Archival Report

Biological Psychiatry: Celebrating 50 Years

Genome-wide Association Study of Maximum Habitual Alcohol Intake in >140,000 U.S. European and African American Veterans Yields Novel Risk Loci

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ABSTRACT

BACKGROUND: Habitual alcohol use can be an indicator of alcohol dependence, which is associated with a wide range of serious health problems.

METHODS: We completed a genome-wide association study in 126,936 European American and 17,029 African American subjects in the Veterans Affairs Million Veteran Program for a quantitative phenotype based on maximum habitual alcohol consumption.

RESULTS: *ADH1B,* on chromosome 4, was the lead locus for both populations: for the European American sample, rs1229984 ($p = 4.9 \times 10^{-47}$); for African American, rs2066702 ($p = 2.3 \times 10^{-12}$). In the European American sample, we identified three additional genome-wide–significant maximum habitual alcohol consumption loci: on chromosome 17, rs77804065 ($p = 1.5 \times 10^{-12}$), at *CRHR1* (corticotropin-releasing hormone receptor 1); the protein product of this gene is involved in stress and immune responses; and on chromosomes 8 and 10. European American and African American samples were then meta-analyzed; the associated region at *CRHR1* increased in significance to 1.02×10^{-13}, and we identified two additional genome-wide significant loci, *FGF14* ($p = 9.86 \times 10^{-9}$) (chromosome 13) and a locus on chromosome 11. Besides *ADH1B*, none of the five loci have prior genome-wide significant support. Post–genome-wide association study analysis identified genetic correlation to other alcohol-related traits, smoking-related traits, and many others. Replications were observed in UK Biobank data. Genetic correlation between maximum habitual alcohol consumption and alcohol dependence was 0.87 ($p = 4.78 \times 10^{-9}$). Enrichment for cell types included dopaminergic and gamma-aminobutyric acidergic neurons in midbrain, and pancreatic delta cells.

CONCLUSIONS: The present study supports five novel alcohol-use risk loci, with particularly strong statistical support for *CRHR1.* Additionally, we provide novel insight regarding the biology of harmful alcohol use.

Keywords: ADH1B, CRHR1, Genome-wide association study, Habitual alcohol use, Million Veteran Program

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The Million Veteran Program (MVP) is a U.S. Department of Veterans Affairs (VA) initiative with a goal of recruiting at least 1 million VA health care beneficiaries, creating a database of genomic and phenotypic information useful for increasing understanding of health and disease (1). The sample is linked both to the VA's extensive electronic health record and to self-report survey information specific to the MVP study. The MVP is particularly valuable for elucidating health problems that are highly prevalent in military veterans, including alcohol use disorder (AUD) and harmful alcohol use.

DSM-IV alcohol dependence (AD), which in DSM-5 is the more severe type of AUD, is moderately heritable; genome-wide association studies (GWASs) of AD and habitual alcohol use have been conducted in European (2–8), African (2,5,6), and East Asian (6,9–13) ancestry populations. Most studies of AD diagnosis have been in small samples, but one reported on ~16,000 subjects (2), and the Psychiatric Genomics Consortium has completed a mega-analysis for AD (14). This AD mega-analysis included 14,904 AD case and 37,944 control subjects from 28 case-control and family-based studies.

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Although this study consistently detected AD polygenic architecture, *ADH1B* risk alleles were the only loci identified, perhaps owing to the heterogeneity across the cohorts included (14). Alcohol consumption is the major risk factor for AD and has medical importance per se. For example, alcohol consumption, even in the normal range ("social" drinking), bears a direct relationship to decline in several cognitive measures (15). Studies of large database samples, including the UK Biobank (4), have focused on alcohol consumption, and their findings have implications for AD risk. Associations with variants mapped to genes that encode alcohol metabolizing enzymes—generally *ADH1B* variants in European American (EUR) and African American (AFR) subjects (16,17), as well as *ALDH2**rs671 (18) in Asians—have been observed consistently. Some studies have reported associations at other loci with various alcohol-related traits (2,4,8); these reports are comparatively few. One meta-analysis of alcohol drinking (>105,000 EUR individuals) identified associations of daily alcohol intake with *KLB, GCKR,* and *CDH13* (8). The GWAS of alcohol consumption in the UK Biobank sample (4) of >112,000 is the largest to date; this study considered only EUR subjects, and the phenotype was based on average weekly alcohol consumption. Genome-wide significant (GWS) associations were identified at several alcohol dehydrogenase loci, in addition to other loci including *GCKR*, *CADM2*, and *FAM69C*.

In the present investigation, we studied the genetic architecture of an alcohol-consumption phenotype—maximum habitual ("in a typical month") alcohol use, or MaxAlc—in the MVP sample (19). We used two strategies to increase power for risk-variant identification: a large sample size and substantial informativity of the phenotype. We included 143,965 MVP participants, and we used MaxAlc defined as a quantitative phenotype. A different phenotype, maximum number of drinks consumed in any 24-hour lifetime period, has previously been studied (5,20). The trait definitions differ in that MaxAlc reflects typical habitual (daily) maximum usage, as opposed to the maximum use ever, which might be on a single occasion. Heaviness of habitual alcohol use may be more correlated with risk of AD than maximum number of drinks consumed in any 24-hour lifetime period (21). Accordingly, we expected that our analysis would be informative regarding the mental and physical consequences of excessive alcohol consumption and AD.

METHODS AND MATERIALS

Subject Recruitment

Participants were enrollees in the MVP (1) (Table 1). Users of the Veterans Health Administration health care system received invitational mailings, had encounters with MVP staff while receiving clinical care, or both. Inclusion criteria were ability and willingness to provide informed consent. Research involving MVP in general is approved by the VA Central Institutional Review Board; the current project was approved by local institutional review boards in Boston, San Diego, and West Haven.

Two optional surveys were designed to augment data contained in the electronic health record. The MVP Baseline Survey elicits information regarding demographic factors, family pedigree, health status, lifestyle habits, military experience, medical history, family history of specific illnesses, and physical features. The MVP Lifestyle Survey contains questions from validated instruments, in domains selected to provide information on environmental exposures, dietary and other habits, sleep and exercise habits, and sense of well-being. This latter instrument includes the following item: "In a typical month, what is/was the largest number of drinks of alcohol (beer, wine, and/or liquor) you may have had in one day?" The response to this item was used to define the phenotype in the present study, referred to here as MaxAlc. All EUR and AFR subjects who responded to the questionnaire were included. Differences between respondents and non-respondents among MVP participants are shown in Supplemental Table S1.

