

Cross-Trait Integration of Fine-Mapped Signals From 30 Brain-Related Genome-Wide Association Studies Prioritizes DRD2 as a Pleiotropic Network Hub

Kenneth Blum

`drd2gene@ariel.ac.il`

Ariel University

Alireza Sharafshah

Universidade Federal do Estado do Rio de Janeiro

Kai-Uwe Lewandrowski

The Origen Institute of Neurobiology and Genetics

Morgan P. Lorio

Orlando College of Osteopathic Medicine

Panayotis K. Thanos

University at Buffalo, State University of New York

Rafael Rea

University of California San Diego

Edward J. Modestino

Curry College

David Baron

Western University of Health Sciences

Rossano Kepler Alvim Fiorelli

Universidade Federal do Estado do Rio de Janeiro

Sergio Schmidt

Universidade Federal do Estado do Rio de Janeiro

Igor Elman

Ariel University

Jonathan S. Vogelgsang

Harvard Medical School

Keerthy Sunder

University of California, Riverside, School of Medicine

Albert Pinhasov

Ariel University

Jia A. Blum

The Origen Institute of Neurobiology and Genetics

Abdalla Bowirrat

Ariel University

Paul R. Carney

University of Missouri, School of Medicine

Thomas Simpatico

University of Vermont

Marlene Oscar Berman

Boston University Chobanian & Avedisian School of Medicine

Kyriaki Thanos

University at Buffalo, State University of New York

Álvaro Dowling

The Origen Institute of Neurobiology and Genetics

Rafaela Dowling

The Origen Institute of Neurobiology and Genetics

Alexander P. L. Lewandrowski

University of Southern California

João Paulo M. Bergamaschi

Universidade de São Paulo

Shaurya Mahajan

The Origen Institute of Neurobiology and Genetics

Yatharth Mahajan

The Origen Institute of Neurobiology and Genetics

Margaret A. Madigan

The Origen Institute of Neurobiology and Genetics

Mark S. Gold

Washington University in St. Louis, School of Medicine

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Abstract

Shared genetic architecture may contribute to the co-occurrence of psychiatric, cognitive, behavioral, pain, and substance-related phenotypes, yet prioritizing pleiotropic loci across heterogeneous genome-wide association studies (GWAS) remains difficult. We developed an exploratory three-level framework comprising trait-specific Bayesian fine-mapping, cross-trait signal integration, and gene prioritization, followed by GTEx brain cis-expression quantitative trait locus, ClinPGx, STRING protein-interaction, and enrichment annotation. Thirty public GWAS data sets representing more than 20 brain-related phenotypes were analyzed. The sum of reported sample sizes was 10,613,558, but this aggregate does not represent unique participants because cohorts may overlap. The workflow retained 999 tag variants and 860 gene entries, yielding 474 unique genes, including 193 shared across at least two traits. Fifty-four variants occurred in at least three phenotypes, and 608 genomic intervals overlapped across data sets. Broad regions on chromosomes 6 and 11 were represented across 20 traits. The chromosome 11 interval included DRD2; rs2514218 occurred in eight data sets. GTEx annotation supported 97 genes, 77 of which formed an interconnected STRING network; 29 genes had pharmacogenomic annotations. DRD2 was prioritized as a network hub. These findings support DRD2 as a hypothesis-generating pleiotropic network candidate rather than a solitary determinant of behavior. Independent replication, correction for cohort overlap and annotation-density bias, ancestry-matched LD analyses, and functional validation are required.

Introduction

Genome-wide association studies (GWAS) have enabled systematic investigation of common genetic variation across complex brain-related phenotypes. Cross-trait approaches can identify recurrent loci and genes that may contribute to neuropsychiatric, behavioral, cognitive, pain, and substance-related outcomes. However, linkage disequilibrium (LD), noncoding variation, heterogeneous phenotypes, and overlapping cohorts complicate the translation of association signals into biologically interpretable candidates. We therefore developed an integrative framework combining trait-specific Bayesian fine-mapping, cross-trait comparison, LD and haplotype characterization, gene prioritization, transcriptomic annotation, pharmacogenomic annotation, protein-interaction analysis, and enrichment assessment. The objective was to identify shared genomic signals and generate testable hypotheses regarding pleiotropic network genes. DRD2 was interpreted as one candidate emerging from the complete pipeline, not as a prespecified causal determinant or solitary gene for addiction or mental illness.

Materials & Methods

2.1. Study Design

A comprehensive multi-trait genome-wide association study (GWAS) fine-mapping framework was developed to identify shared genetic variants and pleiotropic genes across diverse brain-related phenotypes. Thirty publicly available GWAS datasets representing more than 20 brain-related

phenotypes were analyzed using a custom Python-based computational pipeline. The framework consisted of three analytical stages: trait-specific fine-mapping, cross-trait integration and locus refinement, and gene prioritization. Following generation of a Final Gene List (FGL), downstream analyses including transcriptomics (GTEx cis-eQTL), pharmacogenomics (PGx), protein-protein interactions (PPIs), and enrichment assessments were performed to evaluate the biological and translational relevance of prioritized genes.

2.2 GWAS datasets, traits, and sample sizes

We obtained 30 publicly available GWAS data sets from the GWAS Catalog, representing more than 20 brain-related phenotypes. The reported sample sizes ranged from 94 to 2,776,348. Their arithmetic sum was 10,613,558; because cohorts may overlap across GWAS and several related phenotypes may derive from shared consortia, this value is an aggregate data-set count rather than a unique-participant count. The final submission should provide the accession number, source publication, ancestry, genome build, phenotype definition, sample size, and download date for every data set in a supplementary Table 1. The workflow analyzed each data set separately before cross-trait comparison; recurrence therefore indicates representation across data sets and does not necessarily constitute independent replication. The results from Level 1 multi-trait GWAS fine-mapping are summarized in Table 1.

[Insert Table 1]

Table 1
Summary of results from level 1 multi-trait GWAS fine mapping.

Trait	Total SNPs	Sig. SNPs	Loci	Primary (CkI)	Tag SNPs (CkII)	Tag Causal SNPs	Unique Genes
Trait1	29	0	0	29	0	0	0
Trait2	693	416	228	50	263	39	34
Trait3	904	368	193	50	233	47	33
Trait4	657	647	547	50	180	23	23
Trait5	2683	1912	711	50	1482	48	50
Trait6	7583	6385	1484	50	5888	45	28
Trait7	5967	4590	976	50	4230	50	53
Trait8	276	50	34	50	23	23	16
Trait9	614	226	98	50	156	44	33
Trait10	498	433	236	50	251	21	25
Trait11	201	166	94	50	96	47	37
Trait12	1068	472	342	50	198	39	38
Trait13	3102	2405	888	50	1934	48	25
Trait14	37	3	3	37	0	0	0
Trait15	8	3	3	8	0	0	0
Trait16	251	242	6	50	242	50	7
Trait17	400	318	131	50	245	47	39
Trait18	131	13	11	50	4	4	3
Trait19	1241	1046	320	50	884	49	48
Trait20	2307	1648	741	50	1189	45	55
Trait21	29	29	25	29	8	8	7
Trait22	1086	924	638	50	430	40	30
Trait23	58	8	8	50	0	0	0
Trait24	146	51	46	50	10	10	7
Trait25	1578	751	333	50	550	44	55
Trait26	4636	2361	688	50	1938	49	49

Trait	Total SNPs	Sig. SNPs	Loci	Primary (CkI)	Tag SNPs (CkII)	Tag Causal SNPs	Unique Genes
Trait27	4553	2360	687	50	1938	49	49
Trait28	998	705	297	50	522	50	35
Trait29	88	77	54	50	39	30	27
Trait30	3729	2241	601	50	1901	50	54

Checkpoint I and checkpoint II are abbreviated CkI and CkII, respectively.

2.3 Fine-Mapping Pipeline

The Multi-Trait Fine-Mapping Framework was developed as a Python-based computational platform for the identification of pleiotropic loci, candidate causal variants, and biologically relevant genes across multiple brain-related phenotypes. The framework operates through a three-level analytical workflow including trait-specific fine-mapping, cross-trait integration, and gene prioritization. The primary objective of the workflow was to progressively reduce the dimensionality of GWAS summary statistics while preserving variants with the highest probability of biological relevance and causal involvement. The analytical process started with importing GWAS summary statistics from multiple independent brain-related traits. During data ingestion, an automated harmonization procedure standardized column names and data structures across datasets. Required variables included SNP identifier (rsID), chromosome number, genomic coordinates, association p-value, and either effect size estimates (β) or odds ratios (OR). Other variables such as sample size, mapped genes, cytoband annotations, and functional annotations were also considered. Quality-control (QC) procedures were subsequently performed to ensure data consistency. Duplicate SNPs were removed while retaining the record with the lowest p-value. Variants lacking valid chromosomal coordinates, genomic positions, or association statistics were excluded. Following preprocessing, the cleaned datasets were subjected to trait-specific analyses (Level 1).

Level 1: Trait-Specific Fine-Mapping (Singleton GWAS fine-mapping): At the first level, each trait was analyzed independently. Genome-wide association signals were evaluated by statistical transformation of summary statistics and Bayesian fine-mapping procedures. Genome-wide significant variants were identified according to the conventional threshold of $p < 5 \times 10^{-8}$. Significant variants were then clustered into genomic loci using a distance-based approach in which neighboring significant variants were grouped within predefined chromosomal intervals. For each locus, Bayesian fine mapping was performed using Wakefield Approximate Bayes Factors (ABFs) which allowed estimation of posterior inclusion probabilities (PIPs) for unique variants. Variants were subsequently ranked based on their posterior probabilities of causality, and 95% credible sets were generated for each locus. The resulting high-confidence variants were retained within a Primary SNP List constituted the first checkpoint (CkI) of the analytical workflow.

Level 2: Cross-Trait Integration and Locus Refinement: The second level focused on the identification of genetic signals shared among all entered databases. Primary SNP Lists generated during Level 1 were compared across all uploaded datasets to detect common variants. Simultaneously, genomic loci were evaluated for coordinate overlap to identify regions associated with multiple phenotypes. Loci presented across a minimum number of 3 traits were designated as candidate pleiotropic loci. To further refine candidate regions, linkage disequilibrium (LD) and haplotype analyses were accomplished by population-based reference panels derived from the 1000 Genomes Project (1KG). Pairwise LD matrices were generated using both r^2 and D' statistics. Variants exhibiting strong LD relationships were grouped into LD blocks, whereas haplotype structures were reconstructed applying a Haploview-like Solid Spine of LD strategy. Within each LD block, representative tag SNPs were selected according to association significance and PIP. This refinement procedure substantially reduced redundancy among highly correlated variants and generated a set of Tag-Causal SNPs representing the second checkpoint (CkII) of the framework.

Level 3: Gene Prioritization: Tag variants were mapped to genes using GWAS annotations and genomic coordinates. Gene lists were merged while phenotype-specific annotations were retained. Genes occurring across multiple phenotypes were classified as pleiotropic. The resulting Final Gene List served as the input for downstream functional and pharmacogenomic annotation. These outputs prioritize candidates but do not establish causality.

2.4 Downstream Analysis

Following generation of the FGL, two complementary downstream modules were implemented to characterize the functional and translational significance of prioritized genes including GTEx-based and PGx-based assessments.

2.4.1 GTEx-Based Functional Annotation

Transcriptomic annotation was done by resources derived from the Genotype-Tissue Expression (GTEx) project version 8 (v8). The objective of this module was to determine whether prioritized variants influence gene regulation, expression, or splicing patterns across human tissues. The analyses included cis-expression quantitative trait loci (cis-eQTLs), splice quantitative trait loci (sQTLs), and tissue-specific expression profiling. Genes exhibiting significant regulatory associations were flagged as functionally supported candidate genes, which in turn provided mechanistic evidence linking GWAS loci to biological pathways relevant to brain-related traits.

2.4.2 Pharmacogenomics (PGx) Annotation

Genes retained in the Final Gene List were queried against ClinPGx. Pharmacogenomic annotations were used to identify genes previously linked to drug efficacy, adverse reactions, or treatment response. The resulting subset was considered pharmacogenomically annotated rather than clinically actionable unless the underlying source specifically supported an actionability designation.

2.4.3 Protein–Protein Interaction Analysis

Protein–protein interaction (PPI) analysis was performed to investigate functional relationships among genes retained in the Final Gene List (FGL). Interaction networks were generated using the STRING database, allowing the identification of highly connected genes and biologically relevant subnetworks. Network topology and connectivity metrics were evaluated to identify hub genes potentially involved in shared neurobehavioral pathways. Genes exhibiting extensive interaction patterns were prioritized for further interpretation and integration with pharmacogenomic and enrichment analyses.

2.4.4 Pathway, Gene Ontology, and Disease Enrichment Analyses

Functional enrichment analyses characterized pathways, Gene Ontology terms, and disease annotations overrepresented in the prioritized gene set. The final submission must specify the exact tool, database versions, background gene universe, statistical test, and multiple-testing correction. Enrichment results were interpreted as annotation overrepresentation, not evidence of pathway activation, suppression, or disease prediction.

2.5 Statistical Analysis

All statistical calculations were performed within the program framework using standardized analytical procedures. Association significance was evaluated using consensus GWAS p-value threshold ($p < 5 \times 10^{-8}$). To standardize statistical evidence across studies, p-values were transformed into Z-scores using inverse normal transformation: $Z = \Phi^{-1}(1 - p/2)$ [where Φ^{-1} represents the inverse cumulative distribution function of the standard normal distribution]. For datasets reporting odds ratios, beta coefficients were estimated as: $\beta = \ln(\text{OR})$. Standard errors were reconstructed from confidence intervals (CI) or association statistics when not directly available. Bayesian fine-mapping was performed using Wakefield Approximate Bayes Factors (ABFs). For each variant ABF calculated based on the following equation:

$$\text{ABF} = \sqrt{V/(V + W)} \times \exp[(Z^2 W)/(2(V + W))]$$

[where V represents the variance of the effect estimate and W denotes the prior variance parameter.]

Posterior inclusion probabilities (PIPs) for all variants within the same locus were subsequently calculated as:

$$\text{PIP}_i = \text{ABF}_i / \sum \text{ABF}$$

Candidate causal variants were prioritized according to PIP values and assembled into 95% credible sets by accumulating posterior probabilities until: $\sum \text{PIP} \geq 0.95$.

LD was quantified using pairwise r^2 and D' statistics. Variants exhibiting $r^2 \geq 0.80$ were considered highly correlated and assigned to the same LD block. Haplotype structures were reconstructed using Haploview-inspired Solid Spine of LD criteria based on D' thresholds. For enrichment analyses,

significance values were transformed into “ $-\log_{10}P$ ” scores to facilitate visualization and comparison across pathways and tissues. Enrichment magnitude was represented by Normalized Enrichment Scores (NES) allowing direct comparison of pathway activation or suppression across biological contexts. Together, these statistical metrics provided complementary measures of association significance, effect magnitude, posterior probability of causality, linkage disequilibrium structure, enrichment strength, and biological relevance throughout the multi-trait fine-mapping workflow.

