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Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders

Liability to alcohol dependence (AD) is heritable, but little is known about its complex polygenic architecture or its genetic relationship with other disorders. To discover loci associated with AD and characterize the relationship between AD and other psychiatric and behavioral outcomes, we carried out the largest genome-wide association study to date of DSM-IV-diagnosed AD. Genome-wide data on 14,904 individuals with AD and 37,944 controls from 28 case–control and family-based studies were meta-analyzed, stratified by genetic ancestry (European, $n = 46,568$; African, $n = 6,280$). Independent, genome-wide significant effects of different *ADH1B* variants were identified in European (rs1229984; $P = 9.8 \times 10^{-13}$) and African ancestries (rs2066702; $P = 2.2 \times 10^{-9}$). Significant genetic correlations were observed with 17 phenotypes, including schizophrenia, attention deficit–hyperactivity disorder, depression, and use of cigarettes and cannabis. The genetic underpinnings of AD only partially overlap with those for alcohol consumption, underscoring the genetic distinction between pathological and nonpathological drinking behaviors.

Excessive alcohol use is a leading contributor to morbidity and mortality. One in 20 deaths worldwide is attributable to alcohol consumption, as is 5.1% of the global burden of disease[1]. AD, as defined by the Fourth Edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[2], is a serious psychiatric disorder characterized by tolerance, withdrawal, loss of control over drinking, and excessive alcohol consumption despite negative health and social consequences. Among alcohol drinkers, 12% meet criteria for DSM-IV AD during their lifetimes[3]. In the United States, only 25% of those with AD ever receive treatment[4].

AD is moderately heritable (49% by a recent meta-analysis)[5] and numerous genome-wide association studies (GWAS) have aimed to identify loci contributing to this genetic variance (see ref. [6] for a review). According to one study, common single-nucleotide polymorphisms (SNPs) are responsible for as much as 30% of the variance in AD[7], but few have been identified to date. Variants in the genes responsible for alcohol metabolism, especially *ADH1B* and *ALDH2*, have been strongly implicated[8–13]. The association between AD (and related drinking phenotypes) and rs1229984, a missense SNP (Arg48His) in *ADH1B* that affects the conversion of alcohol to acetaldehyde, represents one of the largest common-variant effect sizes observed in psychiatry, with the His48 allele accelerating ethanol metabolism and affording an approximately threefold reduction in likelihood of AD across numerous studies[8,10]. Another functional polymorphism, rs671 in *ALDH2* (Glu504Lys), strongly affects alcohol metabolism by blocking conversion of acetaldehyde to acetate and has an even stronger effect on risk for AD, but is rare except in some Asian populations[8,12,13] *ADH1B* and *ALDH2* polymorphisms, however, only explain a small proportion of the heritable variation in AD in populations of European or African ancestry.

In this study, the Substance Use Disorders working group of the Psychiatric Genomics Consortium (PGC-SUD[14]) compiled the largest numbers of carefully diagnosed alcohol-dependent individuals and alcohol-exposed controls to date, from both case–control and family studies. These included substantial numbers of people with European ancestry (EU, $n = 46,568$, including 38,686 unrelated individuals) and people with admixed African-American ancestry (AA, $n = 6,280$, including 5,799 unrelated individuals) subjects. AD diagnoses were derived from clinician ratings or semistructured interviews following DSM-IV[2] criteria. Each study was subjected to stringent quality control before conducting GWAS within each population of each study, followed by a genome-wide meta-analysis. We estimated the SNP-heritability (h^2_g) of AD and examined the extent to which aggregate genetic variation in AD is related to traits from 45 other GWAS, including continuous measures of alcohol consumption. We also examined whether polygenic risk scores (PRS) derived from these analyses predicted alcohol dependence and related measures of problem drinking in three independent samples.

Results

GWAS meta-analyses. The transancestral discovery meta-analysis of GWAS of AD in 28 cohorts (Table 1 and Supplementary Table 1) identified a genome-wide significant (GWS; $P < 5 \times 10^{-8}$) association in the *ADH* gene cluster on chromosome 4 (Fig. 1 and Table 2). Examining this locus in each population (Fig. 2), rs1229984 in *ADH1B* was the strongest associated variant from the analysis in EU ($z = -7.13$, $P = 9.8 \times 10^{-13}$), while rs2066702, also in *ADH1B*, was the most significant variant in AA ($z = -5.98$, $P = 2.2 \times 10^{-9}$). Transancestral modeling reinforced the robust effects of rs1229984 and other *ADH1B* SNPs on liability to AD across inverse-variance weighted, random effects, and Bayesian models (Supplementary Fig. 1 and Supplementary Table 2).

Clumping the *ADH* locus for linkage disequilibrium (LD; $r^2 < 0.1$ within 500 kb) suggested multiple independent signals in both populations, with the differing leading alleles reflecting different LD structures and allele frequencies in each population (Table 2 and Supplementary Fig. 2). Conditional analyses controlling for rs1229984 and rs2066702 had limited power, but results showed limited attenuation of effect sizes between marginal and conditional analyses, consistent with the existence of additional independent effects in the region (Supplementary Table 3 and Supplementary Fig. 3). Suggestive independent signals in the

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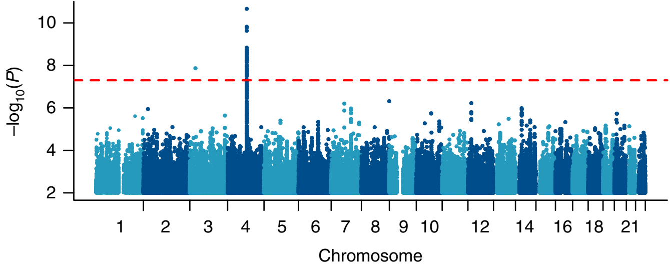


Fig. 1 | Manhattan plot of discovery transancestral meta-analysis showing strong evidence for rs1229984 in *ADH1B*. Results from the discovery meta-analysis of all cohorts (n_{case} = 14,904; $n_{control}$ = 37,944) for association of genome-wide SNPs with AD under a fixed effects meta-analysis weighted by effective sample size. Dashed red reference line indicates GWS after correction for multiple testing ($P < 5 \times 10^{-8}$).

genotyped cohorts included trialleleic variant rs894368 (marginal $z = -4.57$, $P = 4.9 \times 10^{-6}$; conditional $z = 4.53$, $P = 5.8 \times 10^{-6}$) and insertion rs112346244 (marginal odds ratio = 0.912, s.e. = 0.024, $z = -3.81$, $P = 1.4 \times 10^{-4}$; conditional odds ratio = 0.883, s.e. = 0.025, $z = -5.05$, $P = 4.5 \times 10^{-7}$; Supplementary Table 3). Several additional variants that were prioritized in the conditional analysis, while not significant, were in moderate to strong LD with rs698 (marginal odds ratio = 1.115, s.e. = 0.021, $z = 5.19$, $P = 2.1 \times 10^{-7}$; conditional odds ratio = 1.084, s.e. = 0.021, $z = 3.78$, $P = 1.6 \times 10^{-4}$), a functional *ADH1C* variant with a role in AD[8,11].

A single novel SNP on chromosome 3, rs7644567, also reached GWS in the meta-analysis ($z = 5.68$, $P = 1.36 \times 10^{-8}$; Supplementary Fig. 4). Potential biological associations with rs7644567, including chromatin contacts (Supplementary Fig. 5) and cerebellar expression of *RBMS3*, are summarized in Supplementary Methods. However, rs7644567 did not replicate in two independent AA samples (Yale–Penn 2 and Collaborative Study on the Genetics of Alcoholism (COGA) African-American Family GWAS (AAfGWAS)) or the independent FINRISK cohort; all three replication cohorts estimated effects of the minor allele in the opposite direction of the discovery meta-analysis (Supplementary Table 4; see Supplementary Information). The SNP is also rare in most EU samples (minor allele frequency (MAF) < 0.01), with the current GWAS results primarily attributable to AA cohorts, along with the Finnish Twin cohort (FinnTwin) and the Finnish Nicotine Addiction Genetics Project (NAG-Fin). The EU cohorts in the discovery meta-analysis show no evidence of association of AD with the SNPs in strongest LD with rs7644567 in African (rs13098461; $z = 0.27$, $P = 0.79$) or Finnish (rs9854300; $z = 0.10$, $P = 0.92$) reference samples (Supplementary Methods). Based on the clear lack of replication, there is insufficient evidence to conclude that rs7644567 is associated with AD based on the current results.

There was limited genome-wide evidence for heterogeneity across all cohorts, within ancestry, between ancestries, or between study designs within ancestry (Supplementary Methods and Supplementary Figs. 6–8). Evidence for inflation from population stratification or other confounding was also limited in the discovery meta-analysis ($\lambda = 0.962$; Supplementary Fig. 9) and within EU ($\lambda = 1.053$, LD score regression (LDSR) intercept = 1.018) and AA ($\lambda = 1.007$, LDSR intercept = 0.991–0.997; Supplementary Methods). Gene-level association testing with MAGMA[15] did not identify any additional significant genes in EU or AA (Supplementary Table 5 and Supplementary Methods), likely due to lack of power.

