Fibromyalgia (FM): Barbosa et al., 2012; Cohen et al., 2009; Fernandez-de-las Penas et al., 2012; Finan et al., 2011; Martinez-Jauand et al., 2013; Matsuda et al., 2010; Vargas-Alarcon et al., 2007 // Low Back Pain (LBP): Jacobsen et al., 2012; Omair et al., 2012; Omair et al., 2015; Rut et al., 2014 // Migraine: Cargnin et al., 2013 // Post-Operative Pain (POP): Rut et al. (2014) // Temporomandibular Joint Disorders (TMD): Diatchenko et al., 2005; Erdal et al., 2003; Meloto et al., 2015; Michelotti et al., 2014; Smith et al., 2011
DBH (dopamine beta-hydroxylase)	Cubells et al., 2004	Migraine: Fernandez et al., 2006; Fernandez et al., 2009; Ghosh et al., 2013; Lea et al., 2000
DRD1 (dopamine receptor 1)	Kim et al., 2007	
DRD2 (dopamine beta-receptor 2)	Chen et al., 2011; Goldman et al., 1998; Meyers et al., 2013; Wiesbeck et al., 2006	Migraine: Del Zompo et al., 1998; Ghosh et al., 2013; Peroutka et al., 1998
DRD4 (dopamine beta-dopamine 4)	George et al., 1993; Le Foll et al., 2009; Paterson et al., 1999	Migraine: de Sousa et al., 2007; Del Zompo et al., 1998; Mochi et al., 2003 // TMD: Aneiros-Guerrero et al., 2011
MAOA (monoamine oxidase A)	Tikkanen et al., 2010	FM: Gursoy et al., 2008 // TMD: Mutlu et al., 2005
	Opioidergic Mechanisms	
OPRM1 (opioid receptor mu 1)	Arias et al., 2006; Bart et al., 2005; Schwantes-An et al., 2016	LBP: Hasvik et al., 2014; Omair et al., 2015 // POP: Janicki et al., 2006; Kolesnikov et al., 2013; Olsen et al., 2012
	Glutamate Mechanisms	
GAD1 (glutamate decarboxylase 1)	Loh et al., 2006; Tabakoff et al., 2009	
GRIA1 (glutamate receptor ionotropic receptor AMPA type subunit 1)		Migraine: Cargnin et al., 2014; Formicola et al., 2010; Maher et al., 2013
GRIA3 (glutamate receptor ionotropic receptor AMPA type subunit 3)		Migraine: Formicola et al., 2010; Maher et al., 2013
GRIN2 (glutamate receptor ionotropic receptor NMDA type subunit 2)	Domart et al., 2012	
LRP1 (low density lipoprotein receptor-related protein 1)		Migraine: Esserlind et al., 2015; Ghosh et al., 2013
MEF2D (myocyte enhancer factor 2D)		Migraine: Esserlind et al., 2015
	Dysregulation of Brain Reward System	
	GABA Mechanisms	
GABRA2 (gama-aminobutyric acid type A receptor subunit alpha-2)	Covault et al., 2004; Drgon et al., 2006; Edenberg et al., 2004; Lappalainen et al., 2005; Matthews et al., 2007; Soyka et al., 2008	

Gene	Study Citation(s) for Alcohol Use Disorder	Study Citation(s) for Chronic Pain
GABRB3 (gama-aminobutyric acid type A receptor subunit beta-3)		FM: Smith et al., 2012 // Migraine: Netzer et al., 2008; Oswell et al., 2008; Russo et al., 2005
GABRG3 (gama-aminobutyric acid type A receptor subunit gamma-3)	Dick et al., 2004	
SCN1A (sodium voltage-gated channel alpha subunit 1)		Migraine: Persico et al., 2015
	Dysregulation of Brain Stress System	
	Corticotropin-Releasing Mechanisms	
CRHBP (corticotropin releasing hormone binding protein)		FM: Holliday et al., 2010
CRHR1 (corticotropin releasing hormone receptor 1)	Treutlein et al., 2006	
MC2R (melanocortin receptor type 2)		FM: Holliday et al., 2010
	Opioidergic Mechanisms	
OPRK1 (opioid receptor kappa 1)	Gerra et al., 2007; Xuei et al., 2006	
	Neuropeptide Y (Anit-Stress / Stress-Buffering) Mechanisms	
NPY (neuropeptide Y)	Kovanen et al., 2010; Lappalainen et al., 2002	

Table 2

SNPs near the Overlapping Genes Extracted from Genome-wide Association Data on Alcohol Use Disorder (AUD) and Chronic Pain (CP)

