Genetics of Alcoholism

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Abstract

Purpose of review: We review the search for genetic variants that affect the risk for alcohol dependence and alcohol consumption.

Recent findings: Variations in genes affecting alcohol metabolism *(ADH1B, ALDH2)* are protective against both alcohol dependence and excessive consumption, but different variants are found in different populations. There are different patterns of risk variants for alcohol dependence *vs*. consumption. Variants for alcohol dependence, but not consumption, are associated with risk for other psychiatric illnesses.

Summary: *ADH1B* and *ALDH2* strongly affect both consumption and dependence. Variations in many other genes affect both consumption and dependence – or one or the other of these traits -- but individual effect sizes are small. Evidence for other specific genes that affect dependence is not yet strong. Most current knowledge derives from studies of European-ancestry populations, and large studies of carefully phenotyped subjects from different populations are needed to understand the genetic contributions to alcohol consumption and alcohol use disorders.

Introduction

Excessive alcohol consumption and alcohol use disorders (AUDs) take enormous tolls on individuals and societies. WHO estimates that 3 million deaths each year (5.3% of all deaths) are attributable to harmful use of alcohol, along with 5.1% of the global burden of disease[1]. About 50% of the liability for AUDs is heritable[2], but – as is typical for complex genetic traits – the genetic risk is spread among a large number of variants in many genes, with most variants having very small effects (genetic risk ratios < 1.05). Despite AUDs being associated with two of the strongest single-locus genetic effects observed in psychiatry – of functional variants in the alcohol dehydrogenase (*ADH1B*) and aldehyde dehydrogenase 2 (*ALDH2*) genes – the identification of additional loci of smaller effect has been difficult. Key functional variants in *ADH1B* increase the rate at which ethanol is metabolized into acetaldehyde (which has aversive effects), and a functional variant in *ALDH2* essentially blocks its ability to remove acetaldehyde, leading to a strong aversive reaction[3]. These variants reduce excessive drinking by causing aversive reactions, and thereby reduce the risk for AUDs. Disulfiram inhibits ALDH2 and thereby causes an aversive reaction that strongly reduces drinking[3].

The difficulty in identifying other loci of smaller effect is in part due to heterogeneity of the disorder. A diagnosis of AUD, under the current DSM-5 system[4], is obtained when an individual endorses 2 or more of 11 possible criteria that encompass not just aspects of excessive drinking (e.g., tolerance, drinking larger amounts or for longer than expected) but also loss of control over drinking (e.g., giving up important activities to drink) and drinking despite serious physical and emotional consequences. There are many different combinations of symptoms of varying nature and severity that can result in an AUD diagnosis, which might be due to different constellations of genetic effects and thereby contribute to the difficulty in gene discovery. Additionally, we expect most risk variants relevant for alcohol use behaviors to have small to very small effect sizes. Population heterogeneity is also a factor: different populations may have different risk variants or even different risk genes. These three factors (among others) affect most complex genetic traits, raising the difficulty of gene identification. To overcome these fundamental challenges and elucidate the genetic contributions to risk, large sample sizes will be necessary. But obtaining large samples in which AUDs have been carefully assessed has proven difficult. It is far easier to obtain large samples with data on alcohol consumption, but that does not address key issues relevant to dependence. Most individuals who drink do not become dependent; in the US, about 12% of those who drink alcohol meet criteria for alcohol

dependence at some point in their lives[5]. These non-dependent drinkers contribute the bulk of the data for population-based samples where AUD per se is not assessed.