Heritability and genetic correlations. Liability-scale SNP-heritability of AD was estimated at $h^2_g = 0.090$ (s.e. = 0.019, $z = 4.80$, $P = 8.02 \times 10^{-7}$) in the meta-analysis of unrelated EU samples. Exclusion of the *ADH1B* locus did not substantially modify this estimate ($h^2_g = 0.089$, s.e. = 0.0185). Nominally significant polygenic signal for the meta-analysis of unrelated AA individuals was observed based on LDSR with scores computed from 1000 Genomes Project African populations ($z = 2.12$, $P = 0.017$), but the quantitative estimate of h^2_g was unstable depending on the choice of reference panel, reflecting the challenge of correctly specifying LDSR and robustly modeling LD for the AA population (Supplementary Methods).

Significant genetic correlation with AD in EU was observed for 17 traits after correction for multiple testing ($P < 1.11 \times 10^{-3}$ for 45 tested traits; Fig. 3 and Supplementary Table 6). The largest positive correlations were with smoking initiation ($r_g = 0.708$, s.e. = 0.134, $P = 1.3 \times 10^{-7}$) and lifetime cannabis initiation ($r_g = 0.793$, s.e. = 0.217, $P = 2.5 \times 10^{-4}$), as well as with other psychiatric disorders, especially schizophrenia ($r_g = 0.357$, s.e. = 0.054, $P = 3.2 \times 10^{-11}$), attention deficit–hyperactivity disorder ($r_g = 0.444$, s.e. = 0.097, $P = 4.2 \times 10^{-6}$), and depression ($r_g = 0.561$, s.e. = 0.085, $P = 3.5 \times 10^{-11}$). Educational attainment ($r_g = -0.468$, s.e. = 0.066, $P = 9.7 \times 10^{-13}$) and age at first birth (higher values indicate that participants were older when they had their first child; $r_g = -0.626$, s.e. = 0.104, $P = 2.0 \times 10^{-9}$) showed significant inverse genetic correlation with AD, suggesting that liability to AD risk was genetically related to lower educational attainment and lower age at which the participant had his or her first child.

Unexpected patterns of genetic correlation were observed when comparisons were made to other alcohol-related measures, indicating that those measures reflect aspects of alcohol use that are genetically distinguishable. AD was genetically correlated with alcohol consumption in a meta-analysis of the Alcohol Genome-wide Association (AlcGen) and Cohorts for Aging and Research in Genomic Epidemiology Plus (CHARGE+) consortia[16] ($r_g = 0.695$, s.e. = 0.155, $P = 6.9 \times 10^{-6}$), but only modestly with alcohol consumption from the recent large UK Biobank analysis[17] ($r_g = 0.371$, s.e. = 0.092, $P = 5.2 \times 10^{-5}$). No significant genetic correlation was observed between AD and a recent GWAS of the alcohol use disorders identification test (AUDIT) in a 23andMe cohort[18] ($r_g = 0.076$, s.e. = 0.171, $P = 0.656$), perhaps due to the low levels of drinking and drinking-related problems in that population[18]. AD is, however, nominally genetically correlated with GWAS of delay discounting in the 23andMe sample[19] ($r_g = 0.487$, s.e. = 0.178, $P = 6.0 \times 10^{-3}$).

Association with *ADH1B* expression. Based on the strong observed association with rs1229984 and rs2066702, we examined whether other variants affecting *ADH1B* expression (expression quantitative trait loci) were also associated with AD using GTEx v7 results (https://www.gtexportal.org/)[20]. Three variants, rs11939328 (EU, $P = 0.78$; AA $P = 0.98$; transancestral (trans), $P = 0.78$), rs10516440 (EU, $P = 3.97 \times 10^{-6}$; AA, $P = 1.97 \times 10^{-3}$; trans, $P = 4.72 \times 10^{-8}$), and rs7664780 (EU, $P = 0.87$; AA, $P = 0.083$; trans, $P = 0.405$), were selected after LD-informed clumping and the exclusion of variants in LD ($r^2 > 0.1$) with the GWS coding alleles rs1229984 and rs2066702. Of these, only rs10516440 (AD conditional analyses: EU, $P = 1.34 \times 10^{-3}$; AA, $P = 0.013$; trans, $P = 7.44 \times 10^{-5}$) was a significant multitissue expression quantitative trait locus in random effects analysis for *ADH1B* (fixed effects test statistic $S_{FE} = 319.4$, heterogeneity test statistic $S_{Het} = 27.6$, combined $P = 1.4 \times 10^{-76}$), *ADH1A* ($S_{FE} = 139.4$, $S_{Het} = 6.6$, combined $P = 6.72 \times 10^{-33}$), and *ADH1C* ($S_{FE} = 167.3$, $S_{Het} = 8.9$, combined $P = 1.9 \times 10^{-39}$). Rs10516440 is an LD proxy ($r^2 > 0.9$) of rs6827898 (Table 2) in populations of European and African descent. These variants are both located in an intergenic region in the *ADH* gene cluster between *ADH1C* and *ADH7*. In line with the fact that the protective coding alleles are associated with increased activity of the enzyme encoded by *ADH1B*, the major allele rs10516440*A was associated with increased *ADH1B* expression and reduced AD risk.

Table 1 | Descriptive statistics for cohorts in the meta-analysis of AD

Dataset	PMID	Male (%)	Ages (years)	EU				AA			
				n total		*n* unrelated		*n* total		*n* unrelated	
				Case	Control	Case	Control	Case	Control	Case	Control
Case–control: logistic regression											
Comorbidity and Trauma Study	23303482	56%	18–67	572	817	572	817	–	–	–	–
Christchurch Health and Development Study	23255320	48%	16–30	112	500	112	500	–	–	–	–
COGA case-control cohort (COGA-cc)	20201924	54%	18–79	583	363	583	363	–	–	–	–
Family Study of Cocaine Dependence	18243582	51%	18–60	266	174	266	174	255	241	255	241
German Study of the Genetics of Alcoholism (GESGA)	19581569	65%	18–84	1,314	2,142	1,314	2,142	–	–	–	–
Gene-Environment Development Initiative (GEDI): Great Smoky Mountains Study (GSMS)	8956679	57%	9–26	42	565	42	565	–	–	–	–
Center on Antisocial Drug Dependence	25637581	70%	13–20	400	577	400	577	51	51	51	51
Phenomics and Genomics Sample	28371232	57%	18–74	37	523	37	523	–	–	–	–
Collaborative Study on the Genetics of Nicotine Dependence (COGEND Nico)	17158188	34%	25–82	135	272	135	272	46	232	46	232
COGEND Study of Addiction: Genetics and Environment (COGEND SAGE)	20202923	37%	18–77	311	225	311	225	104	103	104	103
Spit For Science	24639683	36%	>18	252	1,863	252	1,863	74	841	74	841
NIAAA	n/a	67%	>18	442	206	442	206	404	110	404	110
Mayo Clinic Center for the Individual Treatment of Alcohol Dependence	25290263	55%	≥18	378	646	378	646	–	–	–	–
Alcohol Dependence in African Americans	n/a	57%	18–69	–	–	–	–	794	297	794	297
Family-based, twins, and siblings: generalized estimating equations											
Brisbane Longitudinal Twin Study	23187020	43%	18–30	60	938	51	546	–	–	–	–
GEDI Virginia Twin Study on Adolescent Behavioral Development (VTSABD)	9294370	38%	8–32	209	503	188	318	–	–	–	–
Minnesota Center for Twin and Family Research	23942779	41%	16–21	609	2,100	553	1,274	–	–	–	–
Center for Education and Drug Abuse Research	21514569	63%	16–34	59	200	54	152	–	–	–	–
Swedish Twin Registry	23137839	47%	40–83	76	8,311	76	6,112	–	–	–	–
Yale-Penn	24166409	58%	16–79	1,094	301	1,004	252	–	–	–	–
Family-based, large, or complex pedigrees: logistic mixed model											
COGA family cohort (COGA-fam)	23089632	45%	12–88	605	682	168	138	–	–	–	–
Australian Alcohol and Nicotine Studies	21529783	45%	18–82	1,571	3,069	1,111	805	–	–	–	–

Continued

Table 1 | Descriptive statistics for cohorts in the meta-analysis of AD (continued).

Dataset	PMID	Male (%)	Ages (years)	EU				AA			
				n total		*n* unrelated		*n* total		*n* unrelated	
				Case	Control	Case	Control	Case	Control	Case	Control
Irish Affected Sib Pair Study of Alcohol Dependence	15770118	50%	17–84	721	1,814	436	1,802	–	–	–	–
Yale–Penn	24166409	51%	16–79	–	–	–	–	1,607	1,070	1,263	933
Summary statistics											
Netherlands Study of Depression and Anxiety & Netherlands Twin Registry	18197199	31%	>18	390	1,633	390	1,633	–	–	–	–
Finnish Nicotine Addiction Genetics Project (NAG-Fin)	17436240	52%	30–92	439	1,137	439	1,137	–	–	–	–
FinnTwin12	17254406	47%	20–27	88	874	88	874	–	–	–	–
National Longitudinal Study of Adolescent to Adult Health (Add Health)	25378290	47%	24–34	768	2,981	768	2,981	–	–	–	–
Helsinki Birth Cohort Study	16251536	43%	56–70	36	1,583	36	1,583	–	–	–	–
Total				**11,569**	**34,999**	**10,206**	**28,480**	**3,335**	**2,945**	**2,991**	**2,808**

Overview of numbers of individuals with AD (cases) and controls from each cohort in the current analysis, including the number of genetically unrelated individuals. Cohorts are listed by study design and analysis method. Sample sizes are listed after quality control exclusions and stratified by ancestry group. PubMed identifiers (PMID) are listed for previous publications describing each cohort, along with the percentage of male samples and the age range in the cohort.

