Genome-wide association and functional studies identify 46 novel loci for alcohol consumption and suggest common genetic mechanisms with neuropsychiatric disorders

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ABSTRACT

Excessive alcohol consumption is one of the main causes of death and disability worldwide. Alcohol consumption is a heritable complex trait. We conducted a genome-wide association study (GWAS) of alcohol use in ~480,000 people of European descent to decipher the genetic architecture of alcohol intake. We identified 46 novel, common loci, and investigated their potential functional significance using magnetic resonance imaging data, gene expression and behavioral studies in *Drosophila*. Our results identify new genetic pathways associated with alcohol consumption and suggest common genetic mechanisms with several neuropsychiatric disorders including schizophrenia.

Excessive alcohol consumption is a major public health problem that is responsible for 2.2% and 6.8% age-standardized deaths for women and men respectively[1]. Most genetic studies of alcohol use focus on alcohol dependency, although the burden of alcohol-related disease mainly reflects a broader range of alcohol consumption behaviors in a population[2]. Small reductions in alcohol intake could have major public health benefits; a recent study reported that even moderate daily alcohol may have significant impact on mortality[3].

Alcohol consumption is a heritable complex trait[4], but genetic studies to date have identified only a small number of robustly associated genetic variants [5-8]. These include variants in the aldehyde dehydrogenase gene family, a group of enzymes that catalyze the oxidation of aldehydes[9], including a cluster of genes on chromosome 4q23 (*ADH1B, ADH1C, ADH5, ADH6, ADH7*)[6].

Here, we report a GWAS meta-analysis of alcohol intake (g/day) among people of European ancestry drawn from UK Biobank (UKB)[10], the Alcohol Genome-Wide Consortium (AlcGen) and the Cohorts for Heart and Aging Research in Genomic Epidemiology Plus (CHARGE+) consortia. Briefly, UKB is a prospective cohort study of ~500,000 individuals recruited between the ages of 40-69 years. Participants were asked to report their average weekly and monthly alcohol consumption through a self-completed touchscreen questionnaire[10]. Based on these reports, we calculated the gram/day (g/d) alcohol intake (**Online Methods**). Participants were genotyped using a customized array with imputation from the Haplotype Reference Consortium (HRC) panel[11], yielding ~7 million common single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) ≥ 1% and imputation quality score [INFO] ≥ 0.1. After quality control (QC) and exclusions (**Online Methods**) we performed GWAS of alcohol consumption using data from 404,731 UKB participants of European descent under an additive genetic model (**Online Methods and Supplementary Table 1**). We found that genomic inflation in the UKB analysis was λ_{GC}=1.45, but did not adjust for inflation as the LD score regression intercept was 1.05, indicating that this was due to polygenicity rather than to population stratification[12]. The estimated SNP-wide heritability of alcohol consumption in the UKB data was 0.09.

We also carried out GWAS in 25 independent studies from the AlcGen and CHARGE+ consortia including 76,111 participants of European descent for which alcohol g/d could be calculated (**Supplementary Table 2**). Various arrays were used for genotyping, with imputations performed using either the 1,000 Genomes Reference Panel or the HRC platforms (**Supplementary Table 3**). After QC, we applied genomic control at the individual study level and obtained summary results for ~7 million SNPs with imputation quality score ≥ 0.3 (**Online Methods**).

We combined the UKB, AlcGen and CHARGE+ results using a fixed effects inverse variance weighted approach for a total of 480,842 individuals[13]. To maximize power, we performed a single-stage analysis to test common SNPs with MAF ≥ 1%. We set a stringent *P*-value threshold of $P < 5 \times 10^{-9}$ to denote significance in the combined meta-analysis[14], and required signals to be significant at $P < 5 \times 10^{-7}$ in UKB, with same direction of effect in UKB and AlcGen plus CHARGE+, to minimize false positive findings. We excluded SNPs within 500kb of variants reported as genome-wide significant in previous GWAS of alcohol consumption[5,6], identified novel loci by requiring SNPs to be independent of each other (LD $r^2 < 0.1$), and selected the sentinel SNP within each locus according to lowest *P*-value (**Online Methods**).

We then tested for correlations of alcohol-associated SNPs with Magnetic Resonance Imaging (MRI) phenotypes of brain, heart and liver, and gene expression. Associations of the sentinel SNPs with other traits/diseases were investigated and *Drosophila* mutant models used to test for functional effects on ethanol-induced behavior.

RESULTS

Our meta-analysis identified 46 novel loci associated with alcohol consumption (log transformed g/day) **(Fig. 1 and Table 1**). We discovered eight additional variants in the combined analysis at nominal genome-wide significance ($P < 1 \times 10^{-8}$) that may also be associated with alcohol intake (**Supplementary Table 4**). The most significantly associated variant, rs1991556 ($P < 4.5 \times 10^{-23}$), is an intronic variant in *MAPT* gene that encodes the microtubule-associated protein tau, and was found through Phenoscanner not only to be associated with dementia[15] and Parkinson's disease[16,17], but also with neuroticism, schizophrenia[18]and other conditions[19-21] (**Online Methods, Fig. 2 and Supplementary Table 5**). The second most significantly associated variant is rs1004787 ($P < 6.7 \times 10^{-17}$), near *SIX3* gene, which encodes a member of the sine oculis homeobox transcription factor family involved in eye development[22]. The third SNP is rs13107325 ($P < 1.3 \times 10^{-15}$), a missense SNP in *SLC39A8*, a gene that encodes a member of the SLC39 family of metal ion transporters, which has been associated with schizophrenia[23] as well as inflammatory bowel disease, cardiovascular and metabolic phenotypes [24 25-27] in previous GWAS (**Fig. 2 and Supplementary Table 5**).

Another of our most significant variants, an intronic SNP rs7121986 ($P < 6.2 \times 10^{-14}$) in *DRD2*, encodes the dopamine receptor D2 that has been associated with cocaine addiction, neuroticism and schizophrenia[18]. We also found significant associations with SNP rs988748 ($P < 4.4 \times 10^{-9}$) in the gene encoding BDNF (brain-derived neurotrophic factor) and rs7517344, which is near *ELAVL4* ($P = 2.0 \times 10^{-10}$), the gene

product of which is involved in BDNF regulation[28]. Previous studies have suggested that variation in *BDNF* is a genetic determinant of alcohol consumption and that alcohol consumption modulates BDNF expression[29].

Additionally, we found association of alcohol consumption with SNP rs838145 ($P < 3.2 \times 10^{-15}$), which has been associated with macronutrient intake in a previous GWAS[30]. This variant is localized to *IZUMO1*, a locus of around 50kb that spans a number of genes including *FGF21*, whose gene product FGF21 is a liver hormone involved in the regulation of alcohol preference, glucose and lipid metabolism[31]. We previously reported significant association of alcohol intake with SNP rs11940694 in *KLB*, an obligate receptor of FGF21 in the brain[5], and strongly replicated that finding here ($P = 3.3 \times 10^{-68}$).

As well as variants in *KLB*, we found support ($P < 1 \times 10^{-5}$) for association of common variants in all four of the other previously reported alcohol intake-related loci (**Supplementary Table 6**). These replicated loci include SNP rs6943555 in *AUTS2* ($P = 2.9 \times 10^{-6}$) and variants in the alcohol dehydrogenase locus (lowest $P = 1.2 \times 10^{-125}$). In addition, we found a novel alcohol intake-related SNP rs1421085 in *FTO* in high LD ($r^2 = 0.92$) with a variant reported previously as genome-wide significant for association with alcohol dependence[32].

