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Genetics of alcohol use disorder: a review

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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 suggested 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.

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

Early molecular genetics studies

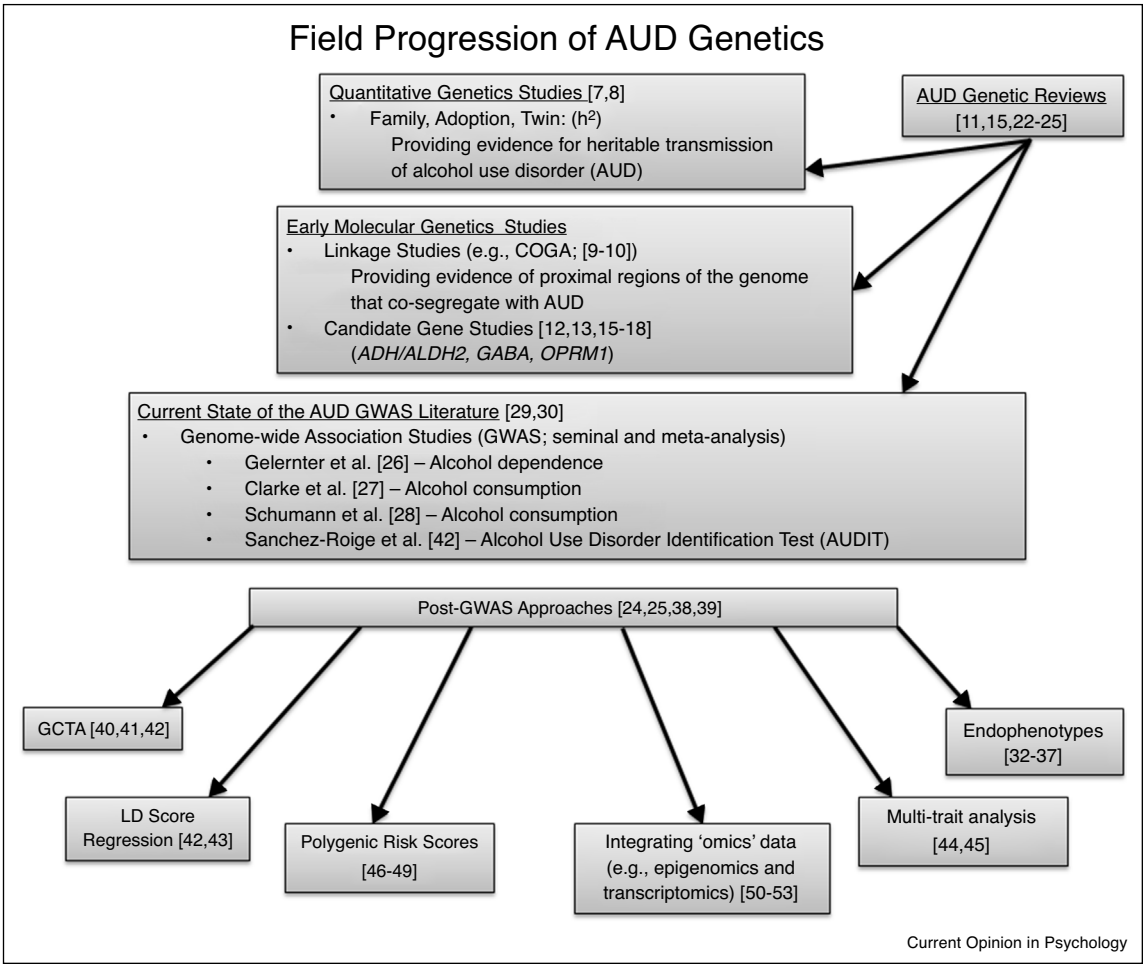
Given such findings, molecular genetics studies have attempted to identify specific variation within the genome related to increased risk for AUD. Early work in the field focused on genome-wide linkage and candidate gene association studies. The former relies on family-based samples to identify regions 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 [9,10,11••], 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 × environment interactions attempting to model the moderating effects of environmental variables on the relations between candidate gene variants and AUD risk [19]. Further, these

[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.

Figure 1



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

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 ($p = 5.0 \times 10^{-8}$) 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••,23••,24••,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