Associations with other GWS loci. We examined results for the eight independent variants associated at GWS levels with alcohol consumption in the UK Biobank[17] (Supplementary Table 7). Among the UK Biobank findings, three of the four reported variants in the *ADH* region of chromosome 4 (rs145452708, a proxy for rs1229984 with $D'=1$, rs29001570 and rs35081954) were associated in the present study with AD (*P* values ranging from 3.5×10^{-5} to 2.3×10^{-10}) with sign-concordant effects; the remaining variant was excluded from our analysis due to MAF < 0.01. The UK Biobank lead variant in *KLB*, rs11940694, was nominally associated with AD ($P=0.0097$), though this did not surpass multiple-testing correction for the eight GWS alcohol consumption loci. We saw little evidence ($P>0.2$) for association of AD with the reported loci at *GCKR* and *CADM2*, which may be due to differences in power for the given effect size or because these genes exert an influence on liability to consume alcohol but not later problems. The locus on chromosome 18 showed limited regional association with AD, but the index variant was not present in our analysis because it no longer appears in the 1000 Genomes Project Phase 3 reference panel[21].

Polygenic risk score analyses. PRS based on our meta-analysis of AD were significantly predictive of AD outcomes in all three tested external cohorts. PRS derived from the unrelated EU GWAS predicted up to 0.51% of the variance in past month alcohol use disorder in the Avon Longitudinal Study of Parents and Children (ALSPAC; $P=0.0195$; Supplementary Fig. 10a) and up to 0.3% of problem drinking in Generation Scotland ($P=7.9\times10^{-6}$; Supplementary Fig. 10b) as indexed by the CAGE (Cutting down, Annoyance by criticism, Guilty feelings, and Eye-openers) questionnaire. PRS derived from the unrelated AA GWAS predicted up to 1.7% of the variance in alcohol dependence in the COGA AAfGWAS cohort ($P=1.92\times10^{-7}$; Supplementary Fig. 10c).

Notably, PRS derived from the unrelated EU GWAS showed much weaker prediction (maximum $r^2=0.37\%$, $P=0.01$; Supplementary Fig. 10d) in the COGA AAfGWAS than the ancestrally matched AA GWAS-based PRS despite the much smaller discovery sample for AA. In addition, the AA GWAS-based AD PRS also still yielded significant variance explained after controlling for other genetic factors (r^2 = 1.16%, P = 2.5 × 10^{-7}). Prediction of CAGE scores in Generation Scotland remained significant and showed minimal attenuation ($r^2=0.29\%$, $P=1.0\times10^{-5}$) after conditioning on PRS for alcohol consumption derived from UK Biobank results[17]. In COGA AAfGWAS, the AA PRS derived from our study continued to predict 1.6% of the variance in alcohol dependence after inclusion of rs2066702 genotype as a covariate, indicating independent polygenic effects beyond the lead *ADH1B* variant (Supplementary Methods).

Power analysis. Power analyses indicated that the current meta-analysis is expected to have at least 41% power to detect very common variants (MAF ≥ 0.25) with odds ratios ≥ 1.10 at $P<5\times10^{-8}$ and 63% power for $P<1\times10^{-6}$ (Supplementary Fig. 11). Power at $P<1\times10^{-6}$ is relevant because only five loci reach that threshold in the current meta-analysis. Power is lower for less-common variants (MAF ≤ 0.05) even with odds ratios ≥ 1.20 at $P<1\times10^{-6}$ (60% power) and $P<5\times10^{-8}$ (38% power).

For perspective, power computations using the observed distribution of top effects for other large GWAS of polygenic traits suggest that we observed significantly fewer GWS loci for AD than would be expected if the loci had true effect sizes and allele frequencies similar to schizophrenia (expected: 25.4 loci, 95% confidence interval: 21–30) or obesity (expected: 8.9 loci, 95% confidence interval: 6–12), but not fewer than would be expected for effect sizes similar to major depression (Supplementary Methods and Supplementary Table 8).

Discussion

To our knowledge, this is the largest GWAS of rigorously defined AD to date, comprising 14,904 AD individuals and 37,944 controls. We identified known loci in *ADH1B* that differed between EU and AA, as well as previously uncharacterized genetic correlations between AD and psychiatric disorders (for example, schizophrenia), tobacco and cannabis use, and social (for example, socioeconomic deprivation) and behavioral (for example, educational attainment) outcomes. Analyses also revealed a genetic distinction between GWAS results for alcohol consumption and AD.

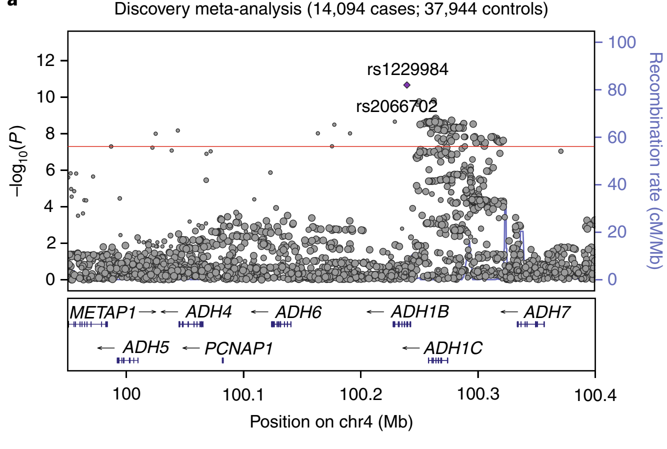
Table 2 | Top ten loci from the meta-analyses of AD by ancestry

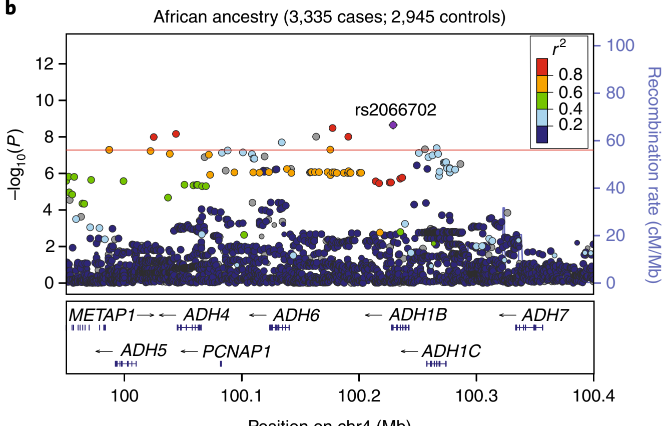
SNP	Chr	BP	A1	A2	Gene	A1 allele frequency		INFO score		Effect size (OR)		Discovery meta-analysis *P* value		
						EU	AA	EU	AA	EU	AA	EU	AA	Trans
Top clumped variants in transancestral meta-analysis (14,904 cases; 37,944 controls)														
rs7644567*	3	29201672	A	G	*RBMS3*	0.964	0.705	0.96	1.00	–	1.229	3.94×10^{-4}	6.64×10^{-6}	**1.36×10^{-8}**
rs2066702	4	100229017	A	G	*ADH1B*	–	0.215	–	0.99	–	0.731	–	**2.21×10^{-9}**	**2.21×10^{-9}**
rs1229984	4	100239319	T	C	*ADH1B*	0.040	0.014	0.90	0.91	0.486	0.912	**9.79×10^{-13}**	3.48×10^{-1}	**2.18×10^{-11}**
rs1789912	4	100263942	T	C	*ADH1C*	0.418	0.132	1.00	1.02	1.106	1.211	1.98×10^{-7}	1.32×10^{-3}	**1.47×10^{-9}**
rs6827898	4	100295863	A	G	(*ADH* region)	0.123	0.112	0.96	0.94	1.145	1.270	5.21×10^{-7}	9.31×10^{-4}	**2.97×10^{-9}**
rs894368	4	100309313	A	C	(*ADH* region)	0.309	0.386	0.99	0.96	0.887	0.981	**1.93×10^{-8}**	9.73×10^{-1}	3.30×10^{-7}
rs2461618	7	68667233	A	G	–	–	0.088	–	0.98	–	0.669	–	6.30×10^{-7}	6.30×10^{-7}
rs116338421	8	145761256	C	G	*ARHGAP39*	–	0.172	–	0.97	–	0.755	–	4.86×10^{-7}	4.86×10^{-7}
rs79171978	12	17798824	C	G	–	0.099	0.027	0.99	0.99	1.201	1.016	5.47×10^{-8}	8.18×10^{-1}	5.98×10^{-7}
rs8017647	14	32456358	T	C	–	0.792	0.565	1.00	0.99	0.901	0.923	8.05×10^{-6}	4.71×10^{-2}	1.03×10^{-6}
Top clumped variants in African ancestry meta-analysis (3,335 cases; 2,945 controls)														
rs5781337	1	223883425	CA	C	–	0.263	0.212	0.98	0.93	1.007	0.664	8.85×10^{-1}	1.62×10^{-7}	6.59×10^{-2}
rs143258048	3	75982870	A	AC	*ROBO2*	–	0.028	–	0.88	–	0.490	–	1.86×10^{-6}	–
rs3857224	4	100129685	T	C	*ADH6*	0.315	0.585	0.99	1.00	0.970	0.814	2.40×10^{-1}	5.86×10^{-7}	2.36×10^{-3}
rs2066702	4	100229017	A	G	*ADH1B*	–	0.215	–	0.99	–	0.731	–	**2.21×10^{-9}**	**2.21×10^{-9}**
rs2461618	7	68667233	A	G	–	–	0.088	–	0.98	–	0.669	–	6.30×10^{-7}	6.30×10^{-7}
rs116338421	8	145761256	C	G	*ARHGAP39*	–	0.172	–	0.97	–	0.755	–	4.86×10^{-7}	4.86×10^{-7}
rs79016499	11	93010988	T	C	–	–	0.066	–	0.93	–	1.729	–	1.36×10^{-6}	–
rs10784244	12	62035165	G	A	–	0.153	0.484	1.00	1.00	1.041	1.226	6.26×10^{-2}	1.04×10^{-6}	2.49×10^{-4}
rs17199739	16	25444288	G	A	–	0.176	0.096	0.99	0.96	0.994	0.693	4.25×10^{-1}	1.11×10^{-6}	8.66×10^{-3}
rs740793	17	3846353	G	A	*ATP2A3*	0.453	0.350	0.97	0.97	0.996	1.370	4.66×10^{-1}	1.48×10^{-6}	3.44×10^{-1}
Top clumped variants in European ancestry meta-analysis (11,569 cases; 34,999 controls)														
rs1229984	4	100239319	T	C	*ADH1B*	0.040	0.014	0.90	0.91	0.486	0.912	**9.79×10^{-13}**	3.48×10^{-1}	**2.18×10^{-11}**
rs3811802	4	100244221	G	A	*ADH1B*	0.454	0.529	0.96	0.96	1.162	0.914	**2.40×10^{-8}**	2.19×10^{-2}	1.22×10^{-4}
rs113659074	4	100252308	T	G	*ADH1B*	0.068	0.093	0.98	0.95	0.800	1.166	1.54×10^{-6}	6.63×10^{-2}	2.99×10^{-4}
rs1229863	4	100252386	A	T	*ADH1B*	0.174	0.038	0.99	0.99	1.145	1.254	7.80×10^{-7}	4.26×10^{-2}	9.28×10^{-8}
rs1154445	4	100288521	G	T	(*ADH* region)	0.425	0.134	0.97	0.99	1.137	1.211	1.80×10^{-7}	2.63×10^{-2}	**1.48×10^{-8}**
rs6827898	4	100295863	A	G	(*ADH* region)	0.123	0.112	0.96	0.94	1.145	1.270	5.21×10^{-7}	9.31×10^{-4}	**2.97×10^{-9}**
rs894368	4	100309313	A	C	(*ADH* region)	0.309	0.386	0.99	0.96	0.887	0.981	**1.93×10^{-8}**	9.73×10^{-1}	3.30×10^{-7}
rs79171978	12	17798824	C	G	–	0.099	0.027	0.99	0.99	1.201	1.016	5.47×10^{-8}	8.18×10^{-1}	5.98×10^{-7}
rs4388946	12	17935154	C	A	–	0.240	0.297	0.99	0.98	1.137	0.950	7.14×10^{-7}	1.87×10^{-1}	7.05×10^{-5}
rs34929220	15	69769635	T	C	*DRAIC*	0.690	0.937	0.90	0.94	0.893	1.028	1.02×10^{-6}	8.38×10^{-1}	7.38×10^{-6}