Results

3.1 Multi-Trait Fine-Mapping Results

Application of the cross-trait fine-mapping framework to 30 brain-related GWAS data sets identified 999 tag variants and 860 primary gene entries. After gene mapping and deduplication, 474 unique genes remained, including 193 represented across at least two traits. Cross-data-set comparison identified 54 variants present in at least three phenotypes and 608 overlapping genomic intervals. Because source cohorts may overlap, these counts reflect cross-data-set recurrence rather than fully independent replication.

Among the overlapping loci, two genomic regions demonstrated the strongest cross-trait enrichment: chromosome 6 (6:25120440–33889314) and chromosome 11 (11:112793134–114173783), each represented across 20 analyzed traits. The chromosome 11 locus contained the dopamine D2 receptor gene (DRD2), where variants including rs2514218 exhibited broad representation across multiple phenotypes, supporting its role as a highly shared genetic signal. Additional recurrent variants, including rs13107325 within SLC39A8, were also identified across numerous datasets, further demonstrating the pleiotropic nature of the detected loci.

GTEx cis-eQTL annotation supported 97 genes across brain tissues. Seventy-seven of these genes formed an interconnected STRING network, and 29 had pharmacogenomic annotations. DRD2 was prioritized as a network hub. These database-derived annotations provide convergent functional support but are not independent experimental validation and may be influenced by literature and annotation density.

Pathway enrichment analyses further implicated dopaminergic signaling and substance use-related pathways among the most significantly enriched biological processes. Notably, pathways associated with nicotine effects on dopaminergic neurons and alcohol use disorder exhibited strong enrichment signals, supporting the involvement of shared reward-related mechanisms across multiple phenotypes. Collectively, these findings demonstrate that large-scale multi-trait fine-mapping can identify shared genetic mechanisms across diverse brain-related traits and highlight DRD2 as one of the most prominent pleiotropic genes emerging from an unbiased genomic analysis.

3.2 Cross-Trait Overlap and Shared Loci

Cross-trait integration analyses revealed substantial genetic overlap among the 30 brain-related phenotypes included in this study. Comparison of Primary SNP Lists generated during Level 1 fine-mapping identified 54 tag-causal SNPs present in at least three independent phenotypes, providing evidence for widespread pleiotropy across neuropsychiatric, behavioral, cognitive, and addiction-related traits (Table 2).

Table 2
Common SNPs across traits
($k \geq 3$).

rSID	N TRAITS
rs13107325	8
rs13217619	6
rs144447022	5
rs4646776	5
rs56113850	5
rs1051730	4
rs10519203	4
rs1229984	4
rs2066702	4
rs4129585	4
rs4298967	4
rs4665972	4
rs4702	4
rs671	4
rs67981811	4
rs75782365	4
rs8034191	4
rs11072774	3
rs115329265	3
rs116137698	3
rs11637630	3
rs11667314	3
rs11783093	3
rs11793831	3
rs12731986	3
rs12907546	3

rSID	N TRAITS
rs13195402	3
rs141342723	3
rs1421085	3
rs144553930	3
rs151267808	3
rs1906252	3
rs2075633	3
rs2138445	3
rs2273500	3
rs2352974	3
rs2668733	3
rs28606370	3
rs34706883	3
rs3747207	3
rs458806	3
rs4856605	3
rs55834529	3
rs6449140	3
rs6452785	3
rs73229093	3
rs738408	3
rs738409	3
rs7623659	3
rs7746199	3
rs9401452	3
rs9467711	3
rs951740	3
rs993137	3

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Among the identified regions, the chromosome 6 locus (6:25120440–33889314) emerged as one of the most extensively shared genomic intervals. This region was represented across numerous analyzed phenotypes and contained variants spanning multiple genes, including CMAHP, CARMIL1, SCGN, SLC17A1, H2BC4, H2AC6, and HFE. The recurrence of this locus across diverse traits suggested the presence of common biological mechanisms contributing to multiple brain-related phenotypes.

To further characterize the chromosome 6 region, linkage disequilibrium (LD) analyses were performed using pairwise r^2 statistics. As shown in Fig. 1, multiple variants within the locus demonstrated strong LD relationships, indicating a highly structured genomic region with correlated genetic signals. The persistence of LD across numerous SNPs suggests that these variants may collectively contribute to the observed cross-trait associations rather than acting as isolated genetic signals.

Haplotype reconstruction further supported the integrity of the chromosome 6 locus by identifying a large, conserved haplotype block spanning the region (Fig. 2). The extensive Solid Spine D' structure indicates that many variants within this interval are co-inherited, reflecting strong haplotypic organization and supporting the hypothesis of a shared genetic architecture underlying multiple phenotypes. Together, the LD and haplotype analyses provide complementary evidence that chromosome 6 represents a major pleiotropic locus identified through the multi-trait GWAS fine-mapping framework.

While chromosome 6 demonstrated substantial cross-trait enrichment, chromosome 11 (11:112793134–114173783) emerged as an equally important shared locus. This region contained several recurrent variants observed across multiple phenotypes and encompassed the dopamine D2 receptor gene (DRD2), a well-established candidate gene implicated in reward processing, addiction, and psychiatric disorders. Consequently, the chromosome 11 locus was selected for more detailed characterization in subsequent analyses.

3.3 DRD2 Shared Locus Analysis

The chromosome 11 interval (11:112,793,134 – 114,173,783) overlapped across 20 of the 30 data sets and included DRD2 as well as neighboring NCAM1-region genes. Variant rs2514218 in the DRD2 region occurred in eight data sets: behavior, cognition, autism spectrum disorder, attention-deficit/hyperactivity disorder, bipolar disorder, psychotic disorder, schizophrenia, and depressive disorder. These related phenotypes and potentially overlapping cohorts warrant cautious interpretation. The cross-trait SNP coverage of the chromosome 11 locus is shown in Fig. 3.

The distribution of variants across this locus revealed that rs2514218 represented the most widely shared SNP within the DRD2 region, while four additional SNPs were present across five phenotypes. The recurrence of these variants across multiple neurobehavioral traits suggests the presence of a shared genetic signal contributing to common biological mechanisms underlying diverse psychiatric and behavioral phenotypes.

Linkage disequilibrium analysis demonstrated several highly correlated variant clusters within the chromosome 11 region. The most significant LD block (Block 5) was centered around lead SNP rs7935745 and spanned genomic coordinates 11:112,995,184–113,042,089 within the NCAM1 region. This block was represented across multiple phenotypes, indicating substantial conservation of association signals across traits. The observed LD structure supports the existence of coordinated inheritance patterns among variants within this genomic interval and further strengthens evidence for a shared pleiotropic locus. [Figure 4]

Haplotype analysis further supported the biological significance of the chromosome 11 locus. The strongest haplotype block (H1) was defined by lead SNP rs1447463 and spanned coordinates 11:112,857,617–112,896,664, encompassing the genes LINC02763 and NCAM1-AS2. The presence of a conserved haplotype structure indicates that multiple variants within this region are co-inherited and may collectively contribute to the observed cross-trait associations. Together, the LD and haplotype analyses demonstrate that chromosome 11 represents a highly structured genomic region with extensive cross-trait sharing. [Figure 5]

DRD2 was located within a highly shared interval and contained the most recurrent variant identified in that region. However, LD and haplotype blocks also involved adjacent NCAM1-region sequences; the chromosome 11 signal therefore cannot be attributed to DRD2 alone. Cross-trait recurrence, functional annotation, and network position jointly prioritized DRD2 as a candidate pleiotropic node for further investigation.

3.4 Final Gene Prioritization

Following cross-trait integration and locus refinement, tag-causal SNPs were mapped to their corresponding genes to generate a comprehensive gene-level representation of the identified association signals. Across all 30 analyzed phenotypes, a total of 474 unique genes were identified. To prioritize genes with the greatest likelihood of contributing to shared biological mechanisms, genes observed across multiple phenotypes were classified as pleiotropic genes and incorporated into the Final Gene List (FGL). This prioritization strategy reduced the candidate gene set to 193 overlapping genes shared across two or more traits, representing the principal biological output of the multi-trait GWAS fine-mapping framework (Table 3).

Table 3
Overlapping (pleiotropic) genes in Final Gene List.

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
DRD2	Trait29; Trait30; Trait5; Trait8	rs1107162; rs1116313; rs11214677; rs4936277; rs61902811; rs61902812; rs7111031; rs7123334	11q23.2
SLC39A8	Trait19; Trait2; Trait20; Trait22; Trait26; Trait27; Trait5; Trait7	rs13107325; rs13135092; rs35225200; rs6855246	4q24
ABCA1	Trait28; Trait6	rs2575876	9q31.1
ABT1	Trait26; Trait27	rs9379897	6p22.2
ACTL11P	Trait19; Trait20	rs7613360	3p21.31
ADAM1A	Trait5; Trait9	rs78069066	12q24.13
ADH1B	Trait3; Trait5; Trait8; Trait9	rs1154433; rs1229984; rs1693457; rs1789882; rs1789891; rs2066702; rs2075633; rs904092	4q23
ADH1C	Trait3; Trait8	rs1154433; rs1612735; rs1789891	4q23
AFG1L	Trait19; Trait20	rs9384679	6q21
AK3	Trait4; Trait9	rs385893	9p24.1
ALDH2	Trait10; Trait13; Trait5; Trait6; Trait8; Trait9	rs4646776; rs671	12q24.12
APOE	Trait13; Trait28; Trait5	rs429358; rs7412; rs769449	19q13.32
ATP2B1	Trait10; Trait13; Trait6	rs12230074; rs12579302; rs17249754	12q21.33
ATXN2	Trait10; Trait13	rs3184504; rs597808	12q24.12
ATXN2L	Trait19; Trait20	rs2008514; rs28888764	16p11.2
BANK1	Trait19; Trait2	rs34592089; rs35225200; rs6855246	4q24
BARHL2	Trait29; Trait5; Trait7	rs10922907; rs12089815; rs1526480; rs2166171	1p22.2
BCL3	Trait10; Trait6	rs1531517	19q13.32
BDNF	Trait12; Trait20	rs11030104; rs6265	11p14.1
BDNF-AS	Trait12; Trait20	rs11030104; rs6265	11p14.1
BORCS7- ASMT	Trait20; Trait25; Trait4; Trait5	rs28606370; rs7085104	10q24.32

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
BRAP	Trait5; Trait8; Trait9	rs11066001; rs3782886	12q24.12
BSN	Trait2; Trait5; Trait7	rs11917431; rs11921590; rs1873625; rs34762726; rs7625857	3p21.31
BSN-DT	Trait11; Trait3	rs11130204	3p21.31
BTN2A1	Trait25; Trait26; Trait27	rs13195402	6p22.2
BTN3A1	Trait19; Trait25; Trait26; Trait27	rs41266839; rs75782365	6p22.2
BTN3A2	Trait19; Trait26; Trait27	rs9467711	6p22.2
BUD13	Trait28; Trait6	rs509728; rs61905084	11q23.3
CACNA1C	Trait19; Trait25; Trait26; Trait27	rs11062161; rs11062170; rs4298967	12p13.33
CACNA1C-AS4	Trait26; Trait27	rs11062161	12p13.33
CACNA1C-IT3	Trait19; Trait25; Trait26; Trait27	rs4298967	12p13.33
CADM2	Trait12; Trait20; Trait3; Trait4; Trait5; Trait7	rs34495106; rs3911063; rs4856605; rs62250712; rs62250713; rs66568921; rs993137	3p12.1
CALN1	Trait19; Trait7	rs35069269; rs56150095	7q11.22
CAMKMT	Trait11; Trait5; Trait8	rs472140; rs540606; rs570436	2p21
CD83P1	Trait26; Trait27	rs13195636; rs140365013	6p22.1
CDKN2B-AS1	Trait2; Trait30	rs10757270; rs1537375; rs2891168; rs4977575	9p21.3
CEACAM16-AS1	Trait10; Trait6	rs1531517	19q13.32
CELSR2	Trait28; Trait6	rs12740374; rs7528419	1p13.3
CERT1	Trait28; Trait6	rs200174418; rs3846663	5q13.3
CHRNA3	Trait11; Trait12; Trait13; Trait3	rs1051730; rs11637630; rs28681284; rs542137493; rs938682	15q25.1
CHRNA4	Trait11; Trait13; Trait3	rs13036436; rs142852579; rs151176846; rs2273500; rs6011779	20q13.33

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
CHRNA5	Trait11; Trait12; Trait13; Trait3	rs16969968; rs2036527; rs2229961; rs55781567; rs56219480	15q25.1
CHRNA3	Trait11; Trait13; Trait3	rs10958725; rs1451240; rs1530848; rs1979140; rs34456987; rs35599391; rs9792277	8p11.21
CHRNA4	Trait11; Trait13; Trait3; Trait5	rs11072774; rs12440014; rs12902602; rs547290720	15q25.1
CLDN2	Trait5; Trait9	rs7057398	Xq22.3
CNNM2	Trait12; Trait20; Trait26; Trait27; Trait4; Trait5	rs28606370; rs7092200; rs75970938; rs79668541	10q24.32
COQ8B	Trait11; Trait3	rs117003019	19q13.2
CRABP1	Trait11; Trait13; Trait3	rs2002403; rs72736802	15q25.1
CRHR1	Trait2; Trait7	rs17689882; rs62057107	17q21.31
CRLF3P1	Trait12; Trait20; Trait5	rs1368550; rs266058	2q12.1
CYP2A6	Trait11; Trait12; Trait13; Trait3; Trait5; Trait6	rs111645190; rs113029345; rs11667314; rs116921376; rs117824460; rs11878604; rs11881918; rs12459249; rs140980078; rs28399442; rs28399448; rs28399462; rs55921593; rs56113850; rs7247098; rs7247903; rs8102683	19q13.2
CYP2A7	Trait12; Trait13	rs111645190; rs113029345; rs117824460; rs7247098; rs7247903; rs8102683	19q13.2
CYP2B7P	Trait12; Trait13	rs10425738; rs56129017; rs76935404; rs8100418	19q13.2
CYP2F2P	Trait11; Trait12; Trait13; Trait3; Trait5	rs111825958; rs11667314; rs116921376; rs11878604; rs11881918; rs12459249; rs140980078; rs147400515	19q13.2
CYP2G1P	Trait11; Trait12; Trait13	rs10425738; rs113919192; rs4803402; rs56129017; rs8100418	19q13.2
DBH	Trait11; Trait3	rs1108581; rs111596452; rs2007153	9q34.2
DCC	Trait17; Trait24; Trait30	rs16955910; rs4632195; rs7227069; rs8084280	18q21.2
ECM1P1	Trait4; Trait9	rs35954307; rs385893	9p24.1
EGLN2	Trait11; Trait3; Trait5	rs144553930	19q13.2