Table 1. Demographic Characteristics of Million Veteran Program EUR (*n* = 126,936) and AFR (*n* = 17,029) Enrollees With Completed Baseline and Lifestyle Surveys

	EUR (*n* = 126,936)	AFR (*n* = 17,029)
Age, Years		
18–29	937 (0.7)	97 (0.6)
30–39	2667 (2.1)	524 (3.1)
40–49	6250 (4.9)	1702 (10.0)
50–59	16,407 (12.9)	5207 (30.6)
60–69	56,805 (44.8)	6708 (39.4)
70–79	28,237 (22.2)	2139 (12.6)
80+	15,519 (12.2)	646 (3.8)
Missing	114 (0.1)	6 (0.0)
Mean (SD)	66.2 (11.4)	60.3 (10.6)
Median	66	61
Sex		
Male	118,752 (93.6)	14,981 (88.0)
Female	8070 (6.4)	2041 (12.0)
Missing	114 (0.1)	7 (0.0)
Ethnicity, Self-identified		
Hispanic	1325 (1.0)	204 (1.2)
Non-Hispanic	124,603 (98.2)	16,603 (97.5)
Unknown	894 (0.7)	216 (1.3)
Missing	114 (0.1)	6 (0.0)
Marital Status		
Married	72,873 (57.4)	6278 (36.9)
Divorced	21,294 (16.8)	3603 (21.2)
Civil commitment	521 (0.4)	79 (0.5)
Never married	7814 (6.2)	1812 (10.6)
Widowed	8269 (6.5)	848 (5.0)
Separated	1713 (1.3)	941 (5.5)
Cohabitating	3006 (2.4)	257 (1.5)
Missing	11,446 (9.0)	3211 (18.9)

Values are *n* (%).
AFR, African American; EUR, European American.

Phenotype Distribution

Phenotype distribution is shown in Supplemental Figure S1.

Genotyping and Microarray

Genotyping was accomplished via a 723,305–single nucleotide polymorphism (SNP) Affymetrix Axiom biobank array

(Thermo Fisher Scientific, Waltham, MA), customized for the MVP (1,22). Additional information is provided in Supplemental Methods.

GWAS Analyses

We performed single variant tests using RVTESTS software (23), including the first 10 principal components, age, and sex as covariates in the linear regression association analyses, separately for EUR and AFR. The significance threshold was $p = 5 \times 10^{-8}$.

Post-GWAS Analyses. To investigate shared genetic and molecular mechanisms, we tested genetic overlap (i.e., shared risk alleles) of MaxAlc with a wide range of phenotypes. Genetic correlations were calculated using the linkage disequilibrium score regression method (LDSC) (https://github.com/bulik/ldsc) (24). LDSC results regarding 232 traits were extracted from the data available at LD Hub version 1.4.0 (http://ldsc.broadinstitute.org/ldhub/) (25). Genetic correlations for an additional 1547 traits were calculated using the GWAS summary association results available at https://sites.google.com/broadinstitute.org/ukbbgwasresults; these GWASs used data from ~337,000 unrelated British individuals from the UK Biobank (26).

To explore further the functional role of the GWS variants identified, we conducted an expression quantitative trait locus (eQTL) analysis using GTEx V7 data (27). False discovery rate (FDR) correction (28), MAGMA (29), FUMA (30), and eQTL analyses are described further in the Supplemental Methods.

RESULTS

We identified an unusual instance of Hardy-Weinberg disequilibrium. *ADH1B* rs1229984, the most consistently associated alcohol risk variant in European populations (16), was initially excluded from analysis because it deviated from Hardy-Weinberg equilibrium (HWE) expectations ($p = 1.4 \times 10^{-43}$). This variant is functional (31), presents very strong allele frequency differences among human populations (32), and has undergone selection in Asian and European populations (17,33), although there is an open debate about the presence of convergent evolution in Europeans (34). Because *ADH1B* rs1229984 is the most relevant locus associated with alcohol drinking behaviors that has a very well-established causative mechanism (17), we investigated the cause for Hardy-Weinberg disequilibrium further to avoid unnecessary exclusion of this variant, which would have highlighted the association of other variants in the same region due to the LD without reflecting the real causal mechanism. This is described in the Supplemental Results.

Primary GWAS Analysis

We observed 7.8% SNP-based heritability ($p = 1.01 \times 10^{-40}$) calculated on the basis of the summary association data in "G1" EUR via LDSC regression (see Supplement for definition of "G1"). As with other large-scale GWASs (25), an inflated λ_{gc} value was observed in the summary association data ($\lambda_{gc} = 1.16$) (Supplemental Figure S2). The LDSC intercept was 1.011 (SE = 0.0091), however, demonstrating that this inflation was due to polygenicity and not to population stratification, phenotype distribution, or other confounders (25). In the smaller AFR sample ($n = 17{,}029$), no effect of polygenicity was observed in the summary association data ($\lambda_{gc} = 1.01$) (Supplemental Figure S3). Four independent GWS regions were identified in "G1" EUR (Figure 1). The lead region was on chromosome 4, lead SNP rs1229984 ($p = 4.9 \times 10^{-47}$) (Figure 2A), at gene *ADH1B* (beta subunit, class I alcohol dehydrogenase). GWS SNPs mapped to numerous loci in the region, so we performed conditional analysis for these loci using genome-wide complex trait analysis (GCTA) with EUR summary statistics and 1000G Genome Project data as reference LD. This analysis confirmed that there are only four independent signals, that is, no associated region reflected more