Conditional analysis using Genome-wide Complex Trait Analysis (GCTA) did not reveal any independent secondary signals related to alcohol consumption. Among ~14,000 individuals in the independent Airwave cohort[33] (**Online Methods**), 7% of the variance in alcohol consumption was explained by the novel and known common variants. Using weights from our analysis, we constructed an unbiased weighted genetic risk score (GRS) in Airwave (**Online Methods**) and found a strong association of the novel and known variants on alcohol consumption levels ($P = 2.75 \times 10^{-14}$), with mean difference in sex-adjusted alcohol intake of 2.6 g/d comparing the top vs the bottom quintile of the GRS (**Supplementary Table 7**).

Associations with MRI imaging phenotypes

We performed single-SNP analyses of the imaging phenotypes in UKB (**Online Methods**) to investigate associations of our novel variants with MRI of brain (N=9,702), heart (N=10,706) and liver (N=8,479). With Bonferroni correction (corrected *P*-value 6.6×10^{-6}, corresponding to 0.05/46 SNPs*164 imaging phenotypes), we found significant positive associations between rs13107325 and the volumes of multiple brain regions; the strongest associations were with putamen (left:

$P = 2.5 \times 10^{-45}$, right: $P = 2.8 \times 10^{-47}$), ventral striatum (left: $P = 9.5 \times 10^{-53}$, right: $P = 9.6 \times 10^{-51}$) and cerebellum (strongest association for left I-IV volume; $P = 1.2 \times 10^{-9}$) (**Supplementary Table 8**); similar findings were also recently reported in a GWAS on brain imaging in UKB[34]. The other significant association was for rs1991556 with the parahippocampal gyrus ($P = 1.2 \times 10^{-6}$).

We then tested these brain regions for association with alcohol consumption and found a significant effect for the left ($P = 2.0 \times 10^{-4}$) and right ($P = 2.6 \times 10^{-4}$) putamen. Finally, we used data from N= 8,610 individuals and performed a mediation analysis using a standard three-variable path model, bootstrapping 10,000 times to calculate the significance of the mediation effect of putamen volume for genetic influences on alcohol consumption (**Online Methods**). We found evidence that the effect of SNP rs13107325 in *SLC39A8* on alcohol intake is partially mediated via its association with left (beta=-0.27; $P = 1.9 \times 10^{-3}$) and right (beta=-0.26; $P = 1.7 \times 10^{-3}$) putamen volume (**Fig. 3 and Supplementary Table 9**).

We did not find any significant associations of novel SNPs with either cardiac (left ventricular mass or end diastolic volume or right ventricular end diastolic volume) (**Supplementary Table 10**) or liver fat measures on MRI (**Supplementary Table 11**), after adjustment for multiple testing.

Effects of SNPs on gene expression

We carried out expression quantitative trait loci eQTL analyses using the Genotype-Tissue Expression (GTEx) and the UK Brain Expression Consortium (UKBEC) datasets; 34 of the 53 novel and known SNPs associated with alcohol consumption have a significant effect on gene expression in at least one tissue, including 33 SNPs that affected gene expression in the brain (**Supplementary Tables 12 and 13, and Supplementary Fig. 1-4**). We found that the most significant eQTLs often do not involve the nearest gene and that several of the SNPs affect expression of different genes in different tissues (**Supplementary Fig. 4**). For example, SNP rs1991556 in the *MAPT* gene affects expression of 33 genes overall, with most significant effects on the expression of the non-protein coding genes *CRHR1-IT1 (*also known as *C17orf69* or *LINC02210*) and *LRRC37A4P*, near *MAPT*, across a wide range of tissues including brain, adipose tissue and skin ($P = 7.2 \times 10^{-126}$ to $P = 2.5 \times 10^{-6}$) **(Supplementary Fig. 4)**. Similarly, the A-allele at SNP rs2071305 within *MYBPC3* affects the expression of several genes and is most significantly associated with increased expression of *C1QTNF4* across several tissues ($P = 1.9 \times 10^{-25}$ to $P = 8.4 \times 10^{-5}$).

Several of these eQTLs were found to affect expression of genes known to be involved in reward and addiction. SNP rs1053651 in the *TCAP-PNMT-STARD3* gene cluster affects expression of the *PPP1R1B* gene (also known as *DARPP-32*) which encodes a protein that mediates the effects of dopamine in the mesolimbic reward pathway[35]. Other known addiction-related genes include *ANKK1* and *DRD2* (affected by SNP rs7121986) implicated in alcohol and nicotine dependence[36,37], *CRHR1* (affected by SNP rs1991556) involved in stress-mediated alcohol dependence[38,39] and *PPM1G* (SNP rs1260326) whose epigenetic modification was reported to be associated with alcohol abuse[40].

Over-representation enrichment analyses based on functional annotations and disease-related terms indicated that genes whose expressions are affected by the identified eQTLs are most significantly enriched for terms related to abdominal cancers (n = 91), motor function (n= 5) and cellular homeostasis (n= 22) (**Supplementary Fig 5**).

Other traits and diseases

Using LD score regression[12], we assessed genetic correlations between alcohol consumption and 235 complex traits and diseases from publicly available summary GWAS statistics (**Online Methods and Supplementary Table 14**). The strongest positive genetic correlations based on false discovery rate $P < 0.02$ were found for smoking (r_g= 0.42, $P = 1.0 \times 10^{-23}$) and HDL cholesterol levels (r_g= 0.26, $P = 5.1 \times 10^{-13}$). We also found negative correlations for sleep duration (r_g= -0.14, $P = 3.8 \times 10^{-7}$) and fasting insulin levels (r_g= -0.25, $P = 4.5 \times 10^{-6}$). A significant genetic correlation was also found with schizophrenia (r_g= 0.07, $P = 3.9 \times 10^{-3}$) and bipolar disorder (r_g= 0.15, $P = 5.0 \times 10^{-4}$) (**Supplementary Table 14**). Over-representation enrichment analysis using WebGestalt[41] showed that our list of novel and known variants are significantly enriched in several diseases and traits including developmental disorder in children ($P < 7.3 \times 10^{-5}$), epilepsy ($P < 1.4 \times 10^{-4}$), heroin dependence ($P = 5.7 \times 10^{-4}$) and schizophrenia ($P < 8.4 \times 10^{-4}$) (**Supplementary Fig. 6**). The result of Mendelian randomization analysis (**Online methods**) to assess a potential causal effect of alcohol on schizophrenia risk, using the inverse variance weighted approach, was not significant ($P = 0.089$), with large heterogeneity of the estimates of the tested variants.