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
EIF4EBP2P3	Trait19; Trait20; Trait25; Trait7	rs12206087; rs1487445; rs17814604; rs1906252; rs2388334; rs6931604; rs901630; rs9320913; rs9375298	6q16.1
EPHX2	Trait11; Trait3	rs149467044	8p21.1
FADS1	Trait10; Trait25; Trait28	rs174566; rs174567; rs28456	11q12.2
FADS2	Trait10; Trait25; Trait28	rs174566; rs174567; rs174592; rs28456	11q12.2
FAM163B	Trait11; Trait13; Trait3	rs111596452; rs112270518; rs113927489; rs56116178; rs75596189	9q34.2
FGF5	Trait10; Trait6	rs12509595; rs13149993	4q21.21
FOXO3	Trait19; Trait20	rs9384679	6q21
FOXP1	Trait20; Trait4	rs11720703	3p13
FOXP2	Trait17; Trait2; Trait20; Trait21; Trait24	rs10229691; rs10266297; rs10280045; rs117717824; rs1456031; rs1476535; rs1563408; rs2049604; rs7797335	7q31.1
FTO	Trait22; Trait26; Trait27; Trait5; Trait8; Trait9	rs11075992; rs11642015; rs1421085; rs1558902; rs3751812; rs7185735; rs8043757; rs8050136; rs9928094	16q12.2
FURIN	Trait17; Trait20; Trait26; Trait27; Trait29	rs11372849; rs17514846; rs4702	15q26.1
GCKR	Trait25; Trait28	rs1260326	2p23.3
GGT1	Trait5; Trait9	rs2006094; rs2330805	22q11.23
GULOP	Trait11; Trait3; Trait5; Trait6	rs11783093; rs149467044; rs56372821; rs59724122; rs73229093; rs7838316	8p21.1
H2AC15	Trait25; Trait26; Trait27	rs34706883	6p22.1
H3C9P	Trait19; Trait26; Trait27	rs9467711	6p22.2
HBS1L	Trait4; Trait9	rs56293029; rs9389269	6q23.3
HCG15	Trait17; Trait26; Trait27	rs116757206; rs11961509	6p22.1
HCN1	Trait26; Trait27	rs10035564; rs7702731	5p12
HECTD4	Trait10; Trait5; Trait6; Trait9	rs11066280; rs2074356; rs77768175	12q24.13

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
HNRNPA1P1	Trait26; Trait27	rs13195636; rs140365013	6p22.1
HYKK	Trait11; Trait13; Trait3; Trait5	rs10519203; rs11852372; rs34684276; rs8034191	15q25.1
IP6K1	Trait17; Trait7	rs11130221; rs7431106; rs7618501	3p21.31
IREB2	Trait11; Trait13; Trait3	rs141502139; rs2002403; rs72736802	15q25.1
ITIH1	Trait26; Trait27	rs2710323	3p21.1
KCNK3	Trait10; Trait6	rs1275984	2p23.3
KRT8P21	Trait17; Trait4	rs11210146; rs4233093; rs4274014	1p31.1
LINC00533	Trait19; Trait25; Trait26; Trait27	rs116137698; rs145410455	6p22.1
LINC01012	Trait19; Trait26; Trait27	rs141342723	6p22.1
LINC01360	Trait11; Trait17; Trait25; Trait29; Trait3; Trait30; Trait5	rs10789373; rs10890020; rs11210229; rs12031120; rs12042444; rs12128161; rs12129573; rs12731986; rs7520239; rs7523829	1p31.1
LINC01830	Trait17; Trait20; Trait4	rs10865093; rs1355178; rs4074442; rs5015511; rs59145082; rs6759922	2p24.1
LINC01833	Trait11; Trait5; Trait8	rs1004787; rs472140; rs540606; rs570436	2p21
LINC01875	Trait12; Trait20; Trait22	rs12463617; rs13021737; rs13028310; rs35796073; rs6711012; rs6711254	2p25.3
LINC02210-CRHR1	Trait2; Trait24; Trait30; Trait7	rs17426174; rs17689882; rs55938136; rs62057061; rs62057107	17q21.31
LINC02238	Trait11; Trait17; Trait29; Trait3; Trait5	rs10789373; rs11210229; rs12031120; rs12042444; rs12128161; rs12731986; rs7520239	1p31.1
LINC02609	Trait29; Trait5; Trait7	rs10922907; rs12089815; rs1526480; rs2166171	1p22.2
LINC02661	Trait29; Trait8	rs1415556; rs1591660; rs7906104	10q25.1
LINC02702	Trait28; Trait6	rs509728; rs61905084	11q23.3
LINC02796	Trait17; Trait19; Trait20; Trait22; Trait25; Trait30	rs1432639; rs2568952; rs2568957; rs2568958; rs2568960; rs3128341; rs4233093; rs7531118	1p31.1

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
LINC03003	Trait16; Trait17; Trait25; Trait26; Trait27; Trait30	rs144447022; rs145108206; rs150817755; rs3130820; rs9257566	6p22.1
LINC03142	Trait19; Trait20; Trait25; Trait7	rs10429537; rs10733389; rs11793831; rs7868984	9p21.3
LPL	Trait28; Trait6	rs10106652; rs1011685; rs13702; rs15285; rs287; rs6999158; rs7826306; rs79108221	8p21.3
MAD1L1	Trait17; Trait20; Trait26; Trait27; Trait30; Trait4	rs10235664; rs34809719; rs3823624; rs58120505; rs62434666; rs6460944; rs868754	7p22.3
MAPKAPK5	Trait5; Trait9	rs78069066	12q24.13
MAPT-AS1	Trait2; Trait7	rs17689882; rs62057107	17q21.31
METAP2P1	Trait11; Trait12; Trait20; Trait3; Trait6	rs10427255; rs13009175; rs1533426; rs1949330; rs2138445; rs6430080; rs6756212; rs7421123; rs9287372; rs961414	2q22.3
MFSD4B	Trait12; Trait20; Trait4; Trait5	rs240955; rs458806	6q21
MIR137HG	Trait19; Trait25	rs1702294; rs1782810	1p21.3
MIR2113	Trait19; Trait20; Trait25; Trait7	rs12206087; rs12211582; rs1487445; rs17813294; rs17814604; rs1906252; rs1933720; rs2388334; rs4587178; rs6931604; rs901630; rs9320747; rs9320913; rs9401452	6q16.1
MIR4432HG	Trait20; Trait4; Trait5	rs1344293; rs2668733	2p16.1
MMS22L	Trait19; Trait20; Trait7	rs12211582; rs17813294; rs1933720; rs4587178; rs9320747; rs9401452	6q16.1
MORC4	Trait5; Trait9	rs7057398	Xq22.3
MORF4L1	Trait11; Trait3	rs17243470	15q25.1
MPHOSPH9	Trait26; Trait27	rs1615350; rs1716180; rs1790135	12q24.31
MRPS30	Trait26; Trait27	rs10035564; rs7702731	5p12
MST1R	Trait19; Trait20	rs7613360	3p21.31
MTNR1B	Trait26; Trait27	rs10830963	11q14.3
MYB	Trait4; Trait9	rs9389269	6q23.3
NAA25	Trait5; Trait9	rs11066132	12q24.13

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
NCAM1	Trait12; Trait13; Trait17; Trait20; Trait26; Trait27; Trait29; Trait3; Trait5; Trait6	rs1320670; rs1836799; rs1892983; rs1940701; rs1940712; rs1940713; rs1940714; rs1940720; rs2155646; rs2186709; rs4439551; rs4479020; rs4480572; rs7106434; rs7127528; rs7128314; rs7935745; rs7938812; rs7945073; rs9919557; rs9919558	11q23.2
NCAM1-AS2	Trait11; Trait17	rs10891480; rs2186710	11q23.2
NEGR1	Trait19; Trait20	rs12128707; rs1486091	1p31.1
NIHCOLE	Trait16; Trait20; Trait25; Trait30	rs10053368; rs10057459; rs10078807; rs10479296; rs10479297; rs12187903; rs12658007; rs12658019; rs12658032; rs12658451; rs13162928; rs13166408; rs13166522; rs1363101; rs1363102; rs1363105; rs1372500; rs1421665; rs1583953; rs191800971; rs2018142; rs21126; rs30266; rs325502; rs35949602; rs410915; rs416223; rs55649128; rs62362442; rs72776989; rs72780741	5q21.2
NOP56P1	Trait19; Trait26; Trait27	rs115329265	6p22.1
NUP62CL	Trait5; Trait9	rs12688091	Xq22.3
OR12D3	Trait26; Trait27	rs114071887	6p22.1
OR2AD1P	Trait17; Trait26; Trait27	rs116757206; rs11961509	6p22.1
OR5BA1P	Trait17; Trait7	rs12807250; rs2509805	11q12.1
OR5V1	Trait26; Trait27	rs114071887	6p22.1
PDE4B	Trait16; Trait29; Trait3	rs11585651; rs1937437; rs1937438; rs1937440; rs1937458; rs2186123; rs2310752; rs2310819; rs2503207; rs3009872; rs4503327; rs4554696; rs6421482; rs6694912; rs7519259; rs7527901; rs7528604; rs7547416	1p31.3
PGBD1	Trait16; Trait26; Trait27	rs33932084; rs6905391	6p22.1
PLA2G10KP	Trait19; Trait20	rs2008514; rs28888764	16p11.2
PNPLA3	Trait4; Trait5; Trait9	rs2294915; rs3747207; rs738408; rs738409	22q13.31
POLR1HASP	Trait19; Trait26; Trait27	rs151267808	6p22.1
POM121L2	Trait19; Trait2; Trait26; Trait27	rs13207082; rs7746199	6p22.1

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
PPP1R3B-DT	Trait10; Trait28	rs2169387; rs4841132	8p23.1
PRDM8	Trait10; Trait6	rs12509595; rs13149993	4q21.21
PRSS1	Trait5; Trait9	rs35031873; rs3857776; rs4726575; rs55833042; rs60095957	7q34
PRSS2	Trait5; Trait9	rs138700403; rs2855983; rs35031873; rs4145394; rs4726580; rs55833042; rs58854468; rs6464530; rs78907924	7q34
PSMA4	Trait11; Trait12; Trait13	rs1052035; rs2036527; rs59133824; rs59683676	15q25.1
PTPRF	Trait19; Trait20; Trait4; Trait5	rs673253; rs951740	1p34.2
RAB4B-EGLN2	Trait11; Trait3; Trait5	rs144553930	19q13.2
RBM6	Trait19; Trait20	rs2240329	3p21.31
RCL1	Trait4; Trait9	rs35954307	9p24.1
RERE	Trait2; Trait30	rs2401137; rs301799	1p36.23
REV3L	Trait12; Trait20; Trait4; Trait5	rs240955; rs458806	6q21
RHOA	Trait11; Trait19; Trait20; Trait3; Trait7	rs11130190; rs7623659	3p21.31
RIPPLY1	Trait5; Trait9	rs7057398	Xq22.3
RN7SKP19	Trait17; Trait25; Trait30; Trait4	rs10890020; rs11210146; rs12129573; rs4274014; rs7523829	1p31.1
RNA5SP94	Trait20; Trait4; Trait5	rs1344293; rs2668733	2p16.1
RNU2-62P	Trait25; Trait26; Trait27	rs55834529	6p22.1
RNU6-334P	Trait16; Trait20; Trait25; Trait30	rs10053368; rs10057459; rs10078807; rs10479296; rs10479297; rs12187903; rs12658007; rs12658019; rs12658032; rs12658451; rs13166522; rs1363101; rs1363102; rs1363105; rs1421665; rs191800971; rs2018142; rs21126; rs30266; rs325502; rs410915; rs416223; rs62362442; rs72780741	5q21.2
RPH3A	Trait5; Trait9	rs77753011	12q24.13

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
RPL37P11	Trait10; Trait6	rs1275984	2p23.3
RPL6P5	Trait11; Trait12; Trait20; Trait3; Trait6	rs10427255; rs13009175; rs1533426; rs1949330; rs2138445; rs6430080; rs6756212; rs7421123; rs9287372; rs961414	2q22.3
RPL8P1	Trait19; Trait26; Trait27	rs141342723	6p22.1
RPSAP2	Trait19; Trait26; Trait27	rs115329265	6p22.1
RSPO3	Trait10; Trait12	rs11756347; rs1936805; rs7766106	6q22.33
SEMA3F	Trait19; Trait3	rs1046953; rs11711407; rs2624839	3p21.31
SEMA3F-AS1	Trait19; Trait20; Trait4; Trait7	rs13100903; rs2526384; rs2526398	3p21.31
SEMA6D	Trait11; Trait20; Trait29; Trait3; Trait4; Trait5	rs12902636; rs12907546; rs281280; rs8034190; rs9646181	15q21.1
SH2B3	Trait10; Trait13	rs3184504; rs7310615	12q24.12
SLC17A3	Trait26; Trait27	rs13198474	6p22.2
SLC2A9	Trait10; Trait13; Trait6	rs6449140	4p16.1
SMARCA4	Trait28; Trait6	rs114821903; rs143020224; rs8106503	19p13.2
SMIM19	Trait11; Trait13; Trait3	rs10958725; rs1451240; rs1979140; rs34456987; rs35599391; rs9792277	8p11.21
SNX17	Trait10; Trait25; Trait6; Trait9	rs4665972	2p23.3
ST3GAL3	Trait19; Trait24	rs12410155; rs3952787; rs7511800	1p34.1
TCF4	Trait24; Trait30	rs12967143; rs1348047	18q21.2
TENM2	Trait11; Trait20; Trait3; Trait4	rs2336895; rs986391	5q34
TET2	Trait19; Trait20	rs55838312	4q24
TET2-AS1	Trait19; Trait20	rs55838312	4q24
TMEM161B-DT	Trait20; Trait4; Trait5	rs6452785	5q14.3
TMEM18	Trait12; Trait20; Trait22	rs12463617; rs13021737; rs13028310; rs35796073; rs6711012; rs6711254	2p25.3

Gene	Overlapping Traits	Tag Causal SNP(s)	CHR POS
TMEM182	Trait12; Trait20; Trait5	rs1368550; rs266058	2q12.1
TMPRSS5	Trait29; Trait30; Trait5; Trait8	rs11214677; rs4936277; rs61902811; rs61902812; rs7111031; rs7123334	11q23.2
TRAFD1	Trait5; Trait9	rs12231737	12q24.13
TRAIP	Trait19; Trait20; Trait7	rs2352974	3p21.31
TRBV29-1	Trait5; Trait9	rs4726575; rs60095957; rs6953502	7q34
TRIB1AL	Trait28; Trait6	rs28601761; rs2954021; rs2980888	8q24.13
TRIM27	Trait26; Trait27	rs182812355	6p22.1
TSNARE1	Trait17; Trait25; Trait26; Trait27	rs4129585	8q24.3
UGT2B10	Trait12; Trait26; Trait27	rs10000284; rs10023464; rs2926036; rs294775; rs835309	4q13.2
UGT2B15	Trait12; Trait26; Trait27	rs10000284; rs10023464; rs294775	4q13.2
VN1R11P	Trait25; Trait26; Trait27	rs55834529	6p22.1
VRK2	Trait26; Trait27; Trait30	rs1568452; rs2678879; rs2717043	2p16.1
WBP1L	Trait26; Trait27	rs12571643	10q24.32
Y_RNA	Trait17; Trait22	rs10992729; rs495828	9q22.31; 9q34.2
ZKSCAN4	Trait26; Trait27	rs17720293	6p22.1
ZNF322	Trait26; Trait27; Trait30	rs57440165; rs9379897	6p22.2
ZSCAN12	Trait19; Trait25; Trait26; Trait27	rs67981811	6p22.1
ZSCAN16-AS1	Trait25; Trait30	rs68188794; rs71537572	6p22.1
ZSCAN26	Trait26; Trait27	rs2799079	6p22.1
ZSCAN31	Trait16; Trait19; Trait20; Trait25; Trait26; Trait27; Trait30	rs13217619; rs7752448; rs853676; rs853679; rs853681; rs853682; rs853685	6p22.1

Each trait here means a distinct dataset of GWAS.