Top ten nominally independent variants from the discovery transancestral (trans.; $n_{case}=14{,}904$; $n_{control}=37{,}944$) meta-analysis and the discovery meta-analyses in AA ($n_{case}=3{,}335$; $n_{control}=2{,}945$) and EU ($n_{case}=11{,}569$; $n_{control}=34{,}999$) ancestry cohorts, respectively. Independent variants are identified based on clumping for LD (pairwise $r^2<0.1$) in 1000 Genomes Project Phase 3 data[21]. EU results are clumped using European ancestry reference samples, AA results are clumped using African ancestry reference samples from the American Southwest, and transancestral results are clumped using merged European and African ancestry reference samples. *P* values and allele frequencies are reported from two-tailed tests of association with AD in fixed-effects meta-analyses weighted by effective sample size. Bold *P* values indicate GWS after correction for multiple testing within the analysis ($P<5\times10^{-8}$). Odds ratios (OR) and INFO scores are reported from the meta-analyses of the subset of unrelated individuals within each ancestry. Variants are sorted by chromosome (Chr) and base pair (BP) position for genome build hg19, with genes annotated by Ensembl VEP[49]. Allele frequency and OR are given with respect to allele 1 (A1). SNPs included in the transancestral meta-analysis were not conditioned on being analyzed in both the EU and AA analyses. For instance, a SNP of strong effect in one group may not be sufficiently common or well-imputed for analysis in the other ancestral group (for example, rs2066702 is not found in non-African populations but is among the top ten in the transancestral analysis due to strong effects in the AA group). For rs7644567 (denoted with *), the SNP did not pass quality control in a sufficient number of cohorts to meet the minimum sample-size requirement for inclusion in the EU-only analyses—it is only represented among EU cohorts by summary statistics from two Finnish cohorts—but allele frequency, INFO score, and meta-analyzed *P* values from the Finnish summary statistics are reported since they contribute to the transancestral meta-analysis.

Although larger sample sizes can be amassed by focusing on quantitative measures of consumption, only the upper tail is relevant to AD (as a medical diagnosis), and even that does not capture other aspects of disordered drinking (for example, loss of control, withdrawal) directly. Conversely, cases derived from electronic medical records (for example, International Classification of Diseases (ICD) codes) result in a high rate of false negatives, while self-screening instruments (for example, AUDIT scores) are best suited to analyses of disordered drinking when a sufficiently high threshold or score cutoff is applied to focus on severity. Our study has the advantage of greater diagnostic precision via use of semistructured interviews to diagnose AD systematically in a majority of the constituent studies and therefore greater interpretability in the context of clinically important AD.

The GWS SNPs reaffirm the importance of functional variants affecting alcohol metabolism to the risk of AD. The top association in *ADH1B*, rs1229984, is a missense variant that is amongst the most widely studied in relation to alcohol use, misuse, and





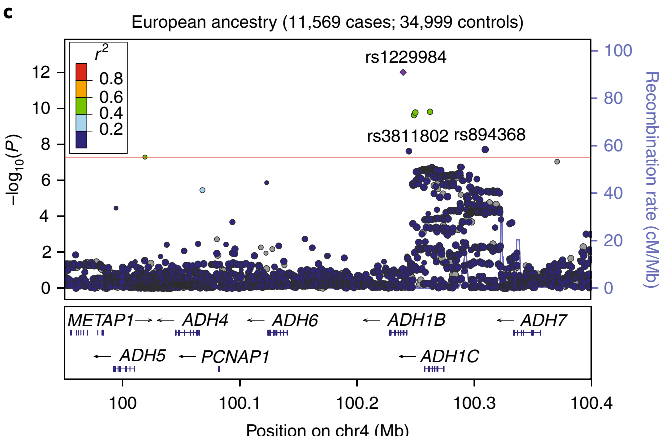


Fig. 2 | Regional plots for the *ADH1B* locus (rs1229984) in the transancestral discovery, AA, and EU meta-analyses. a–c, Results of fixed effects meta-analysis with effective sample-size weights for the *ADH1B* locus in (**a**) all cohorts ($n_{case}=14{,}904$; $n_{control}=37{,}944$); (**b**) AA cohorts ($n_{case}=3{,}335$; $n_{control}=2{,}945$); and (**c**) EU cohorts ($n_{case}=11{,}569$; $n_{control}=34{,}999$). Red reference line indicates the GWS threshold after correction for multiple testing within each analysis ($P<5\times10^{-8}$). Within ancestry, colored points reflect the degree of LD (pairwise r^2) to the index variant (purple diamond) in 1000 Genomes Project reference data[21] for individuals of (**b**) African or (**c**) European ancestry, respectively. LD structures in the two ancestries differ, so for the transancestral sample (**a**), LD is not given, indicted by gray points. Two-tailed tests used for all analyses. Chr4, chromosome 4.

dependence[8–10]. The resulting amino acid substitution (Arg48His) increases the rate at which alcohol dehydrogenase 1B oxidizes ethanol to acetaldehyde[8]. Studies on Asian populations in which the derived allele is common demonstrated strong protection against the development of AD[8,9,13]. In EU and AA, the protective allele is present at much lower frequencies (EU, MAF = 0–4%; AA, MAF < 1%); nevertheless, recent large-scale studies have shown an association between this locus and alcohol consumption and problems at GWS levels in EU with similar effect size[8–10]. The lead variant in AA cohorts, rs2066702 (Arg370Cys), is another functional missense variant in *ADH1B*, and it also encodes an enzyme with an increased rate of ethanol oxidation[8]. The allele encoding Cys370 is common in AA, but rare in other populations[8]. Our results clearly show that these two different functional SNPs in *ADH1B* both affect risk for alcoholism, with their relative importance dependent upon allele frequency in the population studied. There is a suggestion of additional independent effects in the chromosome 4 region, but larger studies will be needed to evaluate this.

