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Genetics of Alcohol Use Disorder: A Review

Joseph D. Deak, **Alex P. Miller**, and **Ian R. Gizer**

Department of Psychological Sciences, University of Missouri, 210 McAlester Hall, Columbia, MO 65211

Abstract

Alcohol use disorder (AUD) represents a significant and ongoing public health concern with 12-month prevalence estimates of ~5.6%. Quantitative genetic studies suggest a heritability of approximately 50% for AUD, and as a result, significant efforts have been made to identify specific variation within the genome related to the etiology of AUD. Given the limited number of replicable findings that have emerged from genome-wide linkage and candidate gene association studies, more recent efforts have focused on the use of genome-wide association studies (GWAS). These studies have demonstrated that hundreds of variants across the genome, most of small effect ($R^2 < 0.002$), contribute to the genetic etiology of AUD. The present review describes the initial, though limited, successes of GWAS to identify loci related to risk for AUD as well as other etiologically relevant traits (e.g., alcohol consumption). In addition, "Post-GWAS" approaches that rely on GWAS data to estimate the heritability and co-heritability of traits, test causal relations between traits, and aid in gene discovery are described. Together, the described research findings illustrate the importance of molecular genetic research on AUD as we seek to better understand the mechanisms through which genetic variation leads to increased risk for AUD.

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5; [1)]) defines alcohol use disorder (AUD) as a single spectrum of problematic use and clinically significant impairment based on endorsement of 2 or more of 11 criteria assessing behavioral and physical manifestations of heavy alcohol use[1]. Recent estimates indicate that 5.6% of individuals meet criteria for a past year AUD [2], resulting in significant social, economic and public health costs [3,4]. In addition to the importance of environmental influences [5,6], quantitative genetic studies examining the impact of familial transmission of liability for AUD have consistently demonstrated a substantial genetic component to the disorder

Corresponding Author: Ian R. Gizer, 210 McAlester Hall, Columbia, MO 65211, (573), 882-5427, gizeri@missouri.edu.

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[1]Due to space constraints the present review will use the term AUD to refer to both DSM-5 defined alcohol use disorder and DSM-IV defined alcohol dependence. The latter required the presence of 3+ symptoms out of 7 to meet diagnostic threshold.

([7]; see Figure 1) with a recent meta-analysis reporting a heritability of approximately 50% [8].

EARLY MOLECULAR GENETICS STUDIES

Given such findings, molecular genetics studies have attempted to identify specific variation within the genome related to increased risk for AUD. Early work in the field focused on genome-wide linkage and candidate gene association studies. The former relies on family-based samples to identify regions of the genome that co-segregate with the disorder of interest. For example, the Collaborative Study of the Genetics of Alcoholism (COGA) relied on a large sample of families enriched for alcohol dependence to identify regions of chromosome 4 containing the alcohol dehydrogenase (ADH) gene which encodes the ADH isozymes that metabolize alcohol into acetaldehyde and a cluster of GABA receptor genes [9–11], respectively.

Linkage studies are limited in terms of their spatial resolution, and thus, association studies that measure differences in allele frequencies between ‘case’ and ‘control’ populations were also pursued. Early association studies focused on a limited number of variants in or near genes selected *a priori* for their biological relevance to the trait of interest or physical location in the genome informed by prior linkage results. Though findings of associations between AUD and variants in or near alcohol metabolizing genes (e.g., *ADH1B* and *ALDH2*; [12,13]) have been some of the most commonly demonstrated effects [14], overall the linkage and candidate gene literatures are characterized by inconsistencies in replication [15], including those reported for the chromosome 4 GABA gene cluster [16], and the μ opioid receptor gene (*OPRM1*; [17,18]). These inconsistent findings have tempered expectations and investment in both linkage and candidate gene studies.

Notably, many of these same limitations can be applied to candidate gene studies of gene x environment interactions attempting to model the moderating effects of environmental variables on the relations between candidate gene variants and AUD risk [19]. Further, these studies may introduce additional challenges associated with accurate measurement of the environment and a lack of protections against Type I error when multiple tests are conducted in the pursuit of indirect replications (e.g., nearby variants or similar environments; [20]).

