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Toxicogenomics of Bisphenol A and Neurodevelopmental Disorders

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<http://dx.doi.org/10.5772/intechopen.68415>

Abstract

Bisphenol A (BPA) has been widely used in many industrial and consumer products and is known as an endocrine-disrupting chemical. To find the underlying genetic basis and molecular mechanisms of BPA-associated neurodevelopmental disorders (NDs), this chapter addressed the toxicogenomics of BPA with publicly accessed Comparative Toxicogenomics Database. The present results indicated that the key cellular components (CC) of the nervous system such as neuron, synapse, dendrite and axon are common in CC annotation; the commonly found molecular functions are neurotransmitter receptor or transducer binding or activity; and the main common biological processes include synaptic signalling, cognition, learning or memory, behaviour, the development of nervous system and brain. Neuroactive ligand-receptor interaction, dopaminergic, glutamatergic and serotonergic synapses, monoamine transport and synaptic vesicle pathway were the common pathways. Simultaneously, the BPA-disease may share the common pathways with drug addictions such as cocaine addiction. Unique pathways might also contribute to the BPA action in different NDs such as one carbon metabolism and detoxification of oxidative stress in Down syndrome. Although GO and pathway results indicate some common annotations, the predicted PPI molecular function clusters are quite different for each ND. In addition, some of the NDs share the same transcription factors (TFs) and miRNAs, which indicate these disorders have the similar expression profiles. Finally, chemicals having comparable interacting genes to BPA should be considered.

Keywords: bisphenol A, toxicogenomics, neurodevelopmental disorders

1. Introduction

The critical windows of vulnerability during human brain development are mainly from the third trimester to at least 2–3 years after birth [1]. Any developmental neurotoxicant exposure during this critical window has the possibility to cause various clinical neurodevelopmental disorders (NDs) in humans (e.g. autism, anxiety disorder, schizophrenia, dyslexia and epilepsy). Bisphenol A (BPA), as a proved endocrine-disrupting chemical, has been widely used as the plasticizer in many consumer products made of polycarbonate plastic such as baby bottles, tableware, food containers and water bottles. BPA can also be found in breast milk [2, 3]. Infants and children were found to have the highest estimated daily intake of BPA per body weight [4, 5]. A review by Healy et al. [6] affirmed that the potential for non-dietary sources make a substantial contribution to the total daily BPA exposure in young children and recommended risk-assessment models implement new frameworks, which specifically address exposure and hazard in early childhood. Pinson et al. [7] reviewed the human and rodent data on the neurodevelopmental alterations of BPA, and found that mostly reported effects were social and sexual behaviour and cognition that were unique to humans. The related mechanisms reported included the disruption of thyroid function, alterations of neurotransmitters levels, calcium signalling and neurotoxicity. Given the extensive BPA exposure during the critical windows of the brain development and the possible neurodevelopmental alterations, here we explore the possible genetic basis and the molecular mechanisms of BPA-associated NDs.

2. BPA-gene interactions and neurodevelopmental disorders

Comparative toxicogenomics database (CTD, <http://ctdbase.org>) is a robust, publicly available database that aims to advance understanding about how environmental exposures affect human health with manually curated information about chemical-gene/protein interactions, chemical-disease and gene-disease relationships, with functional and pathway data to aid in the development of hypotheses about the mechanisms underlying environmentally influenced diseases [8]. In this work, all BPA-gene/protein interactions were downloaded from CTD, in which BPA-gene/protein interactions associated to the following 17 NDs were selected as our targeted NDs for further analysis according to MESH ID used in CTD— anxiety disorders (AD), attention deficit and disruptive behaviour disorders (ADDBD), autism spectrum disorder (ASD), bipolar disorder (BD), developmental disabilities (DD), Down syndrome (DS), foetal alcohol spectrum disorders (FASD), intellectual disability (ID), language development disorders (LDD), learning disorders (LD), motor skills disorders (MSD), obsessive-compulsive disorder (OCD), pervasive child development disorders (PCDD), schizophrenia (Sch), speech disorders (SD), stereotypic movement disorder (SMD) and Tourette syndrome (TS). Thus, BPA-gene/protein interactions associated to these 17 NDs were collected for further analysis.

According to the reference score on relationships between chemicals-genes, genes-diseases and chemicals-diseases [9], we found that ID was most likely having the atypical connectivity with BPA (**Table 1**). Inference BPA interacted genes were up to 119. Inference score of more