Functional studies in *Drosophila*

Based on our GWAS and brain imaging findings we took forward SNP rs13107325 in *SLC39A8* (alias *Zip8* gene) for additional testing in *Drosophila*, which employ conserved mechanisms to modulate ethanol-induced behaviors[42,43]. First, we overexpressed human *Zip8* using a Gal4-driver that included expression in neurons

involved in multiple ethanol-induced behaviors[43]. Flies carrying *ics*^{Gal4}/+ *UAS-hZip8/+* showed a slight, but significant, resistance to ethanol-induced sedation compared to control flies (P = 0.026; N = 16 per genotype). Ethanol tolerance, induced with repeat exposures spaced by a 4-hour recovery, was unchanged in these flies (**Fig. 4a**). We next used the same Gal4-driver to knock down the endogenous *Drosophila* ortholog of *hZip8*, namely *dZip71B*. This caused the flies to display naïve sensitivity to ethanol-induced sedation, and in addition, these flies developed greater tolerance to ethanol upon repeat exposure (P = 0.0003; N = 8 per genotype) (**Fig. 4b**). To corroborate this phenotype, we then tested flies transheterozygous for two independent transposon-insertions in the middle of the *dZip71B* gene (**Supplementary Fig. 7**) and found that these *dZip71B*$^{Mi\ /\ MB}$ flies also displayed naïve sensitivity (P = 0.006) and increased ethanol-induced tolerance (P = 0.032), compared to controls (N = 8 each) (**Fig. 4c**).

DISCUSSION

Our discovery utilizing data on common variants from over 480,000 people of European descent has greatly extended our knowledge of the genetic architecture of alcohol intake, increasing the number of loci by nearly 10-fold to 46. We found loci involved in neuropsychiatric conditions such as schizophrenia, Parkinson's disease and dementia, as well as *BDNF* where gene expression is affected by alcohol abuse. Our findings illustrate that large-scale studies of genetic associations with alcohol intake in the general population, rather than in alcohol dependency alone, can provide new insights into genetic mechanisms regulating alcohol consumption.

We highlight the role of the highly pleiotropic *MAPT* and *SLC39A8* genes in the genetics of alcohol consumption. *MAPT* plays a key role in tau-associated dementia[44] and both genes are also implicated in other neuropsychiatric conditions including neuroticism, schizophrenia and Parkinson's disease[16-18]. The *SLC39A8* gene encodes a member of the SLC39 family of metal ion transporters. The encoded protein is glycosylated and found in plasma membrane and mitochondria, and is involved in the cellular transport of zinc, modulation of which could affect microglial inflammatory responses[45]. Our gain- and loss-of-function studies in *Drosophila* indicate a potential causal role of *SLC39A8* in alcohol drinking behavior. The MRI brain imaging demonstrates a significant association of SNP rs13107325 in the *SLC39A8* gene and putamen volume differences, and these structural differences appear to partially mediate associations of rs13107325 with alcohol consumption. The putamen has been associated with alcohol consumption and the withdrawal syndrome after chronic administration to rodents and non-human primates[46]. Putamen volume differences have also been associated with both schizophrenia and psychosis[47,48] and robust

association between SNP rs13107325 in *SLC39A8* and schizophrenia was reported in a previous GWAS[23].

We also report SNP rs7121986 near *DRD2* as a novel alcohol intake variant in GWAS. The gene product of *DRD2*, D2 dopamine receptor, is a G protein-coupled receptor on post-synaptic dopaminergic neurons that has long been implicated in alcoholism[49]. In addition, we identify SNP rs988748 in *BDNF* as a novel alcohol intake variant; BDNF expression is differentially affected by alcohol exposure in animal models[50,51]. Both genes (along with *PPP1R1P*) are centrally involved in reward-mediating mesocortico-limbic pathways and both are implicated in the development of schizophrenia. For example, there is a robust GWAS association between schizophrenia and SNP rs4938021 in *DRD2* (in perfect LD with our novel alcohol intake-related variant rs7121986) and *DRD2* appears to be pivotal in network analyses of genes involved in schizophrenia[52]. Taken together, our results suggest that there are shared genetic mechanisms between the regulation of alcohol intake and susceptibility to schizophrenia, as well as other neuropsychiatric disorders. In this regard, large prospective epidemiological studies report a three-fold risk of schizophrenia in relation to alcohol abuse[53].

We previously reported genome-wide significant associations of alcohol intake with *KLB*, and identified a liver-brain axis linking the liver hormone FGF21 with central regulation of alcohol intake involving β-Klotho receptor (the gene product of *KLB*) in the brain[5]. Here, we identify a significant variant near *FGF21* gene and strongly replicate the previously reported *KLB* gene variant, strengthening the genetic evidence for the importance of this pathway in regulating alcohol consumption.

The LD score regression analysis showed a positive genetic correlation between alcohol consumption, smoking and HDL cholesterol levels. This confirms previous findings that reported an almost identical genetic correlation of alcohol consumption with number of cigarettes per day[54]. Furthermore, the observed genetic correlation with HDL levels is consistent with previous observations of an association between alcohol consumption and HDL[55,56], including results of a Mendelian randomization study that suggested a possible causal role linking alcohol intake with increased HDL levels[57]. Finally, we found a genetic correlation (inverse) between sleep duration and alcohol consumption, an association previously reported only in a few small epidemiological studies[58]. We could not test for a genetic association between alcohol and risk of alcohol-related cancers[59] because of limited availability of summary data. However, our gene-set enrichment analysis showed a significant enrichment for genes related to abdominal cancers.

Strengths of our study include its size, detailed attention to the alcohol phenotype, dense coverage of the genome through imputation, incorporation of brain and other imaging data to explore potential mechanisms and confirmatory *Drosophila* functional genetic studies. Over 80% of the data came from UKB, which combines high-quality phenotypic data and imputed genome-wide genetic data with strict attention to quality control[60]. We adopted a stringent approach to claim novel variants involving a conservative *P*-value threshold, internal replication in UKB and consistent direction of effect with the other studies, to minimize the reporting of false positive signals.

However, since alcohol intake is socio-culturally as well as genetically determined, it is influenced by other lifestyle and environmental factors which may modify or dilute the genetic signal. A key limitation is that assessment of alcohol intake relies on self-report, which is prone to errors and biases including recall bias and systematic under-reporting by heavy drinkers[61,62]. Furthermore, questionnaires on alcohol intake covered a short duration (e.g. day or week) at a single period, which may not be representative of broader drinking patterns of cohort participants. We harmonized data across cohorts by converting alcohol intake into a common metric of g/d, with imputation as necessary in UKB for participants reporting consumption of small amounts of alcohol. Taking this approach, we were able to detect strong genetic associations with alcohol intake that explained 7% of the variance in alcohol in an independent cohort, while our GRS analysis indicates that individuals in the lower fifth of the GRS distribution were consuming daily approximately one third of a standard drink (2.6 g/d alcohol) less compared with those in the upper fifth.

In summary, in this large study of genetic associations with alcohol consumption, we identified common variants in 46 novel loci with several of the genes expressed in the brain as well as other tissues. Our findings suggest that there may be common genetic mechanisms underpinning regulation of alcohol intake and development of a number of neuropsychiatric disorders including schizophrenia. This may form the basis for greater understanding of observed associations between excessive alcohol consumption and schizophrenia[63].