CURRENT STATE OF THE AUD GWAS LITERATURE

Recent advances in genotyping microarray technologies have allowed for genome-wide coverage at reduced cost, thus resulting in a shift from linkage and candidate gene studies to a greater focus on genome-wide association studies (GWAS) to investigate the genetic risk for AUD. Using current methods, these studies individually test for an association between a phenotype of interest and ~7,000,000 variants across the genome. Despite their promise, many GWA studies conducted thus far have resulted in inconsistent findings, partially attributable to the complex genetic architecture of AUD. More specifically, traits with complex inheritance patterns, such as AUD, tend to demonstrate high levels of polygenicity in which hundreds of variants across the genome, each exhibiting a small effect size ($R^2 < 0.005$), contribute to the genetic etiology of that trait [21]. The ready detection of these

variants is further complicated by challenges with achieving genome-wide significance thresholds (p=5.0×10^{-8}) that account for the testing of multiple genetic variants across the genome. As a result, many published GWAS of AUD have lacked adequate power to robustly detect associations at the genome-wide level [22–25].

To address these challenges, current efforts have focused on assembling larger sample sizes via consortia-led meta-analyses of GWAS datasets to increase power. While genome-wide significant loci for the AUD diagnosis have been limited to variants in the *ADH1B* and *ADH1C* genes (e.g., [14,26]), other etiologically relevant traits have proven more successful [24,25]. For example, the largest published GWAS of alcohol consumption to date (UK Biobank, N=112,117; [27]), reported significant associations with 14 loci. Results included a replication with variants in the *ADH1B* and *ADH1C* genes (rs145452708; p=1.15×10^{-30}), as well as novel variants in the *GCKR* (rs1260326; p=1.34×10^{-21}), *KLB* (rs11940694; p=8.14×10^{-19}), and *CADM2* (rs9841829; p=3.36×10^{-10}) genes. Notably, these findings replicated those from two previous GWAS of alcohol consumption [28], one of which included a large trans-ancestral sample [29], demonstrating the influence of these susceptibility loci across multiple populations. These results illustrate the power that increased sample sizes can have on detecting and replicating genetic variants involved in AUD etiology. Notably, these studies only represent those that have been published thus far, with ongoing efforts from groups such as the Psychiatric Genomics Consortium Substance Use Disorder (PGC-SUD) Working Group [30] soon to be published as well.

Despite these advances, the molecular genetic investigation of the AUD diagnosis faces multiple challenges moving forward. Perhaps the largest challenge is the way in which the AUD diagnosis is operationalized. The DSM-5 [1] currently requires the endorsement of any 2 of 11 criteria to reach the diagnostic threshold for AUD at the mild severity level. This necessarily introduces high levels of heterogeneity into the AUD phenotype, even at the moderate level (4+ symptoms), and given that the genetic influences underlying AUD may not be shared equally across all symptoms [31], likely reduces the statistical power of GWAS focusing on the AUD diagnosis.

One potential approach for addressing heterogeneity in the AUD diagnosis is examining endophenotypes that focus on specific facets of AUD. Broadly speaking, endophenotypes can be thought of as any measurable component between genotype and the disorder of interest. For example, one well-established AUD endophenotype is level of response (LR) to alcohol, defined as the extent to which a specific blood alcohol level produces responses typically associated with alcohol intake (e.g.,[32]). LR is genetically influenced, and a low LR is a significant predictor of AUD risk [33–35]. Currently, studies focusing on endophenotypes have been limited to smaller samples (e.g., [36,37]), and thus, replicable findings are limited. As sample sizes increase, endophenotypes will likely play a larger role in gene discovery and will certainly be important for understanding the mechanisms through which genetic variation leads to increased risk for AUD.

POST-GWAS APPROACHES

In addition to gene discovery, recent molecular genetics research has focused on modeling the aggregate effects of variants across the genome and leveraging other types of ‘omics’

data to further our understanding of the genetic architecture underlying AUD. Often referred to as “Post-GWAS” approaches, these methods have been used to demonstrate the highly polygenic nature of alcohol-related traits, estimate the heritability and co-heritability of traits, test causal relations between traits, and aid in gene discovery [25,38].