Disease name	Inference BPA-interacted genes (n)	Inference score	Reference count
ID	ACBD6, ADK, ADRA2B, AHI1, ALDH5A1, AP4E1, AP4M1, APC, ARL14EP, ASCC3, ASCL1, BBS7, BDNF, CA8, CACNA1G, CALCA, CAPN10, CASP2, CCBE1, CCNA2, CIC, CNDP1, CNKSR1, COL18A1, DEAF1, DISC1, DNMT3A, DOCK8, DYNC1H1, EEF1B2, ELP2, ENTPD1, ERLIN2, FAM126A, FASN, FGFR2, FMR1, FOLR1, FRY, GAMT, GNAS, GON4L, GRIN2B, HDAC4, HEXA, HIST3H3, INPP4A, INPP5E, KCNA2, KDM5A, KDM5C, KDM6B, KIF1BP, KIF7, L2HGDH, LAMA1, LARP7, LETM1, LINS1, MAN1B1, MCC, MECP2, MED13L, MEF2C, METTL23, MFSD2A, NAGLU, NDST1, NF1, NRXN1, NSD1, PARP1, PAX6, PDHX, PECR, PEX6, PMM2, POLR3B, PRKCG, PRKRA, PTCHD1, PTEN, RAB39B, RABL6, RALGDS, RGS7, SC5D, SCAPER, SCN8A, SETBP1, SHANK2, SHANK3, SIN3A, SLC2A1, SLC31A1, SLC4A10, SNX14, SRD5A3, SRGAP3, STRA6, SURF1, SYNGAP1, TAF2, TH, TMCO1, TMEM135, TRMT1, TSEN2, TSEN34, TSEN54, TTI2, UBR7, UROC1, VIP, VRK1, WDR45B, WDR62, ZBTB40, ZCCHC8 (119)	86.31	51
LD	ACHE, APOD, APP, BCL2, CAMKMT, GRIA1, HMOX1, HTR1A, HTR7, IL1B, IL1RN, KL, MAPT, MECP2, MICU1, MT1, NF1, PARK2, PDE1B, PNOC, POR, PSEN1, RNF135, SIGMAR1, SLC17A6, SLC17A7, SYP, TH, TRH, VEGFA (30)	30.96	39
Sch	ACOT6, ADAMTS3, ADCY7, ADGRF4, AHI1, AKT1, ALS2CL, APOE, AVP, BDNF, BTG1, CAMK2B, CASP4, CCDC137, CCL2, CELF2, CFAP65, CHD4, CHI3L1, CLINT1, CNR1, COL3A1, COMT, CP, CPLX1, CPLX2, DAO, DGCR2, DISC1, DIXDC1, DLG1, DPYD, DRD1, DRD2, DRD3, DRD4, DTNBP1, EDEM2, EIF5, ESAM, FAM3D, FASTKD5, FGFR1, GABRA6, GABRB2, GABRD, GAD1, GAD2, GIF, GPR153, GRIK2, GRIK5, GRIN2B, GRIN2D, GRM2, GRM3, GSK3A, GSK3B, HCAR2, HLA-DRB1, HNRNPA3, HP, HRH1, HTR2A, HTR6, HTR7, IL1B, IL2RA, IL6, IL6R, INPP5A, KDM2B, KDR, KLF12, KPNA1, LAMA1, LAMA2, LGR4, LRP1, MAGI2, MAOB, MET, MTHFR, MTOR, ND4, NDUFV2, NKAPL, NOS1, NPRL2, NR3C1, NRG1, NRG3, NRGN, NRIP1, NRXN1, NTF3, NTNG1, NTNG2, NTRK1, NTSR1, OXTR, PAK2, PCM1, PDE4B, PHB, PIK3CB, PITPNM1, PLCB1, PLCL2, PLXNA2, PML, PRODH, PVALB, RB1CC1, RELN, RGS12, RGS4, RGS9, RTN4, RTN4R, SAP30BP, SBNO1, SDF4, SELENBP1, SLC26A7, SLC6A1, SLC6A3, SLC6A4, SP4, SPATA5, SRSF1, SYN2, SYP, TAAR6, TAC1, TEK5, THBS1, TNF, TP53, TPH1, TRAK1, TRRAP, TSPAN18, UGT1A3, VIPR2, VPS35, VPS39, WDR11, ZKSCAN4, ZNF565 (150)	30.91	86
ASD	AVPR1A, BDNF, C3ORF58, CEP41, CHD8, CIRBP, CXORF36, DHCR24, DIO2, DIO3, DLG4, DLX1, DNMT3A, DNMT3B, DPP6, DPYD, EN2, FOXP1, GABRB3, GRIN2B, GTF2I, HEY1, HFE, IL1RAPL1, ITGB3, JARID2, LAMC3, LRRN3, LRRTM3, MEF2C, MTNR1A, NRXN1, NRXN2, NTSR1, OXTR, PCDH9, PTCHD1, RELN, RYR2, SCN1A, SFSWAP, SHANK3, SIN3A, SNTG2, SOX5, SOX9, TBL1X, TET1, TET3, TSHZ3, UPP2 (51)	24.05	29
AD	ADORA2A, APP, CARTPT, CHRNA5, CHRN2, CNR1, CRH, CRHR2, CRP, DIXDC1, DNMT1, DRD2, EOMES, FOS, GABRA2, GLO1, GNB1, GRM8, HTR7, MAGI2, MDK, MECP2, MIF, NPS, NPY, NPY1R, OXT, PAM, SERPINA1, SHANK1, SLC6A3, SLC6A4, TNF, UCN (34)	21.95	52
SMD	CRH, MEF2C, TRH (3)	13.04	3
BD	AKR1C4, ANK3, BDNF, BHLHE40, CACNA1C, COMT, CPLX1, CPLX2, DIXDC1, DRD1, DRD5, GRIK2, GRK3, GSK3A, GSK3B, HTR2A, INS, MTHFR, NDUFV2, NR3C1, NTNG1, NTNG2, NTRK1, NTRK2, PDE4B, POMC, PVALB, RELN, S100B, SERPINA1, SLC5A3, SLC6A4, SNAP25, SP4, TAC1, TACR1, TENM4, TRPC3, TSHB (39)	12.32	31