URLs

GTEx: www.gtexportal.org
UKBEC: http://www.braineac.org/
WebGetstalt: http://www.webgestalt.org
IPA: www.qiagen.com/ingenuity
PhenoScanner: http://www.phenoscanner.medschl.cam.ac.uk (Phenoscanner integrates results from the GWAS catalogue: https://www.ebi.ac.uk/gwas/ and GRASP: https://grasp.nhlbi.nih.gov/)

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Conflicts/Disclosures

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Alcgen and Charge+ contributor: (ARIC): A.C.M., M.R.B., B.Y., D.E.A., (CHS): B.M.P., R.N.L., T.M.B., J.A.B., (FHS): D.L., C.L., (GAPP/Swiss-AF/Beat-AF): S.Thériault, S.A., D.C., L.R., M.Kühne, (GENOA): S.L.R.K., J.A.S., W.A., S.M.R., (GRAPHIC): N.J.S., C.P.N., P.S.B., (GS): A.M.M., T-K.C., C.H., D.P., (HBCS): L.J., S.Tuominen, M.M.P., J.G.E., (HRS): D.R.W., S.L.R.K., J.D.F., W.Z., J.A.S., (MESA): X.G., J.Y., A.W., J.I.R., (METSIM): M.L., A.S., J.Vangipurapu, J.K., (FUSION): M.B., K.L.M., L.J.S., A.U.J., (NESDA): B.W.J.H.P., Y.M., (NFBC): M-R.J., J.Veijola, M.Männikkö, J.A., (ORCADES): H.C., P.K.J, (VIKING): J.F.W., K.A.K., (Croatia-VIS): I.R., O.P., (Croatia-KORCULA): C.H., (PREVEND): N.V., P.v.d.H, (OZALC): M.G.N., J.B.W., P.A.L., A.C.H., (SHIP): A.T., H.J.G., S.E.B., G.H., (TRAILS-pop): A.J.O, I.M.N., (TRAILS-CC): C.A.H., H.Snieder , (TwinsUK): T.D.S, M.Mangino, (YFS): L-P.L., M.Kähönen, O.T.R., T.L.

All authors critically reviewed and approved the final version of the manuscript

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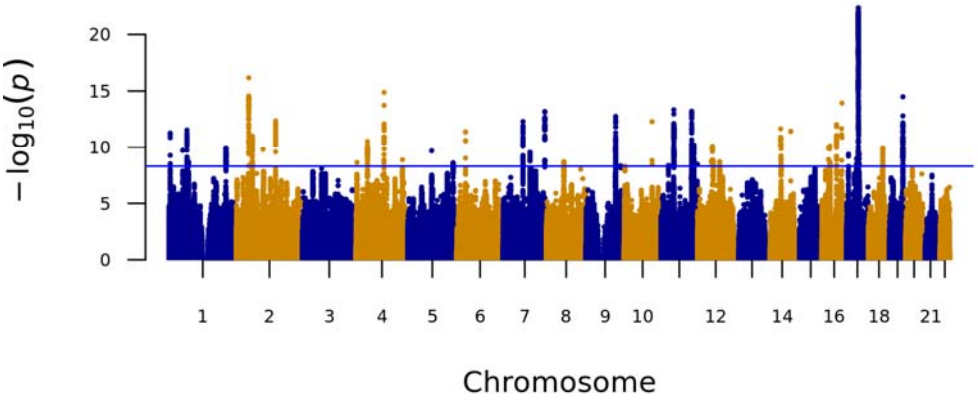
Figure 1. **Manhattan plot showing *P*-values from discovery genome-wide association meta-analysis with alcohol intake (g/d) among 480,842 individuals across UK Biobank, AlcGen and CHARGE+, excluding known variants.** The *P*-value was computed using inverse variance fixed effects models. The y axis shows the $-\log_{10} P$ values and the x axis shows their chromosomal positions. Horizontal blue line represents the threshold of $P = 5 \times 10^{-9}$.



568 **Figure 2**. **Association of alcohol intake loci with other traits**. Plot shows results
569 from associations with other traits which were extracted from the PhenoScanner
570 database for the 46 novel sentinel SNPs including proxies in Linkage Disequilibrium
571 ($r^2 \geq 0.8$) with genome-wide significant associations.

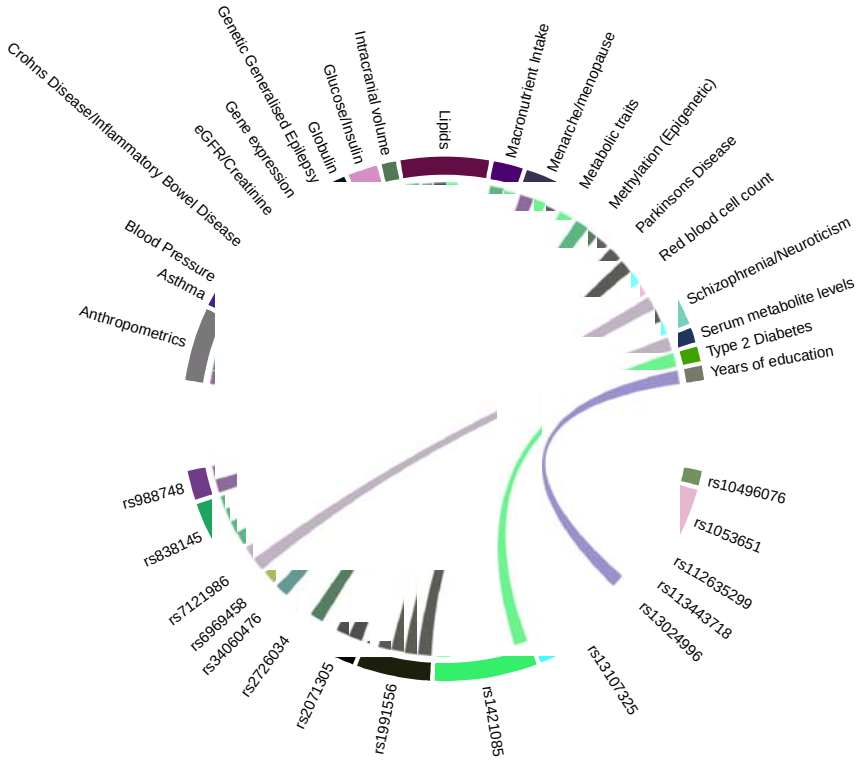


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Figure 3. **Mediation effect of bilateral putamen on the relationship between SNP rs13107325 and alcohol intake**. Left putamen is indicated by the green color whereas the right putamen by the red. a presents the association between rs13107325 and putamen, b is the association between putamen and alcohol consumption, c the association of rs13107325 and alcohol consumption, c' is the association between rs13107325 and alcohol consumption after excluding the effect of putamen, and ab is the mediation effect. The significance of the effect is based on bootstrapping. We provide the z-statistic for each relationship combined with *P*-values (** as $P < 0.005$, * as $P < 0.1$).

