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Invited review

# Genetic studies of alcohol dependence in the context of the addiction cycle

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ABSTRACT

Family, twin and adoption studies demonstrate clearly that alcohol dependence and alcohol use disorders are phenotypically complex and heritable. The heritability of alcohol use disorders is estimated at approximately 50–60% of the total phenotypic variability. Vulnerability to alcohol use disorders can be due to multiple genetic or environmental factors or their interaction which gives rise to extensive and daunting heterogeneity. This heterogeneity makes it a significant challenge in mapping and identifying the specific genes that influence alcohol use disorders. Genetic linkage and (candidate gene) association studies have been used now for decades to map and characterize genomic loci and genes that underlie the genetic vulnerability to alcohol use disorders. These approaches have been moderately successful in identifying several genes that contribute to the complexity of alcohol use disorders. Recently, genome-wide association studies have become one of the major tools for identifying genes for alcohol use disorders by examining correlations between millions of common single-nucleotide polymorphisms with diagnosis status. Genome-wide association studies are just beginning to uncover novel biology; however, the functional significance of results remains a matter of extensive debate and uncertainty. In this review, we present a select group of genome-wide association studies of alcohol dependence, as one example of a way to generate functional hypotheses, within the addiction cycle framework. This analysis may provide novel directions for validating the functional significance of alcohol dependence candidate genes.

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**Contents**



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## 1. Introduction

Alcoholism is a chronic relapsing disorder characterized by a loss of volitional control over consumption, impaired decision-making, pathological preoccupation with alcohol seeking at the expense of healthier forms of behavior and a compulsive drive for harmful drinking in the face of serious life consequences (e.g., deteriorating health, job and family loss). The Diagnostic and Statistical Manual of the American Psychiatric Association, fourth edition (DSM-IV), established criteria for both alcohol dependence (alcoholism) and alcohol abuse. Research studies based on diagnosis compare those who meet or do not meet criteria for alcohol dependence. Alcohol dependence is defined by the presence of three or more of a set of seven criteria. Alcohol abuse is defined by the presence of two out of four criteria in the absence of meeting criteria for dependence. The recent publication of DSM-5 in 2013 combined the two separate diagnoses of alcohol abuse and alcohol dependence from the DSM-IV into a single dimensional diagnosis of alcohol use disorder (AUD) with mild, moderate, and severe sub-classifications. In DSM−5, anyone meeting any two of eleven criteria during a specified period received the diagnosis of AUD where severity is based on the number of criteria met.

The prevalence of AUD (or alcohol dependence in DSM-IV parlance) has increased in the last decade in the general population of United States adults, 18 years of age or older. Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) reported that the DSM-IV 12-month and lifetime prevalence rates in 2001−2002 increased from 8.5% to 30.3%, respectively to 12.7% and 43.6% in 2012 through 2013, respectively (Grant et al., 2015). Despite the increase in AUD over the last decade, many individuals never seek or receive evidence-based treatments. The major reasons are due to fears of stigmatization and the surprisingly still commonly held belief that alcohol dependence is not a medical condition that can be effectively treated with medications or behavioral therapies (Cohen et al., 2007). This situation amounts to a clear treatment exigency that is only exacerbated by the limited number of approved and effective pharmacotherapies that currently exist for alcohol dependence. One promising avenue to ameliorate the treatment gap would be to provide many novel pharmacotherapies that have diverse mechanisms of action that are well-tolerated and effective. This strategy has merit because the arrival of many novel pharmacotherapies for depression over the last 30 years, for example, helped catalyze a transformation in the way depression is perceived and treated. In this regard, the power of high-throughput discovery based methods from disciplines such as genomics can be used to identify many new drug targets (Kingsmore et al., 2008; Sanseau et al., 2012).

Phenotypic variability in AUD is influenced by two major components: (1) environment and (2) genes. AUD are significantly polygenic and are highly heterogeneous making it a great challenge to define a specific universal set of genetic and environmental factors that influence risk across every population affected. Therefore, AUD are not unlike other common complex diseases or disorders such as diabetes, asthma or cancer. The ubiquitous problem of pervasive heterogeneity observed in many common diseases including AUD has ushered in the era of personalized medicine which is hoped to replace the largely unsuccessful one-size fits all approach to treatment. In this regard genomic medicine is particularly relevant to fulfilling the goals of tailoring treatments based on an individual's genomic makeup. This is highly relevant to expanding the range of pharmacotherapies for the significantly unmet medical needs of those affected with a AUD.

Although the DSM, now in its 5th edition, has provided a standardized and reliable way of diagnosing AUD and other substance use disorders, there still remains a great amount of heterogeneity that is uncaptured and the DSM in general has not fully integrated the many advances on the neuroscience and genetics of AUD (Litten et al., 2015). Unfortunately, there is burgeoning evidence that the new AUD construct for DSM-5 has further increased the heterogeneity existing in the DSM. A recent study showed that the DSM-5 specific categories of “moderate” to “severe” AUD corresponds to what was previously captured by “alcohol dependence”; the addition of a “mild” AUD category represents a diagnostic label of unknown clinical relevance (Compton et al., 2013). Therefore, attempts have recently been made to move towards a neuroscience-based framework for addictive disorders with the goal of establishing more biological and genetically relevant domains that one day could be incorporated into a diagnostic framework (Kwako et al., 2016). In particular, a more biologically-based diagnostic framework for AUD will undoubtedly aid discovery of more effective pharmacotherapies by reducing patient heterogeneity, for example. To this end, one of the most useful paradigms for conceptualizing AUD and drug addiction is taken from advances in the understanding of the neurocircuitry of addiction and the impact on the brain reward, stress, and executive function systems. (Koob and Volkow, 2016). As such, addiction has been defined as a three stage cycle containing: (1): binge/intoxication, (2): withdrawal/negative affect and (3): preoccupation/anticipation stages that represent distinct neurocircuitry and functional domains. Initial use of alcohol is driven by positive reinforcement mechanisms that involves patterns of binge-and-intoxication. Alcohol or stimuli associated with alcohol act as a positive reinforcer, to strengthen behavior, which engages the mesolimbic dopamine and opioid reward systems in the central nervous system. In addition, engagement of the dorsal striatum during alcohol addiction is thought to help to solidify habitual behaviors associated with drug seeking and taking. Namely, neuroadaptations in the dorsal striatum involve changes in glutamate, GABA and the endocannabinoid system (Koob and Volkow, 2010). After a period of repeated binge/intoxication neuroadaptations occur leading to a negative emotional state (e.g., anxiety, depression, anhedonia) induced by alcohol withdrawal. Negative reinforcement mechanisms predominately drive behavior where