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Genome-wide analyses reveal shared genetic architecture and novel risk loci between opioid use disorder and general cognitive ability

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ABSTRACT

Background: Opioid use disorder (OUD), a serious health burden worldwide, is associated with lower cognitive function. Recent studies have demonstrated a negative genetic correlation between OUD and general cognitive ability (COG), indicating a shared genetic basis. However, the specific genetic variants involved, and the underlying molecular mechanisms remain poorly understood. Here, we aimed to quantify and identify the genetic basis underlying OUD and COG.

Methods: We quantified the extent of genetic overlap between OUD and COG using a bivariate causal mixture model (MiXeR) and identified specific genetic loci applying conditional/conjunctional FDR. Finally, we investigated biological function and expression of implicated genes using available resources.

Results: We estimated that ~94% of OUD variants (4.8k out of 5.1k variants) also influence COG. We identified three novel OUD risk loci and one locus shared between OUD and COG. Loci identified implicated biological substrates in the basal ganglia.

Conclusion: We provide new insights into the complex genetic risk architecture of OUD and its genetic relationship with COG.

1. Introduction

Opioid use disorder (OUD) is a chronic, relapsing multifactorial disorder with a major public health impact across the world, due to its high morbidity and mortality and its increasing prevalence over the past decades (Babu et al., 2019; Degenhardt et al., 2009; Strang et al., 2020; Wollman et al., 2017, 2015). The disease mechanisms of OUD are not well characterised and there is an extensive clinical overlap with other substance use and mental disorders and traits, including reward-related risk taking and negative affect (Sheffield et al., 2018). Cognitive dysfunction is associated with OUD, and is suggested as a feature of the disorder (Strang et al., 2020). Individuals with OUD exhibit poorer performance across different cognitive domains including attention and executive function (Baldacchino et al., 2012; Ersche et al., 2006; Wollman et al., 2019). Of clinical importance, the cognitive difficulties may impede treatment adherence and functional outcomes (Li et al., 2013; Passetti et al., 2008). However, OUD is also reported among people with higher education (Baldisseri, 2007), indicating that cognitive

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dysfunction may not necessarily be a prerequisite of OUD, suggesting a more mixed picture. Moreover, both OUD and cognitive ability are associated with the same brain regions including basal ganglia structures (Strang et al., 2020; Zhao et al., 2018), indicating a potential common neurobiological basis (Smith et al., 2009; Zhu et al., 2016).

Both OUD and cognitive function are heritable, with SNP-based heritability (h^2_{SNP}) estimates at 11.0% (Kember et al., 2022), 11.3% (Zhou et al., 2020) and 12.8% (Deak et al., 2022) for OUD and 19.0% for general cognitive ability (COG) (Savage et al., 2018), a measure that accounts for approximately 40–50% of the variation across cognitive domains (Davies et al., 2015). To date, genome-wide association studies (GWAS) have identified 14 risk loci for OUD (Kember et al., 2022) and more than two hundred loci for COG (Davies et al., 2018; Lam et al., 2019; Savage et al., 2018). GWAS analyses show significant negative genetic correlations of 0.3–0.4 between OUD and COG, indicating that genetic risk of OUD is linked to lower cognitive performance (Deak et al., 2022; Zhou et al., 2020). Indeed, the genetic susceptibility of addiction may relate to cognitive dysfunction including lower executive functioning (Bogdan et al., 2023). However, while methods determining SNP-phenotype-associations are highly valuable for mapping the unique and shared genetic architecture of complex human phenotypes as well as the potential biological mechanisms involved, they do not inform on the underlying causal relationships between phenotypes, for which tools such as mendelian randomization (MR) (Sanderson et al., 2022) are necessary. A recent MR study reported a significant causal relationship between educational attainment (EDU) and OUD, in which low EDU was found to be causative to OUD (Zhou et al., 2020). However, in the same study the authors did not find a statistically significant causal relationship between cognitive performance and OUD. Kember and colleagues (2022) did however find a negative causal relationship between both EDU, cognitive performance and OUD using an expanded MVP dataset on OUD. Despite the evidence for a common genetic basis between cognitive dysfunction and OUD, the specific genetic loci jointly influencing OUD and cognition remain to be determined. One exception is a high-risk variant (rs4702, *FURIN*) for OUD which has been associated with decreased cognitive ability (Lam et al., 2019). The identification of specific variants is key for understanding the biological mechanisms of their shared genetic variance. Moreover, despite the assembly of large-scale cohorts, the variants discovered in both of these phenotypes only explain a minor fraction of the estimated common variants underlying their heritability (Davies et al., 2018; Kember et al., 2022).