Recent methodological advances have made possible the estimation of single nucleotide polymorphism (SNP) -based heritability (h^2_{SNP}) and genetic correlations between traits using genotype-level data or GWAS summary statistics. These approaches provide an estimate of the additive genetic variance that can be explained by common SNPs (i.e., those with a minor allele frequency >0.01) rather than the broad-sense heritability estimates typically reported in twin studies, which can include other types of genetic effects (e.g., rare variation, epistasis; [39]). Thus, h^2_{SNP} estimates provide an indication of the upper limit of GWAS as an approach for identifying genetic variation contributing to the etiology of a trait, and are typically smaller than heritability estimates obtained from twin studies. To illustrate, Genome-wide Complex Trait Analysis (GCTA;[40]) uses individual-level genotype data to estimate the genetic similarity of each participant-pair within a sample to create a genomic similarity matrix. This matrix is then used to partition variation in a trait into an h^2_{SNP} component and a residual. One of the first such studies conducted on alcohol-related traits reported an h^2_{SNP} estimate of 16% for AUD [41]. More recently, larger GWAS examining Alcohol Use Disorder Identification Test (AUDIT) scores [42] and alcohol consumption [27] have found h^2_{SNP} estimates of 12% and 13%, respectively. An alternative method, linkage disequilibrium (LD) score regression [43], requires only GWAS summary statistics to estimate h^2_{SNP} as well as the genetic correlation between traits of interest. For example, a recent study demonstrated a positive genetic correlation (rG= 0.40) between alcohol consumption and smoking status [27]. Notably, another study showed that AUDIT scores showed a positive genetic correlation with both alcohol consumption (rG=0.68) and AUD status (rG=0.68), suggesting strong genetic overlap between these phenotypes [42]. This is of particular importance given that combined GWAS of these alcohol measures are currently underway using recently developed meta-analytic methods that capitalize on correlated traits to further increase statistical power (e.g., [44,45]).

Another commonly used method of modeling GWAS data that has shown promise in understanding the genetic architecture of complex traits is the creation of polygenic risk scores (PRSs). Briefly, PRSs are generated by selecting variants in a discovery sample that meet a predetermined significance threshold for association with a trait of interest (e.g., alcohol response). Using an independent sample, PRSs are then calculated by combining genotype data across the selected variants in an additive fashion to create an aggregate measure of genetic risk that can then be tested for a relation to the same or a second etiologically-relevant trait. Within the substance use literature, this approach has been most widely applied to tobacco use with PRS based on smoking quantity shown to predict nicotine dependence (e.g., [46]), as well as alcohol and other substance use disorders more broadly (e.g., [47]). Additionally, PRSs for variants associated with alcohol use have been found to predict AUD status (14) as well as alcohol-related problems [48,49]. Notably, the utility of the PRS approach for studying the etiology of AUD will continue to grow as GWAS sample sizes, and thus the predictive power of their PRSs, increase.

In addition to the described advances studying genetic variation in aggregate, there has also been rapid development in methods leveraging other types of 'omics' data (e.g., epigenomics, transcriptomics) in hopes of promoting gene discovery and aiding interpretation of GWAS findings [24]. As an example of the latter, it has become routine for researchers to explore whether an associated variant also shows a relation with gene expression by querying databases such as GTEx [50]. For example, in the GWAS of alcohol consumption described above, the authors found that the most highly associated variant in *CADM2* (rs9841829) was correlated with the expression of this gene in both lung and adipose tissue, supporting a regulatory role for this variant. Similar databases cataloguing other types of 'omics' data can also be queried (e.g., DNA methylation, epigenetic signatures) to aid in the interpretation of significant associations.

