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 respectively¹. 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 population². 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 mortality³.

Alcohol consumption is a heritable complex trait⁴, but genetic studies to date have identified only a small number of robustly associated genetic variants⁵⁻⁸. These include variants in the aldehyde dehydrogenase gene family, a group of enzymes that catalyze the oxidation of aldehydes⁹, 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 questionnaire¹⁰. 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) panel¹¹, yielding ~7 million common single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) $\geq 1\%$ 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 $\lambda_{GC}=1.45$, 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 stratification¹². 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 individuals¹³. To maximize power, we performed a single-stage analysis to test common SNPs with MAF $\geq 1\%$. We set a stringent P -value threshold of $P < 5 \times 10^{-9}$ to denote significance in the combined meta-analysis¹⁴, 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 dementia¹⁵ and Parkinson's disease^{16,17}, but also with neuroticism, schizophrenia¹⁸ and other conditions¹⁹⁻²¹ (**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 development²². 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 schizophrenia²³ as well as inflammatory bowel disease, cardiovascular and metabolic phenotypes²⁴⁻²⁵⁻²⁷ 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 schizophrenia¹⁸. 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 regulation²⁸. Previous studies have suggested that variation in *BDNF* is a genetic determinant of alcohol consumption and that alcohol consumption modulates BDNF expression²⁹.

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 GWAS³⁰. 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 metabolism³¹. We previously reported significant association of alcohol intake with SNP rs11940694 in *KLB*, an obligate receptor of FGF21 in the brain⁵, 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 dependence³².

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 cohort³³ (**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:

114 $P = 2.5 \times 10^{-45}$, right: $P = 2.8 \times 10^{-47}$), ventral striatum (left: $P = 9.5 \times 10^{-53}$, right: $P =$
115 9.6×10^{-51}) and cerebellum (strongest association for left I-IV volume; $P = 1.2 \times 10^{-9}$)
116 (**Supplementary Table 8**); similar findings were also recently reported in a GWAS
117 on brain imaging in UKB³⁴. The other significant association was for rs1991556 with
118 the parahippocampal gyrus ($P = 1.2 \times 10^{-6}$).

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

128 We did not find any significant associations of novel SNPs with either cardiac (left
129 ventricular mass or end diastolic volume or right ventricular end diastolic volume)
130 (**Supplementary Table 10**) or liver fat measures on MRI (**Supplementary Table**
131 **11**), after adjustment for multiple testing.

132 **Effects of SNPs on gene expression**

133 We carried out expression quantitative trait loci eQTL analyses using the Genotype-
134 Tissue Expression (GTEx) and the UK Brain Expression Consortium (UKBEC)
135 datasets; 34 of the 53 novel and known SNPs associated with alcohol consumption
136 have a significant effect on gene expression in at least one tissue, including 33 SNPs
137 that affected gene expression in the brain (**Supplementary Tables 12 and 13, and**
138 **Supplementary Fig. 1-4**). We found that the most significant eQTLs often do not
139 involve the nearest gene and that several of the SNPs affect expression of different
140 genes in different tissues (**Supplementary Fig. 4**). For example, SNP rs1991556 in
141 the *MAPT* gene affects expression of 33 genes overall, with most significant effects
142 on the expression of the non-protein coding genes *CRHR1-IT1* (also known as
143 *C17orf69* or *LINC02210*) and *LRRC37A4P*, near *MAPT*, across a wide range of
144 tissues including brain, adipose tissue and skin ($P = 7.2 \times 10^{-126}$ to $P = 2.5 \times 10^{-6}$)
145 (**Supplementary Fig. 4**). Similarly, the A-allele at SNP rs2071305 within *MYBPC3*
146 affects the expression of several genes and is most significantly associated with
147 increased expression of *C1QTNF4* across several tissues ($P = 1.9 \times 10^{-25}$ to $P = 8.4 \times$
148 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-STAR3* 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 pathway³⁵. 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 abuse⁴⁰.