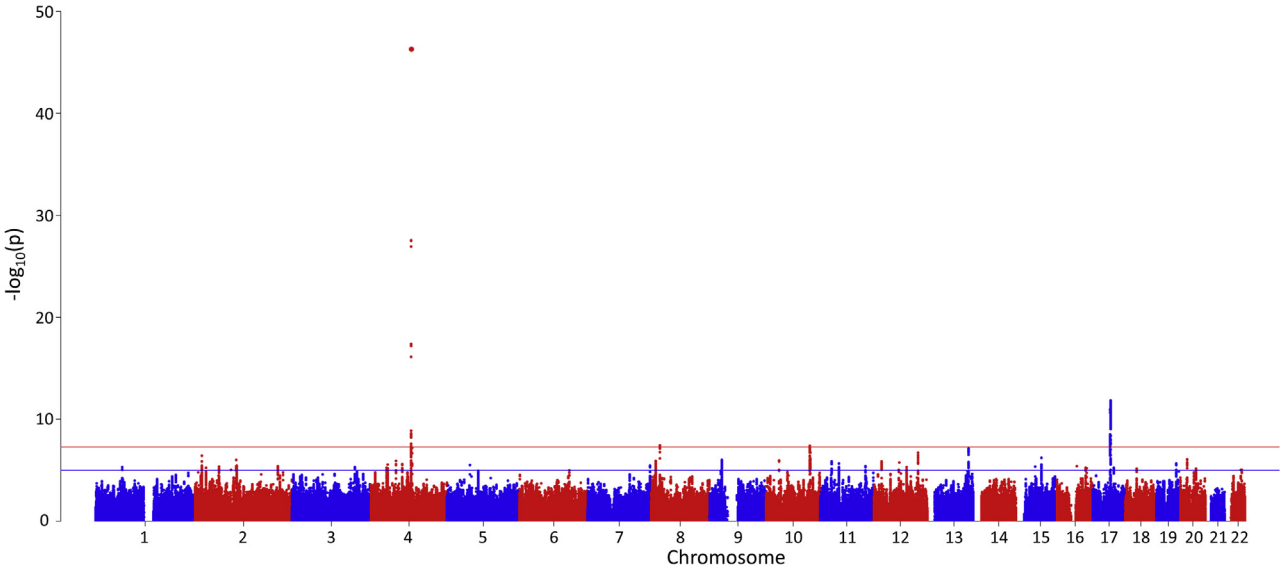

Figure 1. Manhattan plot.

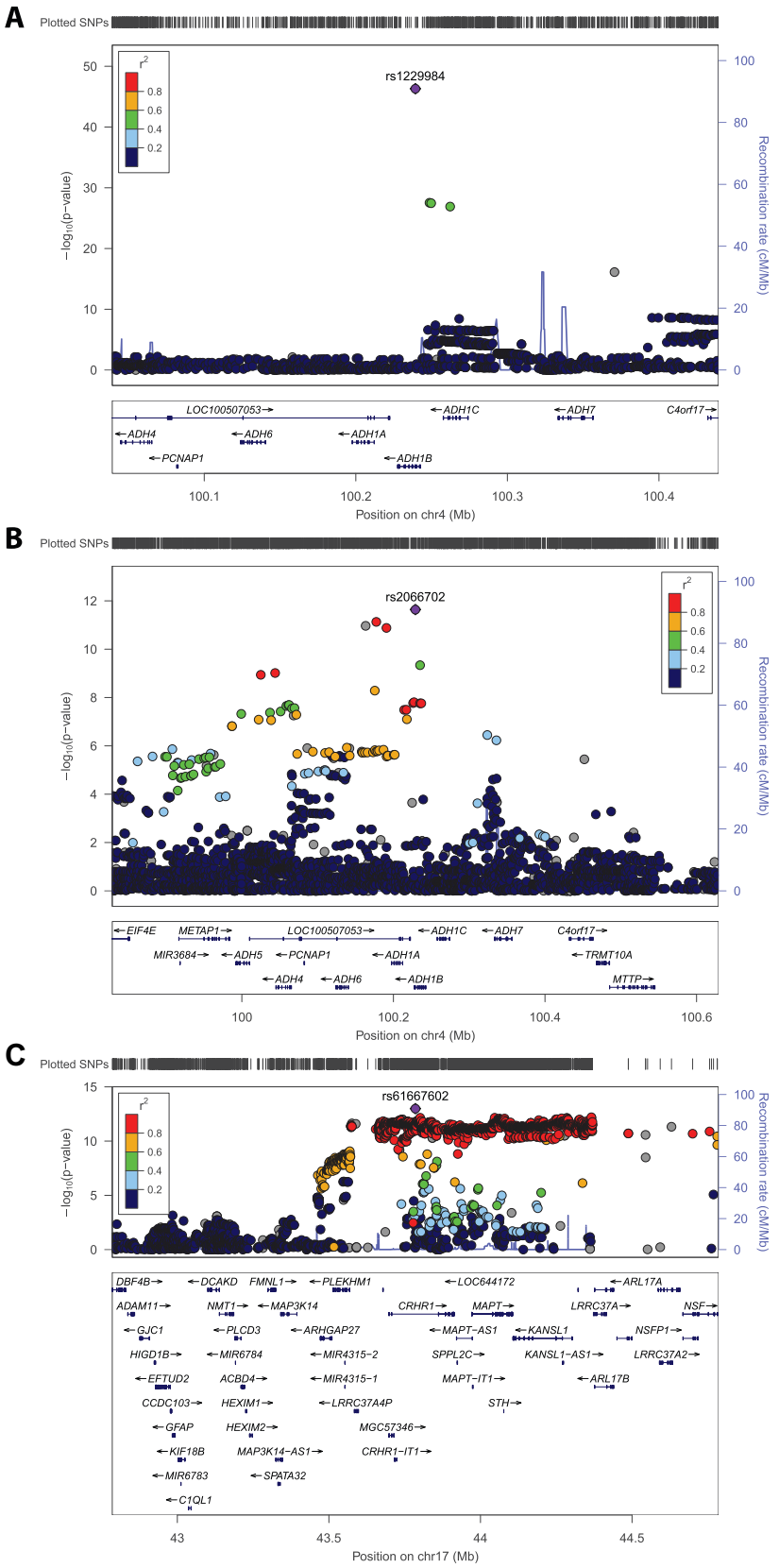

Figure 2. Regional Manhattan plots: **(A)** Chromosome 4 alcohol dehydrogenase genes, European Americans. **(B)** Chromosome 4 alcohol dehydrogenase genes, African Americans. **(C)** Meta-analysis of European and African Americans, chromosome 17 (*CRHR1*) region. SNP, single nucleotide polymorphism.