Overlapping Gene	SNPs reported in previous AUD literature	Authors (AUD)	SNPs reported in previous CP literature	Authors (CP)
ABO	rs657152	Heath et al., 2011	rs647800	Gormley et al., 2016
ADAMTSL1	rs10756991	Gelernter et al., 2014	rs1539000, rs4977338	Cox et al., 2012
ADRA1A	chr8:26608070, rs10101664, rs10105967, rs17088266, rs61670721	Kapoor et al., 2013	rs1048101	Peters et al., 2013
AJAP1	rs66989617	Gelernter et al., 2014	rs10915528	Cook-Sather et al., 2014
AKAP6	rs17412116	Wang et al., 2012	rs981524	Docampo et al., 2014
AP2A1	rs1001281	Kapoor et al., 2013	rs1273644, rs1674139	Gormley et al., 2016
AUTS2	rs6943555	Schumann et al., 2011	chr7:69991038:I	Gormley et al., 2016
C10orf11	rs10762705	Wang et al., 2013	rs11001775	Cox et al., 2012
C1D	rs9807970, rs13385536, rs17034884	Gelernter et al., 2014	rs1503245	Cook-Sather et al., 2014
C2	rs644045, rs685031	Gelernter et al., 2014	rs36221133, rs184265581	Gormley et al., 2016
C7orf10	rs142530316, rs17620991, rs17688247, rs17688571, rs34994199, rs66651482, rs67648979	Mbarek et al., 2015	rs186166891, rs10234636, rs77410344, rs4723954, rs12533531, rs12532479, rs12670267, rs144002785, rs11531504, rs10435164, rs80157425, rs17171694, rs77024938, rs141208879, rs147040642, rs10951637, rs17171696, rs138268186, rs1319467, rs12669577	Gormley et al., 2016
CACNA1A	rs16050	Gelernter et al., 2014	rs10405121, rs11669746, rs12611029, rs2302080, rs4926144, rs77626158, rs8112530	Gormley et al., 2016
CACNA2D1	rs3216242	Gelernter et al., 2014	rs11971008	Docampo et al., 2014
CDH13	rs11640875	Biernacka et al., 2013; Treutlein et al., 2009	rs1559437	Gormley et al., 2016
CNTNAP2	rs851712, rs115707642, rs181335610, rs4726948, rs76164032, rs76687983, rs7811006	Gelernter et al., 2014; Lind et al., 2010	rs10277969	Cook-Sather et al., 2014
COX7C	rs6888626	Zuo et al., 2012	rs2195349	Cook-Sather et al., 2014
CSMD1	rs11783062, rs79575989, rs34123713, rs35473038, rs35542721, rs4105690, rs6993088, rs7461469	Gelernter et al., 2014; Kapoor et al., 2013; Wang et al., 2013	rs1545821	Cook-Sather et al., 2014
DOK6	rs11151517, rs7230078, rs112429852, rs143744549, rs147997033, rs59387400, rs73970243, rs73970248	Gelernter et al., 2014	rs8083908	Cook-Sather et al., 2014
DSCAML1	rs553637, rs117266385	Gelernter et al., 2014; Wang et al., 2013	rs528431	Cox et al., 2012

Overlapping Gene	SNPs reported in previous AUD literature	Authors (AUD)	SNPs reported in previous CP literature	Authors (CP)
ESR1	rs6902771	Biernacka et al., 2013; Treutlein et al., 2009	rs7745737	Cook-Sather et al., 2014
FAM155A	rs142728746, rs146932814, rs16971278, rs16971285, rs74612847, rs76569829, rs79922539, rs7993103, rs9520352, rs9555412, rs9555413, rs9559170, rs9587393	Gelernter et al., 2014	rs9301200, rs9558976	Cox et al., 2012
FREM1	rs3747534	Gelernter et al., 2014	rs1032474, rs4415414	Cox et al., 2012
FUT9	rs4132260	Wang et al., 2013	rs7775100, rs9485644, rs2493357, rs7753933, rs716192, rs7746369, rs4304170, rs78878034, rs4563725, rs2387151, rs4002794, rs9390810, rs1570774, rs9322635, rs9404179, rs9498927, rs9498926, rs7740119, rs7745151, rs57583838	Gormley et al., 2016
GRIA4	rs2508467	Karpyak et al., 2012	rs10502058, rs10895837, rs17104711, rs2510177, rs642544	Peters et al., 2013
GRK5	rs12780837	Gelernter et al., 2014	rs7071131, rs7076992, rs7077224, rs7090417, rs928670	Gormley et al., 2016
HLA-DRA	rs9268628, rs9268644, rs2239803, rs9268644	Gelernter et al., 2014	rs116618786	Gormley et al., 2016
HTR7	rs7916403	Zlojutro et al., 2011; Zuo et al., 2014	rs2800143	Cox et al., 2012
IL-1RN	rs2232354	Gelernter et al., 2014	rs315952, rs454078	Peters et al., 2013
KIAA0040	rs1057239, rs1057302, rs1894709, rs6425323, rs6701037, rs1057239, rs1057302, rs1894709, rs1057239, rs1894709	Zuo et al., 2012	rs10798341, rs10912903, rs12084108, rs12143530, rs2205603, rs2205604, rs2272784, rs3766681, rs3766683, rs3766684, rs3766685, rs3766687, rs3766688, rs3766692, rs3766694, rs6674635, rs6677931, rs6677935, rs760486	Gormley et al., 2016
KLHL29	rs150875373	Gelernter et al., 2014	rs4665597, rs13011734	Gormley et al., 2016
MAGI2	rs990527	Gelernter et al., 2014	rs11979133	Cox et al., 2012
MRPS21	rs12747669, rs140449835, rs12747669, rs140449835, rs1694374, rs494041, rs573351	Gelernter et al., 2014	rs1694374, rs580159, rs497128, rs1260398, rs8006, rs471738, rs11205359, rs1776273, rs543179, rs471657, rs494952, rs573351, rs1776275, rs11811885, rs494041, rs2762860, rs496203, rs3818978, rs500812, rs1694375	Gormley et al., 2016
MYO3B	rs741283	Gelernter et al., 2014	rs6730459, rs76973106	Cox et al., 2012, Gormley et al., 2016
NCOR2	rs1244096	Gelernter et al., 2014	rs11057627, rs12231617, rs1271309, rs3782266, rs4765566, rs951976	Gormley et al., 2016
NOS1AP	rs4480334	Gelernter et al., 2014	rs16859092	Cook-Sather et al., 2014
NOTCH4	rs2071279, rs2071280, rs9267820, rs9267830, rs9267831, rs9267832, rs9267833	Gelernter et al., 2014	rs6936346	Cox et al., 2012
OXR1	rs6996005, rs7819358	Kapoor et al., 2013	rs1453227, rs6469074	Yamaguchi et al., 2014
PCSK2	rs112910132	Gelernter et al., 2014	rs6514790, rs8120978, rs8121922	Gormley et al., 2016