Disease name	Inference BPA-interacted genes (n)	Inference score	Reference count
SD	GRIN2A, MFSD2A, TTPA (3)	12.24	3
DS	CALCA, CXCL8, GATA1, GSTM2, MTHFR, MTR, NTF3, PRDX2, PRDX6, RCAN1, S100B, SLC19A1, SOD1, VIP (14)	9.35	10
TS	DRD3, SLITRK1 (2)	8.31	2
MSD	AKAP5, CAMKMT, FGFR2, OGG1, PTEN, SHANK1 (6)	7.05	6
OCD	BDNF, CCKBR, HOXB8, HTR1D, HTR2A, SLC6A4, SLITRK5 (7)	5.95	7
ADDBD	DRD4, S100B (2)	4.03	2
LDD	BCL11A, DPYD, ERF, FOXP2, GRIN2A, KCNA2, NRXN1, PTEN, SETBP1, SHANK3 (10)	3.52	10
DD	ARFGAP1, CAMKMT, CBL, CHRNA4, CNTN4, DOCK8, DRD2, KCNQ2, KCNT1, LRP2, MECP2, NANS, NTRK2, PMP22, PNKP, PTEN, SHANK3, SLC2A1, SLC33A1, SLC4A4, SLC6A8, STAMBP (22)	2.99	24
FASD	CAT, NOS1 (2)	2.49	2
PCDD	DRD4, MECP2, MKL2 (3)	2.47	3

ID: intellectual disability; LD: learning disorders; Sch: schizophrenia; ASD: autism spectrum disorder; AD: anxiety disorders; SMD: stereotypic movement disorder; BD: bipolar disorder; SD: speech disorders; DS: Down syndrome; TS: Tourette syndrome; MSD: motor skills disorders; OCD: obsessive-compulsive disorder; ADDBD: attention deficit and disruptive behavior disorders; LDD: language development disorders; DD: developmental disabilities; FASD: foetal alcohol spectrum disorders; PCDD: pervasive child development disorders.

Table 1. Selected neurodevelopmental diseases and related BPA-interacted genes.

than 20 was found for LD, Sch, ASD and AD, whereas it was less than 10 for DS, TS, MSD, OCD, ADDBD, LDD, DD, FASD and PCDD. The results showed that it was only two inference BPA interacted genes for TS, ADDBD and FASD, and in total, 403 BPA bi-interacted genes were curated. A total of 563 BPA-mRNA bi-interactions were found, in which 240 expressions were down-regulated, 169 up-regulated and 153 were altered (not mentioned up or down) regulation. Simultaneously, eighty-one BPA-protein bi-interactions, two protein-BPA bi-interactions and eight BPA-DNA methylation interactions were reported.

3. Microarray data and differently expressed gene screening

To explore the possible clinical application of the genes curated, we used Gene Expression Omnibus (<http://www.ncbi.nlm.nih.gov/geo/>) and ArrayExpress (<http://www.ebi.ac.uk/arrayexpress>) to find the microarray data for peripheral blood, and special tissue gene expression profiling in NDs. The differently expressed genes (DEGs) in each ND samples were identified. If more than one microarray dataset is found, all the datasets are integrated to perform the meta-analysis for the DEGs. Based on the inference scores and the counts of inference BPA-interacted genes, we only selected ID, LD, Sch, ASD, AD and BD as our target diseases for the possible microarray data.

We only found some common genes for BD between CTD and the microarray data. It was in the GSE46449 [10] and only four common genes (BDNF, CACNA1C, CPLX2, HTR2A, SP4) were found. Therefore, the existing microarray data is not enough for further annotation.

4. Gene function enrichment analysis

The curated genes in CTD for each ND were uploaded to DAVID 6.8 Beta (<https://david-d.ncifcrf.gov/tools.jsp>). Homo sapiens were used as the background population. The gene ontology (GO) and pathway were analysed [11, 12]. Simultaneously, WikiPathways and Reactome of EnrichR [13, 14] were used for duplicated pathway prediction. STRING (<http://string-db.org>) is a database of known and predicted protein-protein interactions (PPI), and can be used to predict the functional associations between proteins [15]. Based on the information provided by the STRING database, all genes related to each neurodevelopmental disorder are used to construct a PPI network. The functional molecules in the PPI network are subsequently identified by the molecular complex detection (MCODE) plugin [16] of Cytoscape [17]. The MCODE is a well-known automated method to find highly interconnected subgraphs as molecular complexes or clusters in a PPI network. The proteins in each module will be transferred in Genemania app [18] to predict the possible target proteins or biomarkers.

4.1. Intellectual disability

Of the 119 interacted genes, 117 were bi-interacted. GO analysis with these 117 genes indicated that BPA bi-interacted genes are involved in the biological processes (BP) such as cognition, the development of nervous system, head, brain, forebrain, pallium, telencephalon and embryonic organ (**Table 2**). Other BPs included learning or memory, behaviour (social, single- or multi-organism), intraspecies interaction between organisms, embryonic organ morphogenesis, regulation of synapse structure or activity and neuron apoptotic process. Of the BPs, nervous system development was also reported in a recent study on systematic phenomics analysis for the genes muted in ID by Kochinke et al. [19]. Some genes possibly involved in the cellular component (CC) of somatodendritic compartment and the molecular functions (MF) of chromatic binding. Pathway analysis only found MECP2 and associated Rett Syndrome in WikiPathways, in which six BPA bi-interacted genes were involved. This might suggest that ID and Rett syndrome possess the same pathway.