Although there have been many candidate gene studies directed at AUDs, most have been equivocal. The most robust associations were the effects of functional variants in alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) genes that affect alcohol metabolism[3, 6-13] (Figure 1). These findings are among the very few that have survived from the candidate gene era to today's era of genome-wide studies. Variants in *ADH1B* and *ADH1C* that increase the rate of oxidation of ethanol to acetaldehyde, and variants in *ALDH2* that decrease the rate of acetaldehyde oxidation to acetate, exert strong protective effects[3] (Figure 1). The frequencies of these variants, and therefore the effects they exert on risk, differ greatly among populations, with the *ALDH2* variant (rs671) common in East Asia but rare outside Asia[3]. Similarly, one functional variant in *ADH1B* (rs1229984) is common in East Asia (>70%), less common in populations from the Middle East (~20%), even less common in Europe (<4%) and rare or even absent in Africa[3]. A different functional variant in *ADH1B* (rs2066702) is relatively common in many populations from Africa (up to 28%) but rare elsewhere[3]. These variants exert a degree of protection via enzymatic regulation of rapid conversion of alcohol to acetaldehyde (ADH) or reduced clearance of acetaldehyde to acetate (ALDH), with accumulating acetaldehyde resulting in aversive sensations upon alcohol intake.

Recent studies

Variants mapped to *ADH* and *ALDH* genes exert strong effects, but much of the variation in risk for AUDs and also alcohol consumption lies elsewhere in the genome. Genomewide association studies (GWAS) have sought to identify those variants. Some have focused on alcohol consumption (e.g., drinks/week), which is a measure relatively easy to obtain. Because of the wide recognition of the medical consequences of alcohol use, such measures are available even in many studies unrelated to addictions. There are difficulties with drinks/week as a phenotype, however: it may be asked of a recent period (week, month), a typical period during the past year, or the period of maximum consumption during the lifetime. These may differ quite a bit, and short-term or unrepresentative periods may miss information more closely related to problem drinking episodes, or even represent them inaccurately (e.g., reductions in recent drinking due to treatment). For genetic studies, we really want information about trait, rather than state. Lifetime dependence diagnoses are trait measures; current alcohol consumption is a state measure. The disparity between typical and problematic consumption is further widened in

most population-representative samples, in which most of the individuals are at the low end of the intake spectrum; thus genetic discoveries might relate more closely to determinants of low levels of drinking.

Nonetheless, GWAS of alcohol consumption have been successful at identifying loci. Two large meta-analyses identified variants in *AUTS2*[14] and *KLB*[15]. The largest published GWAS of alcohol consumption was conducted with data on 112,117 participants from the UK Biobank[16]; it identified 14 loci, including variants in *ADH1B/ADH1C/ADH5* (likely due to the functional variant in *ADH1B*[3]), *KLB, GCKR, CADM2, FAM69C, STPG2* and *DNAJB14*; gene-based analyses also implicated *DRD2* and *PDE4B*. [Larger ones are expected soon.] Using a slightly expanded set of items, another GWAS of the consumption subscale of the Alcohol Use Disorders Identification Test[17] (AUDIT-C, questions 1-3, quantity and frequency of drinking) found additional novel variants in *CPS1* and *RFC1*[13].

A recent large GWAS[13] and meta-analysis of total AUDIT scores in subjects from the UK Biobank and 23andme also showed significant SNPs in the *ADH1B* region, replicated *KLB* and *GCKR*, and revealed novel loci including *JCAD, CRHR1* and *SLC39A13*. Working with the UK Biobank data, the authors suggest that total AUDIT score – which goes beyond consumption and includes measures of medical harm as well (see below) -- can be used as a proxy for dependence, with the best balance of higher numbers and reasonable specificity when controls are defined as AUDIT ≤ 4 and cases as AUDIT ≥ 12. This study is among the first to delineate the genetic distinctions between consumption and problem drinking in a large population cohort. There were important differences between the AUDIT-C and the AUDIT-P (questions 4-10, which asks about problems arising from excessive drinking, such as guilt or remorse after drinking, inability to stop drinking, failure to do what was expected due to drinking, and memory loss/blackouts and injuries during drinking). Some loci were common to both, including SNPs in the *ADH* region that conditional analyses indicated were driven by *ADH1B* (rs1229984), but some loci were specific to only one sub-scale. AUDIT-C showed stronger genetic correlation with alcohol consumption (r_g = 0.92, *vs*. 0.76 for AUDIT-P)[13]. The genetic correlation between AUDIT-P and alcohol dependence (r_g = 0.63) was far greater than the correlation with either total AUDIT (r_g = 0.39) or AUDIT-C (r_g = 0.33). Notably, AUDIT-P showed significant positive genomewide genetic correlations with several psychiatric disorders, including higher risk for depression, and with higher neuroticism, lower educational achievement and lower subjective well-being. On the other hand, higher genetic liability to the AUDIT-C was related to lower genetic risk for depression and to higher educational achievement[13].