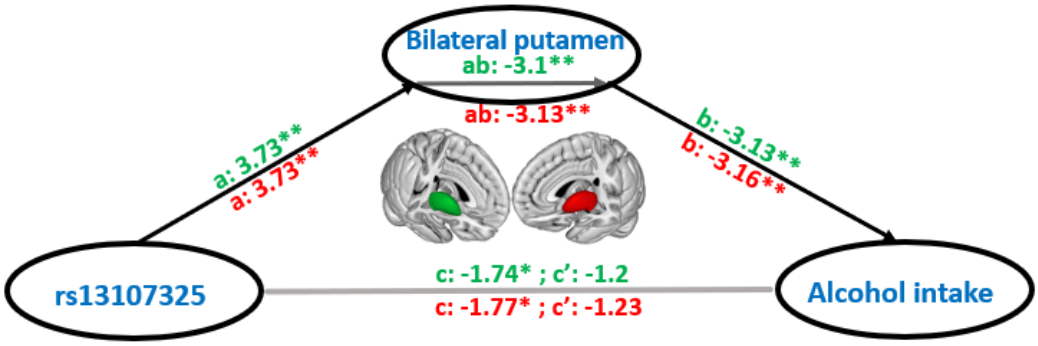
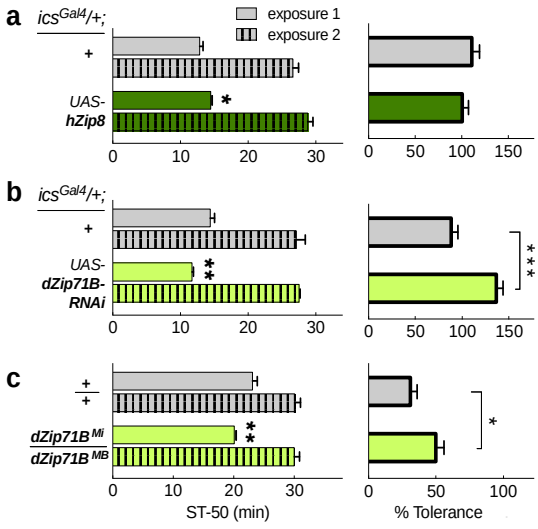


Figure 4. Comparison of *Zip8* alcohol phenotypes in *Drosophila*. Flies were exposed to 100/50 Ethanol/Air vapor for 30 min for exposure 1, and the time to 50% loss of righting was determined (ST-50, sedation time). After recovery on food for 4 hours, flies were re-exposed to the same vapors, and the second ST-50 recorded (left side). The resulting increase in ST-50, i.e. tolerance, is shown on the right. In a) overexpressed human *hZIP8* in *ics*-expressing cells flies are compared against controls whereas in b) knockdown of the fly ortholog *dZip71B* is compared against controls. In c) flies carrying two transposon insertions in the endogenous *dZip71B* gene are compared against controls. Significance levels: ***P <0.001, **P <0.01, **P <0.05. Actual P-values are presented in the text



ONLINE METHODS

UK Biobank data

We conducted a Genome Wide Association Study (GWAS) analysis among 458,577 UKB participants of European descent, identified from a combination of self-reported and genetic data. The details of the selection of the participants has been described elsewhere[14]. These comprise 408,951 individuals from UKB genotyped at 825,927 variants with a custom Affymetrix UK Biobank Axiom Array chip and 49,626 individuals genotyped at 807,411 variants with a custom Affymetrix UK BiLEVE Axiom Array chip from the UK BiLEVE study, which is a subset of UKB. For our analyses, we used SNPs imputed centrally by UKB using the Haplotype Reference Consortium (HRC) panel.

Alcohol intake

We calculated the alcohol intake as grams of alcohol per day (g/d) based on self-reported alcohol drinking from the touch-screen questionnaire. The quantity of each type of drink (red wine, white wine, beer/cider, fortified wine, spirits) was multiplied by its standard drink size and reference alcohol content. Drink-specific intake during the reported drinking period (a week for frequent drinkers defined as: daily or almost daily/once or twice a week/three or four times a week; or a month for occasional drinkers defined as: one to three times a month/special occasions only) was summed up and converted to g/d alcohol intake for all participants with complete response to the quantitative drinking questions. The alcohol intake for participants with incomplete response was imputed by bootstrap resampling from the complete responses, stratified by drinking frequency (occasional or frequent) and sex.

Participants were defined as life-time non-drinkers if they reported 'never' on the question on alcohol drinking frequency (UKB field 1558) and 'no' for the question on former drinker (UKB field 3731); they were excluded from further analysis. Participants with daily alcohol consumption > 500 grams we considered outliers and they were dropped from the analyses. We also excluded participants with missing covariates, leaving data on 404,732 individuals. We $\log_{10}$ transformed g/d alcohol and sex-specific residuals were derived from the regression of $\log_{10}$ transformed g/d alcohol on age, age^2, genotyping chip and weight.

UKB genetic analysis

We performed linear mixed modeling using BOLT-LMM software[64], under an additive genetic model, for associations of measured and imputed SNPs with alcohol consumption (sex-specific residuals of the $\log_{10}$ transformed g/d variable). Model building was based on SNPs with MAF > 5%, call rate > 98.5% and HWE P > 1 x 10^{-}

[6]. SNPs were imputed using the HRC panel with imputation quality INFO score > 0.1. We estimated the LD score regression (LDSR) intercept to access the degree of genomic inflation beyond polygenicity as well as the lambda inflation factor λ_{GC}[65].

The Alcohol Genome-Wide Consortium (AlcGen) and the Cohorts for Heart and Aging Research in Genomic Epidemiology Plus (CHARGE+) consortia

We analyzed available GWAS data from 25 independent studies (N=76,111) from the AlcGen and the CHARGE+ consortia. All study participants were of reported European ancestry and data were imputed to either the 1000 Genome Project or the HRC panel. Alcohol intake in g/d was computed and the $\log_{10}$ transformed residuals were analyzed as described above. Study names, cohort information and general study methods are included in Supplementary Table 2 and 3.

All studies were centrally quality-controlled using easyQC[66]. Finally, we analyzed data on ~7.1 M SNPs at MAF >1% and imputation quality score (Impute [Info score] or Mach [r^2]) > 0.3. Genomic control (GC) was applied at study level. We synthesized the available GWAS using a fixed effects inverse variance weighted meta-analysis and summary estimates were derived for AlcGen and CHARGE+.

One-stage meta-analysis

We performed a one-stage meta-analysis applying a fixed-effects inverse variance weighted meta-analysis using METAL[67] to obtain summary results from the UKB and and the AlcGen plus CHARGE+ GWAS, for up to N=480,842 participants and ~7.1 M SNPs with MAF ≥ 1% for variants present in both the UKB data and AlcGen and CHARGE+ meta-analysis. The LDSR intercept (standard error), in the discovery meta-analysis was 1.05 and no further correction was applied.

Previously reported (known) SNPs

We looked up in the GWAS catalog (http://www.ebi.ac.uk/gwas/) and identified 17 SNPs that associated with alcohol consumption at genome-wide significance level ($P < 5 \times 10^{-8}$). We enhanced the list by reference to a recent GWAS by Clarke et al[6] that was not covered by the GWAS catalog at the time of the analysis, reporting 14 additional rare and common novel SNPs. Together with a SNP in *RASGRF2* shown to be associated with alcohol-induced reinforcement[68], we found 31 previously reported alcohol consumption related SNPs.

Novel loci

According to locus definition of i) SNPs within ±500kb distance of each other; ii) SNPs in linkage disequilibrium LD ($r^2 > 0.1$) calculated with PLINK, we augmented the list of known SNPs to all SNPs present within our data, not contained within the

previously published loci. We further excluded SNPs in the HLA region (chromosome 6, 25-34Mb) due to its complex LD structure. We performed LD clumping in PLINK on 4,515 unknown SNPs with $P < 1 \times 10^{-8}$ using an $r^2 > 0.1$ and distance threshold of 500kb. We further grouped the lead SNPs within 500kb from each other into the same loci and selected the SNP with smallest *P*-value from the locus as sentinel SNP.