PPI analysis found four molecular modules (**Figure 1**). TSEN2, TSEN34, TSEN54 and VRK1 were involved in module 1. TSEN2, TSEN34 and TSEN54 are tRNA splicing endonuclease subunits and can interact through physical interaction or co-expression. VRK1 might interact with TSEN2, TSEN34 and TSEN54 through the same pathway, physical interaction or co-expression. CLP1 and TSEN15 can physically interact with TSEN2, TSEN34 and TSEN54 [20–22], therefore, BPA has the potential to interact with these two genes. BPA might also interact with WARS and WARS2 because of their predicted interaction with TSEN34 [23, 24]. WARS and WARS2 are involved in the tryptophan metabolic pathway, which have been reported to appear to provide a unifying biochemical basis for ASDs [25]. Tryptophan is a precursor of important compounds,

Term	Count	P value	FDR	Genes
BP				
Cognition	16	2.49E-10	4.53E-07	DEAF1, VIP, MEF2C, PTCHD1, TH, NF1, MECP2, PRKCG, NRXN1, PTEN, SHANK2, SHANK3, GRIN2B, GNAS, STRA6, SYNGAP1
Learning or memory	14	4.79E-09	8.72E-06	DEAF1, VIP, MEF2C, TH, NF1, MECP2, PRKCG, NRXN1, PTEN, SHANK2, SHANK3, GRIN2B, STRA6, SYNGAP1
Nervous system development	39	1.56E-08	2.85E-05	FGFR2, MEF2C, DEAF1, NAGLU, BBS7, NDST1, PTCHD1, KCNA2, TH, PAX6, MFSD2A, PTEN, BDNF, FOLR1, INPP5E, ADRA2B, CASP2, KIF1BP, DISC1, APC, DNMT3A, ALDH5A1, NF1, FMR1, MECP2, AHI1, PRKCG, NRXN1, SHANK2, SHANK3, FRY, ASCL1, HDAC4, SLC4A10, WDR62, SCN8A, SYNGAP1, KDM6B, FAM126A
Head development	22	2.28E-08	4.14E-05	MEF2C, FGFR2, NAGLU, BBS7, NDST1, PTCHD1, NF1, TH, PAX6, MECP2, AHI1, MFSD2A, NRXN1, PTEN, SHANK3, ASCL1, SLC4A10, WDR62, STRA6, CASP2, DISC1, KDM6B
Brain development	21	4.94E-08	0.0001	MEF2C, FGFR2, NAGLU, BBS7, NDST1, PTCHD1, NF1, TH, PAX6, MECP2, AHI1, MFSD2A, NRXN1, PTEN, SHANK3, ASCL1, SLC4A10, WDR62, CASP2, DISC1, KDM6B
Single-organism behaviour	16	9.96E-08	0.0002	DEAF1, VIP, MEF2C, KCNA2, TH, NF1, MECP2, PRKCG, NRXN1, PTEN, SHANK2, SHANK3, SLC4A10, GRIN2B, STRA6, SYNGAP1
Forebrain development	15	2.10E-07	0.0004	FGFR2, MEF2C, NDST1, PTCHD1, NF1, TH, PAX6, MFSD2A, PTEN, SHANK3, ASCL1, SLC4A10, WDR62, DISC1, KDM6B
Behaviour	18	2.56E-07	0.0005	DEAF1, VIP, MEF2C, NAGLU, PTCHD1, KCNA2, TH, NF1, MECP2, PRKCG, NRXN1, PTEN, SHANK2, SHANK3, SLC4A10, GRIN2B, STRA6, SYNGAP1
Central nervous system development	22	9.19E-07	0.0017	MEF2C, FGFR2, NAGLU, BBS7, NDST1, PTCHD1, ALDH5A1, NF1, TH, PAX6, MECP2, AHI1, MFSD2A, NRXN1, PTEN, SHANK3, ASCL1, SLC4A10, WDR62, CASP2, DISC1, KDM6B
Social behaviour	7	9.59E-07	0.0017	PTCHD1, TH, MECP2, NRXN1, PTEN, SHANK2, SHANK3
Intraspecies interaction between organisms	7	9.59E-07	0.0017	PTCHD1, TH, MECP2, NRXN1, PTEN, SHANK2, SHANK3
Pallium development	10	1.74E-06	0.0032	MEF2C, ASCL1, WDR62, NF1, TH, PAX6, MFSD2A, PTEN, KDM6B, DISC1
Embryonic organ morphogenesis	12	3.27E-06	0.0060	FGFR2, MEF2C, NAGLU, NDST1, BBS7, FOLR1, PRKRA, TH, PAX6, AHI1, STRA6, GNAS
Learning	9	4.59E-06	0.0084	DEAF1, NF1, TH, MECP2, STRA6, NRXN1, SYNGAP1, SHANK2, SHANK3