In the present study, we investigated the genetic relationship between OUD and COG by analysing the largest GWAS on these phenotypes (Kember et al., 2022; Savage et al., 2018) using statistical approaches that can measure genetic overlap beyond genetic correlation. First, we applied the bivariate causal mixture model MiXeR (Frei et al., 2019) to quantify the number of unique and shared genetic variants between the phenotypes, allowing for mixed effect directions. Second, we applied the conditional/conjunctional false discovery rate (cond/conjFDR) approach (Andreassen et al., 2013a; Smeland et al., 2020b), leveraging the substantial power in the COG GWAS to improve the power to discover OUD risk loci and OUD loci jointly associated with COG. The cond/conjFDR approach has successfully identified overlapping loci between several complex phenotypes, including substance use and other psychiatric disorders (Andreassen et al., 2013a, 2013b; Holen et al., 2023; Icick et al., 2022; Smeland et al., 2017; Wiström et al., 2022). Finally, we applied recently developed functional annotation tools, V2G and FUMA to characterize the molecular pathways involved.

2. Material and methods

2.1. GWAS Samples

We obtained publicly available independent GWAS summary statistics for OUD and COG. The main OUD sample comprised 19,978 International Classification of Diseases (ICD) diagnosed OUD cases and 282,607 opioid-exposed controls (Kember et al., 2022) from the Million Veteran Program, while the latest GWAS of COG included 269,867 individuals (Savage et al., 2018) (see Supplementary Information for details). To assess the consistency of the results, we repeated the genetic overlap analyses using a different OUD GWAS, wherein most controls had unknown opioid-exposure status (Deak et al., 2022). Furthermore, to assess the specificity of the observed genetic overlap between OUD and COG, we also conducted overlap analyses using GWAS of educational attainment (EDU) (Okbay et al., 2022) and household income (HI) (Hill et al., 2019), both of which are genetically correlated with COG (Hill et al., 2019). All GWAS data were from individuals of European ancestry. An overview of the samples is shown in Table 1. The Norwegian National Research Ethics Committee for the South-East Norway Region has evaluated the current protocol and found that no additional institutional review board approval was needed because no individual data were used.

2.2. Mixture model (MiXeR) analysis of genetic architecture

We used MiXeR, which builds on a probabilistic Gaussian mixture model that assumes that a given data set can be modelled as a "mixture" of predefined components (zero and non-zero effect on a trait), each with its own Gaussian distribution and a threshold of 90% heritability to avoid extrapolating model parameters into variants with infinitesimally small effects. The model accounts for minor allele frequency, sample size, effects of LD structure, genomic inflation due to cryptic relatedness, and sample overlap. In addition to estimating the number of variants influencing distinct and shared components of the traits' genetic architecture, we also estimated the genetic correlation between the traits in the shared component irrespective of effect directions and correlation of effect sizes. Finally, we estimated discoverability, that is, the variance of effect size per "trait influencing" variant. The accuracy of the model was evaluated using the Akaike information criterion (AIC), Q-Q plots and log-likelihood curves. Additional details on the MiXeR method can be found in the Supplementary Information and previous publications (Frei et al., 2019; Hindley et al., 2022).

Table 1
Genome-wide association studies used in the present analyses. OUD = opioid use disorder; COG = general cognitive ability; EDU = educational attainment; HI = household income; MVP = Million Veteran Program; PGC = Psychiatric Genomics Consortium; CTG = Complex Trait Genetics lab; SSGAC = Social Science Genetic Association Consortium; UKBB = UK Biobank; ICD = International Classification of Diseases; DSM = Diagnostic and Statistical Manual of Mental Disorders.

Phenotype	Consortium	Sample size	Reference
OUD, one ICD code. Exposed controls	MVP	19,978 cases 282,607 controls	(Kember et al., 2022)
OUD, either two outpatient or one inpatient ICD code, or DSM-assessedOUD diagnosis. Unscreened controls	MVP, PGC, iPSYCH, FinnGen, Partners Biobank, BioVU, Yale-Penn 3	15,251 cases 538,935 controls	(Deak et al., 2022)
COG	CTG	269,867 continuous trait	(Savage et al., 2018)
EDU	SSGAC	1131,881 continuous trait	(Lee et al., 2018)
HI	UKBB	286,301 continuous trait	(Hill et al., 2019)