The only other locus to reach significance was rs7644567 on chromosome 3, primarily driven by AA cohorts. The locus failed to replicate in two small, independent AA samples, and in the only European cohort with even a modest allele frequency (FINRISK), the effect was in the opposite direction. There have also been discussions about whether the standard GWAS significance threshold should be applied to the more genetically diverse African-ancestry cohorts[22,23] and about the possibility of confounding from nonlinear relationships between phenotypes and ancestry-informative markers like rs7644567 in admixed samples[24], all of which increase our skepticism regarding this finding. There is, therefore, insufficient evidence at this time to conclude that rs7644567 is associated with alcohol dependence. Analyses of much larger samples of African ancestry will be needed to resolve this.

Despite limited SNP-level findings, there is significant evidence for polygenic effects of common variants in both EU and AA cohorts. The estimated $h^2_g=0.09$ for AD in EU is only modestly lower than those recently reported for alcohol consumption ($h^2_g=0.13$)[17] and AUDIT scores ($h^2_g=0.12$)[18], and it is comparable to estimates derived for cigarettes-per-day[25]. Our h^2_g estimate is lower than that of a prior report[7], likely reflecting a combination of differences in estimation method (genomic relatedness matrix restricted maximum likelihood (GREML) versus LDSR) and greater heterogeneity in ascertainment strategy across samples in the current study (see refs [26–28]). The latter is especially relevant in comparing h^2_g from that prior single cohort to our meta-analysis, which included cohorts with a wide range of ages at ascertainment, cultural environments, and ascertainment strategies, including enrichment for other substance use disorders. Similarly to other psychiatric disorders (for example, schizophrenia), a much larger sample size will potentially aid in overcoming across-sample heterogeneity and will capture a greater proportion of genetic variance.

Comparing our GWAS to recent GWAS of alcohol consumption measures suggests that the liability underlying normative patterns of alcohol intake and AD are only partially overlapping. Genome-wide genetic correlations were significantly < 1 with log-scaled alcohol consumption by participants in AlcGen and CHARGE+ Consortia cohorts[16] ($r_g=0.695$, s.e. = 0.15, one-tailed $P=0.024$ for $r_g<1$) and in the UK Biobank[17] ($r_g=0.371$, s.e. = 0.092, one-tailed $P=3.2\times10^{-12}$ for $r_g<1$). We also observed only partial replication of the eight loci significantly associated with consumption in the UK Biobank, with strongest results from SNPs in the *ADH* region, including a proxy for rs1229984. In addition, there was no significant correlation with GWAS of log-scaled AUDIT scores in 23andMe participants[18] ($r_g=0.076$, s.e. = 0.171, two-tailed $P=0.656$). Subsequent analyses suggest these estimates are sensitive to sample characteristics, with somewhat higher genetic correlations reported in analysis of alcohol consumption in the full UK Biobank[29] ($r_g=0.75$) and of AUDIT in combined data from 23andMe participants and UK Biobank[30] ($r_g=0.39$). Notably, initial UK Biobank data includes a subset of participants recruited for a study of smoking and lung function in the

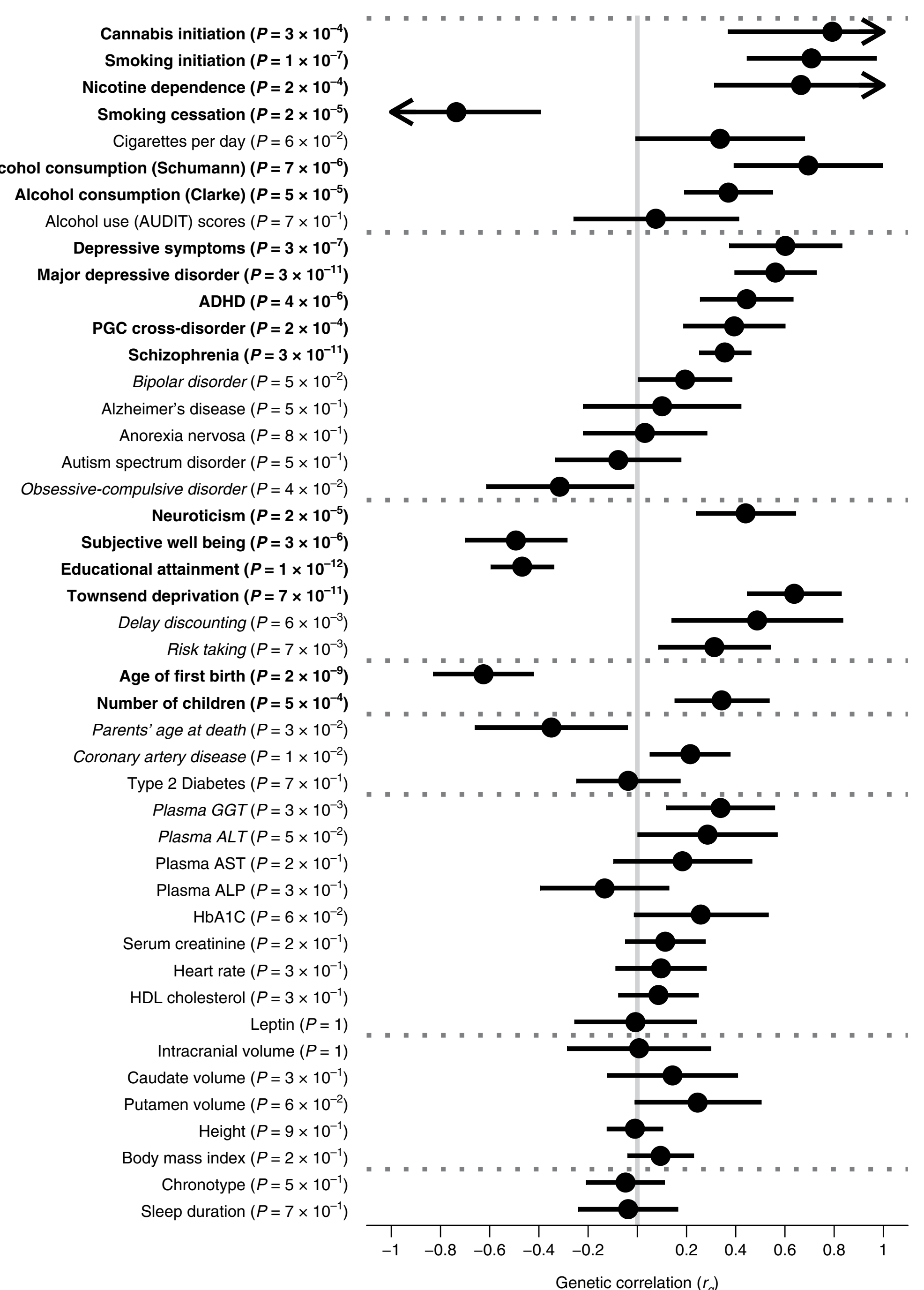


Fig. 3 | Genetic correlations between 45 traits and alcohol dependence in Europeans. Genetic correlation results from LDSR with the meta-analysis of AD in unrelated EU individuals ($n_{case}=10{,}206$; $n_{control}=28{,}480$). After Bonferroni correction, significant correlations were observed with 17 traits and disorders ($P<1.1\times10^{-3}$; bold), with nominally significant results for eight additional traits and disorders ($P<0.05$; italics) based on two-tailed tests of the estimated genetic correlation with block jackknife standard errors. Error bars indicate 95% confidence intervals; arrows indicate intervals extending above 1 or below –1. Vertical gray reference line corresponds to the null hypothesis of no genetic correlation with AD. Phenotypes are organized by research domain. ADHD, attention deficit–hyperactivity disorder; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

first analysis[17], which may have resulted in collider bias[31] and contributed to the initial lower genetic correlation.

One key factor in interpreting the differences between these traits and AD is that the distribution of consumption levels and AUDIT scores can be highly skewed in population samples, with most individuals at the low (nonpathological) end of the spectrum. This effect may be especially pronounced among the older, healthy volunteers of the UK Biobank cohort[32] and in the 23andMe cohort, which is more educated and has higher socioeconomic status than the general US population[18]. We hypothesize that the variants that affect consumption at lower levels may differ substantively from those that affect very high levels of consumption in alcohol dependent individuals, who are also characterized by loss of control over intake[33]. This appears to be the case in studies that used specific cut-offs to

harmonize AUDIT scores with AD data[30,34]. The larger of these studies[30] reports that the genetic correlation between AD and AUDIT scores is maximized at an AUDIT cutoff ≥ 20 (with controls defined as those scoring ≤ 4; r_g = 0.90). Notably, that study also found that a score reflecting items related to problem drinking (AUDIT-P) resulted in a stronger genetic correlation (r_g = 0.64) than a score related to alcohol consumption alone (r_g = 0.33). The strong genetic correlation of AD with lower educational attainment and lower socioeconomic status (i.e., higher Townsend deprivation), in contrast to positive genetic correlations of education with consumption[17] and AUDIT scores related to consumption[30], further underscore this distinction between normative or habitual levels of alcohol intake and diagnosed AD, at least in the respective populations studied.

The current analysis identified robust genetic correlation of AD with a broad variety of psychiatric outcomes. This correlation was strongest for aspects of negative mood, including neuroticism and major depression, as also seen in twin studies[35,36] and through recent specific molecular evidence for pleiotropy[37,38]. Taken together with evidence from other recent genomic studies[37], and with null correlations for other GWAS of alcohol consumption but not for measures of problem drinking (for example, AUDIT-P), these findings suggest that major depression may primarily share genetic liability with alcohol use at pathological levels.