In an interesting twist on the usual approach, a study from the VA Million Veteran Program used the firmly established association of *ADH1B* (rs1229984 in European Americans, rs2066702 in African Americans[12]) to examine how AUDIT-C and ICD codes perform as phenotypes for harmful alcohol use[18]. They determined that in the veteran population, high (≥8) age-adjusted AUDIT-C score correlated better than ICD diagnostic codes with the *ADH1B* variants.

Alcohol dependence is a more severe form of AUD (i.e., 3 or more of 7 criteria in DSM-IV), that affects about 10-12% of drinkers. It is a serious psychiatric disorder that is ascertained by much more detailed interviews than the AUDIT (e.g. SSAGA[19], SSADDA[20]). Since detailed ascertainment requires more effort and is therefore more costly, it is used less frequently than simple state measures of quantity and frequency of use, such as the AUDIT-C. There have been several GWAS of alcohol dependence as well as of criterion counts (**Table 1**). Many have been relatively small (especially when compared to large biobank studies), and findings have been mixed, with limited replication. Notably, several of the first GWAS failed to identify rs1229984 in *ADH1B*, despite its well-documented role. This gap was likely due to both technical challenges (rs1229984 was not on most GWAS arrays and is poorly imputed on some of them) and its relatively low allele frequency in the predominantly European populations that were being investigated[3]. It is common in many Asian populations, and studies there have consistently shown its impact[3]. A targeted genotyping study[7] and a later GWAS and meta-analysis demonstrated the effect of rs1229984 on alcohol dependence[8].

The most recent and largest GWAS of alcohol dependence was led by the Psychiatric Genomics Consortium; it included 14,904 cases and 37,944 alcohol-exposed controls[12]. This study again unequivocally implicated *ADH1B* in the etiology of alcohol dependence, both in Europeans (rs1229984; $p = 9.8 \times 10^{-13}$) and African-Americans (rs2066702; $p = 2.2 \times 10^{-9}$). An important finding was a confirmation that different variants in *ADH1B*, both of which result in amino acid substitutions that have similar effects on alcohol metabolism, were found in the two populations, as a result of large differences in their frequencies and LD patterns. Despite the limited discovery of novel loci, this recent GWAS provided four notable insights. First, it identified genetic correlations between alcohol dependence and a range of psychiatric disorders (e.g., schizophrenia, depression), substance use (e.g., tobacco and cannabis smoking), sociodemographic factors (e.g., education attainment, neighborhood deprivation) and behavioral features (e.g., neuroticism, well-being, age at the birth of one's first child). Second, despite the substantially smaller sample size of the African-American subset of the data, polygenic risk scores derived from this subset were superior predictors (1.7%; $p = 1.9 \times 10^{-7}$) of alcohol

dependence in an independent African-American sample than were risk scores from the much larger European discovery GWAS (0.37%; p = 0.01), confirming the substantial ancestral specificity that was implied by the discovery of different lead SNPs in African-Americans *vs*. Europeans. Third, the genetic correlation with alcohol consumption was modest and variable (0.37 to 0.70). This is, again, a demonstration that there are many genes that affect dependence above and beyond those affecting consumption in the general population. Fourth, despite twin studies suggesting a heritability of 50%, common SNPs explained only 9% of the variance in alcohol dependence. This low SNP-h^2 is consistent with every other psychiatric disorder that has been studied to date, and is expected to increase with increasing sample size and better genomic coverage.

Even though the protective effect of functional loci in *ADH1B* on risk for AUDs is unequivocal, by itself it does not determine risk. The protective effect of the minor allele of rs1229984 on the transition to first intoxication and first DSM-5 symptom is dampened in the presence of drinking peers[21], and childhood trauma moderates the effects of this variant[22].