2.3. Conditional/conjunctional false discovery rate for identification of genetic variants

Using conditional Q-Q plots, we evaluated cross-trait enrichment between OUD and COG. Then we applied condFDR (Andreassen et al., 2013a) to improve discovery of genetic variants associated with OUD, by leveraging genetic overlap with the largest COG GWAS. The condFDR value can be interpreted as the probability that a given SNP is not associated with the primary trait given that the SNP is more strongly or as strongly associated with both phenotypes than observed in the original GWAS. We then computed a conjunctional FDR (conjFDR) statistic, which is determined by repeating the condFDR analysis for both traits after inverting the roles of the primary and secondary trait. The conjFDR is the maximum of the two condFDR statistics and represents the probability that a given SNP is not associated with the primary or secondary trait given that the SNP is more strongly or as strongly associated with both phenotypes than observed in the original GWAS. An FDR level of 0.01 per pair-wise comparison was set for condFDR. We excluded SNPs around the extended MHC region and chromosome 8p23.1 (genome build 19 locations chr6:25119106–33854733 and chr8:7200000–12500000, respectively) before fitting the FDR model, since their intricate regional LD may bias cond/conjFDR estimation (Schwartzman and Lin, 2011). More information about the cond/conjFDR methods can be found in the Supplementary Information, original publications (Andreassen et al., 2014, 2013a) and review (Smeland et al., 2020b).

2.4. Genomic locus definition

We defined independent genetic loci according to the FUMA protocol (Watanabe et al., 2017). Briefly, independent significant genetic variants were identified as variants with conjFDR$<$0.05 and LD $r^2<0.6$ with each other. The SNP with the most significant p-value in the locus was defined as the lead SNP. For each lead variant all candidate variants were identified as variants with LD $r^2\geq0.6$ with the lead variant. For a given lead variant the borders of the genetic locus were defined as min/max positional coordinates over all corresponding candidate variants. Loci were then merged if they were separated by less than 250 kb. LD information was calculated from the 1000 Genomes Project European-ancestry reference panel (Auton et al., 2015). Directional effects of loci were exhibited as concordant or discordant for the traits after comparing z-scores of the lead SNPs. Concordance in the conjFDR analysis would mean that the loci would give risk for both OUD and higher scores on COG. To check for novelty of identified loci we investigated all discovered loci for overlap with previously identified loci using our database of GWAS on the traits investigated in this study. All recent and relevant GWAS for OUD and cognitive phenotypes were included.

2.5. Functional annotation of OUD loci and loci shared between OUD and COG

We applied the open-source Open Targets Genetics application Variant to Gene (V2G) to map lead SNPs to genes, which integrates a variety of functional datasets in a machine-learning approach to identify the most likely causal gene (Mountjoy et al., 2021). We input the lead SNP for each locus and selected the gene with the overall top score for further functional analyses. Due to a relatively modest number of genes resulting from the gene selection approach, gene set analysis was inadequately powered. We did however investigate tissue expression of each individual gene using the application SNP2FUNCTION in FUMA (Watanabe et al., 2017). We further investigated cell-specific expression data of the genes within the human brain using a publicly available RNA-sequencing transcriptome and splicing database (Zhang et al., 2016). The cell types included were fetal and mature astrocytes, neurons, oligodendrocytes, microglia/macrophages, and endothelial cells.

3. Results

3.1. Shared and distinct genetic architecture of OUD and COG

Using MiXeR, we estimated that 5.1 K (sd=0.8 K) "trait influencing" variants affect risk of OUD and twice as many, 10.2 K (sd=0.3 K), influence COG (Supplementary Tables 1–2). Using bivariate MiXeR, we estimated that almost all OUD variants, 4.8 K (sd=0.7 K), were shared with COG, comprising 94 percent of the common variant architecture of OUD. The MiXeR significance testing by comparing AIC of the best fitting MiXeR estimates with a "reference" model yielded positive values, supporting the results (Supplementary Tables 1–3). This is interpreted as evidence that the best fitting MiXeR model is distinguishable from an "infinitesimal model" in which all variants are assumed to be 'causal' (Holland et al., 2020).