Table 2. Most Significant SNPs

Unique ID	rs ID	Chromosome	Position	*p* Value	Start	End	SNPs, *n*	GWAS SNPs, *n*	Lead SNPs	Gene
EUR										
4:100239319:C:T	rs1229984	4	100239319	4.91×10^{-47}	100019089	100638613	111	107	rs1229984	*ADH1B*
8:21811530:C:G	rs7821592	8	21811530	3.63×10^{-8}	21777476	21869727	43	30	rs7821592	*XPO7*
10:110572259:G:T	rs1577857	10	110572259	4.15×10^{-8}	110462973	110635222	116	90	rs1577857	*RNU6-53P*
17:43810896:C:T	rs77804065	17	43810896	1.54×10^{-12}	43463493	44865603	3414	2979	rs77804065; rs199447	*CRHR1*
AFR										
4:100229017:A:G	rs2066702	4	100229017	2.29×10^{-12}	99986965	100263535	54	51	rs2066702	*ADH1B*
Meta-analysis										
4:100239319:C:T	rs1229984	4	100239319	1.07×10^{-49}	100019089	100638613	110	106	rs1229984	*ADH1B*
8:21827162:C:T	rs2291317	8	21827162	2.48×10^{-8}	21777476	21869727	43	30	rs2291317	*XPO7*
10:110572259:G:T	rs1577857	10	110572259	4.15×10^{-8}	110462973	110635222	116	90	rs1577857	*RNU6-53P*
11:28648185:C:T	rs7931459	11	28648185	4.63×10^{-8}	28591168	28704399	172	84	rs7931459	*LOC105376602*
13:102868108:C:T	rs1360983	13	102868108	9.86×10^{-9}	102860527	102911712	51	44	rs1360983	*FGF14*
17:43785349:C:T	rs61667602	17	43785349	1.02×10^{-13}	43463493	44865603	3423	2976	rs61667602; rs1378358	*CRHR1*

AFR, African American; EUR, European American; GWAS, genome-wide association study; ID, identifier; SNP, single nucleotide polymorphism.

than one independent signal. The other three associated regions map to chromosome 17, lead SNP rs77804065 ($p = 1.5 \times 10^{-12}$) (Supplemental Figure S4A), at *CRHR1*, corticotropin-releasing hormone receptor 1, with the protein product of this gene involved in stress and immune responses (numerous additional GWS SNPs were found in the chromosome 17 region, including variants that map to *KANSL1*, KAT8 regulatory NSL complex subunit 1); chromosome 8, lead SNP rs7821592 ($p = 3.6 \times 10^{-08}$) (Supplemental Figure S4B), closest gene *XPO7,* exportin 7, the protein product of which mediates nuclear export of proteins; and chromosome 10, lead SNP rs1577857 ($p = 4.2 \times 10^{-08}$) (Supplemental Figure S4C), at *LOC105378478,* which has unknown function (closest gene, *RNU6-53P*). The MVP includes mostly male subjects (93.6%). Although sex was included as a covariate, male and female subjects differ in their prevalence of and genetic liability to AUDs (35,36), so we evaluated whether inclusion of female subjects affected the results substantively by repeating the analysis excluding female subjects. No major differences were observed between GWASs of both-sexes and male-only samples (Supplemental Table S2).

In the AFR sample, one GWS region was identified, lead SNP *ADH1B**rs2066702 (2.29×10^{-12}) (Figure 2B). Conditional analysis, with AFR LD reference, confirmed that this reflects a single peak.

When EUR and AFR results were meta-analyzed (n = 143,965 subjects total), we identified two additional GWS loci, uncharacterized *LOC105376602* ($p = 4.63 \times 10^{-08}$) on chromosome 11, and *FGF14* ($p = 9.86 \times 10^{-09}$) on chromosome 13 (Supplemental Figure S5B and 5E). In addition, the associated region at *CRHR1* increased in statistical significance to $p = 1.02 \times 10^{-13}$. Comparing EUR results (Supplemental Figure S4A) with EUR-AFR meta-analysis (Figure 2C), we observed different lead variants on chromosome 17, but they both indicated *CRHR1* as a credible gene responsible for the association observed. Results are summarized in Table 2 and more extensively in Supplemental Table S3.

To verify our results in an independent sample, we used summary association data from the AD GWAS conducted by the Psychiatric Genomics Consortium (PGC) (37). Although to date this is the largest AD GWAS, its effective sample size (38) is much smaller than the one used in our analysis (PGC, n = 31,819; MVP, n = 143,965) so there is low statistical power to replicate our findings. Nevertheless, considering our six GWS results in trans-ancestry meta-analysis, we observed GWS replication of the chromosome 4 *ADH1B**rs1229984 association ($p = 2.18 \times 10^{-11}$), a nominal replication of chromosome 10 rs1577857 ($p = 2.44 \times 10^{-3}$), and direction replication (i.e., the loci showed the same effect direction in both MaxAlc and AD) for all loci (Supplemental Table S4). We estimate that the probability to observe a direction replication of all six MVP-identified loci in PGC AD GWAS by chance is 1.7% (Supplemental Figure S6). Leveraging the polygenic architecture of the complex traits investigated, in the EUR sample, MaxAlc in MVP showed $r_g = .87$ with AD in the PGC cohort ($p = 4.78 \times 10^{-9}$) by LDSC. For additional replication, we investigated UK Biobank data regarding nine traits related to alcohol use (Supplemental Table S5). To identify the phenotypes most closely related to MaxAlc, we performed a genetic-correlation analysis and observed the strongest correlation with "amount of alcohol drunk on a typical drinking day" ($r_g = .81$, $p = 5.83 \times 10^{-40}$). Significant correlations were also observed with the other traits, including "frequency of consuming six or more units of alcohol" ($r_g = .70$, $p = 2.72 \times 10^{-30}$), "ever been injured or injured someone else through drinking alcohol" ($r_g = .84$, $p = 8.56 \times 10^{-5}$), and "ever had known person concerned about, or recommend reduction of, alcohol consumption" ($r_g = .64$, $p = 3.79 \times 10^{-14}$). Considering the most strongly genetically correlated alcohol-use trait (i.e., "amount of alcohol drunk on a typical drinking day"), we observed replications (Supplemental Table S4) for chromosome 4 rs1229984 ($p = 3.77 \times 10^{-32}$), chromosome 10 rs1577857 ($p = .027$), and chromosome 17 rs77804065 ($p = 2.67 \times 10^{-6}$) and rs61667602 ($p = 1.25 \times 10^{-6}$).

