Biological Psychiatry: Celebrating 50 Years

Commentary

How Much Do You Drink on Your Heavy Drinking Day?

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Many individuals drink alcohol, but for a fraction of them it causes serious problems, including alcohol dependence (AD) or, more broadly, alcohol use disorder (AUD). Genetic variation influences both consumption (usually described as number drinks per week) and risk for AUD, and genome-wide association studies (GWASs) have examined both, with interesting results. There is an overlap in the underlying genetic variations associated with consumption and AUD, but there are also important differences, particularly in how the genetics relates to other traits. The differences probably arise in part from different timeframes used (consumption usually refers to a recent consumption period, and AUD refers to lifetime) and the selection of individuals to study (population samples vs. targeted recruitment, demographics) as well as from differences between genetic influences on light or moderate drinking versus the loss of control characteristic of AUD.

Consumption (drinks per week) can be obtained from food questionnaires in studies focused on other traits, asking about the last week, month, or year, and may not reflect the period of heaviest or most problematic drinking. AUD focuses on lifetime diagnoses, based on the compulsive nature of drinking and the problems caused by it, as defined in the Diagnostic and Stastical Manual (DSM) or the International Classification of Diseases (ICD). Electronic medical records are an efficient source of longitudinal data; however, challenges such as inconsistencies in coding remain.

One measure of heavy drinking is the largest number of drinks consumed within 24 hours at any stage in one's life (MaxDrinks). In this issue of *Biological Psychiatry*, Gelernter *et al.* (1) used a phenotype related to MaxDrinks, but instead of asking about a single incident they ask, "In a typical month, what is/was the largest number of drinks of alcohol …you may have had in one day," a phenotype they term MaxAlc. Gelernter *et al.* (1) argue, quite reasonably, that a typical pattern may be more reflective of an individual's risk for AUD than a single incident. Their finding that the genetic correlation between MaxAlc and DSM-IV AD (2) was high (0.87) argues that MaxAlc taps into the genetics of AUD better than drinks per week. MaxAlc showed significant single nucleotide polymorphism (SNP)–based heritability (0.078) in the larger subset of Americans of European descent (EUR) (see below regarding subsetting EUR); this is not far below the 0.090 found for DSM-IV–defined alcohol dependence in Europeans (2).

Gelernter *et al.* (1) examined MaxAlc in a subset of the Million Veteran Program (MVP): 126,936 EUR and 17,019 Americans of African descent (AFR) who answered the single question (above) in a lifestyle survey. The MVP is a valuable resource; it is not, however, a representative sample of the population. There is a highly biased sex ratio, with men constituting 93.6% of EUR and 88.0% of AFR responders. It is also an older sample, with 97% of the participants 40 years of age or older (mean age, approximately 66 years); in this regard, it is comparable to the UK Biobank. About one third reported having no more than 2 drinks on their heaviest drinking day of a typical month, but nearly 40% reported drinking at binge levels (≥5 drinks) at least once in a typical month.

A well-known functional SNP in *ADH1B*, rs1229984, was by far the strongest signal in EUR ($p = 4.0 \times 10^{-47}$). Another functional SNP in the same gene, rs2066702, common in AFR but nearly absent in EUR, was the strongest signal in AFR ($p = 2.3 \times 10^{-12}$). These SNPs have previously been strongly associated with both quantity/frequency measures and AUD (2–6) and MaxDrinks (7). Both minor variants have a protective effect, increasing the rate of ethanol metabolism, which likely transiently increases the aversive acetaldehyde intermediate (3). Both SNPs have extremely uneven distributions across the world (3), which has caused problems in some previous analyses. Many quality control pipelines automatically discard rs1229984 for not being in Hardy-Weinberg equilibrium [e.g., (8,9)]. Gelernter *et al.* (1) explored this. Principal component analysis showed that the violation of Hardy-Weinberg equilibrium was caused by the presence within the EUR of a small group (approximately 2%) that had a minor allele frequency of 0.26, whereas the larger group had a minor allele frequency of 0.03. Omitting the small group from analysis led to the strong finding of association of rs1229984 with MaxAlc. There were many other signals in the region of chromosome 4 where the *ADH* genes cluster, a region with significant linkage disequilibrium (3); conditioning on the lead SNPs in both populations caused other signals in that region to disappear (1). Although not new, these findings strongly reinforce the contribution of these *ADH1B* variants to both drinking and AUD-related phenotypes.