In the bivariate MiXeR model, the AIC differences indicated that the best model fit was indistinguishable compared to the maximum possible overlap (AIC=−0.19), but distinguishable compared to the minimum possible overlap (AIC=3.58; Supplementary Table 3). This indicated with high confidence that the overlap of OUD with COG is not less than estimated but could be larger. Greater power in the OUD dataset will improve this precision. In line with prior work (Deak et al., 2022; Zhou et al., 2020), there was a significant negative genome-wide genetic correlation between the phenotypes: $r_g=-0.38$ (sd=0.02) when considering all variants (Fig. 1), while the genetic correlation within the shared component was even higher, $r_g=-0.58$ (sd=0.05). Using the OUD GWAS dataset largely based on unscreened controls (Deak et al., 2022), we observed consistent estimates of genetic overlap at the genome-wide level using MiXeR compared to the primary analysis, (see Supplementary Results for more details). Similarly, EDU and HI displayed a substantial genetic overlap with OUD akin to that observed for COG, indicating widespread genetic effects of the implicated variants.

3.2. Identification of new OUD loci leveraging boost in power from overlap with COG

In line with the MiXeR estimates, conditional Q-Q plots indicated

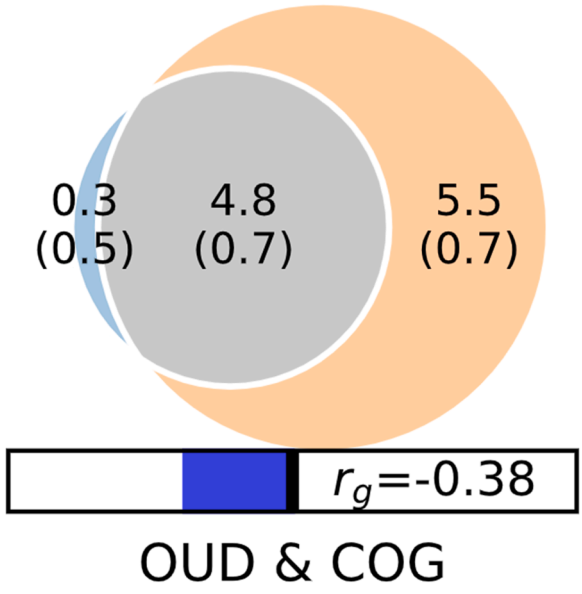

Fig. 1. MiXeR Venn diagram showing the number (in thousands) of shared and disorder-specific trait-influencing variants for opioid use disorder (OUD, light blue), general cognitive ability (COG, orange) and polygenic overlap (grey). The numbers indicate the estimated quantity of 'causal' variants per component, explaining 90% of SNP heritability in each phenotype, followed by the standard deviation. r_g = Genome-wide genetic correlation.

strong bidirectional cross-trait enrichment between OUD and COG (Fig. 2), indicating polygenic overlap. We then applied condFDR to boost discovery of OUD loci conditional on COG and identified a total of 12 loci for OUD at condFDR<0.01, including two novel loci for OUD linked to genes *CPT2* and *CD47* (Table 2).

3.3. Identification of loci jointly associated with OUD and COG

To identify shared risk loci between OUD and COG we performed conjFDR analysis (Fig. 3). We identified in total eight loci jointly associated with OUD and COG at conjFDR<0.05, including one novel OUD risk locus mapping to gene *SLC5A11* (Table 3). All shared loci showed discordant effects between OUD and COG, in line with the negative genetic correlation. Because of the complex LD structure of the extended MHC region, we counted loci within the MHC as one locus. We additionally conducted conjFDR analyses on OUD cohorts with unscreened controls, EDU and HI, and observed 24, 23 and six shared loci with COG respectively (see Supplementary Results for more details).

3.4. Functional characterization

The top genes implicated using Open Targets (Mountjoy et al., 2021) are listed in Tables 2 and 3. The full lists of genes in each locus, identified with Open Targets are listed in Supplementary Tables 16–33. Applying FUMA we found that the lead SNPs were mostly intronic or intergenic variants except for rs4702 which is localized in the 3'UTR of *FES* and may impact post-transcriptional and translational processes. Rs4702 is previously identified for OUD (Deak et al., 2022) and is also a risk variant for schizophrenia, bipolar disorder and major depression (Holen et al., 2023). Another exception was *OPRM1*, which codes for the main opioid receptor (μ) for opioid drugs and is a known exonic variant for OUD (Zhou et al., 2020). Finally, we identified a non-coding intronic RNA, at rs35942385 (*ARHGAP15*). Among the identified loci, many have previously been associated with various cognitive and substance use traits according to the GWAS catalog (Buniello et al., 2018).