Term	Count	P value	FDR	Genes
Regulation of synapse structure or activity	11	4.63E-06	0.0084	MEF2C, BDNF, FMR1, NF1, MECP2, NRXN1, SYNGAP1, PTEN, SHANK2, SHANK3, DISC1
Multi-organism behaviour	7	5.03E-06	0.0092	PTCHD1, TH, MECP2, NRXN1, PTEN, SHANK2, SHANK3
Telencephalon development	11	5.17E-06	0.0094	MEF2C, ASCL1, WDR62, NF1, TH, PAX6, MFSD2A, PTEN, KDM6B, SHANK3, DISC1
Regulation of neuron apoptotic process	10	8.61E-06	0.0157	MEF2C, ASCL1, HDAC4, BDNF, NF1, MECP2, PRKCG, SYNGAP1, PARP1, CASP2
Neuron apoptotic process	10	1.27E-05	0.0231	MEF2C, ASCL1, HDAC4, BDNF, NF1, MECP2, PRKCG, SYNGAP1, PARP1, CASP2
Observational learning	4	1.58E-05	0.0287	NF1, STRA6, NRXN1, SHANK3
Embryonic organ development	13	2.24E-05	0.0408	MEF2C, FGFR2, NAGLU, BBS7, NDST1, FOLR1, PRKRA, TH, PAX6, AHI1, GAMT, STRA6, GNAS
CC				
Somatodendritic compartment	18	1.10E-05	0.0152	VIP, SNX14, KCNA2, FMR1, TH, NF1, PRKCG, NRXN1, PMM2, PTEN, SHANK2, SHANK3, ASCL1, SLC4A10, GNAS, SYNGAP1, SLC31A1, APC
MF				
Chromatin binding	15	1.23E-05	0.0180	TAF2, MEF2C, DNMT3A, FMR1, PAX6, MECP2, CIC, HDAC4, ASCL1, VRK1, SIN3A, KDM5A, HIST3H3, NSD1, KDM6B

Table 2. GO analysis for the genes related to intellectual disability.

such as serotonin, quinolinic acid and kynurenic acid, which are involved in neurodevelopment and synaptogenesis. Decreased tryptophan metabolism may alter brain development, neuro-immune activity and mitochondrial function. In module 2, ASCL1, HDAC4, BDNF, KDM6B, TH, HIST3H3, PAX6 and SIN3A interacted through co-localization, co-expression and physical interactions. TH and KDM6B linked other six node proteins through CALCOCO1 [26]. In module 3, LARP7, GAMT and TRMT1 were interacted by physical interactions, co-expression and predicted, pathway or genetic interaction. In this module, CDK9 plays an import role to link the three genes mainly by physical interactions [27–29], although there was no direct evidence for BPA-CDK9 interaction. CDK9 might associate with ID by JUN binding [30] or by AFF family of RNA-binding proteins [31]. In module 4, PARP1, FASN and PTEN interact through physical interaction, co-expression, predicted, pathway, genetic interaction and shared protein domains. Recent findings have proven that the mTOR pathway is altered in cells with defective DNA repair. PARP1 is related to the accumulation of irreparable DNA damage [32], while PTEN is a phosphatase to mediate switching off the PI3K/Akt/mTOR signalling pathway, which has been reportedly associated with ID [33–35]. FASN (expression of fatty acid synthase) is found negatively correlated with PTEN [36], but the in-between genes were not explored. FASN may co-express with MAST2 [26], PRKDC [26, 37] or BMI1 to physically interact with PTEN.

