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Review

The genetics of alcohol dependence: Advancing towards systems-based approaches

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ABSTRACT

Background: Personalized treatment for psychopathologies, in particular alcoholism, is highly dependent upon our ability to identify patterns of genetic and environmental effects that influence a person's risk. Unfortunately, array-based whole genome investigations into heritable factors that explain why one person becomes dependent upon alcohol and another does not, have indicated that alcohol's genetic architecture is highly complex. That said, uncovering and interpreting the missing heritability in alcohol genetics research has become all the more important, especially since the problem may extend to our inability to model the cumulative and combinatorial relationships between common and rare genetic variants. As numerous studies begin to illustrate the dependency of alcohol pharmacotherapies on an individual's genotype, the field is further challenged to identify new ways to transcend agnostic genomewide association approaches. We discuss insights from genetic studies of alcohol related diseases, as well as issues surrounding alcohol's genetic complexity and etiological heterogeneity. Finally, we describe the need for innovative systems-based approaches (Systems Genetics) that can provide additional statistical power that can enhance future gene-finding strategies and help to identify heretofore-unrealized mechanisms that may provide new targets for prevention/treatments efforts. Emerging evidence from early studies suggest that Systems Genetics has the potential to organize our neurological, pharmacological, and genetic understanding of alcohol dependence into a biologically plausible framework that represents how perturbations across evolutionarily robust biological systems determine susceptibility to alcohol dependence.

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1. Introduction

Alcohol dependence (AD) is defined across all versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), and despite changes in criteria, as a disorder characterized by physiological and psychological effects in individuals who consume large amounts of alcohol (American Psychiatric Association, 1968, 1980, 1987, 2000). Individuals "addicted" to alcohol are likely to demonstrate either or all of the following: (1) a strong urge/craving for the drug, (2) an inability to limit the amount of alcohol they consume, and/or (3) a diagnosis of dependence, as defined by the DSM. Despite the many negative implications of alcohol use, AD continues to be a major public health concern in the United States of America. In fact, as of 2010, 131.3 million Americans (~52%) have been reported as current drinkers of alcohol (Substance Abuse and Mental Health Services Administration, 2011).

In our effort to understand the genetic liability to AD, research has focused on characterizing individual differences in the biological systems that regulate the breakdown of alcohol and the neuronal systems/pathways that are believed to be affected by alcohol. Research on the metabolism of alcohol suggests the involvement of several enzymes. The oxidative pathway involves aldehyde dehydrogenase (ALDH), alcohol dehydrogenase (ADH), cytochrome P450 2E1, and catalase. The non-oxidative pathway involves fatty acid ethyl ester and phospholipidase D. Differences in the functionality of the ALDH and ADH enzymes have been linked to, (1) increased risk for alcohol-induced tissue damage (cirrhosis; Chao et al., 1994), and (2) protection against developing AD (Chen et al., 2009). In the context of brain effects, the acute and chronic effects of alcohol exposure are very important, as the cycle of addiction is dependent upon how an individual responds to repeated alcohol use over time. Based on the body of literature across humans and animals, AD is likely to involve neuronal circuits involved in the Binge/Intoxication, Withdrawal/Negative Affect, and Preoccupation/Anticipation stages of the addiction cycle (Koob and Volkow, 2010); see Fig. 1. In fact, neurotransmitter systems, such as dopamine, glutamate, opioid, serotonin, and γ-aminobutyric acid (GABA) systems, as well as stress response circuits (neuropeptide-Y and corticotropin-releasing factor) and appetite regulating systems are key to alcohol's effects (Hillemacher, 2011). For instance, studies demonstrate that opioid antagonists suppress alcohol drinking (Rosner et al., 2010) and that gamma-aminobutyric acid A receptors ($GABA_A$) mediate the rewarding effects of alcohol (Koob, 2004) and alcohol consumption (Rewal et al., 2012; Tabakoff et al., 2009). Given the role of each of these metabolic and neuronal pathways in alcohol use and addiction, they are regarded as candidate pathways for genetic studies of alcohol. It is believed that individual differences in the genetic code of these and other candidate molecules will provide insight into the risk for AD. Unfortunately, the extant body of animal and human research on alcohol has also demonstrated that alcohol, as a drug, is not specific in its effects, but rather casts a wide net in the human brain. Consequently, susceptibility to AD likely involves a network of genes across several biological systems. This has complicated the elucidation of the genetic mechanisms that drive compulsive drinking, AD, and specific AD characteristics. In the proceeding pages, we highlight the positive and negative findings from molecular genetic studies of AD and the need for analytical and interpretational approaches in the form of Systems Genetics. Systems Genetics has the potential to organize our neurological, pharmacological, and genetic understanding of AD into a biologically plausible framework that represents how perturbations across evolutionarily robust biological systems determine susceptibility to AD.

2. The genetic epidemiology of AD

2.1. Genetic studies of AD

Human genetic studies of alcohol are organized into two broad categories, quantitative genetic (i.e., family and twin studies) and molecular genetic studies. Quantitative genetic studies suggest that genetic differences play an important part in susceptibility to AD. Much of this evidence has been derived from early family-based studies which indicated that first-degree relatives of alcohol dependent cases were several times more likely to be later diagnosed with AD relative to first-degree relatives of control subjects (Bierut et al., 1998). Further, twin and adoption studies suggest that this familial pattern may be attributable to additive genetic factors, which account for roughly 40–60% of the liability for AD (Agrawal and Lynskey, 2008; Knopik et al., 2004). Twin studies also suggest that a large number of genes related to AD also influence other forms of drug dependence (Palmer et al., 2012), as well as other externalizing psychopathologies (Iacono et al., 2008; Young et al., 2000).

As the genotyping technology improved, candidate gene and genomewide association methods were developed as a means to identify genetic variants that confer increased risk for AD. However, due to the etiological complexity of complex traits like AD, newer DNA sequencing methods, in particular, next generation sequencing (NGS) have become increasingly necessary as they provide a more accurate description of both common and rare variants (i.e., be they single nucleotide polymorphisms (SNPs) or structural variants). Both linkage and association studies are heavily focused on genetic variation that can be captured by genomic platforms designed to identify rare and/or common variation within a specific gene or across the entire genome, usually by relying upon linkage disequilibrium (LD). However, both methods have significant differences that affect their interpretation. Linkage studies are often regarded as being more powerful than association