There have also been efforts to combine different types of 'omics' data into a single analysis to aid in gene identification, though few such efforts have been published in the alcohol literature. As an example, PrediXcan models data from GTEx and similar gene expression databases to impute tissue-specific gene-expression based on an individual's genotype data and uses these imputed gene-expression values to test for associations at the gene level [51]. Using this approach, a recent study demonstrated a positive association between hippocampal expression of *CDK3* and delayed discounting, a devaluation of future reward often found to be associated with substance use [52]. As another example, a recent study conducted a combined analysis of methylome-wide association and GWA data in a single sample to identify an association between variants in an intronic region of *CNTN4* and alcohol use [53]. Though the reported associations require replication, these studies provide important illustrations of the progression of molecular genetic investigations of alcohol-related traits.

CONCLUSIONS

Moving forward, continued efforts to integrate large GWAS datasets examining alcohol use remain critical to the detection and replication of genome-wide significant associations. These findings will further our understanding of the genetic etiology of AUD, and will also promote the advancement of "Post-GWAS" approaches seeking to better understand the mechanisms through which genetic variation leads to increased AUD risk. It is hoped that such information will ultimately lead to improved prevention and treatment efforts.

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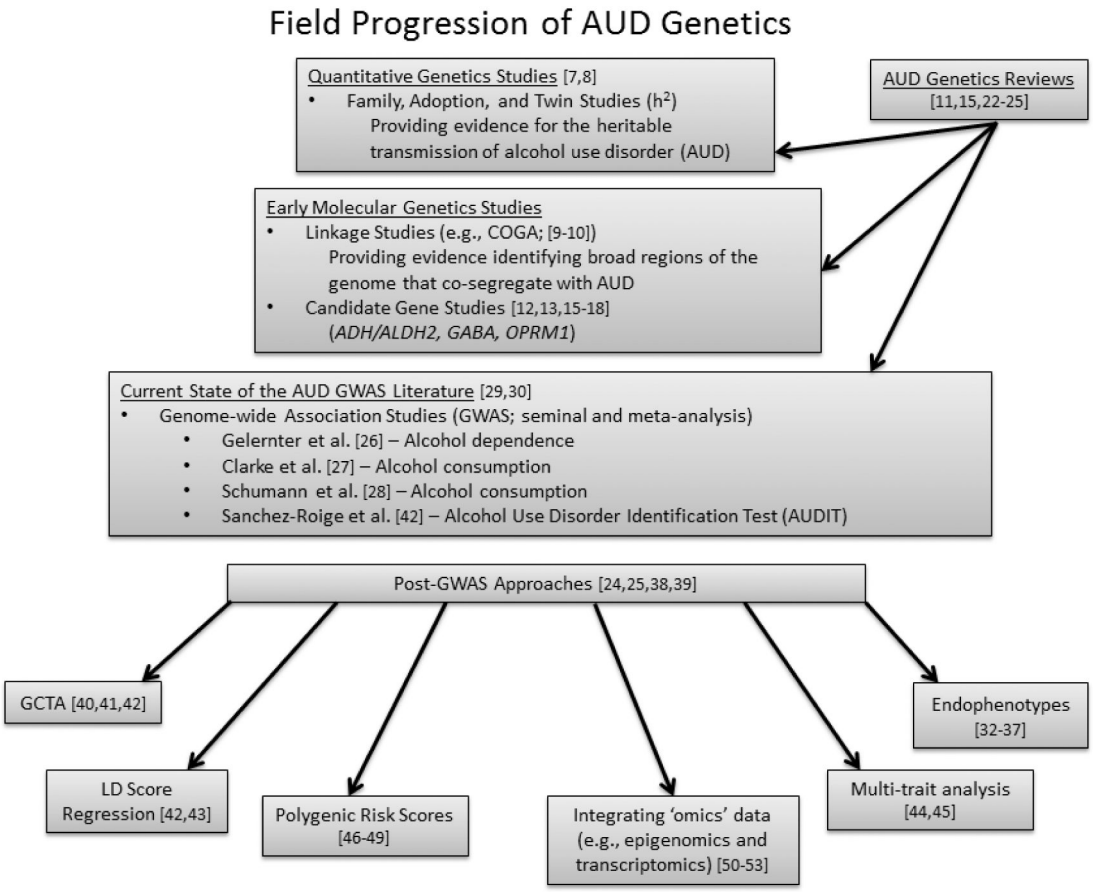

Figure1.

Review of AUD genetics literature.Values correspond with in-text references.