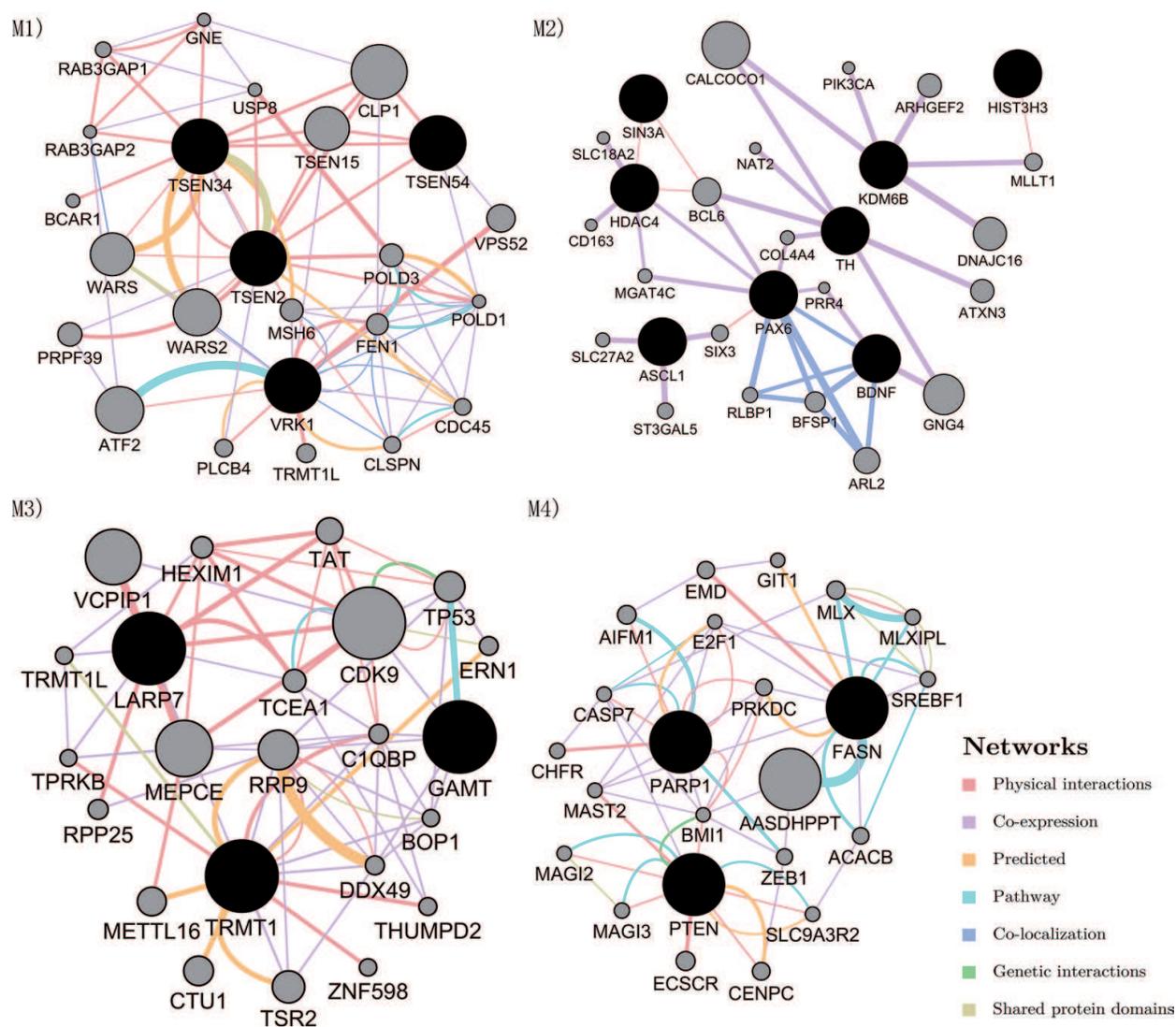


Figure 1. Networks for the genes in PPI MCODE molecular modules for ID.

4.2. Learning disorders

A total of 29 BPA bi-interacted genes related to LD were found. Some of these genes are involved in the BPs such as behaviour, learning or memory, cognition, synaptic-signalling related, cell-cell signalling related, secretion, neuron death or apoptotic-related processes (Table 3). Simultaneously, some of these genes may participate in the CCs such as synapse, presynapse, dendrite, somatodendritic compartment, axon or secretory vesicle. Five KEGG pathways might be influenced by BPA (Table 4). Retrograde endocannabinoid signalling, serotonergic synapse and glutamatergic synapse pathways may be influenced by BPA and involve in LD. Nicotine addiction and Alzheimer's disease may share the same pathway with LD. WikiPathways indicated monoamine transport, synaptic vesicle pathway, MECP2 and associated Rett syndrome pathway might also be influenced. Interestingly, some genes involved in LD are also found in sudden infant death syndrome (SIDS) susceptibility pathways. Reactome pathway confirmed the serotonergic synapse pathway found in KEGG, and additionally suggested that organic anion transporters pathway may be influenced by BPA.

Term	Count	P value	FDR	Genes
BP				
Single-organism behaviour	14	2.98E-14	5.29E-11	SLC17A7, APP, HTR1A, PSEN1, PDE1B, GRIA1, BCL2, MAPT, NF1, TH, MECP2, IL1B, PARK2, TRH
Behaviour	14	2.07E-12	3.67E-09	SLC17A7, APP, HTR1A, PSEN1, PDE1B, GRIA1, BCL2, MAPT, NF1, TH, MECP2, IL1B, PARK2, TRH
Learning or memory	10	9.30E-11	1.65E-07	SLC17A7, APP, PDE1B, PSEN1, GRIA1, NF1, TH, MECP2, IL1B, PARK2
Cognition	10	3.03E-10	5.39E-07	SLC17A7, APP, PDE1B, PSEN1, GRIA1, NF1, TH, MECP2, IL1B, PARK2
Chemical synaptic transmission	12	2.11E-09	3.75E-06	SYP, SLC17A7, ACHE, HTR1A, PNOC, PSEN1, GRIA1, HTR7, NF1, TH, MECP2, PARK2
Trans-synaptic signalling	12	2.11E-09	3.75E-06	SYP, SLC17A7, ACHE, HTR1A, PNOC, PSEN1, GRIA1, HTR7, NF1, TH, MECP2, PARK2
Synaptic signalling	12	2.11E-09	3.75E-06	SYP, SLC17A7, ACHE, HTR1A, PNOC, PSEN1, GRIA1, HTR7, NF1, TH, MECP2, PARK2
Anterograde trans-synaptic signalling	12	2.11E-09	3.75E-06	SYP, SLC17A7, ACHE, HTR1A, PNOC, PSEN1, GRIA1, HTR7, NF1, TH, MECP2, PARK2
Secretion by cell	13	2.26E-08	4.02E-05	SLC17A7, ACHE, APP, HTR1A, PSEN1, HMOX1, NF1, VEGFA, IL1RN, MECP2, IL1B, PARK2, TRH
Cell-cell signalling	15	3.65E-08	6.49E-05	ACHE, TH, IL1RN, NF1, MECP2, PARK2, TRH, SYP, SLC17A7, HTR1A, PNOC, PSEN1, GRIA1, HTR7, IL1B
Secretion	13	9.70E-08	1.73E-04	SLC17A7, ACHE, APP, HTR1A, PSEN1, HMOX1, NF1, VEGFA, IL1RN, MECP2, IL1B, PARK2, TRH
Regulation of cell communication	19	1.13E-07	2.01E-04	ACHE, KL, NF1, IL1RN, MECP2, PARK2, TRH, POR, SYP, APP, CAMKMT, HTR1A, APOD, PSEN1, GRIA1, BCL2, HMOX1, VEGFA, IL1B
Regulation of signalling	19	1.46E-07	2.60E-04	ACHE, KL, NF1, IL1RN, MECP2, PARK2, TRH, POR, SYP, APP, CAMKMT, HTR1A, APOD, PSEN1, GRIA1, BCL2, HMOX1, VEGFA, IL1B
System process	16	1.56E-07	2.78E-04	TH, NF1, MECP2, PARK2, SLC17A7, APP, HTR1A, PNOC, PSEN1, PDE1B, GRIA1, HTR7, BCL2, HMOX1, VEGFA, IL1B
Dicarboxylic acid transport	6	1.68E-07	2.98E-04	SLC17A7, SLC17A6, PSEN1, NF1, IL1B, TRH
Organic hydroxy compound metabolic process	9	2.69E-07	4.79E-04	APP, HTR1A, PDE1B, BCL2, TH, MECP2, IL1B, PARK2, POR
Neuron death	8	4.39E-07	7.81E-04	APP, PSEN1, HMOX1, BCL2, NF1, MECP2, PARK2, SIGMAR1
Locomotory behaviour	7	6.43E-07	1.14E-03	APP, PDE1B, MAPT, TH, MECP2, PARK2, TRH
Response to hypoxia	8	7.59E-07	1.35E-03	HMOX1, BCL2, VEGFA, NF1, TH, MECP2, IL1B, TRH