Overlapping Gene	SNPs reported in previous AUD literature	Authors (AUD)	SNPs reported in previous CP literature	Authors (CP)
PIP5K1B	rs3812537	Gelernter et al., 2014	rs11144442	Gormley et al., 2016
PRDM16	rs760568	Gelernter et al., 2014	rs10218452, rs10797381, rs7518255, rs2075968, rs10909886, rs2376495, rs61759167, rs11587518, rs28594467, rs61759161, rs1393064, rs56304645, rs61759163, rs12745073, rs1393065, rs2493212, rs12136643, rs12038657, rs2651899, rs207195	Gormley et al., 2016
PRPF3	rs1260401, rs1776276	Gelernter et al., 2014	rs2794680, rs698918, rs1260406, rs1776265, rs2794684, rs2794682, rs1694364, rs4926422, rs1260404, rs3125808, rs1260407, rs1260409, rs698914, rs1097066, rs834225, rs1260385, rs1260403, rs698917, rs1776272, rs1260408	Gormley et al., 2016
PTPRD	rs10816057, rs10977546	Gelernter et al., 2014	rs2039331	Cox et al., 2012
RBFOX1	rs1507026, rs1507027, rs1507029, rs28581832, rs4786880, rs7186335, rs7193674, rs7203593, rs76931803, rs8044875, rs9925723	Gelernter et al., 2014	rs1955388	Gormley et al., 2016
RORA	rs79271390	Gelernter et al., 2014	rs4238351	Cook-Sather et al., 2014
RPRD2	rs1260419, rs1776270	Gelernter et al., 2014	rs13374465, rs35784258, rs1617829, rs834241, rs1260392, rs828783, rs4926395, rs1260419, rs11205373, rs832621, rs834234, rs1566225, rs834242, rs11205375, rs12736375, rs7513182, rs11205382, rs1313570, rs10888583, rs834243	Gormley et al., 2016
SEMA6D	rs11856716	Gelernter et al., 2014	rs10519138	Gormley et al., 2016
SERINC2	rs1039630, rs10914386, rs2275435, rs4478858, rs4949400, rs4949402, rs4478858, rs2275436, rs4478858, rs2275435, rs2275436, rs4478858, rs4949400, rs4949402	Biernacka et al., 2013; Zuo et al., 2012; Zuo et al., 2014	rs140137989	Gormley et al., 2016
SERPINC1	rs1799876	Xu et al., 2015	rs12137553, rs12746886	Gormley et al., 2016
SKIV2L	rs419788, rs437179, rs440454	Gelernter et al., 2014	rs115867030, rs116336668	Gormley et al., 2016
SLC9B1	rs66466366	Gelernter et al., 2014	rs10006076	Gormley et al., 2016
TBX19	rs1003502	Yu et al., 2008	rs2268550	Cook-Sather et al., 2014
TCERG1L	rs11017811, rs11017815	Gelernter et al., 2014	rs1176493	Cook-Sather et al., 2014
TMEM132D	rs1000118, rs2218917, rs4759995	Gelernter et al., 2014; Zuo et al., 2012	rs4759808, rs10847807	Cox et al., 2012
TNXB	rs2071293, rs3096695, rs3117181, rs3134954, rs7766862	Heath et al., 2011; Kapoor et al., 2013	rs150223621, rs182129909	Gormley et al., 2016
USP24	rs497159, rs1165238	Biernacka et al., 2013	rs12566055	Cook-Sather et al., 2014

Note. SNPs reported here were limited to the top 20 of each gene