AD was also strongly genetically correlated with poor educational and socioeconomic outcomes and marginally correlated with measures of risk-taking. Nominally significant genetic correlations with delay discounting (i.e., favoring immediate rewards) and risk-taking, and the strong genetic correlation of AD with attention deficit–hyperactivity disorder, cigarette smoking, and cannabis use, may similarly reflect a shared genetic factor for risk-taking and reduced impulse control. Common genetic liability to early, risky behaviors is characteristic of both AD[39] and age of first birth[40]. The observed negative genetic correlation with age of first birth is consistent both with risk-taking and with the significant genetic correlations of AD with lower socioeconomic status, as indexed by higher neighborhood Townsend deprivation score and lower educational attainment. Lower socioeconomic status is correlated with both AD[41] and age of first birth[42], and the current study suggests that shared genetic liabilities may be one potential mechanism for their observed relationship. However, the question of whether these genetic correlations represent causal processes, horizontal pleiotropy, or the impact of unmeasured confounders should be explored in the future[43].

Lower genetic correlations were observed for most biomedical and anthropometric outcomes. Liver enzymes GGT and ALT, once proposed as possible biomarkers for alcohol abuse[44], showed only nominal evidence for genetic correlation with AD, and neither survived multiple-testing correction. Notably, we did not find any association between AD and body-mass index (BMI). Negative genetic correlations with BMI were previously reported for both alcohol consumption[17] and AUDIT scores[18], but there is prior evidence that BMI has differing underlying genetic architectures in the context of AD and outside of that context[45]. The negative genetic correlations observed in those studies are consistent with studies of light to moderate drinking, which is also associated with healthier lifestyle behaviors, while heavy and problematic drinking is typically associated with weight gain[46].

This study benefited from precision in diagnostic assessment of AD, known alcohol exposure in a majority of the controls, and careful quality control that excluded overlap of individuals between studies. Despite these strengths, our sample size was insufficient to identify additional GWS loci robustly. Power analyses indicate that additional SNPs associated with AD are likely to have small effect sizes, smaller than schizophrenia[47] and more consistent with more common psychiatric disorders (for example, major depression[48]). This supports the pressing need for collection of large numbers of well-characterized cases and controls. The differences between our results and the study of AUDIT scores[18] highlight that ascertainment and trait definition are critically important and must be taken into account. Careful study of how screening tools, such as the AUDIT, correlate with genetic liability to AD (as defined by DSM-IV or similar) could substantially boost sample sizes for future AD GWAS. There is also a continued need to characterize the genetic architecture of AD in non-EU populations.

We show a previously unreported genetic distinction between drinking in the pathological range (AD) and habitual drinking that does not cross the threshold into pathology or dependence and does not capture behavioral aspects of disordered drinking. Larger future samples will allow us to uncover additional pleiotropy between pathological and nonpathological alcohol use, as well as between AD and other neuropsychiatric disorders.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41593-018-0275-1.

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Competing interests

L.J.B., A.M.G., J.P.R., J.-C.W. and the spouse of N.L.S. are listed as inventors on Issued US Patent 8080,371, "Markers for Addiction" covering the use of certain SNPs in determining the diagnosis, prognosis, and treatment of addiction. N.W. has received funding from the German Research Foundation (DFG) and Federal Ministry of Education and Research Germany (BMBF); he has received speaker's honoraria and travel funds from Janssen-Cilag and Indivior. He took part in industry-sponsored multicenter randomized trials by D&A Pharma and Lundbeck. M. Ridinger received compensation from Lundbeck Switzerland and Lundbeck institute for advisory boards and expert meetings, and from Lundbeck and Lilly Suisse for workshops and presentations. K.M. received honoraria from Lundbeck, Pfizer, Novartis, and AbbVie. K.M. also received Honoraria (Advisory Board) from Lundbeck and Pfizer and speaker fees from Janssen Cilag. H.K. has been an advisory board member, consultant, or continuing medical education speaker for Indivior, Lundbeck, and Otsuka. He is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was sponsored in the past three years by AbbVie, Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, and Pfizer. H.K. and J.G. are named as inventors on PCT patent application #15/878,640, entitled "Genotype-guided dosing of opioid agonists," filed 24 January 2018. P.F., S.L.E., and members of the 23andMe Research Team are employees of 23andMe. M.A.F. has received grant support from Assurex Health, Mayo Foundation, Myriad, NIAAA, National Institute of Mental Health (NIMH), and Pfizer; he has been a consultant for Intra-Cellular Therapies, Inc., Janssen, Mitsubishi Tanabe Pharma Corporation, Myriad, Neuralstem Inc., Otsuka American Pharmaceutical, Sunovion, and Teva Pharmaceuticals. H.d.W. has received support from Insys Therapeutics and Indivior for studies unrelated to this project, and she has consulted for Marinus and Jazz Pharmaceuticals, also unrelated to this project. T.L.W. has previously received funds from ABMRF. J.N. is an investigator for Janssen and Assurex. M.M.N. has received honoraria from the Lundbeck Foundation and the Robert Bosch Stiftung for membership on advisory boards. M. Ridinger has received honoraria from Lundbeck Switzerland and the Lundbeck Institute for membership of advisory boards and participation in expert meetings, and from Lundbeck and Lilly Suisse for workshops and presentations. N.S. has received honoraria from Abbvie, Sanofi-Aventis, Reckitt Benckiser, Indivior, Lundbeck, and Janssen-Cilag for advisory board membership and the preparation of lectures, manuscripts, and educational materials. Since 2013, N.S. has also participated in clinical trials financed by Reckitt Benckiser and Indivior. N.W. received speaker's honoraria and travel expenses from Janssen-Cilag and Indivior; has also participated in industry-sponsored multicenter randomized trials conducted by D&A Pharma and Lundbeck. W.G. has received symposia support from Janssen-Cilag GmbH, Neuss, Lilly Deutschland GmbH, Bad Homburg, and Servier, Munich, and is a member of the Faculty of the Lundbeck International Neuroscience Foundation (LINF), Denmark. J.A.K. has provided consultations on nicotine dependence for Pfizer (Finland) 2012–2015. In the past three years, L.D. has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior, Mundipharma, and Seqirus. B.M.N. is a member of the scientific advisory board for Deep Genomics and has consulted for Camp4 Therapeutics Corporation, Merck & Co., and Avanir Pharmaceuticals, Inc. A.A. previously received peer-reviewed funding and travel reimbursement from ABMRF for unrelated research.

Additional information

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Methods

Samples. The Substance Use Disorders working group of the Psychiatric Genomics Consortium (PGC-SUD[14]) collected individual genotypic data from 14 case–control studies and nine family-based studies and summary statistics from GWAS of AD from five additional cohorts (Table 1). AD was defined as meeting criteria for a DSM-IV[2] (or, for one cohort, DSM-IIIR[50]; a very similar construct; see Supplementary Note) diagnosis of AD. Diagnoses were derived either from clinician ratings or semistructured interviews. Excepting three cohorts with population-based controls ($n = 7{,}015$), all controls were screened for AD. Individuals with no history of drinking alcohol and those meeting criteria for DSM-IV alcohol abuse were excluded as controls where possible (Supplementary Information and see Nature Research Reporting Summary). This study was approved by the institutional review board (IRB) of Washington University in St. Louis and was conducted in accordance with all relevant ethical regulations. Each contributing cohort obtained informed consent from their participants and received ethics approvals for their study protocols from their respective review boards in accordance with applicable regulations.

Quality control and imputation. Data for the cohorts that shared raw genotypes were deposited to a secure server for uniform quality control (QC). QC and imputation of the 14 case–control studies was performed using the Ricopili pipeline (https://github.com/Nealelab/ricopili). For the nine family-based cohorts, an equivalent pipeline, Picopili (https://github.com/Nealelab/picopili), was developed for QC, imputation, and analysis appropriate for diverse family structures, including twins, sibships, and extended pedigrees (Supplementary Information).

After initial sample and variant QC, principal components analysis (PCA) was used to identify population outliers for exclusion and to stratify samples in each study by continental ancestry. Identified EU and AA ancestry populations were confirmed by PCA using the 1000 Genomes Project reference panel[21] (Supplementary Fig. 12). Ancestry within these two groups was accounted for with principal components. Final sample and variant QC, including filters for call rate, heterozygosity, and departure from Hardy–Weinberg equilibrium (HWE), was then performed within each ancestry group in each cohort. Samples were also filtered for cryptic relatedness and for departures from reported pedigree structures (Supplementary Information and Nature Research Reporting Summary).

Each cohort was imputed using SHAPEIT[51] and IMPUTE2[52], using the cosmopolitan (all ancestries) 1000 Genomes Project reference panel consistent with prior recommendations[53] (see also refs [47,54,55]). Concordance of MAFs with the reference panel was verified before imputation, with SNPs in EU cohorts compared to MAF in European population samples and AA cohorts compared to MAF in African population samples (Supplementary Information). Instances of cryptic relatedness between cohorts were identified and excluded after imputation (Supplementary Information). Imputed SNPs were then filtered for INFO score > 0.8 and allele frequency > 0.01 before analysis.

Association analysis. A GWAS of AD status was performed within each ancestry stratum of each sample using an association model appropriate for the study design (Table 1 and Supplementary Table 1). For case–control studies, GWAS was performed using logistic regression with imputed dosages. For family-based studies of small, simple pedigrees (for example, sibships), association with imputed genotypes was tested using generalized estimating equations (GEE). For more complex pedigrees, imputed genotypes were tested using logistic mixed models. Sex was included as a covariate, along with principal components to control for population structure (Supplementary Information, Supplementary Note, and Supplementary Figs. 13 and 14).