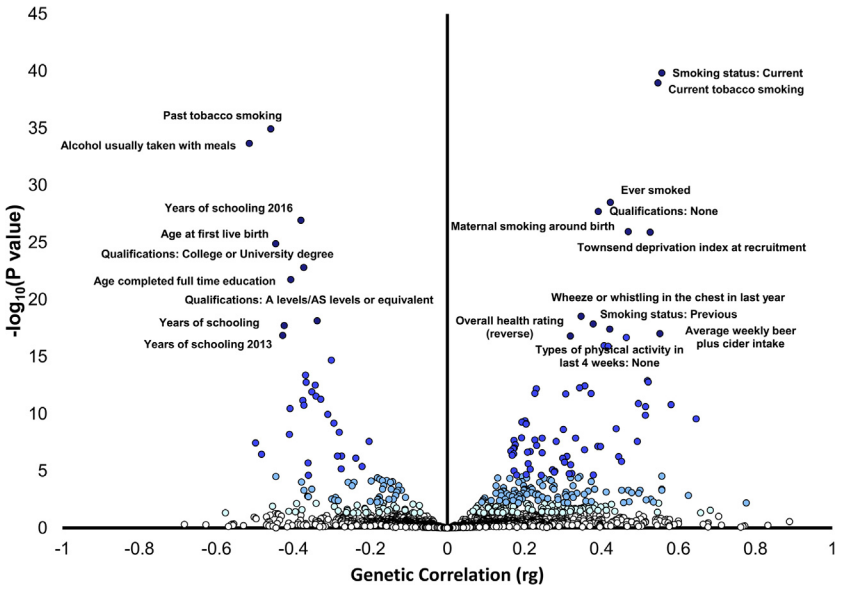

Figure 3. Phenome-wide genetic-correlation analysis. Blue shades corresponds to significance strength, from white, nonsignificant ($p > .05$), to very light blue ($p < .05$), light blue (false discovery rate: $q < 0.05$), to blue (Bonferroni correction $p < 2.81 \times 10^{-40}$), and dark blue (top 20 results). Phenotype labels are included for the top 20 results. A, advanced; AS, advanced subsidiary.

We evaluated possible association of genes identified as associated in previous investigations of alcohol consumption phenotypes: *GCKR, CADM2, FAM69C, KLB,* and *CDH13*. No GWS results were observed, but suggestive results were observed in the EUR sample at two of these loci, *GCKR* ($p_{min} = 5.78 \times 10^{-6}$) and *KLB* ($p_{min} = 5.54 \times 10^{-6}$), and nominally significant signals were observed in the remaining genomic regions (regional Manhattan plots for all five of these are in Supplemental Figure S7). This could be attributable to the polygenic architecture of complex traits, where loci have very small effect sizes, and a much larger sample size will be needed to replicate these loci at a GWS level; or to the difference between MaxAlc and AD, which has a high correlation with PGC AD (see above) and the consumption phenotypes wherein these other markers were identified.

Phenome-wide Genetic Correlations

LDSC revealed significant genetic correlations (FDR: $q < 0.05$) with 238 of nearly 1800 traits (Figure 3, Supplemental Table S6). The most significant observed correlations (Supplemental Table S3 shows all results at FDR: $q < 0.05$) were with respect to smoking and alcohol-drinking traits, where the top correlations were with current smoking status (positive correlation, $r_g = .55$, $p = 1.30 \times 10^{-39}$), the degree of past smoking (past tobacco smoking; negative correlation, $r_g = -.46$, $p = 5.49 \times 10^{-36}$), and "healthy" alcohol-drinking behaviors (e.g., alcohol usually taken with meals; negative correlation, $r_g = -.50$, $p = 5.44 \times 10^{-34}$). Among the other highly significant correlations, several were related to level of education (e.g., years of schooling, $r_g = -.37$ $p = 1.53 \times 10^{-25}$) and socioeconomic status (Townsend deprivation index, $r_g = .53$, $p = 3.69 \times 10^{-27}$). Numerous correlations were also found with measures of physical activity (e.g., no physical activity in the last 4 weeks, $r_g = .41$, $p = 3.06 \times 10^{-17}$). Other noteworthy correlations included mood swings ($r_g = .20$, $p = 1.05 \times 10^{-5}$) and risk taking ($r_g = .20$, $p = 2.74 \times 10^{-5}$). Considering psychiatric traits, we observed significant genetic correlations with depressive symptoms ($r_g = .22$, $p = 4 \times 10^{-4}$), schizophrenia ($r_g = .13$, $p = 0 \times 10^{-4}$), and attention-deficit/hyperactivity disorder ($r_g = .32$, $p = .023$).

Gene-Based Association and Tissue and Cell-type Enrichment Analysis

Gene-based association analysis and tissue and cell type enrichment results are shown in Figures 4 and 5 and described in the Supplemental Methods.

eQTL Analysis

After applying a FDR 5% correction for the variants, genes, and tissues tested, we observed 212 significant eQTLs out of 2855 tests conducted with respect to the GWS loci observed in the trans-ancestry meta-analysis. Considering the top central nervous system (CNS) tissue for each eQTL surviving multiple testing correction (Table 3), we observed 37 significant results. Thirty-four relate to rs61667602 (chromosome 17), associated with the expression of multiple genes, where the strongest significance was mostly observed in the cerebellum transcriptomic profile ($n = 22$ of 34). Additionally, we identified significant eQTLs with respect to rs1360983 on chromosome 13 (*FGF14-AS2*, top CNS tissue: spinal cord) and rs2291317 on chromosome 8 (*BIN3,* top CNS tissue: nucleus accumbens; *FAM160B2,* top CNS tissue: substantia nigra). Consistent with the strong LD with the loci identified in the trans-ancestry meta-analysis, similar eQTL results were observed with respect to the variants identified in the EUR analysis.

DISCUSSION

We report findings from a GWAS of maximum habitual alcohol use from the U.S. MVP sample, in EUR and AFR populations. In the EUR sample, we observed 7.8% SNP-based heritability that is consistent with other large GWASs of alcohol-related traits, which also range from 5% to 10% (14). These

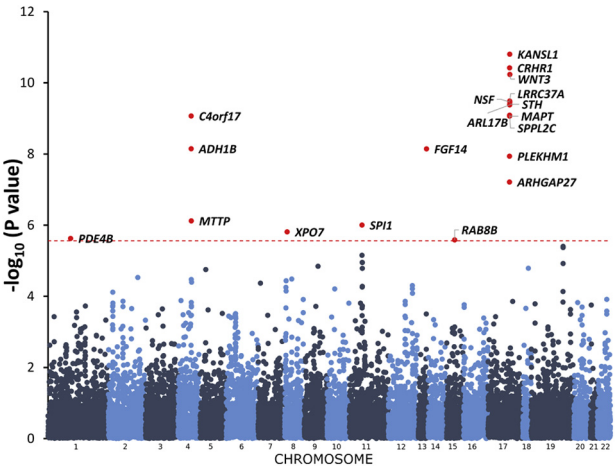

Figure 4. Manhattan plot, gene-based association results.