We explored tissue type expression for the top gene in each locus for both condFDR and conjFDR analysis and discovered nucleus accumbens, anterior cingulate cortex, caudate nucleus, atrial appendage, hippocampus, amygdala, and putamen to survive multiple comparison testing (Supplementary Figure S3). Furthermore, we provide cell-type expression profiles for the major cell types; fetal and mature astrocytes, neurons, oligodendrocytes, microglia, and endothelial cells, in the normal fetal (18.0–18.5 gestational weeks old), and adult (8–63 years old) human temporal cortex, from 6, 12, 1, 5 and 3 patients respectively, for the 15 implicated genes. All major cell types were expressed (Supplementary Figure S4).

Table 2.
The most strongly associated single nucleotide polymorphisms (SNPs) in genomic loci associated with opioid use disorder (OUD) at conditional false discovery rate (condFDR) <0.01 given association with general cognitive ability (COG) after merging regions <250 kb apart into a single locus are shown. Location = Chromosome and base pair position, conditional false discovery rate (FDR) value, V2G = Variant to gene, and OUD novelty status.

Location	Lead SNP	V2G gene	CondFDR	P-value OUD	Novel for OUD
1:53717656	rs12408900	CPT2	2.11E-03	2.03E-07	Yes
2:144208523	rs35942385	ARHGAP15	6.83E-03	6.61E-06	No
3:107960919	rs16854357	CD47	6.25E-03	1.11E-06	Yes
6:29354809	rs3094550	MHC	5.69E-04	1.30E-07	No
6:154360797	rs1799971	OPRM1	9.12E-08	7.68E-13	No
8:143316970	rs13262595	TSNARE1	3.77E-04	2.65E-07	No
11:112869404	rs1940701	NCAM1	1.25E-04	7.99E-08	No
11:113298339	rs2471857	TTC12	9.76E-03	9.18E-07	No
13:31839274	rs9572914	B3GLCT	5.51E-03	4.20E-06	No
15:91426560	rs4702	FES	2.06E-05	2.78E-10	No
16:61631362	rs9635513	CDH8	5.13E-03	1.62E-08	No
20:48583726	rs7272308	SLC9A8	5.28E-03	2.74E-07	No

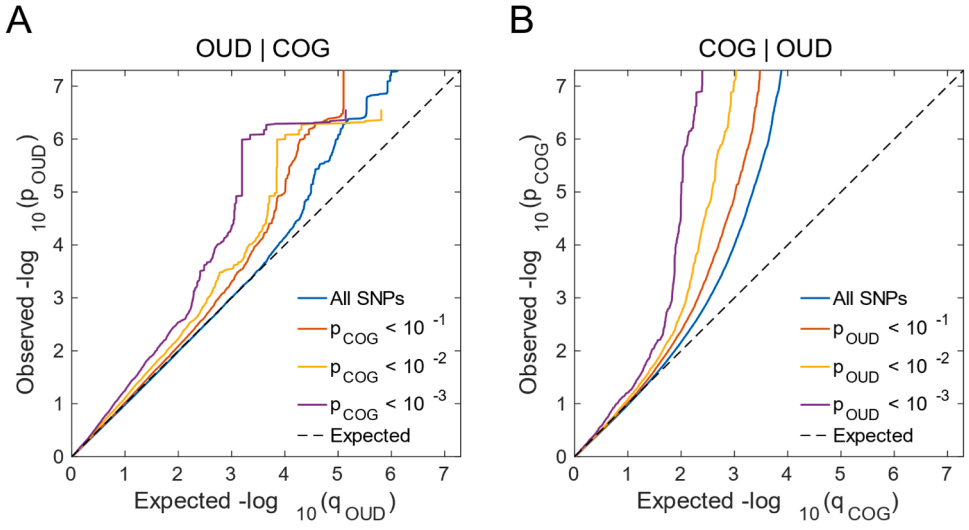

Fig. 2. Conditional Q-Q plots. A) Q-Q plot of nominal versus empirical opioid use disorder (OUD) −log10 p-values (corrected for inflation) below the standard GWAS threshold of $p<5\times10^{-8}$ as a function of the significance of the association with general cognitive ability (COG) at the level of p≤0.1, p≤0.01, p≤0.001, respectively. B. Conditional Q-Q plot of nominal versus empirical COG −log10 p-values (corrected for inflation) below the standard GWAS threshold of $p<5\times10^{-8}$ as a function of significance of association with OUD, at the level of p≤0.1, p≤0.01, p≤0.001, respectively. The blue lines illustrate the standard enrichment for all SNPs irrespective of their association p-value in the second phenotype. The dashed line shows the null hypothesis. Successive leftward deflection for declining nominal p-values from the dashed line of no association, indicates that the proportion of non-null SNPs in OUD increase with higher levels of association with COG, and vice versa.