In addition to this primary analysis, subsets of genetically unrelated individuals were selected from each family-based cohort (i.e., the most severe case in each family, by symptom count, was selected, followed by selection of unrelated/married-in controls) and used to perform a conventional case–control GWAS using logistic regression. This was used in place of the family-based GWAS for estimation of effect sizes and LD score regression analyses (Supplementary Table 2).

Genome-wide meta-analysis. The primary discovery meta-analysis of all ancestry-stratified GWAS ($n_{case} = 14{,}904$; $n_{control} = 37{,}944$) was conducted in METAL[56]. As the different study designs (family vs. case–control) produced effect sizes that were not comparable, results were combined using weighting by effective sample size (Supplementary Information and Supplementary Note). Separate ancestry-specific discovery meta-analyses of EU ($n = 46{,}568$) and AA ($n = 6{,}280$) cohorts were also performed. Heterogeneity was evaluated across all cohorts and between study designs (Supplementary Information).

In addition to the discovery meta-analyses, we conducted meta-analyses for two design subsets. First, we performed sample size weighted meta-analysis of the subset of genetically unrelated individuals in EU ($n = 38{,}686$) and AA ($n = 5{,}799$) cohorts for use in LD score regression (LDSR) analysis. Second, we performed inverse-variance weighted meta-analysis of genetically unrelated individuals in genotyped cohorts to estimate within-ancestry effect sizes for EU ($n = 28{,}757$) and AA ($n = 5{,}799$). These effect sizes were then used to compare transancestral fine mapping results using inverse-variance weighted fixed effects, random effects[57], and Bayesian[58] models (Supplementary Information). Supplementary Table 2 summarizes all of the meta-analytic models considered in the current analysis.

Replication. A novel locus on chromosome 3 was genome-wide significant (GWS) in the transancestral discovery meta-analysis. To seek replication, we examined the association between this locus and DSM-IV AD in two independent AA samples: Yale–Penn 2 (911 individuals with AD; 599 controls; tested using GEE) and COGA AAfGWAS (880 individuals with AD; 1,814 controls; tested using GWAF[59]). Association with AD status, broadly defined using hospital and death records, was also examined in the FINRISK cohort (1,232 individuals with AD; 22,614 controls) using Firth logistic regression[60] (Supplementary Information and Nature Research Reporting Summary).

Power analysis. Post hoc power analysis was performed for odds ratios ranging from 1.05 to 1.30 and across allele frequencies using CaTS[61] with the estimated effective sample size. Power analysis identifies the range of SNP effect sizes the current study was likely to detect at genome-wide significance if such effects exist. Additionally, we made specific comparisons to the distribution of effects for schizophrenia[47], obesity[62], and major depression[48] as meaningful benchmarks to understand the magnitude of effect sizes plausible for AD (Supplementary Information and Nature Research Reporting Summary).

Heritability and genetic correlation analysis. LDSR analysis[63] was performed to estimate the heritability explained by common SNPs in meta-analyses of unrelated EU and AA samples, respectively. LDSR was performed using HapMap3 SNPs and LD scores computed from 1000 Genomes Project reference samples corresponding to each population (Supplementary Information). Conversion of h^2_g estimates from observed to liability scale[64] was performed assuming population prevalences of 0.159 and 0.111 for AD in alcohol-exposed EU and AA individuals, respectively[3]. Gene-level enrichments were also tested with MAGMA[15] (Supplementary Information).

Genetic correlations between AD and 45 traits from LD Hub[25] and other published studies[16–19,65–71] were examined using LDSR with the same unrelated EU meta-analysis (10,206 individuals with AD and 28,480 controls) and precomputed European ancestry LD scores. LDSR compares GWAS results for pairs of traits to estimate the correlation in the genetic liabilities explained by all common SNPs in the LD reference panel. To avoid increasing the multiple-testing burden, redundant or highly correlated phenotypes were reduced by manually selecting the version of the phenotype with the greatest predicted relevance to AD, largest sample size, or highest heritability (Supplementary Information).

Polygenic risk scores. To test the generalizability of the current GWAS results, polygenic risk scores (PRS) were computed in three external cohorts (Supplementary Information and Nature Research Reporting Summary). PRS computed from EU ancestry results were used to predict alcohol dependence in ALSPAC[72,73] and COGA AAfGWAS, and CAGE screener scores in Generation Scotland (GS)[74]. PRS based upon the AA results were used to predict alcohol dependence in COGA AAfGWAS (Supplementary Information).

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SAGE: dbGap phs000092.v1.p1.
COGEND: dbGap phs000404.v1.p1.
GEDI Duke University (GSMS): dbGap phs000852.v1.p1.
Center on Antisocial Drug Dependence: dbGap submission in process.
Spit for Science: dbGap submission in process.
NIAAA: available via https://btris.nih.gov/.
GEDI Virginia Commonwealth University (VTSABD): dbGap submission in process.
Minnesota Center for Twin and Family Research: dbGap phs000620.v1.p1.
Yale–Penn: dbGap phs000425.v1.p1 and phs000952.v1.p1.
See Data Availability for information on accessing other cohorts.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Code availability. Code for GWAS of case/control cohorts with Ricopili is available at https://github.com/Nealelab/ricopili. Code for GWAS of family-based cohorts with Picopili is available at https://github.com/Nealelab/picopili. Code and reference data for LD score regression analyses are available at https://github.com/bulik/ldsc. Effective sample size calculations were implemented using output from PLINK (https://www.cog-genomics.org/plink2), GMMAT (https://content.sph.harvard.edu/xlin/software.html#gmmat), and geepack (https://cran.r-project.org/web/packages/geepack/index.html) in R (https://cran.r-project.org/); stand-alone software for this purpose hasn't been written but example code is available from the first author upon reasonable request.

Data availability

Summary statistics from the genome-wide meta-analyses are available on the Psychiatric Genomics Consortium's downloads page (http://www.med.unc.edu/pgc/results-and-downloads), including the source data for Figs. 1 and 2. Individual-level data from the genotyped cohorts and cohort-level summary statistics will be made available to researchers following an approved analysis proposal through the PGC Substance Use Disorder group with agreement of the cohort PIs; contact the corresponding authors for details. Cohort data are also available from dbGaP except where prohibited by IRB or European Union data restrictions. Expression data used to evaluate variants in *ADH1B* is available from GTEx (https://gtexportal.org/home/). Hi-C data used to evaluate the chromosome 3 variant can be queried with HUGIn (https://yunliweb.its.unc.edu/hugin/). Publicly available genome-wide summary statistics used for testing genetic correlations are accessible through LD Hub (http://ldsc.broadinstitute.org/) or from the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc/results-and-downloads), the Social Science Genetic Association Consortium (SSGAC; https://www.thessgac.org/data), Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA; http://enigma.ini.usc.edu/research/download-enigma-gwas-results/), and the Neale Lab (http://www.nealelab.is/uk-biobank); for availability of summary statistics from other studies, contact the respective authors. The source data for Fig. 3 is included in Supplementary Table 6.

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Reporting Summary

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When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Data collecting (phenotyping and genotyping) was performed previously by each cohort. Details on data collection in each cohort have been described previously, see the Supplementary Information for a full list of references. Broadly, phenotyping was not specifically dependent on specialized software (though may have, for example, been stored in a software system such as REDCap, https://projectredcap.org/), and genotyping was performed using standard genotype calling pipelines outside of the scope of the current study.
Data analysis	Quality control, imputation, and GWAS of case/control cohorts was performed using ricopili (https://github.com/Nealelab/ricopili), which includes wrappers around PLINK, Eigenstrat, LifeOver, SHAPEIT, IMPUTE2, and METAL. Quality control, imputation, and GWAS of family-based cohorts was performed with picopili (https://github.com/Nealelab/picopili), which additionally includes wrappers of PRIMUS, ADMIXTURE, REAP, GMMAT, and geepack. Trans-ancestral meta-analyses were performed with METASOFT and MANTRA. PRSice was used for polygenic risk score analyses. LD score regression analyses were performed with ldsc (https://github.com/bulik/ldsc) and the LD Hub web tool (ldsc.broadinstitute.org). Gene-based analyses were performed with the FUMA web tool (http://fuma.ctglab.nl/), which uses MAGMA. Analyses related to local ancestry calling included scripts from Alicia Martin (https://github.com/armartin/ancestry_pipeline) using HAPI-UR and RFMix. Power analysis was performed using CaTS. Plots were generated using R, LocusZoom (http://locuszoom.org/), LDlink (https://analysistools.nci.nih.gov/LDlink/), and HUGIn (https://yunliweb.its.unc.edu/hugin/).

All of the above are publicly available, with the exception of MANTRA which is available from the method's developer (Andrew Morris). Relevant links and citations are all provided in the manuscript.