To report a SNP as novel signal of association with alcohol consumption:

i) the sentinel SNP has $P < 5 \times 10^{-9}$ in the one-stage meta-analysis;
ii) the sentinel SNP is strongly associated ($P < 5 \times 10^{-7}$) in the UKB GWAS alone;
iii) the sentinel SNP has concordant direction of effect between UKB and AlcGen and CHARGE+ datasets;
iv) The sentinel SNP is not located within any of the previously reported loci

We selected the above criteria i) to iii) to minimize false positive findings including use of a conservative one-stage *P*-value threshold that is an order of magnitude more stringent than a genome-wide significance *P*-value. (The threshold of $P < 5 \times 10^{-9}$ has been proposed e.g. for whole-genome sequencing-based studies.) This approach led us to the identification of 46 sentinel SNPs in total.

Conditional analysis

We conducted locus-specific conditional analysis using the GCTA (Genome-wide Complex Trait Analysis) software (http://cnsgenomics.com/software/gcta). For each of the 46 novel sentinel SNPs, we obtained conditional analysis results for the SNPs with MAF>1% and within 500kb from the sentinel SNP after conditioning on the sentinel SNP. The meta-analysis results of the GWAS in UKB, AlcGen and CHARGE+ were used as input summary statistics and the individual-level genetic data from UKB were used as the reference sample. Results for a SNP were considered conditionally significant if the difference between the conditional *P*-value and the original *P*-value is greater than 1.5-fold ($-\log_{10}P/-\log_{10}(P\_\text{conditional}) > 1.5$ and the conditional *P*-value is smaller than 5×10^{-8}.

Gene expression analyses

To analyze the impact of genetic variants on expression of neighboring genes and identify expression quantitative trait loci (*cis*-eQTLs; i.e., SNPs associated with differences in local gene expression), we used two publicly available databases, the Genotype-Tissue Expression (GTEx) database[69] and the UK Brain Expression Consortium (UKBEC) dataset[70]. We searched these databases for significant variant-transcripts pairs for genes within 1Mb of each input SNP.

With the GTEx database, we tested for *cis*-eQTL effects in 48 tissues from 620 donors. The data described herein were obtained from the GTEx Portal, Release: V7 and used FastQTL[71], to map SNPs to gene-level expression data and calculate q-values based on beta distribution-adjusted empirical *P*-values[72]. A false discovery rate (FDR) threshold of ≤0.05 was applied to identify genes with a significant eQTL. The effect size, defined as the slope of the linear regression, was computed in a normalized space (normalized effect size (NES)), where magnitude has no direct biological interpretation. Here, NES reflects the effects of our GWAS A1 alleles (that are not necessarily the alternative alleles relative to the reference alleles, as reported in the GTEx database). Supplementary Table 12 lists transcripts-SNPs associations with significant eQTL effects.

With the UKBEC dataset that comprises 134 brains (http://www.braineac.org/), we searched for *cis*-eQTLs in 10 brain regions, including the cerebellar cortex (CRBL), frontal cortex (FCTX), hippocampus (HIPP), medulla (specifically inferior olivary nucleus, MEDU), occipital cortex (specifically primary visual cortex, OCTX), putamen (PUTM), substantia nigra (SNIG), thalamus (THAL), temporal cortex (TCTX) and intralobular white matter (WHMT), as well as across all brain tissues (aveALL). MatrixEQTL[73] generated *P*-values for each expression profile (either exon-level or gene-level) against the respective SNP were obtained for the 10 different tissues and overall (aveALL). **Supplementary Table 13** lists transcripts-SNPs associations with a eQTL *P*-value < 0.0045 in at least one brain tissue. Subsequent data analysis was performed in R (http://www.R-project.org/).

We carried out over-representation enrichment analysis using the list of 146 GTEx eQTL genes. Ingenuity pathway analysis (IPA®, QIAGEN Inc.) was performed on this list using ontology annotations from all available databases except those derived from low-confidence computational predictions.

Magnetic Resonance Imaging Data

We used the most recent release of magnetic resonance imaging (MRI) data on brain, heart and liver for UKB participants to investigate genetic associations with the 46 novel SNPs for alcohol consumption.

Brain imaging

Brain MRI acquisition and pre-processing

We used the T1 data from UKB to elucidate volumetric brain structures, including the cortical and the sub-cortical areas. The T1 data were acquired and pre-processed centrally by UKB. The brain regions were defined by combining the Harvard-Oxford

cortical and subcortical atlases[74] (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and the Diedrichsen cerebellar atlas[75] (http://www.diedrichsenlab.org/imaging/propatlas.htm). FAST (FMRIB's Automated Segmentation Tool)[76] was then used to estimate the grey matter partial volume within each brain region. Subcortical region volumes were also modelled by using FIRST (FMRIB's Integrated Registration and Segmentation Tool). More details about the MRI scanning protocol and pre-processing has been provided in UKB documentation (https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf).

Association Analyses

We performed association analyses on N = 9,705 individuals between all novel SNPs and the grey matter volume of brain regions using Pearson correlation, adjusting for age, age^2, sex, age × sex, age^2 × sex, and head size. All, brain volume features, log transformed alcohol intake data (g/d), and the confounders were firstly transformed by using a rank-based inverse Gaussian transformation. Significance levels were set at $P < 0.05$ adjusted using the false-discovery rate method for multiple comparisons.

Mediation analysis

To assess if the effect of a SNP on alcohol consumption is mediated through a brain region, we performed a single-level mediation analysis based on a standard three-variable path model (SNP-brain region-alcohol consumption) with corrected and accelerated percentile bootstrapping 10,000 times to calculate the significance of the mediation effect. We considered as mediator variable the grey matter volume of brain regions that had a significant association on alcohol consumption. We calculated the significance of path a, path b and a*b mediation (SNP-brain region-alcohol consumption) using a multilevel mediation and moderation (M3) toolbox[77,78]

Cardiac Imaging

Cardiac MRI acquisition and pre-processing

Details of the cardiac image acquisition in UKB are reported previously[79]. Cardiac MRI was acquired using a clinical wide bore 1.5T scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) with 48 receiver channels, a 45 mT/m and 200 T/m/s gradient system, an 18-channel anterior body surface coil used in combination with 12 elements of an integrated 32 element spine coil and electrocardiogram gating for cardiac synchronization. A two-dimensional short-axis cardiac MRI was obtained using a balanced steady state free precession to cover the entire left and right ventricle (echo time, 1.10msec; repetition time, 2.6msec; flip angle, 80°; slice thickness, 8mm with 2mm gap; typical field of view, 380×252mm; matrix size, 208×187, acquisition of 1 slice per breath-hold).

The cardiac images were segmented to provide left ventricular mass (LVM), left end-diastolic (LVEDV), left end-systolic volume (LVESV), and right end-diastolic (RVEDV) and right end-systolic volume (RVESV) using a fully convolutional network as described previously[80]. Left (LVEF) and right ventricular ejection fraction (RVEF) were derived from (LVEDV–LVESV)/LVEDV×100 and (RVEDV–RVESV)/RVEDV×100, respectively.

Association Analyses

To test associations between cardiac MRI measures and alcohol consumption-related SNPs, we carried out a regression of LVM, LVEDV, LVEF, RVEDV, and RVEF onto each of the 46 SNPs adjusting for age, sex, height, weight, hypertension, diabetes, and smoking history. Significance levels were set at $P < 0.05$ adjusted using the false-discovery rate method for multiple comparisons.