A Genetic View of Comorbidity with Depression

The co-occurrence of AUD and depression is significant, with a nearly doubling of the risk of either disorder in those with the other[23]. From a clinical viewpoint, the etiology of the elevated co-occurrence of AUD and depression is of considerable importance as treatment for such a dual diagnosis is particularly challenging[24]. AUD can occur secondary to a diagnosis of depression[25], and AUD can result in depression[26]; that is, there are cases where one of these disorders seems to cause the other one. But some of this co-occurrence appears to reflect common genetic liabilities[27, 28]. In the PGC study of alcohol dependence, the SNP based genetic correlation with major depressive disorder (SNP-r_g = 0.56), depressive symptoms (SNP-r_g = 0.60) and neuroticism (SNP-r_g = 0.44) were strong and could indicate shared pathways or networks[12]. One study used alcohol dependence and depression criterion counts to identify a genomewide significant variant in semaforin 3A (*SEM3A*) in African-Americans[29]. Even after accounting for individuals with comorbid AUD, polygenic risk scores (PRS, sometimes called a genetic risk score (GRS), represent the weighted additive effect of multiple independent loci) derived from a large GWAS of major depression predicted up to 2% of the variance in alcohol dependence even after accounting for pleiotropic effects[30]. A collaboration between the

Psychiatric Genomics Consortium's Substance Use Disorders and Major Depressive Disorders working groups recently examined whether high polygenic risk for AUD might be associated with risk for depression, or vice versa, and found that genetic risk for depression exerted a putatively causal effect on liability for alcohol dependence, but not consistently so on quantity or frequency measures of alcohol intake[31]. While this study provides genetically-informed evidence for a causal role of depression in the etiology of pathological drinking, it did not exclude the reverse pathway from alcohol dependence to depression due to differences in sample size across the two studies. These studies pave the way for larger, analyses that might lead to better delineation of the genetic contributions to this comorbidity. But we should not expect a definitive answer with respect to presence of one direction of causation and not the other; that simply is not consistent with clinical observation.

Looking ahead

AUD is a polygenic trait with effect sizes that are closer to the smaller effects observed for major depressive disorder (MDD) than for schizophrenia (SCZ), both also heritable and complex psychiatric disorders.[12] Thus, our expectation is that unlike SCZ where ~37,000 cases resulted in the identification of 108 loci[32], results for AUD will follow the discovery pathway for MDD, where ~136,000 cases were required to identify 44 loci[33]. What does this mean for ongoing gene-identification efforts? To reach the large numbers needed, many studies with different levels of phenotyping, from structured diagnostic interview instruments (e.g., SSAGA, SSADDA), ICD codes derived from electronic health records, and brief screening tools (e.g., AUDIT, CAGE[34]) will need to be combined. This will result in substantial heterogeneity, and the likelihood of some undetected cases among those assigned as controls due to low specificity. Taking the results from such large studies back to carefully phenotyped samples will be necessary to understand the findings better. More studies of ethnically diverse cohorts are needed to better cover the range of variations relevant beyond Europeans; different groups are known to have different variants and allele frequencies, as well as different environments in which they act[3, 12, 35].

Another important observation is that only 9% of the heritability of alcohol dependence was explained by available genome-wide SNPs, despite twin studies indicating that this estimate should be closer to 50%. This observation holds for alcohol consumption and also for nearly all other complex psychiatric phenotypes. One reason for this discrepancy is that twin studies rely on assumptions that may inflate heritability estimates (e.g., random mating). Alternatively,

because genome-wide arrays mostly capture common variants, any heritable variation that is attributable to rarer variants or to structural variants (e.g., copy number variants) is likely to be missed in SNP-based heritability calculations. Additionally, standard GWAS analyses do not take interacting loci into account. A recent paper suggests that as our ability to infer such unmeasured variation improves, more of the heritability of complex traits will be captured[36].