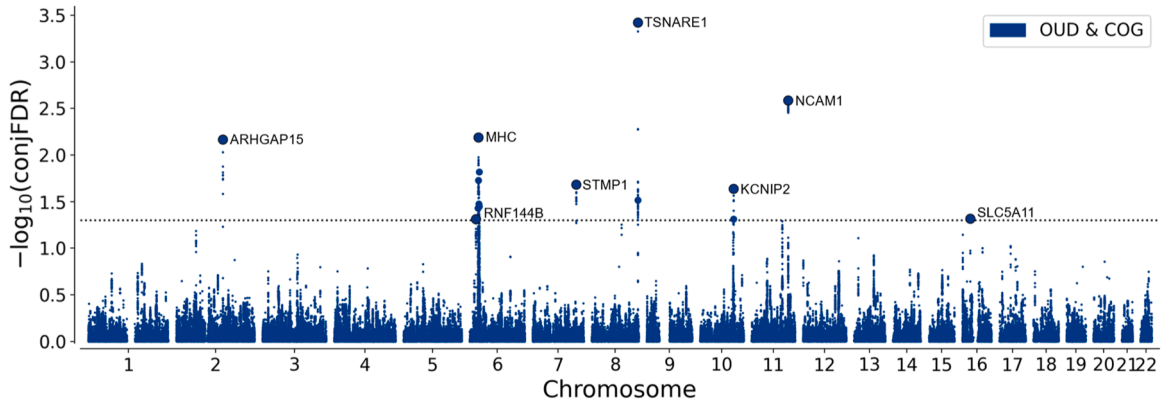

Fig. 3. ConjFDR Manhattan plot. Common genetic variants jointly associated with opioid use disorder (OUD) and general cognitive ability (COG) at conjunctional false discovery rate (conjFDR)<0.05. Manhattan plot showing the –log10 transformed conjFDR values for each SNP on the y-axis and chromosomal positions along the x-axis. The dotted horizontal line represents the threshold for significant shared associations (conjFDR<0.05). Independent lead SNPs are highlighted.

Table 3
Summary data of shared loci identified between opioid use disorder (OUD) and general cognitive ability (COG) at conjunctional false discovery rate (conjFDR) <0.05. Location = Chromosome and base pair position; SNP = single nucleotide polymorphism; V2G = Variant to gene.

Location	Lead SNP	V2G gene	ConjFDR	P-value OUD	P-value COG	Novel for OUD
2:144208523	rs35942385	ARHGAP15	6.83E-03	6.61E-06	6.55E-10	No
6:19078274	rs2842385	RNF144B	4.86E-02	8.32E-05	9.50E-05	No
6:27410422	rs35984974	MHC	6.48E-03	2.57E-06	5.14E-06	No
7:135082751	rs3812281	STMP1	2.07E-02	2.65E-05	4.81E-06	No
8:143316970	rs13262595	TSNARE1	3.77E-04	2.65E-07	9.07E-10	No
10:103726528	rs11191161	KCNIP2	2.31E-02	3.08E-05	3.34E-09	No
11:112892570	rs9919620	NCAM1	2.58E-03	1.65E-07	1.43E-06	No
16:24727064	rs7188873	SLC5A11	4.81E-02	8.77E-05	2.09E-08	Yes

4. Discussion

In the current study we demonstrate a substantial overlap in common genetic variants influencing COG and OUD. Both OUD and COG were highly polygenic, with COG being twice as polygenic (10.2 K variants) as OUD (5.1 K variants). Most of the genetic variants (94%) influencing OUD were shared with COG, indicating a considerable shared genetic basis. Within the shared portion, there was a high negative genetic correlation (r_g =−0.58), indicating that OUD risk variants decrease cognitive performance in the general population. These findings suggest that the genetic etiology of OUD is strongly related to cognitive functioning, representing a large part of its susceptibility. Leveraging the larger COG GWAS dataset and the cross-trait enrichment between these phenotypes, we discovered three novel OUD risk loci, providing new insights into the molecular pathways of OUD. Additionally, we found consistent results with another OUD dataset (Deak et al., 2022), which was largely based on unscreened controls compared to the opioid-exposed controls contributing to the primary OUD dataset (Kember et al., 2022). This indicates that the observed genetic overlap between OUD and COG was not driven by the control definition but reflects true shared genetic effects between these phenotypes. Furthermore, to assess whether the observed genetic overlap was specific to COG, we also conducted MiXeR and conjFDR analyses using GWAS datasets on EDU (Okbay et al., 2022) and HI (Hill et al., 2019). We observed a similar picture of genetic overlap at the genome-wide level where almost all OUD variants were found to influence these behavioural and socioeconomic traits. However, to specifically address whether the genetic association with these traits could drive the genetic overlap between OUD and COG other studies are warranted, using methods such as mendelian randomization or genomic SEM (Grotzinger et al., 2019; Sanderson et al., 2022). The results nevertheless demonstrate that most OUD risk variants are associated with a range of cognitive, behavioural and socioeconomic traits as well as risk of mental disorders (Holen et al., 2023), emphasizing their broad impact on key functional and health-related traits.