SNP-based heritability estimates account for about 15% to 25% of the heritability reported by twin studies (39). The phenotype tested (i.e., "in a typical month, what is/was the largest number of drinks of alcohol [beer, wine, and/or liquor] you may have had in one day?") has genetic overlap with both alcohol consumption (UK Biobank: "amount of alcohol drunk on a typical drinking day" and "frequency of consuming six or more units of alcohol") and with alcohol misuse (PGC: DSM-IV Alcohol Dependence; UK Biobank: "ever been injured or injured someone else through drinking alcohol" and "ever had known person concerned about, or recommend reduction of, alcohol consumption").

Our findings provide strong support for association in the chromosome 4 alcohol dehydrogenase region, for *ADH1B**rs1229984, as has been reported multiple times previously (here with $p = 4.9 \times 10^{-47}$), spanning a lengthy chromosomal region (Figure 2A). A different signal at the same locus, rs2066702 (2.29×10^{-12}) (Figure 2B), was the only GWS result in the AFR sample. We also report three additional regions in the EUR sample, with prior varying, but never GWS, support: a region on chromosome 17 including *CRHR1**rs77804065 ($p = 1.5 \times 10^{-12}$) (Figure 2C); chromosome 8, lead SNP rs7821592 (3.6×10^{-8}), closest to *XPO7*; and at chromosome 10, lead SNP rs1577857 (4.2×10^{-08}), *LOC105378478*, which has unknown function. The transpopulation meta-analysis added two additional novel GWS regions, *FGF14* ($p = 9.86 \times 10^{-09}$) and *LOC105376602* ($p = 4.63 \times 10^{-08}$) (19).

Lead SNP *ADH1B**rs1229984 is a long-established risk locus from the pre-GWAS era that has been strongly confirmed by GWAS (2,6). To identify rs1229984 as the lead variant, we needed to address a data-cleaning dilemma, as this variant was initially excluded from analysis on HWE criteria. Knowing the importance of the variant, we investigated the situation further and discovered two subpopulations within the EUR sample, one with higher rs1229984 minor allele frequency [that clusters with Ashkenazi Jews (40)] and another much larger subpopulation with lower minor allele frequency ("G1"). HWE criteria for this key variant were met within both of these individual subpopulations. In the initial quality control investigation, the violation of HWE expectations was, we conclude, attributable to this demonstrable violation of the random mating assumption (and not to a problem with data quality). We recommend that studies that may have excluded *ADH1B**rs1229984 on HWE grounds examine this same issue.

This variant has support for association many orders of magnitude greater than the next-best-supported independent region on chromosome 17, lead SNP rs77804065, which maps to *CRHR1,* with observed $p = 1.5 \times 10^{-12}$ in the EUR sample. *CHRH1* variants were previously implicated in candidate gene studies of alcohol-use phenotypes (41,42) and in an animal study regarding sensitivity to relapse into alcohol-seeking induced by environmental stress (43). This GWS association signal maps to a well-known 900-kb inversion region (44) containing numerous other genes, some of which could also be considered MaxAlc-candidate loci. The inversion is much less common in Africans (44,45), consistent with the complex evolutionary history at this locus (46), so meta-analysis between the EUR and AFR samples could potentially narrow the associated region greatly, if there is association information in that population as well, even if nonsignificant taken only in the AFR sample. Indeed, the transpopulation meta-analysis showed that statistical significance increased by over an order of magnitude (to 1.02×10^{-13}) with improved evidence for localization of the lead SNP at *CHRH1* (Figure 2C). A similar phenomenon has been observed in narrowing associated regions for schizophrenia when meta-analyzing EUR and Asian GWAS results (47). Gene-based analyses and the replication in the UK Biobank provided additional evidence supporting *CRHR1* as a risk locus.

On chromosome 8, rs7821592, the implicated locus is *XPO7*. Although this locus was identified as being of interest in a prior sparse "pooled GWAS" study of AD (48) and was identified in a study of AD comorbid with bipolar disorder (49), it has never previously been identified for these traits at anything approaching GWS. Finally, in European Americans, rs1577857 (*LOC105378478*) on chromosome 10 has apparently not been reported previously. Although this variant is located in a noncoding RNA gene not previously associated with any human phenotype, the association in the MVP cohort was also replicated in PGC and UK Biobank cohorts. Additionally, the regulatory functional significance of this locus is supported by the fact that the variant is in a DNase I hypersensitivity site detected in 12 different cell types (50).

In the AFR sample, we identified a single region led by *ADH1B* rs2066702 that, like rs1229984 in the EUR sample, is well replicated (2).

The transpopulation meta-analysis added two novel GWS loci: six in the meta-analysis versus only four in the European-only analysis (and one, overlapping with an EUR-associated region, GWS in AFR taken individually, albeit with a different SNP). These were *FGF14* at $p = 9.86 \times 10^{-09}$: a gene implicated in inherited cerebellar ataxias (51), among other traits, which regulates potassium voltage-gated channel subfamily Q members 2 and 3 potassium channels (52); and an uncharacterized RNA gene locus, *LOC105376602* (at $p = 4.63 \times 10^{-08}$). *FGF14* is particularly relevant because *KLB*, a locus previously identified as associated to alcohol consumption (4,6,8,53) and replicated in MVP ($p_{min} = 5.54 \times 10^{-6}$), is a receptor that acts as a targeting signal for several *FGF* genes (54), suggesting the strong possibility of wider involvement of