The resulting FGL contained numerous genes previously implicated in neuropsychiatric disorders, addiction, cognition, and behavioral regulation. Several genes demonstrated extensive cross-trait representation, including **DRD2**, **SLC39A8**, **ALDH2**, **ADH1B**, **BDNF**, **CACNA1C**, **FTO**, and multiple nicotinic acetylcholine receptor genes such as **CHRNA3**, **CHRNA4**, **CHRNA5**, and **CHRNA4**. These genes were associated with diverse phenotypes including substance use disorders, psychiatric disorders, cognitive traits, obesity, and stress-related conditions, supporting their potential roles as pleiotropic contributors to brain-related phenotypes.

Among the prioritized genes, **DRD2** emerged as one of the most notable candidates. DRD2 was observed across multiple phenotypes and was represented by several tag-causal SNPs, including rs1107162, rs1116313, rs11214677, rs4936277, rs61902811, rs61902812, rs7111031, and rs7123334. The repeated identification of DRD2 across independent datasets, combined with its localization within one of the most highly shared genomic loci identified during cross-trait analyses, further supported its prioritization for downstream functional investigation.

The prioritization process also highlighted genes involved in dopaminergic signaling, synaptic transmission, neurotransmitter metabolism, alcohol metabolism, nicotine dependence, and neuronal development. The presence of these genes within the FGL suggests that multiple interconnected biological pathways contribute to the shared genetic architecture observed across neurobehavioral and psychiatric phenotypes. Consequently, the 193-gene FGL served as the foundation for subsequent transcriptomic, pharmacogenomic, protein–protein interaction, and enrichment analyses designed to evaluate the biological relevance and translational significance of the prioritized gene set.

3.5 Functional Validation

3.5.1 GTEx-Based Functional Validation

To evaluate the biological relevance of genes identified through the multi-trait GWAS fine-mapping framework, the 193 pleiotropic genes contained within the Final Gene List (FGL) were subjected to transcriptomic validation using data derived from the Genotype-Tissue Expression (GTEx) Project version 8. Assessment of cis-expression quantitative trait loci (cis-eQTLs), splice quantitative trait loci (sQTLs), and tissue-specific expression profiles identified 97 genes exhibiting significant expression patterns across 13 brain-related GTEx datasets. These genes were considered functionally supported candidates and retained for subsequent downstream analyses (Table 4).

Table 4
Pleiotropic Gene Filter confirmed by GTEx cis-eQTL.

Gene	cis-eQTL evidence	Tissues with eQTL	Min p-value	Max NES
DRD2	Yes	2	6.51E-06	0.398233
ABCA1	Yes	1	4.7E-06	1.80279
ABT1	Yes	1	3.32E-07	0.519014
ADH1B	Yes	2	2.62E-06	0.999069
ADH1C	Yes	3	2.29E-11	1.29688
AK3	Yes	8	2.72E-11	0.552615
ALDH2	Yes	8	1.59E-11	0.689149
APOE	Yes	1	2.87E-07	0.930728
ATP2B1	Yes	3	9.53E-06	1.37055
ATXN2	Yes	1	9.25E-05	1.06775
BANK1	Yes	3	6.92E-06	0.5859
BDNF-AS	Yes	6	6.18E-11	0.384945
BSN	Yes	1	1.29E-05	0.459232
BTN2A1	Yes	8	1.82E-09	0.935893
BTN3A1	Yes	7	5.57E-10	1.34775
BTN3A2	Yes	13	3.54E-28	1.54311
CACNA1C	Yes	4	2.98E-17	2.71529
CADM2	Yes	7	3.62E-13	0.667317
CALN1	Yes	2	5.09E-07	0.633974
CAMKMT	Yes	2	3.82E-06	0.99619
CDKN2B-AS1	Yes	1	1.42E-05	0.519001
CELSR2	Yes	3	1.93E-05	0.405441
CHRNA3	Yes	4	1.32E-36	0.838166
CHRNA4	Yes	10	2.92E-26	1.42129
CHRNA5	Yes	13	1.43E-38	1.54519
CHRNA3	Yes	2	1.43E-15	2.0741
CNNM2	Yes	3	2.23E-06	0.488343

Gene	cis-eQTL evidence	Tissues with eQTL	Min p-value	Max NES
COQ8B	Yes	2	9.63E-10	0.506165
CRABP1	Yes	6	2.46E-14	0.921324
CRHR1	Yes	5	3.03E-07	0.721504
CYP2A7	Yes	6	2.61E-12	0.987195
CYP2B7P	Yes	6	7.44E-09	0.498579
CYP2G1P	Yes	2	2.10E-07	1.14804
DBH	Yes	3	4.98E-21	0.737918
DCC	Yes	1	7.54E-07	0.334799
EGLN2	Yes	1	9.88E-06	0.196735
EPHX2	Yes	13	6.63E-18	1.16942
FADS1	Yes	10	7.63E-33	1.30128
FAM163B	Yes	2	6.18E-17	0.700828
FGF5	Yes	1	1.03E-06	0.262325
FOXO3	Yes	2	5.96E-06	0.23749
FOXP2	Yes	2	1.7E-05	0.978883
FTO	Yes	10	2.35E-27	0.825965
FURIN	Yes	1	1.14E-05	0.407278
GGT1	Yes	11	4.23E-12	2.12487
HBS1L	Yes	11	7.42E-34	0.828918
HCN1	Yes	4	2.65E-06	1.17385
HECTD4	Yes	1	1.68E-06	0.214439
HYKK	Yes	9	9.08E-09	0.450141
IP6K1	Yes	1	0.000105	0.21902
IREB2	Yes	2	3.70E-07	1.85759
KCNK3	Yes	5	1.17E-06	0.332679
LINC00533	Yes	2	1.01E-05	0.62689
LINC01012	Yes	1	5.20E-08	1.51326
LINC01833	Yes	2	6.06E-10	0.550963

Gene	cis-eQTL evidence	Tissues with eQTL	Min p-value	Max NES
LPL	Yes	2	3.73E-06	0.753629
MAPKAPK5	Yes	2	3.80E-09	0.614445
MAPT-AS1	Yes	9	1.07E-21	0.773961
MFSD4B	Yes	5	9.42E-09	0.589668
MIR137HG	Yes	6	7.99E-10	0.68158
MMS22L	Yes	3	8.31E-07	0.814119
MORC4	Yes	1	3.99E-05	0.389008
MORF4L1	Yes	3	3.44E-06	1.27659
MPHOSPH9	Yes	2	4.55E-06	0.613345
MST1R	Yes	8	4.97E-19	1.30972
NAA25	Yes	6	9.25E-24	0.903789
NEGR1	Yes	5	2.61E-09	1.31799
NUP62CL	Yes	1	0.000121	0.287032
PGBD1	Yes	8	2.28E-08	0.602862
PRDM8	Yes	4	1.67E-09	0.429979
PSMA4	Yes	9	2.81E-11	0.850599
RBM6	Yes	13	4.67E-42	1.29883
RCL1	Yes	10	4.76E-12	3.30662
RERE	Yes	7	8.91E-12	1.27768
REV3L	Yes	3	2.66E-11	0.50489
RPH3A	Yes	2	6.82E-06	1.56493
RSPO3	Yes	1	6.97E-05	0.612377
SEMA3F	Yes	2	8.49E-06	0.440419
SEMA3F-AS1	Yes	1	2.75E-05	0.296977
SEMA6D	Yes	1	6.15E-09	0.231853
SLC2A9	Yes	4	8.04E-08	0.347378
SLC39A8	Yes	1	1.78E-07	0.29893
SMIM19	Yes	13	6.98E-35	0.61107

Gene	cis-eQTL evidence	Tissues with eQTL	Min p-value	Max NES
SNX17	Yes	3	7.63E-07	0.24604
ST3GAL3	Yes	1	6.6E-06	0.407754
TENM2	Yes	1	7.94E-06	1.73328
TMEM18	Yes	2	7.96E-07	2.14812
TMPRSS5	Yes	12	9.22E-34	1.20034
TRAFD1	Yes	2	1.61E-06	1.41841
TRIM27	Yes	2	1.5E-05	0.373193
TSNARE1	Yes	13	7.09E-33	1.64578
VRK2	Yes	2	4.90E-08	0.381513
WBP1L	Yes	1	3.91E-07	0.324489
ZNF322	Yes	11	1.74E-22	0.870564
ZSCAN16-AS1	Yes	1	6.92E-07	0.416754
ZSCAN26	Yes	12	5.69E-27	0.677865
ZSCAN31	Yes	13	4.26E-27	1.98266

cis-eQTL evidence = at least one significant cis-eQTL for this gene in the selected tissues (GTEx gtex_v8, ± 100 kb gene-body window).

The GTEx filtering process substantially reduced the candidate gene set while preserving genes with strong evidence of transcriptional activity in neural tissues. Several prioritized genes, including **DRD2**, demonstrated significant expression signatures across multiple brain regions, supporting their potential roles in neuropsychiatric and behavioral phenotypes. [Figure 6]

Collectively, transcriptomic analyses provided independent functional support for the prioritized gene set. Although multiple genes demonstrated strong expression-based evidence, **DRD2** remained consistently represented across GWAS fine-mapping, cross-trait overlap, and GTEx analyses, further supporting its prioritization as a candidate pleiotropic gene. [Figure 7] [Figure 8]

3.5.2 Pharmacogenomic Validation

To assess translational relevance, the GTEx-supported genes were subsequently evaluated using curated pharmacogenomic resources. This analysis identified **29 genes** possessing established pharmacogenomic evidence, indicating potential involvement in therapeutic response, drug metabolism, and precision medicine applications. [Figure 9]

The pharmacogenomic filtering process generated a refined subset of clinically relevant genes associated with addiction, psychiatric disorders, neurotransmission, and behavioral regulation. These findings provided additional support for the translational significance of the prioritized gene set and established the foundation for subsequent network-based analyses.

3.6 Protein–Protein Interaction Analysis

To further investigate the biological relationships among prioritized genes, protein–protein interaction (PPI) analysis was performed using the STRING-MODEL platform. The analysis was conducted on genes that passed transcriptomic validation through GTEx cis-eQTL filtering, allowing assessment of functional connectivity among biologically supported candidates. [Figure 10]

The PPI analysis demonstrated that 77 genes formed a highly interconnected interaction network, indicating substantial functional relationships among prioritized genes. The observed connectivity suggests that many of the identified genes participate in shared biological pathways and molecular processes relevant to neuropsychiatric, behavioral, cognitive, and addiction-related phenotypes.

Within the annotated STRING network, DRD2 had high connectivity and was prioritized as a hub. This finding was consistent with its recurrence in the cross-trait and functional-annotation stages. Network centrality should nevertheless be interpreted in light of annotation-density bias: extensively studied proteins may have more documented interactions than less characterized proteins. Sensitivity analyses that restrict evidence channels or adjust for prior annotation degree would strengthen the inference.

In addition to DRD2, several genes involved in neurotransmission, synaptic signaling, neuronal development, and behavioral regulation contributed to the overall network structure. The presence of these interconnected genes suggests that multiple biological pathways operate cooperatively to influence susceptibility to neurobehavioral and psychiatric traits.

Overall, the PPI analysis provided system-level evidence supporting the biological relevance of the prioritized gene set and reinforced the role of DRD2 as a central candidate gene within the broader network of pleiotropic genetic factors.

3.7 Pathway, Gene Ontology, and Disease Enrichment Analyses

To further characterize the biological significance of the prioritized genes, pathway enrichment, Gene Ontology (GO), and disease association analyses were performed on genes retained following GWAS fine-mapping, GTEx validation, and pharmacogenomic filtering. These analyses were designed to identify biological processes, molecular pathways, and disease phenotypes enriched among the prioritized gene set.

Pathway enrichment analyses revealed significant enrichment of pathways involved in dopaminergic neurotransmission, reward processing, addiction biology, and neuropsychiatric function. Among the

most significantly enriched pathways were Nicotine Effects on Dopaminergic Neurons and Alcohol Use Disorder (AUD), indicating that many of the prioritized genes converge on shared reward-related signaling mechanisms. These findings are consistent with the repeated identification of genes involved in dopaminergic regulation throughout the analytical framework.

Gene Ontology analyses further demonstrate enrichment of biological processes associated with neuronal signaling, synaptic communication, neurotransmitter activity, behavioral regulation, and nervous system function. Collectively, these results suggest that the prioritized genes participate in interconnected biological mechanisms underlying multiple brain-related phenotypes.

Disease enrichment analyses identified significant associations with neuropsychiatric, and substance use disorders, including schizophrenia, bipolar disorder, depressive disorder, nicotine dependence, alcohol-related disorders, and opioid use disorder. The convergence of these disease associations supports the presence of shared genetic architecture across diverse behavioral and psychiatric traits.

Overall, the enrichment analyses provided functional context for the prioritized genes and reinforced the importance of dopaminergic signaling pathways within the broader pleiotropic network identified through the multi-trait GWAS fine-mapping framework. The consistent appearance of **DRD2** across multiple analytical stages further supports its potential role as a central contributor to shared neurobehavioral genetic mechanisms.

Discussion

This exploratory study integrated independently fine-mapped signals from 30 publicly available GWAS data sets spanning neuropsychiatric, behavioral, cognitive, pain, stress, sleep, obesity, and substance-related phenotypes. The workflow retained 999 tag variants, 474 unique genes, and 193 genes represented across at least two traits. Broad regions on chromosomes 6 and 11 overlapped across 20 data sets. The arithmetic sum of source sample sizes exceeded 10 million, but it must not be interpreted as the number of unique participants because cohort overlap was not fully resolved.

The multi-trait analytical workflow identified 999 tag-causal SNPs and 860 primary gene entries, which were subsequently consolidated into 474 unique genes. Among these, 193 genes were classified as pleiotropic genes shared across multiple phenotypes and were retained within the Final Gene List (FGL). Cross-trait integration analyses highlighted two major genomic signals located on chromosome 6 (6:25120440–33889314) and chromosome 11 (11:112793134–114173783). These loci demonstrated extensive overlap across the analyzed phenotypes and contained multiple recurrent variants associated with neurobehavioral and psychiatric traits. The chromosome 11 locus was particularly notable because it encompassed DRD2 and several highly shared variants, including rs2514218, which demonstrated broad representation across multiple phenotypes.