Remaining calculations, most notably the effective sample size calculations used for meta-analyses across study designs/association models, were performed using ad hoc scripts. Example code is available from the first author by request.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Summary statistics from the genome-wide meta-analyses are available on the Psychiatric Genomics Consortium's downloads page (http://www.med.unc.edu/pgc/results-and-downloads), including the source data for Figures 1 and 2. Individual-level data from the genotyped cohorts and cohort-level summary statistics will be made available to researchers following an approved analysis proposal through the PGC Substance Use Disorder group with agreement of the cohort PIs; contact the corresponding authors for details. Cohort data are also available from dbGaP except where prohibited by IRB or European Union data restrictions. Expression data used to evaluate variants in ADH1B is available from GTEx (https://gtexportal.org/home/). Hi-C data used to evaluate the chromosome 3 variant can be queried with HUGIn (https://yunliweb.its.unc.edu/hugin/). Publicly available genome-wide summary statistics used for testing genetic correlations are accessible through LD Hub (http://ldsc.broadinstitute.org/), or from the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc/results-and-downloads), the Social Science Genetic Association Consortium (SSGAC; https://www.thessgac.org/data), Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA; http://enigma.ini.usc.edu/research/download-enigma-gwas-results/), and the Neale Lab (http://www.nealelab.is/uk-biobank); for availability of summary statistics from other studies contact the respective authors. The source data for Figure 3 is included in Supplementary Table S6.

Accession Codes
Comorbidity and Trauma Study (CATS): dbGAP accession phs000277.v1.p1
Center for Education and Drug Abuse Research (CEDAR): dbGAP accession phs001649.v1.p1
Christchurch Health and Development Study (CHDS): dbGAP submission in process
The Collaborative Study on the Genetics of Alcoholism (COGA): dbGaP accession numbers phs000125.v1.p1, phs000763.v1.p1, and phs000976.v1.p1
Study of Addiction: Genetics and Environment (SAGE): dbGAP accession phs000092.v1.p1
Collaborative Genetic Study of Nicotine Dependence (COGEND): dbGAP accession phs000404.v1.p1
Gene-Environment-Development Initiative (GEDI) – Duke University (GSMS): dbGAP accession phs000852.v1.p1
Center on Antisocial Drug Dependence (CADD): dbGAP submission in process
Spit for Science: dbGAP submission in process
NIAAA: available via https://btris.nih.gov/
Gene-Environment-Development Initiative (GEDI) –Virginia Commonwealth University (VTSABD): dbGAP submission in process
Minnesota Center for Twin and Family Research (MCTFR): dbGAP accession phs000620.v1.p1
Yale-Penn: dbGAP accession phs000425.v1.p1 and phs000952.v1.p1

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

Sample size was not predetermined, but instead reflects our best effort to aggregate all possible studies with genome-wide genotype data and robust phenotyping of alcohol dependence according to the DSM-IV criteria used in the current study. This open, international collaboration supported by the Psychiatric Genomics Consortium includes contributions from 28 studies (plus 3 replication cohorts and 2), and to our knowledge represents the largest genome-wide study of alcohol dependence to date.

Based on the available data, we have made efforts to maximize the use of the genotyped samples. This includes developing the infrastructure and appropriate statistical modeling to include both family-based and case/control cohorts in the same genome-wide analysis, and including trans-ancestral analysis of both European and African ancestry individuals.

We have also performed power analysis for the current genome-wide study, as detailed in the manuscript. For instance, we estimate that the full discovery meta-analysis has >80% power to detect variants associated with alcohol dependence with true odds ratios >= 1.15 and minor allele frequency > 0.15. We have also provided comparisons of power with other GWAS (e.g., schizophrenia, depression, obesity). This power and sample size are consistent with successful GWAS of many other complex traits.

Data exclusions	Data exclusions were performed based on (a) failure of pre-determined data quality control criteria and (b) planned phenotype exclusions to avoid confounds in defining alcohol dependence cases and controls. For quality control, individuals were excluded if they were observed to have low genotyping quality (i.e. high missingness rates), excess heterozygosity (an indicator of possible sample contamination or other technical artifacts), or if they deviated from reported family pedigree structures (i.e. excessive mendelian error rates, discordance between genetically-inferred and reported sex, cryptic genetic relatedness to unrelated individuals, or lack of expected genetic relatedness to members of the same pedigree). Observed outliers of genetic ancestry, as determined by principal components analysis, were also excluded in order to avoid the known risk of population stratification in genome-wide studies including such individuals. Ancestries other than African or European were excluded due to insufficient sample size for a meaningful analysis in the currently available data. For phenotype-based exclusions, we omit individuals lacking phenotype information for alcohol dependence, individuals who report never being exposed to alcohol, and individuals meeting criteria for alcohol abuse (i.e. qualifying neither as alcohol dependence cases or healthy controls). Cohorts with other exclusion criteria as part of their original study recruitment are detailed in the Supplementary Information. The metrics used as exclusion criteria were established prior to the analyses, but some thresholds used for exclusion (e.g. threshold from principal components analysis to define ancestry strata) were evaluated during the QC process. All of the above exclusions were made in accordance with the planned study protocol, and are detailed in the manuscript.
Replication	The primary genome-wide significant locus identified in the current study (i.e. the ADH1B locus) is itself a replication of previous studies of alcohol dependence (see manuscript for references). For the novel genome-wide significant locus on chromosome 3, we present more targeted replication analysis from 3 additional cohorts of African and Finnish ancestries relevant to the putative signal. As described in the manuscript, replication was not found. We rely on this lack of replication to conclude that there is not sufficient evidence for an effect of the chr. 3 locus, with the result observed in the discovery sample potentially reflecting confounding from ancestry or an increased multiple testing burden. We also evaluate the consistency of effects in this locus between European and African ancestry cohorts and across study designs as a form of internal replication. These tests find very little evidence of any heterogeneity, indicating that the reported results have generally consistent evidence across ancestry and study design. Polygenic risk score analyses also provide generalizability of the overall results in both European and African ancestry cohorts. In all instances, polygenic risk scores derived from effect sizes in this study successfully predicted alcohol-related phenotypes in other studies as expected. The only instance of poor prediction was that effect sizes from the EA discovery GWAS in this study only weakly predicted alcohol dependence in an independent AA sample (COGA AAfGWAS), which is consistent with prior observations about cross-population polygenic prediction. The strong sample size requirements of the secondary analyses (most notably LD score regression analyses of heritability and genetic correlation to other traits) and dependence on LD reference panels limits options for direct replication of those findings. We instead focus on comparisons to existing GWAS of other alcohol-related phenotypes to get potential insight into how genome-wide results appear to generalize between these phenotypes in different study populations. The compelling findings from those comparisons are a key result for the current analysis and are discussed at length in the manuscript.
Randomization	Randomization of experimental groups was not applicable to this study. The experimental conditions are determined by each individual's genetics, which are fixed at conception. Conceptually this reflects a randomization of the alleles inherited from each individual's parents (i.e. mendelian randomization), but it does not involve randomization of experimental conditions by the researchers in a classical sense. Our study assess the observed association between that natural randomization of genotype and the ascertained phenotype of alcohol dependence.
Blinding	Blinding is not relevant to the current study. Samples were not allocated to different conditions by the researches, and the phenotype ascertainment process is fully separate from the genotyping process.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	The current study encompasses 14,904 cases and 37,944 controls from 28 cohorts in the primary analysis (after quality control), with an additional 2,997 cases and 25,318 controls from 3 replication cohorts and 9,629 individuals in 2 other cohorts used for

polygenic risk score analysis. Details on each cohort are provided in the manuscript, with summary descriptives in Table 1 and full descriptions in the Supplementary Information.

Briefly, included participants represent a mix of ascertainment schemes across cohorts, including both population-based collections and ascertained research cohorts. These include studies of genetically unrelated cases and controls, as well as family-based studies ranging from sibling pairs to extended pedigrees ascertained for enrichment of substance abuse. Overall, the participants include roughly equal numbers of males and females, with ages fully distributed across the lifespan for adults. Participants are from North America, Europe, and Australia and are of European or African ancestry (confirmed in genetic data), with African ancestry individuals predominantly reflecting African-American admixture.

Genome-wide genotype data has been collected for all participants. Most individuals in the primary analysis were analyzed using the individual level genotype data, but a subset (N=9,929 from 5 cohorts) are only represented in summary statistics from their respective cohorts. The 3 replication cohorts are also only analyzed through contributed summary statistics.

Phenotyping criteria vary by cohort (full descriptions in the manuscript supplement), but for most cohorts a standardized measure such as the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) or the Composite International Diagnostic Interview (CIDI) has been administered to ascertain lifetime alcohol dependence status in accordance with DSM-IV diagnostic guidelines. Current treatment data has not been collected for all participants, but is not critical to the current research question of genetic associations with lifetime dependence diagnosis.

Recruitment

Participants were recruited separately for each cohort according to their respective study design. Descriptions of the design for each cohort can be found in the Supplementary Information, along with references to previous publications containing complete details.

Overall, the cohorts represent a mix of population-based cohorts without targeted ascertainment (e.g. birth cohorts from a specified region), cohorts recruited for studies of alcohol dependence (e.g. families of probands from inpatient or outpatient treatment facilities), or cohorts originally recruited for studies of other substance dependence (e.g. cocaine or nicotine) or other phenotypes where measures of alcohol dependence were included in phenotyping (e.g. schizophrenia, high-risk populations involved in the criminal justice system, or pharmacogenetics studies).

These recruitment strategies could yield biases in the results for a given cohort, but the mix of recruitment strategies used across the cohorts is unlikely to produces consistent biases across the current analysis. Instead, any different biases resulting from the variety of recruitment strategies and study designs would be more likely to manifest as heterogeneity or noise in results across the cohorts, potentially reducing power.