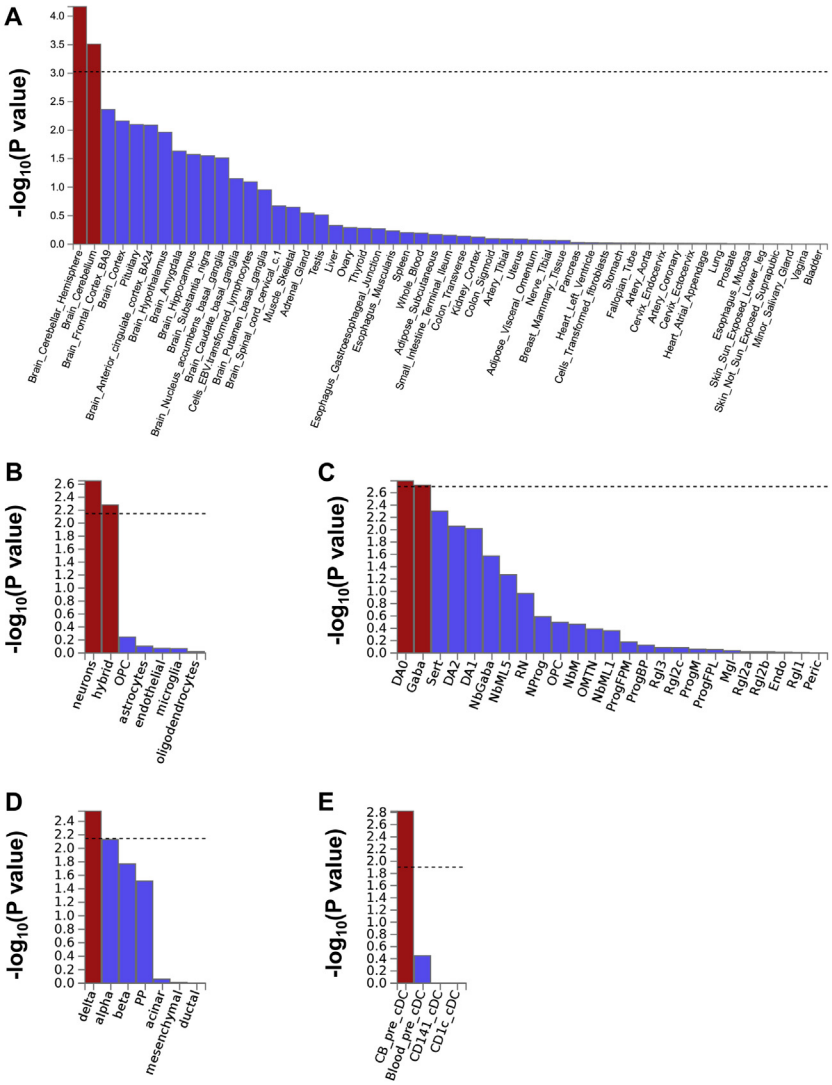

Figure 5. **(A)** Statistical significance of the enrichments for tissue-specific gene expression. Detailed results are reported in Supplemental Table S7. **(B)** Statistical significances for cell types in human cortex from adult samples. "Hybrid" refers to a mixture of oligodendrocyte progenitor cells (OPC), oligodendrocytes, and neurons. Detailed results are reported in Supplemental Table S8. **(C)** Statistical significances for cell types in human midbrain. Detailed results and acronym legends are reported in Supplemental Table S9. **(D)** Statistical significances for cell types in human pancreas. Detailed results are reported in Supplemental Table S10. **(E)** Statistical significances for cell types in conventional dendritic cells (cDC). Detailed results are reported in Supplemental Table S11. BA, Brodmann area.

the fibroblast growth factor family in predisposition to alcohol consumption.

Thus, although our AFR sample was too small for novel locus identification when taken individually, transpopulation meta-analysis was very valuable because of the differences in local LD (allowing improved *CRHR1* region mapping) and additional association information for risk regions apparently in common between these populations.

The phenome-wide genetic-correlation analyses identified correlations with numerous traits including tobacco-smoking behaviors, socioeconomic status, physical activity, reproductive behaviors, fat mass, personality traits, and, to a lesser extent, certain psychiatric disorders. Similar findings have been reported previously, even with small numbers of markers or with *ADH1B**rs1229984 taken individually (55). These genetic relationships of MaxAlc are consistent with the pervasive role of alcohol use and abuse on human morbidity and mortality (56). Gene-based analysis, besides supporting *CRHR1* as noted, supported other genes associated in SNP-based analysis such as *XPO7* and *FGF14,* as well as, for example, *KANSL1,* which maps to the same inversion region as *CRHR1*, and *PDE4B* (phosphodiesterase 4B), previously implicated in other neuropsychiatric disorders. Tissue and human cell-type expression enrichments were noted for cerebellar hemisphere and cerebellum; dopaminergic and gamma-aminobutyric acidergic neurons in human midbrain; and delta cells in pancreas. The cerebellar enrichment is particularly relevant with respect to the known effects of alcohol on this brain region: ethanol is the most common injurious agent to Purkinje cells (57,58). In this context, interindividual variability in the genetic regulation of cerebellum may be linked to the ability to drink large amounts of alcohol. Additionally, alcohol affects the type-A γ-aminobutyric acid receptor, which mediates autocrine signaling mechanisms in pancreatic cells (59). Individuals with high resistance to the effects of ethanol on this system may be able to drink larger amounts of alcohol; subjects at risk for AD tend to have lower levels of response to measures including body sway (60), which is presumably at

Table 3. Significant eQTLs Observed With Respect to the GWS Variants Identified in Trans-ancestry Meta-analysis Considering 13 CNS Tissues