To further evaluate the biological relevance of prioritized genes, downstream analyses were performed using transcriptomic, pharmacogenomic, and network-based approaches. GTEx cis-eQTL analyses

reduced the candidate gene set to 97 functionally supported genes demonstrating significant expression patterns across 13 brain-related tissues. Subsequent pharmacogenomic filtering identified 29 genes with established therapeutic or clinical relevance. Protein–protein interaction analyses further refined these findings by identifying a highly interconnected network of biologically relevant genes. Integration of GWAS fine-mapping, GTEx validation, pharmacogenomic annotation, and network analyses ultimately generated a multidimensional gene set consisting of 24 highly prioritized candidate genes.

DRD2 was prioritized across several analytical dimensions: it was located in a highly shared chromosome 11 interval, rs2514218 recurred across eight data sets, DRD2 had brain cis-eQTL support, and the encoded receptor occupied a central position in the STRING network. This convergence supports DRD2 as a pleiotropic candidate but does not establish it as a causal master regulator. The adjacent NCAM1-region LD and haplotype blocks further argue against assigning the broad chromosome 11 signal to one gene.

The identification of DRD2 as the central hub gene is consistent with decades of evidence implicating dopaminergic signaling in reward processing, addiction vulnerability, behavioral regulation, and numerous neuropsychiatric disorders. In 1990, Blum and Noble first reported an association between the DRD2 Taq1 polymorphism and severe alcoholism [16]. Importantly, DRD2 was not viewed as an “alcoholism gene,” but rather as a reward-related gene involved in broader neurobiological mechanisms underlying motivated behavior. Unlike substances that act through distinct pharmacological pathways, many addictive behaviors ultimately converge on common dopaminergic mechanisms within the mesolimbic reward circuitry. The dopamine D2 receptor has been profoundly implicated in reward processing, reinforcement learning, and vulnerability to substance-seeking behaviors [23–38].

Dysfunction of D2 receptor signaling has been associated with maladaptive seeking behaviors involving alcohol, drugs, nicotine, food, and other compulsive behaviors [23–38]. Decades of research indicate that genetic variation contributes substantially to vulnerability for severe substance-seeking behaviors, suggesting that DRD2 variants may serve as common determinants of compulsive and addictive phenotypes [39]. Consistent with these observations, our analysis identified DRD2 as one of the most extensively connected genes across multiple neurobehavioral and psychiatric phenotypes. Through interrogation of 30 GWAS datasets and extensive database mining, DRD2 repeatedly emerged as a highly connected component within the broader genetic architecture of brain-related disorders.

Dopamine does not function in isolation. D2 receptor signaling is embedded within corticostriatal and mesolimbic circuits that integrate glutamatergic, GABAergic, opioid, serotonergic, endocannabinoid, and other neurotransmitter systems. The present findings are therefore compatible with a network model in which DRD2 contributes to reward-related variation alongside many other genes and environmental influences. The term “Everything Gene Hypothesis” should be understood only as a metaphor for a testable network-centrality proposition, not as a claim that DRD2 determines all behavior or mental illness.

Pathway, Gene Ontology, and disease annotations emphasized dopaminergic, neuronal-signaling, nicotine-related, alcohol-related, and other substance-use categories. These results provide functional context, but enrichment of addiction-related terms is partly expected because alcohol, nicotine, cocaine, heroin, opioid use, and broader substance-related phenotypes were included among the inputs. Enrichment should therefore not be described as independent disease prediction.

4.1. Limitations

This analysis has important limitations. The aggregate sample-size sum does not represent unique participants, and overlapping source cohorts may inflate recurrence. Phenotype definitions, ancestry, genome build, imputation, quality control, and statistical power differed across studies. Several included phenotypes were correlated or derived from related consortia. Fine-mapping depends on allele harmonization, the prior variance, locus definition, and ancestry-matched LD references; the final report must provide these parameters and sensitivity analyses. Transformation of two-sided P values does not retain effect direction when harmonized allelic effects are unavailable. GTEx, ClinPGx, STRING, and enrichment resources are annotation tools rather than experimental validation, and network-degree bias may favor highly studied genes such as *DRD2*. No independent cohort, functional perturbation, prospective validation, or clinical utility analysis was performed. Accordingly, the results should not be used for individual genetic risk prediction or treatment selection.

4.2. Research Implications

If independently replicated, cross-disorder genomic networks may help organize future research around shared biological mechanisms rather than isolated diagnoses. Appropriate next steps include prespecified replication in nonoverlapping cohorts; ancestry-stratified fine-mapping; direct comparison of *DRD2* with other candidate hubs such as *BDNF*, *APOE*, *NCAM1*, and *SLC39A8*; correction for interaction-database annotation degree; integration of chromatin, single-cell, and spatial transcriptomic data; and experimental perturbation of prioritized pathways. Clinical or public-policy implementation would be premature without evidence of predictive validity, clinical utility, and benefit over established assessment methods.

4.3. Translational and Policy Implications

The present findings have several potential implications for translational research and health policy, although they do not support immediate clinical implementation. The prioritization of *DRD2* within a broader pleiotropic network illustrates why complex behavioral, psychiatric, cognitive, pain-related, and substance-use phenotypes should not be attributed to a single genetic variant or gene. Genetic associations should instead be interpreted within polygenic networks that interact with developmental, environmental, social, and clinical exposures. This distinction is particularly important when genetic findings are communicated to patients, clinicians, policymakers, and the public.

A first priority is the development of evidence standards for translating cross-trait genomic findings into clinically meaningful tools. Candidate genes identified through fine-mapping, expression annotation,

pharmacogenomic databases, and protein-interaction networks require replication in independent and ancestrally diverse populations. Prospective studies should determine whether adding genomic information improves prediction beyond established clinical, behavioral, and environmental variables. Clinical testing should not be recommended solely because a gene is recurrent across phenotypes or occupies a central position in an annotated network.

A second priority is improving the diversity and transparency of genomic resources. Many existing GWAS and linkage-disequilibrium reference panels remain disproportionately representative of populations of European ancestry. Policies supporting the inclusion of underrepresented populations, ancestry-matched reference panels, transparent reporting of cohort overlap, and public availability of summary statistics and analytical code would improve reproducibility and reduce the risk that future genomic applications amplify existing health disparities.

A third implication concerns responsible communication and regulation of genetic risk information. DRD2 and related reward-pathway genes have attracted substantial public and commercial interest, but probabilistic associations can be misrepresented as deterministic diagnoses. Genetic findings related to addiction, psychiatric conditions, pain, or behavioral traits should be accompanied by clear statements regarding effect size, uncertainty, ancestry limitations, environmental modification, and the absence of individual-level diagnostic certainty. Regulatory and professional guidance should discourage unsupported single-gene claims and require evidence of analytical validity, clinical validity, and clinical utility before tests are marketed for treatment selection or behavioral-risk prediction.

Finally, these findings support a research framework in which genomic information may eventually be combined with clinical phenotyping, cognitive measures, medication history, environmental exposures, and validated pharmacogenomic evidence. Such integration could ultimately contribute to more individualized prevention and treatment strategies. However, the present analysis is hypothesis-generating. It does not establish that DRD2 testing can diagnose a disorder, predict an individual's behavior, determine treatment eligibility, or guide medication selection. Any movement toward implementation should therefore proceed through independent replication, prospective validation, ethical review, and demonstration of benefit over existing standards of care.

4.4. The Everything Gene Hypothesis

We propose a restrained, testable formulation: DRD2 may occupy a recurrent and highly annotated position within reward-related genomic networks across multiple brain-related phenotypes. The hypothesis predicts that DRD2 will remain comparatively central after correction for cohort overlap, ancestry, correlated phenotypes, LD structure, and annotation density, and that perturbation of DRD2-linked networks will produce measurable effects across more than one neurobehavioral domain. Failure to meet these predictions would argue against exceptional DRD2 centrality.

Conclusion

Cross-trait integration of 30 brain-related GWAS data sets identified 999 tag variants, 474 unique genes, and 193 genes represented across multiple traits. DRD2 was prioritized within a shared chromosome 11 interval through variant recurrence, brain cis-eQTL evidence, pharmacogenomic annotation, and its position within a protein-interaction network.

These findings identify DRD2 as a hypothesis-generating pleiotropic network candidate—not a solitary determinant of behavior, addiction, or mental illness. Cohort overlap, phenotype heterogeneity, linkage-disequilibrium uncertainty, ancestry-related limitations, and annotation-density bias preclude causal or individual-level interpretation.

Independent replication, ancestry-matched fine-mapping, sensitivity analyses, prospective validation, and experimental studies are required before the proposed network-centrality hypothesis can inform risk stratification, clinical care, or health policy. Responsible translation will also require diverse genomic resources, transparent reporting standards, and safeguards against deterministic or unsupported single-gene claims.

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Author Contributions—CRediT Statement

Kenneth Blum: Conceptualization, Investigation, Resources, Supervision, Project administration, Writing—original draft, Writing—review and editing.

Alireza Sharafshah: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Visualization, Writing—original draft, Writing—review and editing.

Kai-Uwe Lewandrowski: Conceptualization, Methodology, Investigation, Supervision, Project administration, Visualization, Writing—original draft, Writing—review and editing.

Morgan P. Lorio: Conceptualization, Validation, Interpretation of results, Writing—original draft, Writing—review and editing.

Panayotis K. Thanos: Conceptualization, Methodology, Validation, Interpretation of results, Supervision, Writing—review and editing.

Rafael Rea: Software, Formal analysis, Data curation, Validation, Visualization, Writing—review and editing.

Edward J. Modestino: Validation, Interpretation of results, Writing—review and editing.

David Baron: Validation, Interpretation of clinical and psychiatric implications, Writing—review and editing.

Rossano Kepler Alvim Fiorelli: Validation, Supervision, Interpretation of clinical implications, Writing—review and editing.

Sergio Schmidt: Methodology, Validation, Supervision, Interpretation of neurocognitive findings, Writing—review and editing.

Igor Elman: Validation, Interpretation of psychiatric and addiction-related findings, Writing—review and editing.

Jonathan S. Vogelgsang: Validation, Interpretation of psychiatric findings, Writing—review and editing.

Keerthy Sunder: Validation, Interpretation of psychiatric and neuroscience implications, Writing—review and editing.

Albert Pinhasov: Methodology, Validation, Interpretation of molecular and neurogenetic findings, Supervision, Writing—review and editing.

Jia A. Blum: Data curation, Investigation, Validation, Writing—review and editing.

Abdalla Bowirrat: Methodology, Validation, Interpretation of neurogenetic findings, Writing—review and editing.

Paul R. Carney: Validation, Interpretation of neurological findings, Writing—review and editing.

Thomas Simpatico: Validation, Interpretation of addiction and behavioral-health implications, Writing—review and editing.

Marlene Oscar Berman: Validation, Interpretation of neurobehavioral and cognitive findings, Writing—review and editing.

Kyriaki Thanos: Investigation, Validation, Literature review, Writing—review and editing.

Álvaro Dowling: Validation, Interpretation of clinical and translational implications, Writing—review and editing.

Rafaela Dowling: Validation, Literature review, Interpretation of clinical implications, Writing—review and editing.

Alexander P. L. Lewandrowski: Investigation, Literature review, Visualization, Validation, Writing—review and editing.

João Paulo M. Bergamaschi: Validation, Interpretation of clinical and translational implications, Writing—review and editing.

Shaurya Mahajan: Formal analysis, Data curation, Investigation, Literature review, Writing—review and editing.

Yatharth Mahajan: Formal analysis, Data curation, Investigation, Literature review, Writing—review and editing.

Margaret A. Madigan: Project administration, Investigation, Literature review, Visualization, Writing—review and editing.

Mark S. Gold: Conceptualization, Validation, Interpretation of addiction and psychiatric implications, Supervision, Writing—review and editing.

All authors reviewed and approved the final manuscript, agreed to be accountable for their respective contributions, and accepted responsibility for the integrity of the work.

Data Availability: Public GWAS summary data and external annotation resources were analyzed. The final submission must provide all accession numbers, stable links, analysis code, program version, parameters, and access conditions.

Ethics Approval: Institutional review exemption was determined by the authors since analysis of public, deidentified GWAS data was performed and reported in summary presentations.

References

1. Bolormaa S, Pryce JE, Reverter A, Zhang Y, Barendse W, Kemper K, Tier B, Savin K, Hayes BJ, Goddard ME (2014) A multi-trait, meta-analysis for detecting pleiotropic polymorphisms for stature, fatness and reproduction in beef cattle. *PLoS Genet* 10(3):e1004198
2. Bonnemaier PW, Leeuwen EM, Iglesias AI, Gharahkhani P, Vitart V, Khawaja AP, Simcoe M, Höhn R, Cree AJ, Igo RP (2019) Multi-trait genome-wide association study identifies new loci associated with optic disc parameters. *Commun biology* 2(1):435
3. Yoshida GM, Yáñez JM (2021) Multi-trait GWAS using imputed high-density genotypes from whole-genome sequencing identifies genes associated with body traits in Nile tilapia. *BMC Genomics* 22(1):57

4. Lindström S, Thompson DJ, Paterson AD, Li J, Gierach GL, Scott C, Stone J, Douglas JA, dos-Santos-Silva I, Fernandez-Navarro P, Verghese J (2014) Genome-wide association study identifies multiple loci associated with both mammographic density and breast cancer risk. *Nat Commun* 5(1):5303
5. Discovery (2013) refinement of loci associated with lipid levels. *Nat Genet* 45(11):1274–1283
6. Liu JZ, Van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S (2015) Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 47(9):979–986
7. Nosková A, Mehrotra A, Kadri NK, Lloret-Villas A, Neuenschwander S, Hofer A, Pausch H (2023) Comparison of two multi-trait association testing methods and sequence-based fine mapping of six additive QTL in Swiss Large White pigs. *BMC Genomics* 24(1):192
8. Hormozdiari F, Kostem E, Kang EY, Pasaniuc B, Eskin E Identifying causal variants at loci with multiple signals of association. In *Proceedings of the 5th ACM Conference on Bioinformatics, Computational Biology, and Health Informatics 2014 Sep 20* (pp. 610–611)
9. Li Z, Zhou X (2025) Towards improved fine-mapping of candidate causal variants. *Nat Rev Genet* 26(12):847–861
10. Servin B, Stephens M (2007) Imputation-based analysis of association studies: candidate regions and quantitative traits. *PLoS Genet* 3(7):e114
11. Benner C, Spencer CC, Havulinna AS, Salomaa V, Ripatti S, Pirinen M (2016) FINEMAP: efficient variable selection using summary data from genome-wide association studies. *Bioinformatics* 32(10):1493–1501
12. Wang G, Sarkar A, Carbonetto P, Stephens M (2020) A simple new approach to variable selection in regression, with application to genetic fine mapping. *J Royal Stat Soc Ser B: Stat Methodol* 82(5):1273–1300
13. Schaid DJ, Chen W, Larson NB (2018) From genome-wide associations to candidate causal variants by statistical fine-mapping. *Nat Rev Genet* 19(8):491–504
14. Nicolae DL, Gamazon E, Zhang W, Duan S, Dolan ME, Cox NJ (2010) Trait-associated SNPs are more likely to be eQTLs: annotation to enhance discovery from GWAS. *PLoS Genet* 6(4):e1000888
15. Grandy DK, Litt M, Allen L et al (1989) The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. *Am J Hum Genet* 45(5):778–785
16. Blum K, Noble EP, Sheridan PJ et al (1990) Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA* 263(15):2055–2060
17. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ (1991) Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch Gen Psychiatry* 48(7):648–654. 10.1001/archpsyc.1991.01810310066012
18. Blum K, Han D, Gupta A, Baron D, Braverman ER, Dennen CA, Kazmi S, Llanos-Gomez L, Badgaiyan RD, Elman I, Thanos PK (2022) Statistical validation of risk alleles in genetic addiction risk severity (GARS) test: early identification of risk for alcohol use disorder (AUD) in 74,566 case–control subjects. *J Personalized Med* 12(9):1385