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 regression¹², 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 WebGestalt⁴¹ 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 behaviors⁴³. 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 dementia⁴⁴ and both genes are also implicated in other neuropsychiatric conditions including neuroticism, schizophrenia and Parkinson's disease¹⁶⁻¹⁸. 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 responses⁴⁵. 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 primates⁴⁶. Putamen volume differences have also been associated with both schizophrenia and psychosis^{47,48} and robust

224 association between SNP rs13107325 in *SLC39A8* and schizophrenia was reported in
225 a previous GWAS²³.

226 We also report SNP rs7121986 near *DRD2* as a novel alcohol intake variant in
227 GWAS. The gene product of *DRD2*, D2 dopamine receptor, is a G protein-coupled
228 receptor on post-synaptic dopaminergic neurons that has long been implicated in
229 alcoholism⁴⁹. In addition, we identify SNP rs988748 in *BDNF* as a novel alcohol
230 intake variant; BDNF expression is differentially affected by alcohol exposure in
231 animal models^{50,51}. Both genes (along with *PPP1R1P*) are centrally involved in
232 reward-mediating mesocortico-limbic pathways and both are implicated in the
233 development of schizophrenia. For example, there is a robust GWAS association
234 between schizophrenia and SNP rs4938021 in *DRD2* (in perfect LD with our novel
235 alcohol intake-related variant rs7121986) and *DRD2* appears to be pivotal in network
236 analyses of genes involved in schizophrenia⁵². Taken together, our results suggest
237 that there are shared genetic mechanisms between the regulation of alcohol intake and
238 susceptibility to schizophrenia, as well as other neuropsychiatric disorders. In this
239 regard, large prospective epidemiological studies report a three-fold risk of
240 schizophrenia in relation to alcohol abuse⁵³.

241 We previously reported genome-wide significant associations of alcohol intake with
242 *KLB*, and identified a liver-brain axis linking the liver hormone FGF21 with central
243 regulation of alcohol intake involving β -Klotho receptor (the gene product of *KLB*) in
244 the brain⁵. Here, we identify a significant variant near *FGF21* gene and strongly
245 replicate the previously reported *KLB* gene variant, strengthening the genetic evidence
246 for the importance of this pathway in regulating alcohol consumption.

247 The LD score regression analysis showed a positive genetic correlation between
248 alcohol consumption, smoking and HDL cholesterol levels. This confirms previous
249 findings that reported an almost identical genetic correlation of alcohol consumption
250 with number of cigarettes per day⁵⁴. Furthermore, the observed genetic correlation
251 with HDL levels is consistent with previous observations of an association between
252 alcohol consumption and HDL^{55,56}, including results of a Mendelian randomization
253 study that suggested a possible causal role linking alcohol intake with increased HDL
254 levels⁵⁷. Finally, we found a genetic correlation (inverse) between sleep duration and
255 alcohol consumption, an association previously reported only in a few small
256 epidemiological studies⁵⁸. We could not test for a genetic association between alcohol
257 and risk of alcohol-related cancers⁵⁹ because of limited availability of summary data.
258 However, our gene-set enrichment analysis showed a significant enrichment for genes
259 related to abdominal cancers.

260 Strengths of our study include its size, detailed attention to the alcohol phenotype,
 261 dense coverage of the genome through imputation, incorporation of brain and other
 262 imaging data to explore potential mechanisms and confirmatory *Drosophila*
 263 functional genetic studies. Over 80% of the data came from UKB, which combines
 264 high-quality phenotypic data and imputed genome-wide genetic data with strict
 265 attention to quality control⁶⁰. We adopted a stringent approach to claim novel variants
 266 involving a conservative *P*-value threshold, internal replication in UKB and consistent
 267 direction of effect with the other studies, to minimize the reporting of false positive
 268 signals.

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

283 In summary, in this large study of genetic associations with alcohol consumption, we
 284 identified common variants in 46 novel loci with several of the genes expressed in the
 285 brain as well as other tissues. Our findings suggest that there may be common genetic
 286 mechanisms underpinning regulation of alcohol intake and development of a number
 287 of neuropsychiatric disorders including schizophrenia. This may form the basis for
 288 greater understanding of observed associations between excessive alcohol
 289 consumption and schizophrenia⁶³.