Several lines of evidence suggest a highly pleiotropic nature of genetic risk underlying mental traits and disorders (Watanabe et al., 2019). The extensive genetic overlap between OUD and COG is in line with recent studies identifying large genetic overlap between mental traits and disorders with a large variation in genetic correlations (Hindley et al., 2022). Our findings comply with the observation that multiple genetic variants with small effect sizes influence many traits to different degrees (Smeland et al., 2020a). While the polygenicity of COG is on the same order of magnitude as schizophrenia (9.6 K), bipolar disorder (8.6 K), depression (14.5 K), OUD is similarly polygenic as ADHD (5.6 K) (Hindley et al., 2022). The lower polygenicity of OUD may indicate less genetic heterogeneity compared to COG, schizophrenia, or depression. This is consistent with COG being influenced by a wide range of brain systems (Deary et al., 2010), while OUD may more specifically result from dysfunctional interplay between reward processing, affect regulation and cognitive functions like executive function (Bogdan et al., 2023). The strong negative genetic correlation between COG and OUD within the shared component is similar to that observed between COG and ADHD (r_g =−0.60), another mental disorder highly linked to cognitive difficulties, while the estimates of the genetic correlation in the shared component exceed those reported for other psychiatric disorders like schizophrenia, bipolar disorders and depression (Hindley et al., 2022). The imperfect correlation within the shared component can be explained by a mixture of concordant and discordant effect directions among the shared variants, which are partially cancelling each other out. Additionally, the variation in the strength of association with OUD and COG will vary across the variants, leading to an imperfect correlation. Finally, the global genetic correlations estimated between OUD and COG are similar to those reported previously using LDSC, demonstrating that OUD risk variants are associated with lower cognitive performance in the population.

Our findings underline how common genetic variants aggregates into genetic risks of developing OUD and decreased COG. Furthermore, as treatment regimens for OUD is implemented, the shared risk of OUD and cognitive dysfunction should be taken into account. Moreover, the knowledge of coinheritance of these traits may aid decision makers in planning public health measures and prevention programs.

Furthermore, using the cond/conjFDR approach we were able to boost discovery of genetic variants linked to OUD, by leveraging the larger GWAS on COG. Seven of the presently discovered loci were not discovered in the original OUD GWAS (Kember et al., 2022), while four loci have been identified in other studies, at lead SNP locations 2:144208523 and 7:135082751 (Heng Xu et al., 2022), 6:19078274 (Deak et al., 2022) and 16:61631362 (Holen et al., 2023), validating these findings. Furthermore, we note that a locus with lead SNP location 16:24727064 was identified by (Gaddis et al., 2022) for opioid addiction, however at a relaxed genome-wide threshold (p-value 3×10^{-6}). The three novel OUD loci were linked to genes *CPT2, CD47* and *SLC5A11*. Among the identified loci, seven implicated genes (*ARHGAP15, CD47, RNF144B, NCAM1, TTC12, B3GLCT, CDH89*) have previously been associated with exogenous substance intake (e.g. (Kember et al., 2022; Saunders et al., 2022)) and also cognitive measures (e.g. (Okbay et al., 2022; Savage et al., 2018)), supporting our findings of shared genetics of OUD and COG. Moreover, eight of the genes (*ARHGAP15, CD47, TSNARE1, NCAM1, TTC12, B3GLCT, FES, CDH8*) have been linked to other psychiatric disorders, demonstrating pervasive cross-disorder influences. Additionally, the highly pleiotropic MHC region has previously been linked to both COG (Savage et al., 2018), psychiatric disorders (Lee et al., 2019) and OUD (Holen et al., 2023).