19. Gold MS, Baron D, Bowirrat A, Blum K (2020) Neurological correlates of brain reward circuitry linked to opioid use disorder (OUD): Do Homo sapiens acquire or have a reward deficiency syndrome? *J Neurol Sci* 418:117137. 10.1016/j.jns.2020.117137
20. Blum K, Bowirrat A, Baron D et al (2024) Identification of stress-induced epigenetic methylation onto dopamine D2 gene and neurological and behavioral consequences. *Gene Protein Dis* 3(1). 10.36922/gpd.1966
21. Blum K, Baron D, Lott L et al (2020) In search of reward deficiency syndrome (RDS)-free controls: the Holy Grail in genetic addiction risk testing. *Curr Psychopharmacol* 9(1):7–21
22. Hamilton PJ, Lim CJ, Nestler EJ, Heller EA (2024) Neuroepigenetic editing. *Methods Mol Biol* 2842:129–152. 10.1007/978-1-0716-4051-7_6
23. Sharafshah A, Blum K, Lewandrowski KU et al (2025) Pharmacoepigenomics in personalized medicine: a hypothesis-generating approach to introduce CpG-PGx SNPs as new candidates for a systematic insight into the genomic-epigenomic-phenomic-pharmacogenomics (G-E-Ph-PGx) axis. *J Pers Med* 15(12):579. 10.3390/jpm15120579
24. Blum K, Sharafshah A, Khalsa J et al (2025) Computational GWAS meta-meta analysis revealing cross talk between cannabis CNR1 and DRD2 receptors optimizing long-term outcomes for cannabis use disorder (CUD) by enhancing dopamine homeostasis promoting high-quality cannabis medicinals. *Res Sq [Preprint]*. 10.21203/rs.3.rs-8140327/v1
25. Sharafshah A, Motovali-Bashi M, Blum K et al (2025) A GWAS meta-meta-analysis and in-depth in silico pharmacogenomic investigations in identification of APOE and other genes associated with pain, anti-inflammatory, and immunomodulating agents in opioid use disorder (OUD) derived from 14.91 million subjects. *Cell Mol Neurobiol* 45(1):76. 10.1007/s10571-025-01587-5
26. Sharafshah A, Lewandrowski KU, Gold MS et al (2025) In silico pharmacogenomic assessment of glucagon-like peptide-1 (GLP-1) agonists and the Genetic Addiction Risk Score (GARS)–related pathways: implications for suicidal ideation and substance use disorder. *Curr Neuropharmacol* 23(8):974–995. 10.2174/011570159X349579241231080602
27. Lewandrowski KU, Blum K, Sharafshah A et al (2025) Genetic and regulatory mechanisms of comorbidity of anxiety, depression and ADHD: a GWAS meta-meta-analysis through the lens of a systems biology and pharmacogenomic perspective in 18.5 million subjects. *J Pers Med* 15(3):103. 10.3390/jpm15030103
28. Sharafshah A, Motovali-Bashi M, Keshavarz P, Blum K (2024) Synergistic epistasis and systems biology approaches to uncover a pharmacogenomic map linked to pain, anti-inflammatory and immunomodulating agents (PALma) in a healthy cohort. *Cell Mol Neurobiol* 44(1):74. 10.1007/s10571-024-01504-2
29. Suresh N, Kantipudi SJ, Ramu D et al (2023) Association between opioid and dopamine receptor gene polymorphisms OPRM1 rs1799971, DAT VNTR 9–10 repeat allele, DRD1 rs4532 and DRD2 rs1799732 and alcohol dependence: an ethnicity-oriented meta-analysis. *Pharmacogenet Genomics* 33(7):139–152. 10.1097/FPC.0000000000000502

30. Lu H, Roeder N, Richardson B et al (2026) Unpredictable chronic mild stress upregulates dopamine receptor expression independent of fatty acid-binding protein 7 gene deletion. *Neurochem Res* 51(3):143. 10.1007/s11064-026-04753-3
31. Androvičová R, Jahn K, Engel J et al (2026) Epigenetic alterations of serotonergic but not dopaminergic signalling in compulsive sexual behaviour disorder. *Behav Brain Res* 497:115872. 10.1016/j.bbr.2025.115872
32. Rose MP, Whitton GM (2026) Depression, anxiety, and genetics shape smoking risk through salience networks. *Psychiatry Res Neuroimaging* 360:112202. 10.1016/j.pscychresns.2026.112202
33. Kigar SL, Lim TV, Turner L et al (2026) Peripheral expression of dopamine genes as a biomarker for cocaine addiction in humans. *Eur Addict Res* 32(1):28–33. 10.1159/000551119
34. Blum K, Lewandrowski KU, Lorio MP et al (2026) Reward deficiency syndrome (RDS): a common neurogenetic trait/state of all addictions: is this the new DSM? *Br J Health Med Res* 13(1):29–62. 10.14738/bjhr.1301.19797
35. Castelli V, Tringali G, Di Bartolomeo M et al (2026) Prenatal THC exposure and binge-like alcohol drinking in early adolescence: from sex-specific drinking vulnerability to abnormal endocannabinoid-dopamine nexus in the nucleus accumbens. *J Psychopharmacol* Published online Febr 27. 10.1177/02698811261420097
36. Teixeira MR, Felício RFM, Assis ISDS et al (2026) Dopaminergic system gene polymorphisms associated with severe obesity and related outcomes: a case-control study in Brazil. *Behav Brain Res* 509:116226. 10.1016/j.bbr.2026.116226
37. Mao J, Chen P, Nie Y (2026) The interaction of negative parenting and DRD2 gene rs1799732 polymorphism on self-control in children and adolescents: development stage differences. *Br J Dev Psychol* 44(2):333–349. 10.1111/bjdp.70020
38. Pascale E, Cimino S, Cerniglia L et al (2026) Disordered eating in early childhood: DRD2 and COMT gene polymorphisms and behavioral features in family trios. *Eat Weight Disord* 31(1):8. 10.1007/s40519-025-01810-8
39. Blum K, Wood RC, Braverman ER, Chen TJ, Sheridan PJ (1995) The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes' theorem. *Funct Neurol* 10(1):37–44
40. Blum K, Braverman ER, Sharafshah A et al (2025) Exploring dopamine as the master regulator of brain circuitry and mental health genome. *Gene Protein Dis* 5. 10.36922/gpd.6557
41. Zhou H, Sealock JM, Sanchez-Roige S et al (2020) Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nat Neurosci* 23(7):809–818. 10.1038/s41593-020-0643-5
42. Efrati Y, Demetrovics Z, Horváth Z et al (2025) Seeking satisfaction among Israeli young adults: the roles of gratification, compensation, reward deficiency syndrome, and compulsivity in relation to addictive behaviors. *Subst Abuse Rehabil* 16:177–191. 10.2147/SAR.S527209
43. Zhang H, Zheng R, Yu B et al (2024) Dissecting shared genetic architecture between depression and body mass index. *BMC Med* 22(1):455. 10.1186/s12916-024-03681-9

44. Jung S, Halvorson MW, Pedersen N, EGOS; NORDiC et al (2025) Rare coding variation in OCD implicates shared genes with other psychiatric disorders. medRxiv [Preprint]. Published online Dec 23. 10.64898/2025.12.22.25342827
45. Ruzzo EK, Pérez-Cano L, Jung JY et al (2019) Inherited and de novo genetic risk for autism impacts shared networks. *Cell* 178(4):850–866e26. 10.1016/j.cell.2019.07.015
46. Bruel AL, Vitobello A, Thiffault I et al (2022) ITS1N1: a novel candidate gene involved in autosomal dominant neurodevelopmental disorder spectrum. *Eur J Hum Genet* 30(1):111–116. 10.1038/s41431-021-00985-9
47. Beauchaine TP, Constantino JN, Hayden EP (2018) Psychiatry and developmental psychopathology: unifying themes and future directions. *Compr Psychiatry* 87:143–152. 10.1016/j.comppsy.2018.10.014
48. Huang QQ, Wigdor EM, Malawsky DS et al (2024) Examining the role of common variants in rare neurodevelopmental conditions. *Nature* 636(8042):404–411. 10.1038/s41586-024-08217-y
49. Evangelou E, Gao H, Chu C et al (2019) New alcohol-related genes suggest shared genetic mechanisms with neuropsychiatric disorders. *Nat Hum Behav* 3(9):950–961. 10.1038/s41562-019-0653-z
50. Rutter M, Silberg J, O'Connor T, Simonoff E (1999) Genetics and child psychiatry: I. Advances in quantitative and molecular genetics. *J Child Psychol Psychiatry* 40(1):3–18
51. Han M, Yuan L, Huang Y et al (2022) Integrated co-expression network analysis uncovers novel tissue-specific genes in major depressive disorder and bipolar disorder. *Front Psychiatry* 13:980315. 10.3389/fpsy.2022.980315
52. Li H, Liu Q, Shan Q et al (2025) Identification of mitochondrial-related causal genes for major depressive disorder via integrating multi-omics. *J Affect Disord* 382:540–548. 10.1016/j.jad.2025.04.124
53. Li J, Cai T, Jiang Y et al (2016) Genes with de novo mutations are shared by four neuropsychiatric disorders discovered from NPdenovo database. *Mol Psychiatry* 21(2):290–297. 10.1038/mp.2015.40
54. Palomo T, Kostrzewa RM, Beninger RJ, Archer T (2007) Genetic variation and shared biological susceptibility underlying comorbidity in neuropsychiatry. *Neurotox Res* 12(1):29–42. 10.1007/BF03033899
55. Ganesh S, Ahmed PH, Nadella RK, ADBS Consortium et al (2019) Exome sequencing in families with severe mental illness identifies novel and rare variants in genes implicated in Mendelian neuropsychiatric syndromes. *Psychiatry Clin Neurosci* 73(1):11–19. 10.1111/pcn.12788
56. Subaran RL, Odgerel Z, Swaminathan R et al (2016) Novel variants in ZNF34 and other brain-expressed transcription factors are shared among early-onset MDD relatives. *Am J Med Genet B Neuropsychiatr Genet* 171B(3):333–341. 10.1002/ajmg.b.32408
57. Thapar A, Harold G, McGuffin P (1998) Life events and depressive symptoms in childhood—shared genes or shared adversity? A research note. *J Child Psychol Psychiatry* 39(8):1153–1158

58. Feng Y, Jia N, Huang P, Hu S, Yang S (2026) Cross-ancestry genetic architecture reveals shared biological pathways of major psychiatric disorders. *Mol Psychiatry* Published online March 17. 10.1038/s41380-026-03541-3
59. Ganesh S, Vemula A, Bhattacharjee S, ADBS Consortium et al (2022) Whole exome sequencing in dense families suggests genetic pleiotropy amongst Mendelian and complex neuropsychiatric syndromes. *Sci Rep* 12(1):21128. 10.1038/s41598-022-25664-7
60. Priyanka, Kumar R, Kumar V et al (2025) Deciphering transcriptomic signatures in schizophrenia, bipolar disorder, and major depressive disorder. *Front Psychiatry* 16:1574458. 10.3389/fpsy.2025.1574458
61. Zhang S, Zhao L, Liao A et al (2024) Investigating the shared genetic architecture between psychiatric disorders and executive function. *Biol Psychiatry Glob Open Sci* 4(6):100392. 10.1016/j.bpsgos.2024.100392
62. Barbash S, Simchovitz A, Buchman AS et al (2017) Neuronal-expressed microRNA-targeted pseudogenes compete with coding genes in the human brain. *Transl Psychiatry* 7(8):e1199. 10.1038/tp.2017.163
63. Nabais MF, Laws SM, Lin T et al (2021) Meta-analysis of genome-wide DNA methylation identifies shared associations across neurodegenerative disorders. *Genome Biol* 22(1):90. 10.1186/s13059-021-02275-5
64. Waszczuk MA, Eaton NR, Krueger RF et al (2020) Redefining phenotypes to advance psychiatric genetics: implications from hierarchical taxonomy of psychopathology. *J Abnorm Psychol* 129(2):143–161. 10.1037/abn0000486
65. Goçi Uka A, Agani F, Blyta A et al (2019) Role of the allelic variation in the 5-hydroxytryptamine receptor 1A (HTR1A) and the tryptophan hydroxylase 2 (TPH2) genes in the development of PTSD. *Psychiatr Danub* 31(2):256–262. 10.24869/psyd.2019.256

Figures

Cross-trait LD blocks (r²) — 6:25120440-33889314

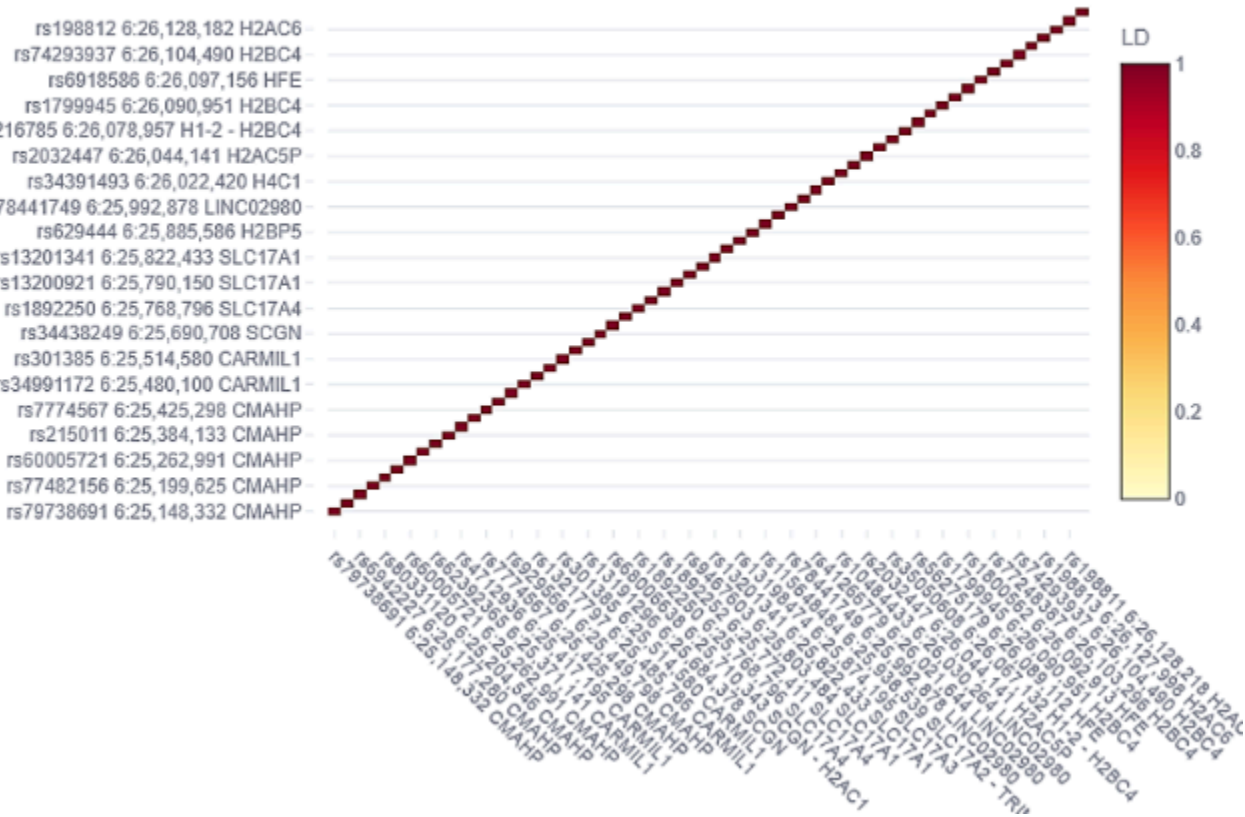


Figure 1

Cross-trait LD block visualization (r²) for locus 6:25120440-33889314.