290 URLs

291 GTEx: www.gtexportal.org
 292 UKBEC: <http://www.braineac.org/>
 293 WebGetstalt: <http://www.webgestalt.org>
 294 IPA: www.qiagen.com/ingenuity
 295 PhenoScanner: <http://www.phenoscaner.medschl.cam.ac.uk> (Phenoscaner
 296 integrates results from the GWAS catalogue: <https://www.ebi.ac.uk/gwas/> and
 297 GRASP: <https://grasp.nhlbi.nih.gov/>)
 298

299

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557

558 **Figure 1. Manhattan plot showing P -values from discovery genome-wide**
 559 **association meta-analysis with alcohol intake (g/d) among 480,842 individuals**
 560 **across UK Biobank, AlcGen and CHARGE+, excluding known variants.** The P -
 561 value was computed using inverse variance fixed effects models. The y axis shows the
 562 $-\log_{10} P$ values and the x axis shows their chromosomal positions. Horizontal blue
 563 line represents the threshold of $P = 5 \times 10^{-9}$.
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567

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

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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

605 **ONLINE METHODS**

606

607 **UK Biobank data**

608 We conducted a Genome Wide Association Study (GWAS) analysis among 458,577
609 UKB participants of European descent, identified from a combination of self-reported
610 and genetic data. The details of the selection of the participants has been described
611 elsewhere¹⁴. These comprise 408,951 individuals from UKB genotyped at 825,927
612 variants with a custom Affymetrix UK Biobank Axiom Array chip and 49,626
613 individuals genotyped at 807,411 variants with a custom Affymetrix UK BiLEVE
614 Axiom Array chip from the UK BiLEVE study, which is a subset of UKB. For our
615 analyses, we used SNPs imputed centrally by UKB using the Haplotype Reference
616 Consortium (HRC) panel.

617

618 *Alcohol intake*

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

630

631 Participants were defined as life-time non-drinkers if they reported ‘never’ on the
632 question on alcohol drinking frequency (UKB field 1558) and ‘no’ for the question on
633 former drinker (UKB field 3731); they were excluded from further analysis.
634 Participants with daily alcohol consumption > 500 grams we considered outliers and
635 they were dropped from the analyses. We also excluded participants with missing
636 covariates, leaving data on 404,732 individuals. We log₁₀ transformed g/d alcohol
637 and sex-specific residuals were derived from the regression of log₁₀ transformed g/d
638 alcohol on age, age², genotyping chip and weight.

639

640 **UKB genetic analysis**

641 We performed linear mixed modeling using BOLT-LMM software⁶⁴, under an
642 additive genetic model, for associations of measured and imputed SNPs with alcohol
643 consumption (sex-specific residuals of the log₁₀ transformed g/d variable). Model
644 building was based on SNPs with MAF > 5%, call rate > 98.5% and HWE P > 1 x 10⁻

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

648 **The Alcohol Genome-Wide Consortium (AlcGen) and the Cohorts for Heart and** 649 **Aging Research in Genomic Epidemiology Plus (CHARGE+) consortia**

650 We analyzed available GWAS data from 25 independent studies (N=76,111) from the
 651 AlcGen and the CHARGE+ consortia. All study participants were of reported
 652 European ancestry and data were imputed to either the 1000 Genome Project or the
 653 HRC panel. Alcohol intake in g/d was computed and the log₁₀ transformed residuals
 654 were analyzed as described above. Study names, cohort information and general study
 655 methods are included in Supplementary Table 2 and 3.

656 All studies were centrally quality-controlled using easyQC⁶⁶. Finally, we analyzed
 657 data on ~7.1 M SNPs at MAF >1% and imputation quality score (Impute [Info score]
 658 or Mach [r²]) > 0.3. Genomic control (GC) was applied at study level. We synthesized
 659 the available GWAS using a fixed effects inverse variance weighted meta-analysis
 660 and summary estimates were derived for AlcGen and CHARGE+.