rs ID	Gene	TSS Distance	Slope	SE	*p* Value	FDR *q*	Top CNS Tissue
rs1360983	*FGF14-AS2*	−178,872	−0.361	0.078	2.00×10^{-5}	1.72×10^{-4}	Spinal cord (cervical c-1)
rs61667602	*LRRC37A2*	−803,528	1.169	0.063	2.29×10^{-36}	4.69×10^{-34}	Cerebellum
	LRRC37A4P	157,648	−1.096	0.061	4.20×10^{-34}	7.89×10^{-32}	Nucleus accumbens (basal ganglia)
	AC005829.1	−559,054	1.132	0.068	1.67×10^{-32}	2.18×10^{-30}	Cerebellum
	KANSL1-AS1	−485,593	1.202	0.072	3.39×10^{-32}	4.05×10^{-30}	Cortex
	AC005829.2	−552,623	1.219	0.076	2.65×10^{-31}	2.45×10^{-29}	Cerebellum
	PLEKHM1	217,234	−0.951	0.062	7.95×10^{-30}	5.43×10^{-28}	Cerebellum
	ARL17A	−871,739	1.130	0.076	5.96×10^{-29}	3.80×10^{-27}	Cerebellum
	MAPK8IP1P2	105,643	1.093	0.083	5.77×10^{-25}	2.30×10^{-23}	Cerebellum
	MAPK8IP1P1	−535,623	1.157	0.085	1.25×10^{-24}	4.78×10^{-23}	Cerebellar hemisphere
	DND1P1	122,112	1.166	0.096	3.14×10^{-22}	9.89×10^{-21}	Cortex
	LINC02210	87,655	0.690	0.059	3.02×10^{-21}	8.66×10^{-20}	Cortex
	SPPL2C	−136,907	0.734	0.067	8.67×10^{-20}	2.18×10^{-18}	Cerebellum
	LRRC37A	−584,750	1.004	0.093	3.42×10^{-19}	7.91×10^{-18}	Cerebellum
	AC091132.1	204,723	−0.922	0.098	4.67×10^{-16}	7.83×10^{-15}	Cerebellum
	FAM215B	−854,812	0.844	0.090	6.89×10^{-16}	1.14×10^{-14}	Cerebellum
	FMNL1	485,759	−0.672	0.074	2.54×10^{-15}	3.87×10^{-14}	Cerebellum
	AC091132.3	176,406	0.757	0.120	6.44×10^{-9}	6.76×10^{-8}	Cerebellar hemisphere
	ARHGAP27	273,562	0.459	0.078	4.94×10^{-8}	4.93×10^{-7}	Nucleus accumbens (basal ganglia)
	AC091132.2	255,139	−0.573	0.101	1.03×10^{-7}	1.00×10^{-6}	Cerebellum
	AC008105.3	486,194	−0.469	0.086	3.15×10^{-7}	2.99×10^{-6}	Cerebellum
	MAPT-AS1	−187,617	0.508	0.096	6.23×10^{-7}	5.72×10^{-6}	Cerebellum
	MAPT	−186,399	−0.316	0.065	3.62×10^{-6}	3.22×10^{-5}	Cerebellum
	CRHR1	86,082	−0.399	0.098	1.01×10^{-4}	8.31×10^{-4}	Putamen (basal ganglia)
	RPS26P8	99,440	0.698	0.169	1.11×10^{-4}	9.12×10^{-4}	Spinal cord (cervical c-1)
	KANSL1	−517,384	0.355	0.090	1.42×10^{-4}	0.001	Cerebellum
	NMT1	656,319	−0.211	0.057	3.44×10^{-4}	0.003	Cerebellum
	NSF	−882,686	−0.158	0.043	3.93×10^{-4}	0.003	Cerebellum
	AC008105.1	466,248	−0.247	0.072	7.87×10^{-4}	0.006	Cerebellum
	AC091132.4	162,179	−0.387	0.118	.001	0.010	Cerebellum
	AC015936.1	760,069	0.575	0.173	.002	0.011	Spinal cord (cervical c-1)
	CR936218.1	−327,330	−0.393	0.122	.002	0.013	Putamen (basal ganglia)
	ACBD4	575,382	−0.175	0.057	.003	0.020	Cerebellum
	PLCD3	574,628	0.189	0.067	.006	0.041	Hypothalamus
	ARL17B	−653,781	0.351	0.127	.007	0.043	Cerebellum
rs2291317	*BIN3*	−699,499	0.212	0.074	.005	0.034	Nucleus accumbens (basal ganglia)
	FAM160B2	−119,533	0.251	0.089	.007	0.043	Substantia nigra

CNS, central nervous system; eQTL, expression quantitative trait locus; FDR, false discovery rate; GWS, genome-wide significant; ID, identifier; TSS, transcription start site.

least in part cerebellar in origin. In a mouse model, it was demonstrated that genetically influenced differences in cerebellar alcohol response affect alcohol consumption (61). eQTL analysis provides further evidence for functional effects of risk loci, particularly those mapped to chromosome 17, in the CNS, particularly the cerebellum.

In summary, we mapped 1) four risk loci for MaxAlc in European Americans, of which only one (*ADH1B*) was previously known; 2) one in African Americans, which was previously known (a different marker in *ADH1B* than in European Americans); and 3) an additional two loci, both novel, in the trans-population meta-analysis. MaxAlc is a clinically meaningful trait that differs from, but is genetically correlated with, DSM diagnosis of AUD. It is unclear to what extent the novel findings are due to the phenotype definition or to the size and other characteristics of the clinical sample. MaxAlc, relating not merely to habitual alcohol use but to maximal habitual use, is more strongly related to the pathological range of alcohol use than some other measures such as the Alcohol Use Disorders Identification Test—Consumption or MaxDrinks (maximum number of drinks consumed in any 24-hour lifetime period) (62). The negative correlation with "healthy" alcohol use behaviors, such as "alcohol usually taken with meals," supports this interpretation.

Although our study is based on a large sample, we are still underpowered to conduct additional analyses to dissect the

differences in the polygenic architecture of excessive drinking behaviors between sexes and age classes. MaxAlc, although a valid and useful phenotype, has previously been used only rarely. The high correlation with AUD per se may encourage more use in future studies, in the context of the results we report here. Additionally, the MVP uses a genotyping array that, while adequate for studies of European Americans, is sparse for African Americans and accordingly leaves much of the genome unstudied (63). This is the case because African Americans are a genetically older population than European Americans and have lower LD genome-wide; hence each SNP tends to query a shorter genomic region. For studies including large African American populations, a more informative array would, ideally, be employed.

Finally, this study demonstrates the tremendous utility of the MVP sample for locus discovery. The large sample and informative set of surveys (combined with electronic health record data, which were not used here) will permit powerful and virtually unprecedented association studies of a vast array of traits and diseases. Furthermore, the inclusion of a sizeable sample of individuals of African descent contributes to additional locus identification opportunities.

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Summary statistics for all genome-wide association study analyses are freely available. The dbGaP accession assigned to the MVP is phs001672.v1.p (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001672.v1.p1). Additionally, investigators who wish to gain access to the individual-level data may contact JG or MBS; access to these data will be available in one of our laboratories on a collaborative basis. MVP is presently working toward developing ways to make individual-level coded data more broadly accessible as allowed by the consent and consistent with the MVP data access policies and procedures.

JG and HRK are named as coinventors on Patent Cooperation Treaty Patent Application No. 15/878,640: "Genotype-guided dosing of opioid agonists," filed January 24, 2018. MBS has in the past 3 years been a consultant for Actelion, Aptinyx, Bionomics, Dart Neuroscience, Healthcare Management Technologies, Janssen, Jazz Pharmaceuticals, Neurocrine Biosciences, Oxeia Biopharmaceuticals, and Pfizer; owns founders shares and stock options in Resilience Therapeutics; and has stock options in Oxeia Biopharmaceuticals. HRK has been an advisory board member, consultant, or continuing medical education speaker for Alkermes, Indivior, and Lundbeck; and is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last 3 years by AbbVie, Alkermes, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, Pfizer, Arbor, and Amygdala Neurosciences. The other authors report no biomedical financial interests or potential conflicts of interest.

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