Several other loci were genome-wide significant in the EUR: rs77804065 on chromosome 17 near *CRHR1*, rs7821592 on chromosome 8, and rs1577857 on chromosome 10. No other loci were significant in the AFR. Meta-analysis of EUR plus AFR strengthened the signal for rs1229984 and for a different SNP within *CRHR1*, rs61667602, and elevated two other SNPs to significance: rs1360983 in *FGF14* and rs7931459 on chromosome 11. Converging evidence was sought from other studies; these were not true replications because the phenotypes differed. There was nominal evidence for the SNP on chromosome 10 ($p = 2.4 \times 10^{-3}$) in the largest meta-analysis to date of AD (2), and a region containing the chromosome 10 finding was significant for drinks per week (6). There was support in the UK Biobank data for loci on chromosomes 10 and 17 for the amount consumed on a typical day and for the frequency of drinking 6 or more drinks in a day, phenotypes with a strong

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Table 1. Comparison of Single Nucleotide Polymorphisms Significant in Gelernter *et al.* (1) That Are Also Reported in Kranzler *et al.* (5)

		p Values							
		Gelernter *et al.*			Kranzler *et al.*				
Gene	rsID	MaxAlc META	MaxAlc EUR	MaxAlc AA	AUDIT-C META[a]	AUDIT-C EUR	AUDIT-C AA	AUD META	AUD EUR	AUD AA
ADH1B	rs1229984	1.1×10^{-49}	4.9×10^{-47}		3.6×10^{-133}	4.8×10^{-102}	1.3×10^{-19}	4.7×10^{-85}	4.5×10^{-74}	4.2×10^{-05}
ADH1B	rs2066702			2.3×10^{-12}				6.4×10^{-15}	1.3×10^{-03}	4.7×10^{-24}
CRHR1[b]	rs61667602; rs77804065	1.0×10^{-13}	1.5×10^{-12}							
FGF14	rs1360983	9.9×10^{-09}								
XPO7[b]	rs2291317; rs7821592	2.5×10^{-08}	3.6×10^{-08}							
RNU6-53P	rs1577857	4.2×10^{-08}	4.2×10^{-08}		2.2×10^{-05}	8.3×10^{-09}	2.6×10^{-01}	3.2×10^{-9}	3.2×10^{-7}	8.7×10^{-3}
LOC105376602	rs7931459	4.6×10^{-08}								
GCKR			5.8×10^{-06}		2.0×10^{-16}	1.7×10^{-16}	.11	2.3×10^{-13}	1.4×10^{-16}	.68
KLB			5.5×10^{-06}		3.1×10^{-9}	3.5×10^{-9}	NA			

AA, Americans of African descent; AUDIT-C, Alcohol Use Disorders Identification Test; EUR, Americans of European descent; META, meta-analysis.
Data assembled from Gelernter *et al.* (1) and Kranzler *et al.* (5), both of which were drawn from the Million Veteran Program. The degree of overlap was not reported in either study.
[a]Kranzler *et al.* (5) meta-analysis included additional populations.
[b]Different top single nucleotide polymorphisms in EUR vs. meta-analysis.

genetic correlation with MaxAlc. Among other SNPs that have been reported associated with quantity/frequency phenotypes, Gelernter *et al.* (1) found good support for *KLB* and *GCKR* (6,9) (both $p < 10^{-5}$) but only nominal support at best for others (*CADM2*, *FAM69C*, and *CDH13*). Neither of two SNPs reported from an earlier GWAS of MaxDrinks (7) was significant.

It is interesting to compare the findings for MaxAlc with those in recent study of AD (assessed from the electronic medical record) and the Alcohol Use Disorders Identification Test (AUDIT-C) (questions 1–3 that relate to quantity/frequency) that was also from the MVP (5). The overlap between the sample analyzed by Gelernter *et al.* (1) and the larger one analyzed by Kranzler *et al.* (5) is not clear. Kranzler *et al.* found 13 significant loci in EUR and 2 in AFR for AUDIT-C and found 10 loci in EUR and 2 in AFR for AD. Several of the SNPs significant for MaxAlc are not significant for either AUDIT-C or AD (Table 1); conversely, there are SNPs significant for either AUDIT-C or AD that are not significant for MaxAlc. Some of the discrepancies are likely related to sample sizes, but a more detailed examination of the relationships among those phenotypes based on the individual data would be instructive.

The genetic correlations between MaxAlc and other traits were also interesting. (Owing to the unfortunate underrepresentation of AFR in most GWASs to date, this could only be studied in EUR.) The strongest positive correlations were with smoking and cannabis initiation, and there were positive correlations with psychiatric disorders, particularly depression, attention-deficit/hyperactivity disorder, and schizophrenia. There were negative correlations with educational attainment. There was a positive correlation with alcohol consumption in two earlier studies (8,9). A previous analysis of AD also found a positive genetic correlation with smoking and with other psychiatric disorders (e.g., schizophrenia, depression) and a negative correlation with educational attainment (2), as did a study of the problem component of the AUDIT-P (questions 4–10) (4) and AD diagnosis extracted from electronic medical record (5). In contrast, studies of consumption (drinks per week) (6) or the consumption component of the AUDIT (questions 1–3) (4,5) found a positive correlation with educational attainment and a negative correlation with depression. This highlights the difference between studies of consumption versus AUD. Some of the discrepancy likely results from the highly skewed consumption in the general population; most people drink at modest levels.

We are still only scratching the surface in our quest to identify genes that contribute to AUD; there are likely hundreds to thousands. Much larger sample sizes are needed, as is an increased focus on AUD diagnosis and severe cases rather than the easier-to-obtain drinks per week measures. The magnitude of the problems caused by excessive drinking and AUDs should be matched with commensurate efforts to understand the underlying biology to improve both prevention and treatment.

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Article Information

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