661 **One-stage meta-analysis**

662 We performed a one-stage meta-analysis applying a fixed-effects inverse variance
 663 weighted meta-analysis using METAL⁶⁷ to obtain summary results from the UKB and
 664 and the AlcGen plus CHARGE+ GWAS, for up to N=480,842 participants and ~7.1
 665 M SNPs with MAF ≥ 1% for variants present in both the UKB data and AlcGen and
 666 CHARGE+ meta-analysis. The LDSR intercept (standard error), in the discovery
 667 meta-analysis was 1.05 and no further correction was applied.

668

669 **Previously reported (known) SNPs**

670 We looked up in the GWAS catalog (<http://www.ebi.ac.uk/gwas/>) and identified 17
 671 SNPs that associated with alcohol consumption at genome-wide significance level (P
 672 < 5×10^{-8}). We enhanced the list by reference to a recent GWAS by Clarke et al⁶ that
 673 was not covered by the GWAS catalog at the time of the analysis, reporting 14
 674 additional rare and common novel SNPs. Together with a SNP in *RASGRF2* shown to
 675 be associated with alcohol-induced reinforcement⁶⁸, we found 31 previously reported
 676 alcohol consumption related SNPs.

677

678 **Novel loci**

679 According to locus definition of i) SNPs within ±500kb distance of each other; ii)
 680 SNPs in linkage disequilibrium LD ($r^2 > 0.1$) calculated with PLINK, we augmented
 681 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.

700

701 **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}).

712

713 **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) database⁶⁹ and the UK Brain Expression Consortium (UKBEC) dataset⁷⁰. We searched these databases for significant variant-transcripts pairs for genes within 1Mb of each input SNP.

719

720 With the GTEx database, we tested for *cis*-eQTL effects in 48 tissues from 620
 721 donors. The data described herein were obtained from the GTEx Portal, Release: V7
 722 and used FastQTL⁷¹, to map SNPs to gene-level expression data and calculate q-
 723 values based on beta distribution-adjusted empirical *P*-values⁷². A false discovery rate
 724 (FDR) threshold of ≤ 0.05 was applied to identify genes with a significant eQTL. The
 725 effect size, defined as the slope of the linear regression, was computed in a
 726 normalized space (normalized effect size (NES)), where magnitude has no direct
 727 biological interpretation. Here, NES reflects the effects of our GWAS A1 alleles (that
 728 are not necessarily the alternative alleles relative to the reference alleles, as reported
 729 in the GTEx database). Supplementary Table 12 lists transcripts-SNPs associations
 730 with significant eQTL effects.

731 With the UKBEC dataset that comprises 134 brains (<http://www.braineac.org/>), we
 732 searched for *cis*-eQTLs in 10 brain regions, including the cerebellar cortex (CRBL),
 733 frontal cortex (FCTX), hippocampus (HIPPO), medulla (specifically inferior olivary
 734 nucleus, MEDU), occipital cortex (specifically primary visual cortex, OCTX),
 735 putamen (PUTM), substantia nigra (SNIG), thalamus (THAL), temporal cortex
 736 (TCTX) and intralobular white matter (WHMT), as well as across all brain tissues
 737 (aveALL). MatrixEQTL⁷³ generated *P*-values for each expression profile (either
 738 exon-level or gene-level) against the respective SNP were obtained for the 10
 739 different tissues and overall (aveALL). **Supplementary Table 13** lists transcripts-
 740 SNPs associations with a eQTL *P*-value < 0.0045 in at least one brain tissue.
 741 Subsequent data analysis was performed in R (<http://www.R-project.org/>).

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

746

747 **Magnetic Resonance Imaging Data**

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

751

752 **Brain imaging**

753

754 *Brain MRI acquisition and pre-processing*

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

cortical and subcortical atlases⁷⁴ (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>) and the
Diedrichsen cerebellar atlas⁷⁵ (<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).