Term	Count	P value	FDR	Genes
Memory	6	7.93E-07	1.41E-03	SLC17A7, PSEN1, GRIA1, TH, MECP2, IL1B
Regulation of neurotransmitter levels	7	8.92E-07	1.59E-03	SLC17A7, ACHE, PDE1B, PSEN1, NF1, TH, PARK2
Regulation of neuron apoptotic process	7	9.19E-07	1.63E-03	PSEN1, HMOX1, BCL2, NF1, MECP2, PARK2, SIGMAR1
Response to decreased oxygen levels	8	9.52E-07	1.69E-03	HMOX1, BCL2, VEGFA, NF1, TH, MECP2, IL1B, TRH
Neuron apoptotic process	7	1.22E-06	2.16E-03	APP, PSEN1, HMOX1, BCL2, NF1, MECP2, PARK2
Response to oxygen levels	8	1.41E-06	2.51E-03	HMOX1, BCL2, VEGFA, NF1, TH, MECP2, IL1B, TRH
Central nervous system development	11	1.65E-06	2.93E-03	SLC17A7, APP, APOD, PSEN1, MAPT, BCL2, NF1, TH, MECP2, IL1B, PARK2
Nitrogen compound transport	10	2.10E-06	3.74E-03	SLC17A7, SLC17A6, PSEN1, NF1, IL1RN, TH, MECP2, IL1B, PARK2, TRH
Learning	6	3.41E-06	6.06E-03	APP, PDE1B, NF1, TH, MECP2, PARK2
Response to oxidative stress	8	4.34E-06	7.72E-03	APP, APOD, PSEN1, MAPT, HMOX1, BCL2, IL1B, PARK2
Regulation of neuron death	7	5.01E-06	8.91E-03	PSEN1, HMOX1, BCL2, NF1, MECP2, PARK2, SIGMAR1
Chemical homeostasis	11	5.20E-06	9.25E-03	SLC17A7, MICU1, APP, PSEN1, KL, HMOX1, BCL2, VEGFA, TH, IL1B, PARK2
CC				
Synapse part	13	4.60E-10	5.87E-07	ACHE, TH, NF1, MECP2, PARK2, SIGMAR1, SYP, SLC17A7, APP, SLC17A6, PSEN1, GRIA1, MAPT
Neuron projection	15	1.09E-09	1.39E-06	TH, NF1, PARK2, SIGMAR1, SYP, SLC17A7, APP, HTR1A, SLC17A6, PNOC, APOD, PSEN1, GRIA1, MAPT, HTR7
Neuron part	16	4.99E-09	6.37E-06	TH, NF1, PARK2, SIGMAR1, SYP, SLC17A7, APP, HTR1A, SLC17A6, PNOC, PDE1B, APOD, PSEN1, GRIA1, MAPT, HTR7
Synapse	13	6.19E-09	7.90E-06	ACHE, TH, NF1, MECP2, PARK2, SIGMAR1, SYP, SLC17A7, APP, SLC17A6, PSEN1, GRIA1, MAPT
Presynapse	9	5.66E-08	7.23E-05	SYP, SLC17A7, APP, SLC17A6, PSEN1, GRIA1, NF1, TH, PARK2
Dendrite	10	2.30E-07	2.94E-04	APP, HTR1A, PNOC, APOD, PSEN1, GRIA1, HTR7, MAPT, NF1, TH
Somatodendritic compartment	11	4.77E-07	6.09E-04	APP, HTR1A, PNOC, APOD, PDE1B, PSEN1, GRIA1, HTR7, MAPT, NF1, TH

Term	Count	P value	FDR	Genes
Axon	9	1.38E-06	1.76E-03	SYP, SLC17A7, APP, PNOC, PSEN1, GRIA1, MAPT, NF1, TH
Secretory vesicle	9	2.35E-06	3.00E-03	SYP, SLC17A7, APP, SLC17A6, GRIA1, VEGFA, TH, IL1B, TRH
MF				
Protein domain specific binding	10	7.72E-07	1.04E-03	SYP, APP, PSEN1, GRIA1, MAPT, BCL2, TH, MECP2, IL1B, PARK2

Table 3. GO analysis for the genes related to learning disorders.