Liver Imaging

Liver MRI acquisition and pre-processing

Details of the liver image acquisition protocol have been reported previously[81]. Briefly, all participants were scanned in a Siemens MAGNETOM Aera 1.5-T MRI scanner (Siemens Healthineers, Erlangen, Germany) using a 6-minute dual-echo Dixon Vibe protocol, providing a water and fat separated volumetric data set for fat and muscle covering neck to knees. For liver proton density fat fraction (PDFF) quantification, an additional single multi-echo gradient slice was acquired over the liver. Liver images were analysed by computing specific ROI for water, fat and T2* by magnitude-based chemical shift technique with a 6-peak lipid model, correcting for T1 and T2*

Association Analyses

We performed association analyses between 46 alcohol consumption-related SNPs and liver PDFF (%), from 8,372 samples, using a linear regression model adjusting for age, age^2, sex, T2D, BMI, genotyping chip and first three PCs. Liver PDDF was firstly transformed by using a rank-based inverse transformation. Significance levels were set at $P < 0.05$ adjusted using the false-discovery rate method for multiple comparisons.

***Drosophila* experiments**

Flies were kept on standard cornmeal/molasses fly food in a 12:12hr light:dark cycle at 25°C. Transgenc flies were obtained from the Bloomington *Drosophila* Stock Center: *UAS-hZip8* BL#66125, *UAS-dZIP71B-TRiP-RNAi*^{HMC04064} BL#55376,

837 *dZip71B*^{MI13940} BL#59234, and *dZip71B*^{MB11703} BL#29928. For behavioral
838 experiments, crosses were set up such that experimental and control flies were sibling
839 progeny from a cross, and both were therefore in the same hybrid genetic background
840 (*w Berlin / unknown*). Flies aged 1-5 days of adult age were collected, exposed to
841 100/50 (flowrates) ethanol/air vapor in the Booze-o-Mat 2 days later, and their loss of
842 righting determined by slight tapping, as described[82]. For tolerance, flies were put
843 back onto regular food after a 30-min initial exposure, and were then re-exposed to
844 the same vapor 4 hours later. Note that tolerance is not connected to initial
845 sensitivity, and flies naively sensitive to ethanol-induced sedation can have no, or a
846 reduced tolerance phenotype. Flies overexpressing *hZip8* (and their sibling controls)
847 were placed at 28°C for two days to increase the expression levels of the transgene, as
848 we did not detect a phenotype when they were kept at 25°C (data not shown). Data
849 from experimental and control flies were compared by Student's t-tests.
850
851 **Effects on other traits and diseases**
852 We queried SNPs against GWAS results included in PhenoScanner, to investigate
853 cross-trait effects, extracting all association results with genome-wide significance at
854 $P < 5 \times 10^{-8}$ for all SNPs in high LD ($r^2 \geq 0.8$) with the 46 sentinel novel SNPs, to
855 highlight the loci with strongest evidence of association with other traits. At the gene
856 level, overrepresentation enrichment analysis (ORA) with WebGestalt[41] on the nearest
857 genes to all alcohol intake loci was carried out.

858 The genetic correlations between alcohol consumption and 235 other traits and
859 diseases were obtained in the online software LD Hub. LD hub is a centralized
860 database of summary-level GWAS results and a web interface for LD score regression
861 analysis

862 To estimate the potential causal effect of alcohol consumption-related variants on
863 schizophrenia, we performed a Mendelian randomization analysis utilizing publicly
864 available GWAS data on schizophrenia and the Mendelian randomization package in
865 R. The effect was estimated using the inverse-variance weighted (IVM) method.
866 Pleiotropy was tested by applying the MR-Egger regression method and heterogeneity
867 statistics were obtained. In presence of heterogeneity the random effects inverse-
868 variance method was applied[83].

869 **Genetic risk scores and percentage of variance explained**
870 We calculated an unbiased weighted genetic risk score in 14,004 unrelated
871 participants in Airwave, an independent cohort with high quality HRC imputed
872 genetic data[33]. We used as weights the beta coefficients of the meta-analysis. We
873 assessed the association of the GRS with alcohol intake and calculated the alcohol
874 consumption levels for individuals in the top vs the bottom quintiles of the

875 distribution. To calculate the percent of variance of alcohol consumption explained by
876 genetic variants, we generated the residuals from a regression of alcohol consumption
877 in Airwave. We then fit a second linear model for the trait residuals with all novel and
878 known variants plus the top 10 principal components, and estimated the percentage
879 variance of the dependent variable explained by the variants.
880
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Table 1: Association results of 46 novel alcohol variants identified through the meta-analysis of UK Biobank and AlcGen and CHARGE+. Results are ordered by *P*-value of combined analysis.