765

766 *Association Analyses*

767 We performed association analyses on N = 9,705 individuals between all novel SNPs
768 and the grey matter volume of brain regions using Pearson correlation, adjusting for
769 age, age², sex, age × sex, age² × sex, and head size. All, brain volume features, log
770 transformed alcohol intake data (g/d), and the confounders were firstly transformed by
771 using a rank-based inverse Gaussian transformation. Significance levels were set at *P*
772 < 0.05 adjusted using the false-discovery rate method for multiple comparisons.

773

774 *Mediation analysis*

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

783

784 **Cardiac Imaging**

785

786 *Cardiac MRI acquisition and pre-processing*

787 Details of the cardiac image acquisition in UKB are reported previously⁷⁹. Cardiac
788 MRI was acquired using a clinical wide bore 1.5T scanner (MAGNETOM Aera,
789 Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) with 48 receiver
790 channels, a 45 mT/m and 200 T/m/s gradient system, an 18-channel anterior body
791 surface coil used in combination with 12 elements of an integrated 32 element spine
792 coil and electrocardiogram gating for cardiac synchronization. A two-dimensional
793 short-axis cardiac MRI was obtained using a balanced steady state free precession to
794 cover the entire left and right ventricle (echo time, 1.10msec; repetition time,
795 2.6msec; flip angle, 80°; slice thickness, 8mm with 2mm gap; typical field of view,
796 380×252mm; matrix size, 208×187, acquisition of 1 slice per breath-hold).

797 The cardiac images were segmented to provide left ventricular mass (LVM), left end-
798 diastolic (LVEDV), left end-systolic volume (LVESV), and right end-diastolic
799 (RVEDV) and right end-systolic volume (RVESV) using a fully convolutional
800 network as described previously⁸⁰. Left (LVEF) and right ventricular ejection fraction
801 (RVEF) were derived from $(LVEDV-LVESV)/LVEDV \times 100$ and $(RVEDV-RVESV)/RVEDV \times 100$, respectively.
802

803

804 *Association Analyses*

805 To test associations between cardiac MRI measures and alcohol consumption-related
806 SNPs, we carried out a regression of LVM, LVEDV, LVEF, RVEDV, and RVEF
807 onto each of the 46 SNPs adjusting for age, sex, height, weight, hypertension,
808 diabetes, and smoking history. Significance levels were set at $P < 0.05$ adjusted using
809 the false-discovery rate method for multiple comparisons.
810

811 **Liver Imaging**

812 *Liver MRI acquisition and pre-processing*

813 Details of the liver image acquisition protocol have been reported previously⁸¹.
814 Briefly, all participants were scanned in a Siemens MAGNETOM Aera 1.5-T MRI
815 scanner (Siemens Healthineers, Erlangen, Germany) using a 6-minute dual-echo
816 Dixon Vibe protocol, providing a water and fat separated volumetric data set for fat
817 and muscle covering neck to knees. For liver proton density fat fraction (PDFF)
818 quantification, an additional single multi-echo gradient slice was acquired over the
819 liver. Liver images were analysed by computing specific ROI for water, fat and T2*
820 by magnitude-based chemical shift technique with a 6-peak lipid model, correcting for
821 T1 and T2*
822

823 *Association Analyses*

824

825 We performed association analyses between 46 alcohol consumption-related SNPs
826 and liver PDFF (%), from 8,372 samples, using a linear regression model adjusting
827 for age, age², sex, T2D, BMI, genotyping chip and first three PCs. Liver PDFF was
828 firstly transformed by using a rank-based inverse transformation. Significance levels
829 were set at $P < 0.05$ adjusted using the false-discovery rate method for multiple
830 comparisons.
831

832

833 ***Drosophila* experiments**

834 Flies were kept on standard cornmeal/molasses fly food in a 12:12hr light:dark cycle
835 at 25°C. Transgenic flies were obtained from the Bloomington *Drosophila* Stock
836 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 described⁸². 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 WebGestalt⁴¹ 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 applied⁸³.

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 data³³. 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.

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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	NPIP6	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: RsID 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