Cross-trait haplotype blocks (D') — 6:25120440-33889314

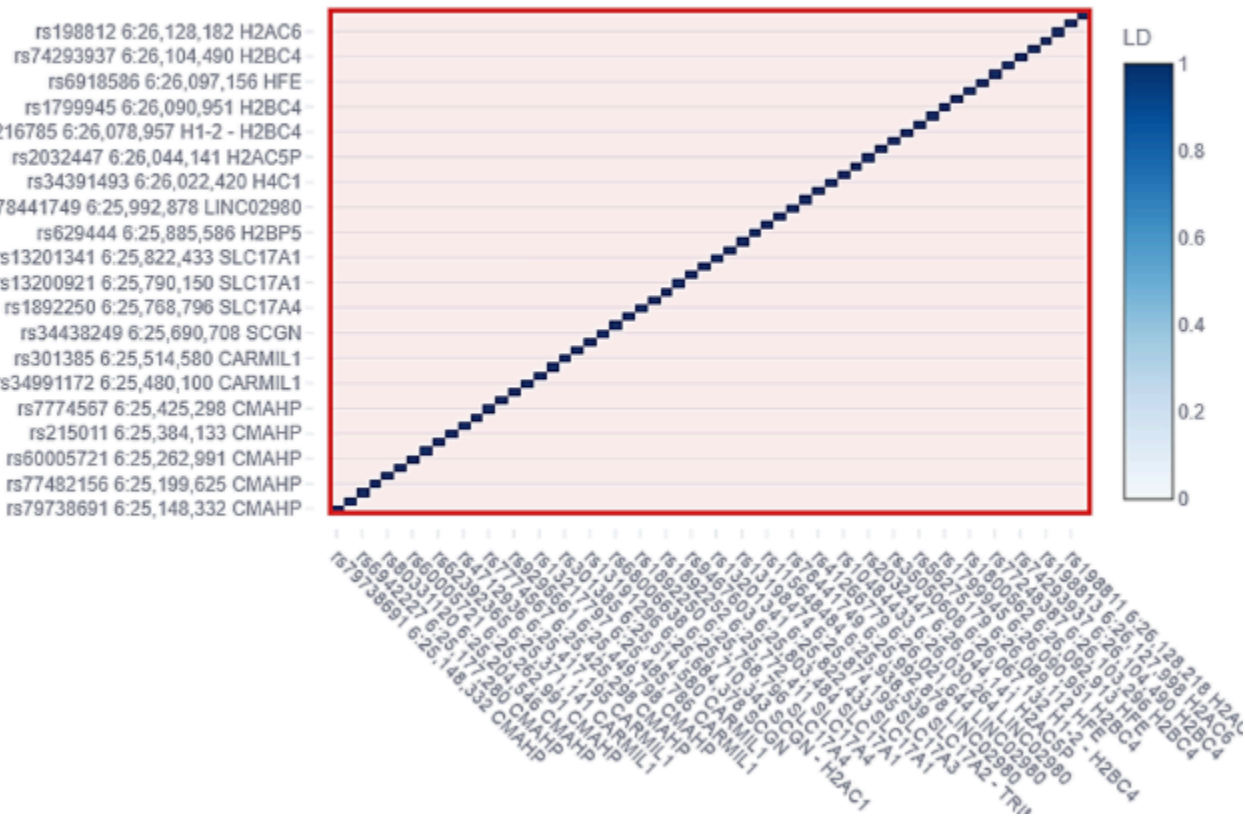


Figure 2

Cross-trait haplotype visualization (Solid Spine D') for locus 6:25120440-33889314. Haploview Solid Spine | D' ≥ 0.80. Red solid = selected block. Gray dotted = other blocks. Axis: rsID / CHR: POS/gene

Cross-trait LD blocks (r²) — 11:112793134-114173783

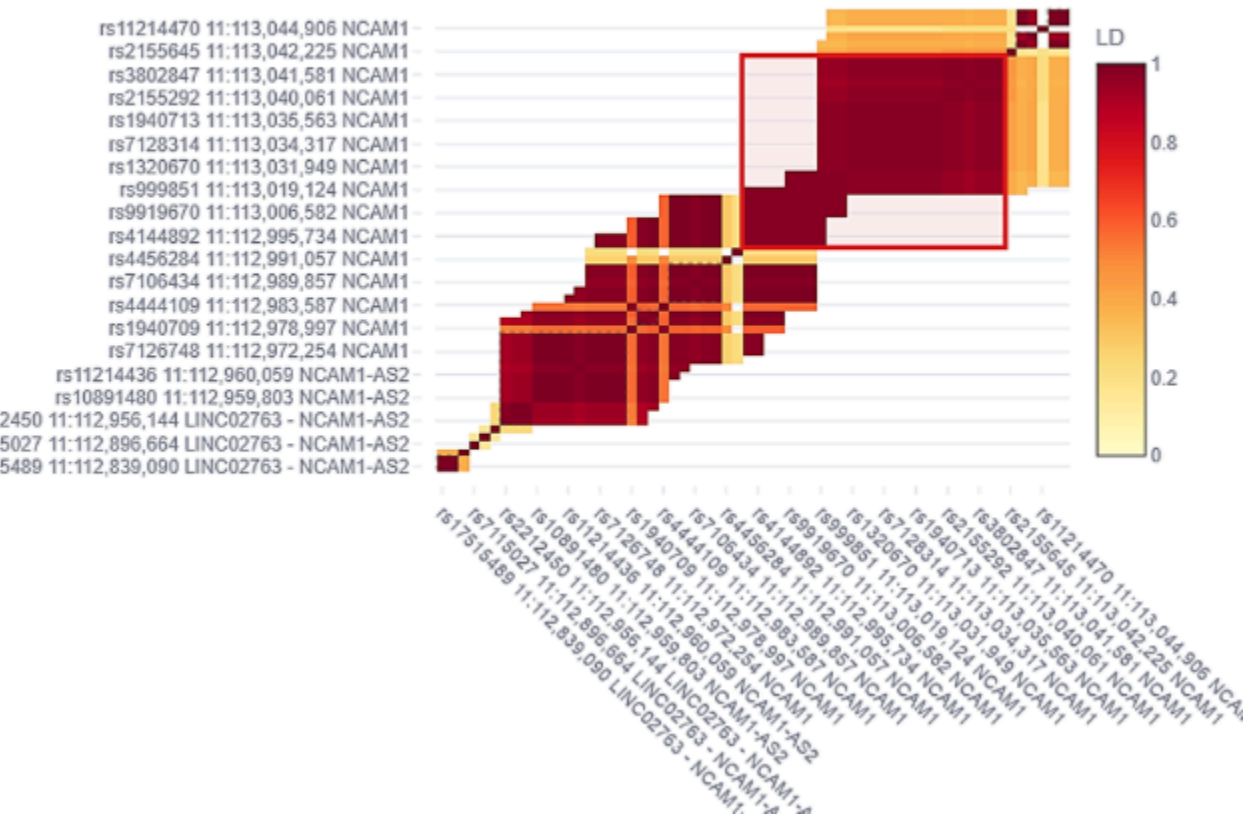


Figure 4

Cross-trait LD block visualization (r^2) for locus 11:112793134-114173783. Ensembl LD: chr11:112,693,654–113,193,654; Pairs: 30589; $r^2 \geq 0.80$. Red solid = selected block. Gray dotted = other blocks. Axis: rsID / CHR:POS / gene.

Cross-trait haplotype blocks (D') — 11:112793134-114173783

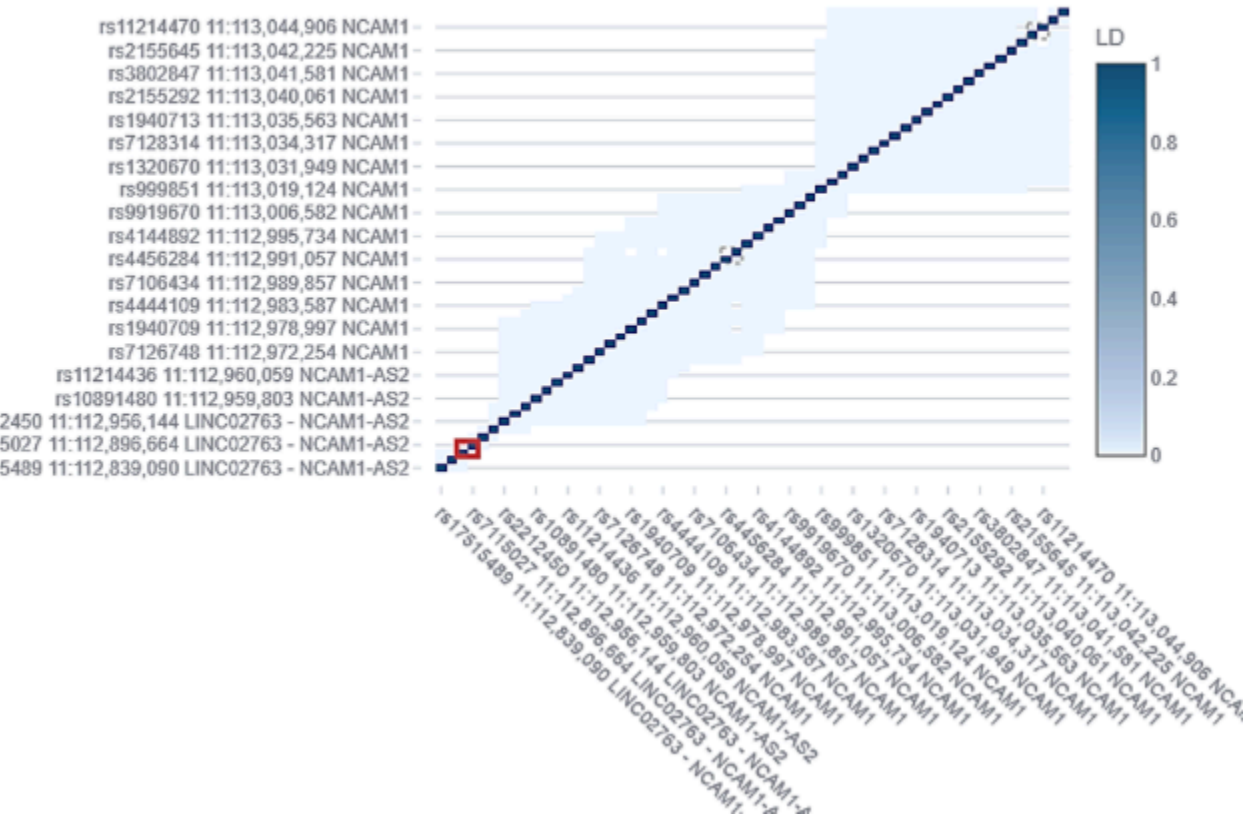


Figure 5

Cross-trait haplotype visualization (Solid Spine D') for locus 11:112793134-114173783. Haploview Solid Spine | $D' \geq 0.80$. Red solid = selected block. Gray dotted = other blocks. Axis: rsID / CHR:POS / gene.

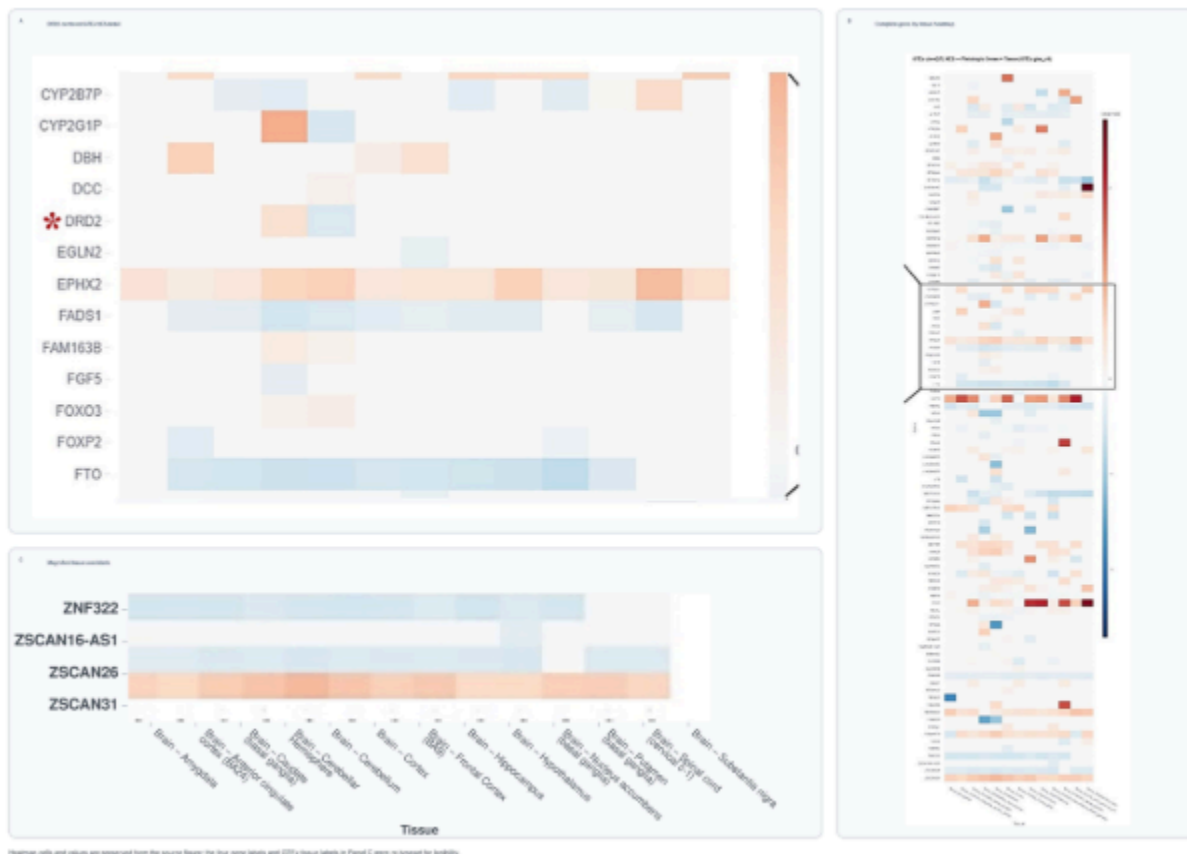


Figure 6

GTEx NES Heatmap. Pleiotropic Candidate Genes × Tissue. Mean NES across all cis-eQTLs for each gene in each tissue. Red = alternative allele increases expression; Blue = decreases. Missing cells = no significant cis-eQTL in that tissue for this gene. Red star specifies DRD2 gene.