leadSNP						Combined			UKB			AlcGen and CHARGE+		
Nearest_Gene	Annotated Gene	rsID_LEAD_SNP	CP	EA	EAF	BETA	SE	P	BETA	SE	P	BETA	SE	P
MAPT	STH	rs1991556	17:44083402	A	0.22	-0.012	0.001	4.5E-23	-0.013	0.001	2.4E-21	-0.011	0.004	4.0E-03
RP11-89K21.1	SIX3	rs1004787	2:45159091	A	0.54	0.009	0.001	6.7E-17	0.009	0.001	1.1E-15	0.007	0.003	1.4E-02
SLC39A8	SLC39A8	rs13107325	4:103188709	T	0.07	-0.016	0.002	1.3E-15	-0.017	0.002	4.8E-16	-0.006	0.006	3.6E-01
IZUMO1, RASIP1, FUT1	IZUMO1	rs838145	19:49248730	A	0.55	-0.008	0.001	3.2E-15	-0.009	0.001	2.4E-15	-0.004	0.003	1.7E-01
na	PSMD7	rs1104608	16:73912588	C	0.43	-0.008	0.001	1.2E-14	-0.009	0.001	4.9E-15	-0.003	0.003	2.5E-01
MYBPC3	MYBPC3	rs2071305	11:47370957	A	0.69	0.009	0.001	4.5E-14	0.009	0.001	3.9E-13	0.007	0.003	3.1E-02
na	DRD2	rs7121986	11:113355444	T	0.37	-0.008	0.001	6.2E-14	-0.008	0.001	1.3E-13	-0.005	0.003	1.1E-01
na	DPP6	rs6969458	7:153489725	A	0.47	0.008	0.001	6.4E-14	0.008	0.001	1.3E-12	0.007	0.003	1.5E-02
RP11-308N19.1	ZNF462	rs74424378	9:109331094	T	0.76	0.009	0.001	1.7E-13	0.009	0.001	4.5E-13	0.006	0.003	8.4E-02
ARHGAP15, AC096558.1, RP11-570L15.2	ARHGAP15	rs13024996	2:144225215	A	0.37	-0.008	0.001	4.4E-13	-0.008	0.001	6.6E-13	-0.004	0.003	1.4E-01
MLXIPL	MLXIPL	rs34060476	7:73037956	A	0.87	-0.011	0.002	5.0E-13	-0.012	0.002	1.4E-13	-0.004	0.004	4.1E-01
na	FAM178A	rs61873510	10:102626510	T	0.33	-0.008	0.001	5.1E-13	-0.008	0.001	9.8E-12	-0.008	0.003	1.7E-02
FTO	FTO	rs1421085	16:53800954	T	0.60	0.008	0.001	9.2E-13	0.007	0.001	1.7E-10	0.010	0.003	9.2E-04
na	PMFBP1	rs11648570	16:72356964	T	0.89	-0.012	0.002	2.1E-12	-0.011	0.002	1.5E-10	-0.013	0.005	3.4E-03
OTX2, RP11-1085N6.6	OTX2	rs2277499	14:57271127	T	0.34	-0.008	0.001	2.2E-12	-0.007	0.001	2.4E-09	-0.012	0.003	9.1E-05
PDE4B	PDE4B	rs2310752	1:66392405	A	0.43	-0.007	0.001	2.8E-12	-0.008	0.001	1.8E-11	-0.006	0.003	4.2E-02
SERPINA1	SERPINA1	rs112635299	14:94838142	T	0.02	-0.025	0.004	3.7E-12	-0.027	0.004	9.8E-12	-0.017	0.010	9.9E-02
na	AJAP1	rs780569	1:4569436	A	0.71	-0.008	0.001	5.2E-12	-0.008	0.001	1.1E-11	-0.005	0.003	1.2E-01
na	VRK2	rs10496076	2:57942987	T	0.37	-0.007	0.001	9.7E-12	-0.007	0.001	1.3E-09	-0.009	0.003	1.6E-03
ACTR10, C14orf37	ACTR10	rs71414193	14:58685301	A	0.19	-0.009	0.001	1.8E-11	-0.008	0.001	5.8E-09	-0.013	0.004	4.5E-04
BEND4	BEND4	rs16854020	4:42117559	A	0.13	0.010	0.002	2.9E-11	0.010	0.002	5.8E-09	0.016	0.005	6.4E-04
na	SORL1	rs485425	11:121544984	C	0.45	-0.007	0.001	6.1E-11	-0.007	0.001	7.3E-11	-0.004	0.003	1.9E-01
SEZ6L2	SEZ6L2	rs113443718	16:29892184	A	0.31	-0.007	0.001	7.4E-11	-0.008	0.001	4.5E-11	-0.003	0.003	2.9E-01
CBX5, RP11-968A15.2	CBX5	rs57281063	12:54660427	A	0.41	0.007	0.001	7.9E-11	0.007	0.001	1.8E-09	0.007	0.003	1.2E-02
na	TNRC6A	rs72768626	16:24693048	A	0.94	0.014	0.002	9.7E-11	0.015	0.002	1.7E-09	0.014	0.006	1.8E-02
SYT14	SYT14	rs227179	1:210216731	A	0.59	-0.007	0.001	1.1E-10	-0.007	0.001	1.4E-09	-0.006	0.003	2.8E-02
TCF4	TCF4	rs9320010	18:53053897	A	0.60	0.007	0.001	1.1E-10	0.007	0.001	1.6E-09	0.007	0.003	2.2E-02
SBK1	NPIPB6	rs2726034	16:28336882	T	0.68	0.007	0.001	1.4E-10	0.007	0.001	1.1E-09	0.006	0.003	4.7E-02
ANKRD36	ANKRD36	rs13390019	2:97797680	T	0.87	0.010	0.002	1.6E-10	0.011	0.002	7.0E-11	0.004	0.005	4.5E-01
na	ELAVL4	rs7517344	1:50711961	A	0.17	0.009	0.001	1.9E-10	0.008	0.001	2.5E-07	0.016	0.004	2.1E-05
LINC00461	MEF2C	rs4916723	5:87854395	A	0.58	0.007	0.001	2.1E-10	0.007	0.001	5.1E-10	0.005	0.003	1.1E-01
ARPC1B, ARPC1A	ARPC1B	rs10249167	7:98980879	A	0.87	0.010	0.002	2.9E-10	0.009	0.002	8.1E-08	0.015	0.004	3.8E-04
EFNB3, WRAP53	EFNB3	rs7640	17:7606722	C	0.80	0.008	0.001	4.3E-10	0.009	0.001	1.3E-09	0.006	0.004	9.9E-02
RP11-501C14.5	IGF2BP1	rs4794015	17:47067826	A	0.41	0.007	0.001	4.3E-10	0.006	0.001	5.4E-08	0.009	0.003	1.2E-03
TCAP, PNMT, STARD3	TCAP	rs1053651	17:37822311	A	0.27	-0.007	0.001	1.1E-09	-0.008	0.001	8.4E-10	-0.003	0.003	2.8E-01
na	AADAT	rs7698119	4:171070910	A	0.49	-0.006	0.001	1.3E-09	-0.006	0.001	1.6E-07	-0.009	0.003	1.6E-03
STAT6, AC023237.1	STAT6	rs12312693	12:57511734	T	0.55	-0.006	0.001	1.5E-09	-0.006	0.001	9.5E-09	-0.005	0.003	5.6E-02
SCN8A	SCN8A	rs7958704	12:51984349	T	0.41	-0.006	0.001	1.6E-09	-0.006	0.001	1.7E-08	-0.006	0.003	3.5E-02
ACSS3	ACSS3	rs11114787	12:81595700	T	0.27	0.007	0.001	2.0E-09	0.007	0.001	2.7E-08	0.007	0.003	2.4E-02
RP11-32K4.1	BHLHE22	rs2356369	8:64956882	T	0.52	-0.006	0.001	2.0E-09	-0.006	0.001	4.1E-08	-0.007	0.003	1.6E-02
ZRANB2-AS2	ZRANB2	rs12031875	1:71585097	A	0.82	-0.008	0.001	2.2E-09	-0.008	0.001	7.6E-08	-0.010	0.004	8.7E-03
MSANTD1, HTT	MSANTD1	rs12646808	4:3249828	T	0.66	0.007	0.001	2.4E-09	0.007	0.001	1.1E-09	0.002	0.003	4.7E-01
TENM2	TENM2	rs10078588	5:166816176	A	0.52	0.006	0.001	2.5E-09	0.006	0.001	4.3E-08	0.007	0.003	1.9E-02
IGSF9B	IGSF9B	rs748919	11:133783232	T	0.79	0.008	0.001	3.3E-09	0.008	0.001	1.0E-08	0.005	0.003	1.1E-01
AC010967.2	GPR75-ASB3	rs785293	2:53023304	A	0.57	-0.006	0.001	3.3E-09	-0.006	0.001	3.2E-08	-0.006	0.003	3.8E-02
BDNF, RP11-587D21.4	BDNF	rs988748	11:27724745	C	0.21	-0.008	0.001	4.4E-09	-0.007	0.001	1.2E-07	-0.010	0.004	8.3E-03

SNP: Single Nucleotide polymorphism; LocusName: Nearest Gene; rsID_LEAD_SNP: Rs ID number of the lead SNP; CP: Chromosome/Position (build hg19/37); EA: Effect allele of the discovered SNP; EAF: Frequency of the effect allele; BETA_comb: Effect size in meta-analysis; SE_comb; Standard Error of the effect in meta-analysis; P_comb: Meta-analysis P-value; BETA_UKB: Effect size in UK Biobank analysis; SE_UKB: Standard Error of the effect in the UK Biobank analysis; P_UKB: UK Biobank analysis P-value;BETA_AlcGenCHARGE+: Effect size in the AlcGen meta-analysis; SE_AlcGenCHARGE+: Standard Error of the effect in the AlcGen meta-analysis; P_AlcGenCHARGE+: AlcGen meta-analysis P-value