The impact of individual genes (other than *ADH1B* and *ALDH2*[3]) is individually very small but cumulatively large. Aggregating the weighted effect of tens of thousands or millions of variants into a PRS can provide a partial index of vulnerability (or resilience). Even such large aggregates of genetic effects have modest predictive power, but they do enable examination of how genetics and environment can interact, and potentially how one can better match prevention and treatment options to an individual. It must, however, be kept in mind that genes do not themselves determine whether someone will become alcoholic. Individuals at high polygenic risk may elect not to consume alcohol and those at low polygenic risk may experience serious life events or other environmental influences that propel them towards AUD. Even in this exciting new era of gene discovery, it is critical to highlight that genetic risk is only a piece of the complex architecture of risk and protective factors that underlie AUD. Some of these may be amenable to treatment interventions. It is reasonable to expect that better knowledge of the genetic risk and protective factors involved may bring such treatment closer to clinical reality.

Table 1: GWAS studies of alcohol use disorders to date. DSM-IV AD = DSM-IV alcohol dependence; DSM-IV AA – DSM-IV alcohol abuse; AUDIT score = total AUDIT score; AUDIT-C = score on AUDIT questions 1-3 (consumption); AUDIT-P = score on AUDIT questions 4-10 (problems); *=not significant at the standard level of 5×10^{-8}.

Author (year)	Ncase/Ncontrol			Definition of AUD	Significant variants	Gene
	European	African-American	Other			
Treutlein[37] (2009)	1460/2332	-	-	DSM-IV AD	rs7590720, rs1344694	*PECR*
Bierut[38] (2010)	1235/1433	662/499	-	DSM-IV AD	-	-
Edenberg[39] (2010)	847/552	345/140	-	DSM-IV AD	-	-
Wang[40] (2013)	2322 subjects from 118 families	-	-	DSM-IV AD criterion count	-	-
Heath[41] (2011)	8209	-	-	DSM-IV AD and DSM-IV AA criteria factor score	-	-
Kendler[42] (2011)	2357	812	-	Alcohol dependence factor score	-	-
Frank[43] (2012)	1333/2168	-	-	DSM-IV AD	rs1789891	*ADH1C*
Zuo[44] (2012)	1409/1518	681/508	-	DSM-IV AD	-	-
McGue[45] (2013)	7188	-	-	DSM symptoms and non-diagnostic problems factor score		
Park[10] (2013)	-	-	Korean (621/750)	DSM-IV AD	rs1442492* rs10516441* rs671*	*ADH7* *ALDH2*
Gelernter[8] (2014)	5131	4629	-	DSM-IV AD criterion count	rs1229984 rs2066702 rs10031423 rs116203444	*ADH1B,* *PDLIM5* *LOC100507053*

					rs28470942 rs925966 rs1493464 rs1856202 rs113683471	
Quillen[46] (2014)	-	-	Chinese (122/473)	DSM-IV AD	rs3782886 rs671	*ALDH2*
Kapoor[47] (2014)	1788 from 118 families	-	-	Age at onset of AD	rs2168784 rs35951/rs35952 rs57083693	Intergenic *ARL15* *UTP20*
Mbarek[48] (2015)	1,374/6,468		-	AUDIT ≥9 (men); ≥6 (women)	-	-
Adkins[49] (2017)	706/1,748	-	-	DSM-IV AD	rs2256485 rs150268941	*COL6A3*
Sanchez-Roige[50] (2017)	20,328	-	-	AUDIT score	-	-
Almli[51] (2017)		1036		AUDIT score	rs1433375	*SCLT1*
Sanchez-Roige[13] (2018)	141,923	-	-	AUDIT score, AUDIT-C & AUDIT-P	rs4953148 rs1260326 rs1920650 rs11940694 rs146788033 rs11733695 rs3114045 rs188514326 rs13135092 rs35040843 rs7078436 rs2293576 rs62062288 rs492602	*LINC01833* *GCKR/SNX17* (many) *KLB* *METAP1* *RP11-696N14.1* *ADH1C* *RP11-588P8.1* *SLC39A8, RN7SL728P* *RP11-700E23.3* *JCAD* (many) *CRHR1* & many (many)
Gelernter[9] (2018)	-	-	Thai: 1045	DSM-IV AD criterion count	rs149212747	*ALDH2 & SH2B3*

Walters[12] (2018)	11569/34,999	3335/2945		DSM-IV AD	rs1229984 (EA) & rs2066702 (AA)	*ADH1B (both alleles)*

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