The implicated genes annotating the novel loci include *CPT2* (1:53717656), which codes for a protein involved in long-chain fatty acid metabolism on the inner mitochondrial membrane. It has not previously been associated with mental disorders nor cognitive measures but with disorders of mitochondrial long-chain fatty acid metabolism (Violante et al., 2010). *CD47,* linked to another novel locus (3:107960919), encodes a membrane protein involved in intracellular calcium concentration increase as cells adhere to extracellular matrix. It may also be involved in membrane transport and signal transduction (Latour et al., 2001). *CD47* is associated with smoking initiation (Saunders et al., 2022), cognitive performance (Lee et al., 2018), EDU (Okbay et al., 2022), schizophrenia (Trubetskoy et al., 2022) and bipolar disorder (Li et al., 2021). *B3GLCT*, linked to the third novel locus (13:31839274), codes for beta-1,3-glucosyltransferase, that transfers glucose to O-linked fucosylglycans on thrombospondin type-1 repeats of several proteins and is thus involved in metabolism of proteins. It is a type II membrane protein and a defect in the gene is highly associated with Peters-plus syndrome (Stelzer et al., 2016). Genome-wide associations include EDU (Okbay et al., 2022), major depression (Howard et al., 2019), bipolar I disorder (Mullins et al., 2021), and cocaine use (Wu et al., 2019). Finally, *SLC5A11 (SMIT2)* (16:24727064), codes for a cotransporter (Na^+ and myo-inositol) in the plasma membrane and is part of a class of proteins that uses ion gradients do drive active transport of nutrients, neurotransmitters, osmolytes, and ions (Roll et al., 2002). The gene product of *SLC5A11* specifically transports inositol into mammalian cells (Su et al., 2023). It has previously not been associated with mental disorders or traits except for opioid dependence at a more relaxed genome-wide threshold (p-value 3×10^{-6}) (Gaddis et al., 2022).

Intriguingly, tissue expression analysis revealed that the mapped genes for OUD and COG were significantly associated with expression in the nucleus accumbens, anterior cingulate cortex, the caudate nucleus, hippocampus, amygdala and putamen (Supplementary Figure S3). These brain tissues are part of the corticostriatal and corticolimbic circuits and may be relevant to OUD pathogenesis. The findings may thus be in line with the Genetically Informed Neurobiology of Addiction model of addiction, as recently proposed (Bogdan et al., 2023), which highlights the role of predisposing genetic factors of addiction in these areas.

The current study has some limitations. We cannot exclude sporadic, non-systematic sample overlap. However, this is unlikely to affect the results to a meaningful extent. Larger datasets for OUD in general and for other cohorts of non-European ancestry in particular are needed to uncover more of the genetic underpinnings of OUD and COG and improve generalizability of results.

5. Conclusions

The present study shows that OUD and COG have largely shared genetic architectures, in which variants linked to lower cognitive performance constitute a major fraction of the genetic architecture underlying OUD. In addition, we identified novel OUD risk variants which may help generate novel hypotheses into molecular mechanisms of OUD. The identified loci implicate genes involved in long-chain fatty acid metabolism, membrane transport, signal transduction, metabolism of proteins and inositol transport. Moreover, the genes are highly expressed in specific brain regions, corroborating a neurobiological basis of OUD. Further genetic research using larger datasets is likely to uncover more of the molecular genetic mechanisms underlying OUD and delineate its relationship with cognition, which may inform the development of new treatment strategies for this patient group, an unmet need in this field.

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Declaration of Competing Interest

OAA has received speaker's honoraria from Sunovion, Lundbeck and Janssen and is a consultant for Cortechs.ai. AMD is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict-of-interest policies. JG is a named inventor on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018 and issued on January 26, 2021 as U.S. Patent No. 10,900,082. JG was paid for editorial work on the journal Complex Psychiatry. Remaining authors have no conflicts of interest to declare.

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Contributors

BH, OAA, and OBS were responsible for the study concept and design. AAS, KSOC, OBS and OAA contributed to the acquisition of summary data. BH, GK, OBS and OAA assisted with data analysis and interpretation of findings. GK and BH prepared figures. BH drafted the manuscript. OAA and OBS provided critical revision of the manuscript for important intellectual content. All authors critically reviewed

content and approved final version for publication.

Code availability

Cond/conjFDR analyses were run with MATLAB 2018b and code is available at https://github.com/precimed/pleiofdr. Version 1.3.7 of the FUMA web tool was used (https://fuma.ctglab.nl/updates). We used the 25 February 2022 release of the OpenTargets web tool (https://genetics.opentargets.org/). Scripts to standardize summary statistics and to produce Manhattan plots were run with python version 3.7.4 (https://github.com/precimed/python_convert).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2023.111058.

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