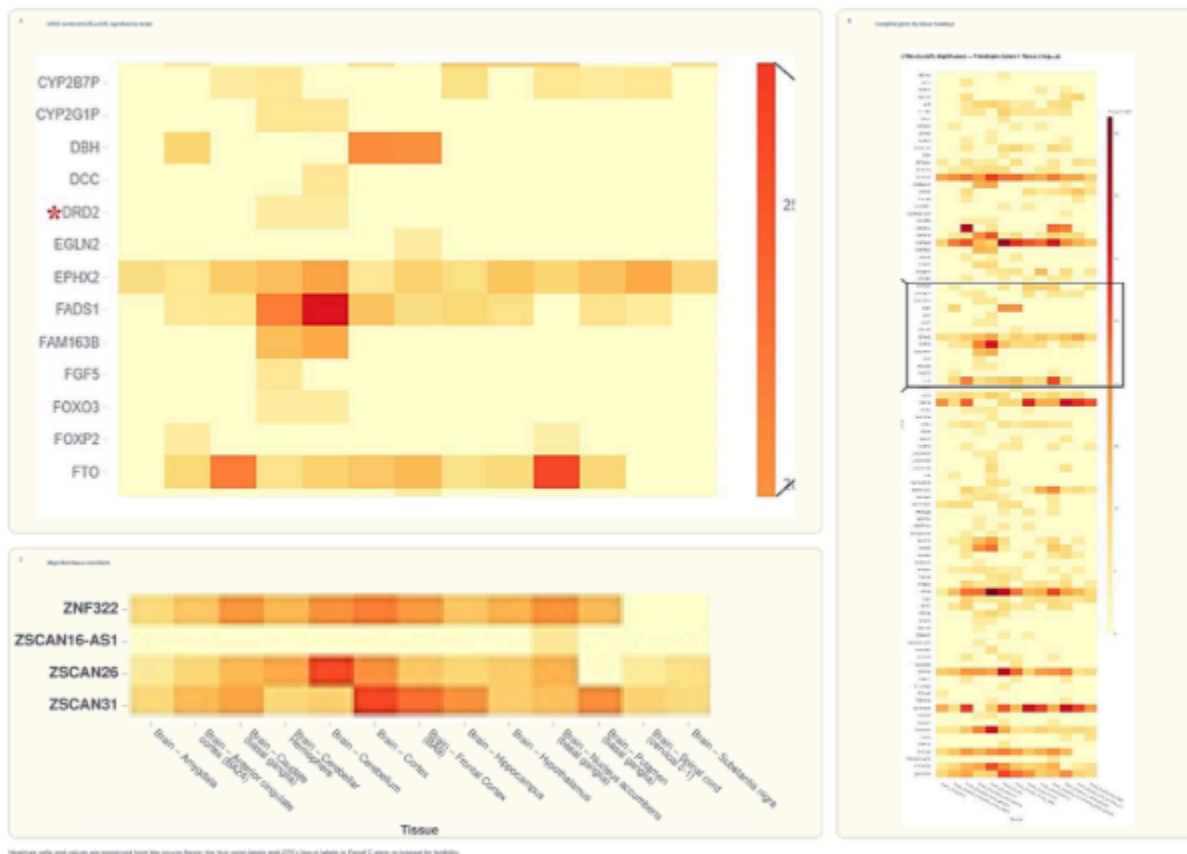


Figure 7

GTEx Significance Heatmap. Pleiotropic Genes $\times$ Tissue ($-\log_{10} p$). Maximum $-\log_{10}(\text{p-value})$ across all cis-eQTLs for each gene in each tissue. Darker = more significant. Genes with consistently dark cells across tissues have the strongest expression-level evidence. Red star specifies DRD2 gene.

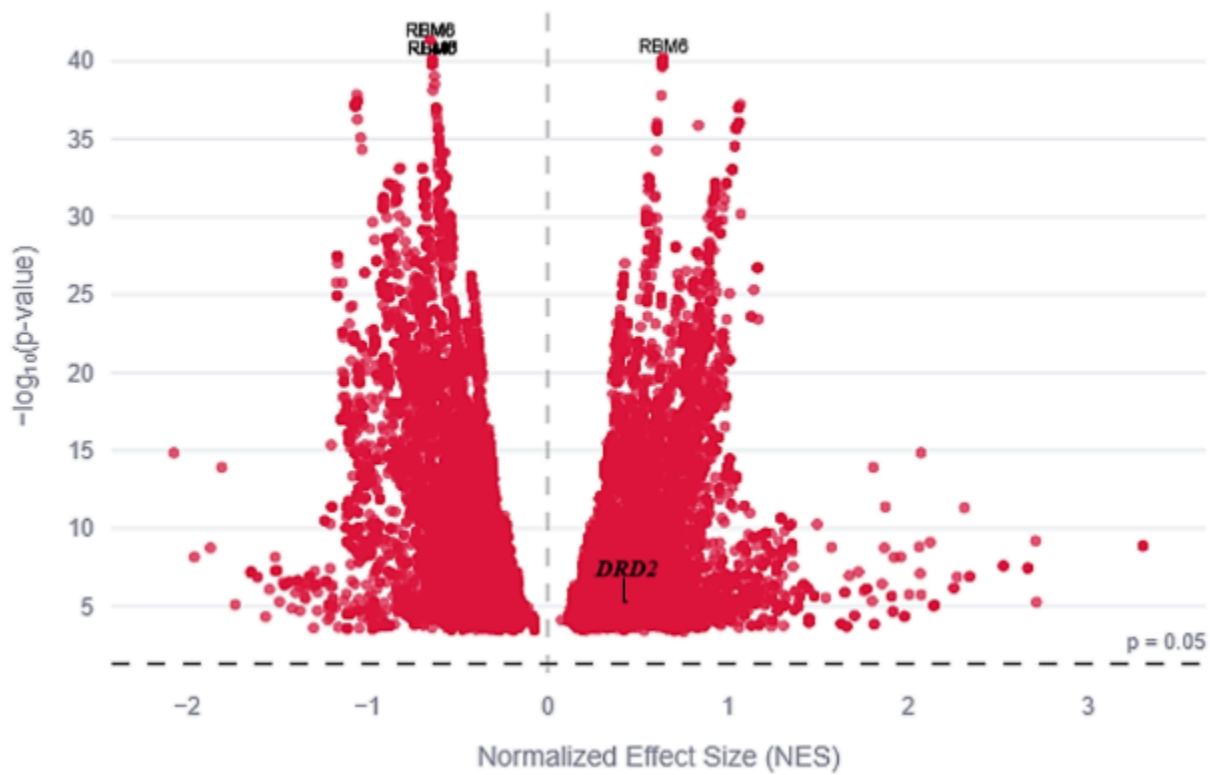


Figure 8

Volcano plot of pleiotropic genes passed by GTEx filter illustrated by Normalized Effect Size (NES) in x-axis and $-\log P$ in y-axis. RBM6 showed in the top and DRD2 is mentioned as the important gene.

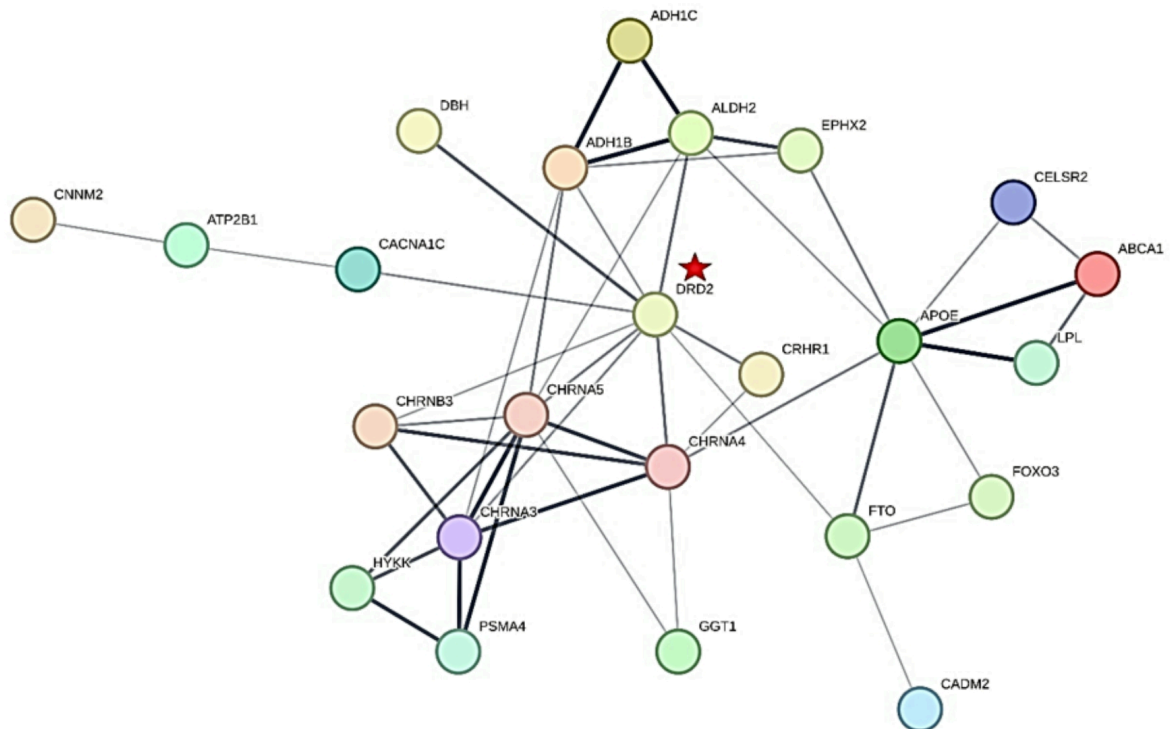


Figure 9

STRING-MODEL of PGx filtering on pleiotropic genes with significant cis-eQTL results from GTEx downstream analyses followed by GWAS fine-mapping.

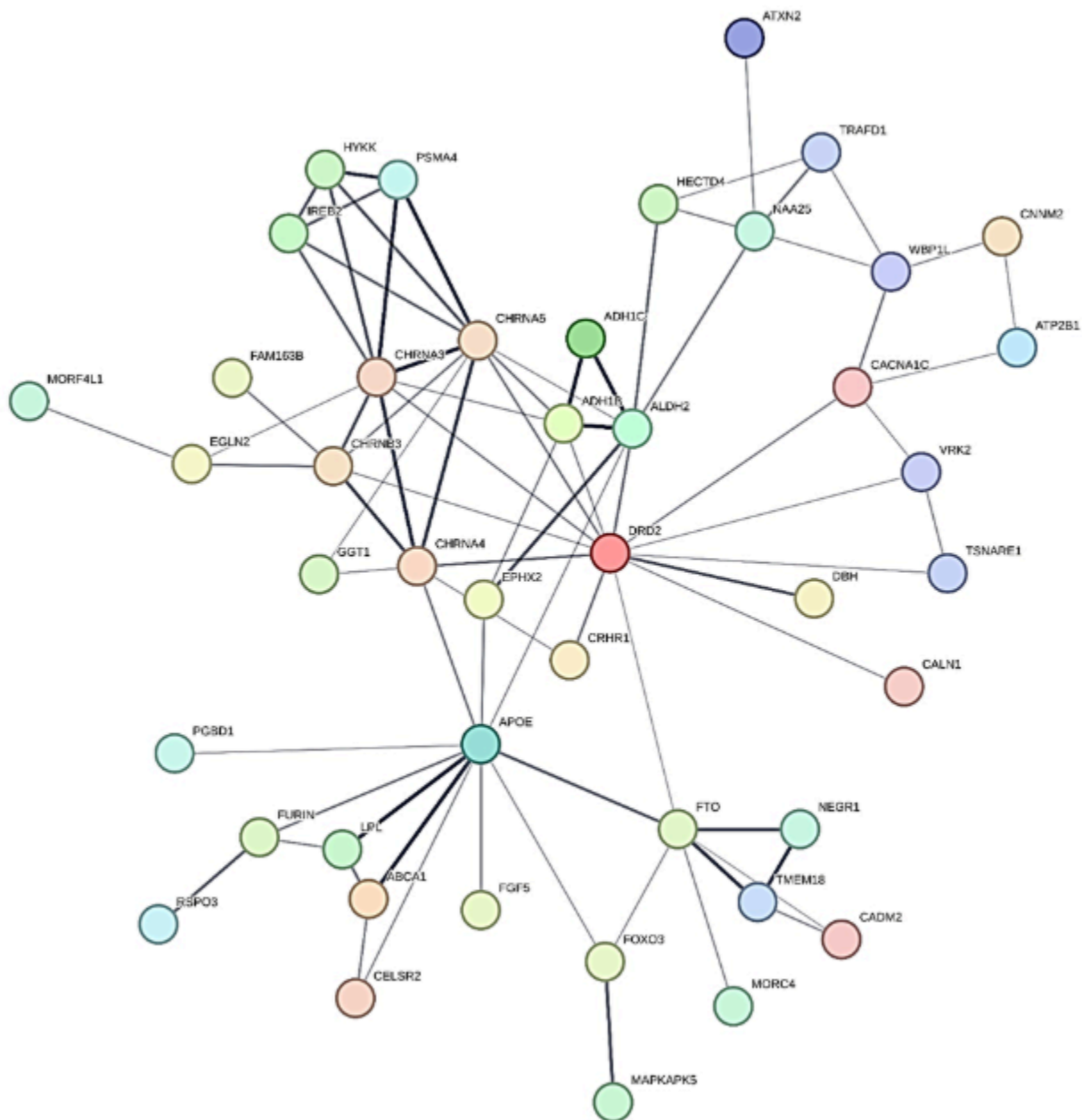


Figure 10

STRING-MODEL of fully connected members of pleiotropic genes with significant GTEx eQTL in 13 brain tissues. DRD2 is the hub gene in this network.