Terms	Count	P value	Genes
KEGG			
Nicotine addiction	3	0.0047	SLC17A7, SLC17A6, GRIA1
Alzheimer's disease	4	0.0088	APP, PSEN1, MAPT, IL1B
Retrograde endocannabinoid signalling	3	0.0278	SLC17A7, SLC17A6, GRIA1
Serotonergic synapse	3	0.0331	APP, HTR1A, HTR7
Glutamatergic synapse	3	0.0348	SLC17A7, SLC17A6, GRIA1
WikiPathways			
SIDS susceptibility pathways	6	2.83E-05	MECP2, IL1RN, TH, IL1B, HTR1A, VEGFA
Integrated pancreatic cancer pathway	5	0.0008	APP, ACHE, BCL2, MAPT, VEGFA
Monoamine transport	3	0.0003	ACHE, TH, IL1B
Synaptic vesicle pathway	3	0.0011	SLC17A6, SLC17A7, SYP
Alzheimer's disease	4	0.0011	APP, IL1B, PSEN1, MAPT
Mecp2 and associated Rett syndrome	3	0.0009	GRIA1, MECP2, NF1
Overview of nanoparticle effects	2	0.0028	BCL2, HMOX1
Reactome			
Organic anion transporters	2	0.0215	SLC17A7, SLC17A6
Serotonin receptors	2	0.0321	HTR1A, HTR7
TRAF6-mediated NF-kB activation	2	0.0631	APP, RNF135
Interleukin-1 signalling	2	0.0932	IL1RN, IL1B
Biocart			
Generation of amyloid b-peptide by PS1	2	0.0427	APP, PSEN1
Deregulation of CDK5 in Alzheimer's Disease	2	0.0427	APP, MAPT

Table 4. Pathway analysis for the genes related to learning disorders.

Only one module was found for LD (**Figure 2: LD**). In this module, HTR1A, MAPT, TH, PARK2 and TRH were interacted by physical interactions, co-expression, predicted, pathway, co-localization, genetic interactions and shared protein domains. PARK2 is known to play a role in neurological development or function and when disturbed can account for LD [38, 39]. TH links PARK2 by sharing the same pathway [40], in which HOXA4 could co-express with TRHR [41], which could co-express with MAPT [42]. Serotonin gene (HTR1A) is also involved in this module, which is consistent with the serotonergic synapse and serotonin receptors pathway in KEGG and Reactome, respectively.

4.3. Schizophrenia

A total of 149 genes related to Sch were found to be BPA bi-interacted. Significant BPs included those found in LD such as behaviour, learning or memory, cognition, synaptic signalling related and cell-cell signalling related. Synaptic transmission-related, cell communication-related and phosphorus metabolic processes were also found (**Table 5**). Like LD, the genes participate in synapse, presynapse, dendrite, somatodendritic compartment and axon cellular components. Other CCs include cell body, intrinsic or integral component of plasma membrane, synaptic membrane and plasma membrane region. Unlike LD with little significant MFs found, Sch showed many significant MFs including the activity of signal transducer, neurotransmitter receptor, transmembrane-signalling receptor, molecular transducer, glutamate receptor and dopamine neurotransmitter receptor, dopamine or catecholamine binding. The same as LD, WikiPathways found that BPA could be linked to Sch through Alzheimer's disease, monoamine transport and SIDS susceptibility pathways (**Table 6**). The KEGG pathways such as neuroactive ligand-receptor interaction, cocaine addiction, dopaminergic synapse, cAMP signalling pathway and calcium-signalling pathway were also found to be significant. Reactome pathways included transmission across chemical synapse, amine ligand-binding receptors, neuronal system and signalling by GPCR, PDGF, FGFR4, FGFR3, FGFR1 or EGFR.

Five molecular modules were found for Sch (**Figure 3**). In module 1, 24 genes were connected by predicted, co-expression, physical interaction, co-localization, shared protein domains and pathway and genetic interactions. Almost all these genes showed co-expression [43, 44] and genetic interactions [45]. Except these 24 genes, GRID2, GRIK3 and GRIK4 might also be influenced by BPA because of their shared protein domains with GRIK2, GRIK5, GRIN2D, GRM2 and GRM3 and genetic interactions. KCNJ12 might also be interacted by BPA because of predicted, co-expression, genetic interactions and physical interactions. KCNJ12 has been reported may involve in the candidate pathway of Sch [46]. IL6, HP, AKT1, GSK3B, TNF, PIK3CB, and TP53 are composites of module 2. AKT/GSK3 pathway in which AKT1 and GSK3B has been reportedly associated in Sch [47]. TP53, as a key element in maintaining genomic stability and cell apoptosis and having been evidently proved a Sch susceptibility gene, linked TNF, AKT1 and GSK3B by direct co-expression, physical interactions and genetic interactions. Other genes such as AKT2 and DVL1 in this module might also interact with BPA because of the co-expression of AKT2 and PIK3CB [37], and DVL1 and AKT1 [48]. In module 3, SLC6A3, GAD1, COMT and RELN were involved through physical interaction, co-expression, predicted, pathway, co-localization and shared protein domains. LRPAP1, ITGB1, DAB1, PAFAH1B3,

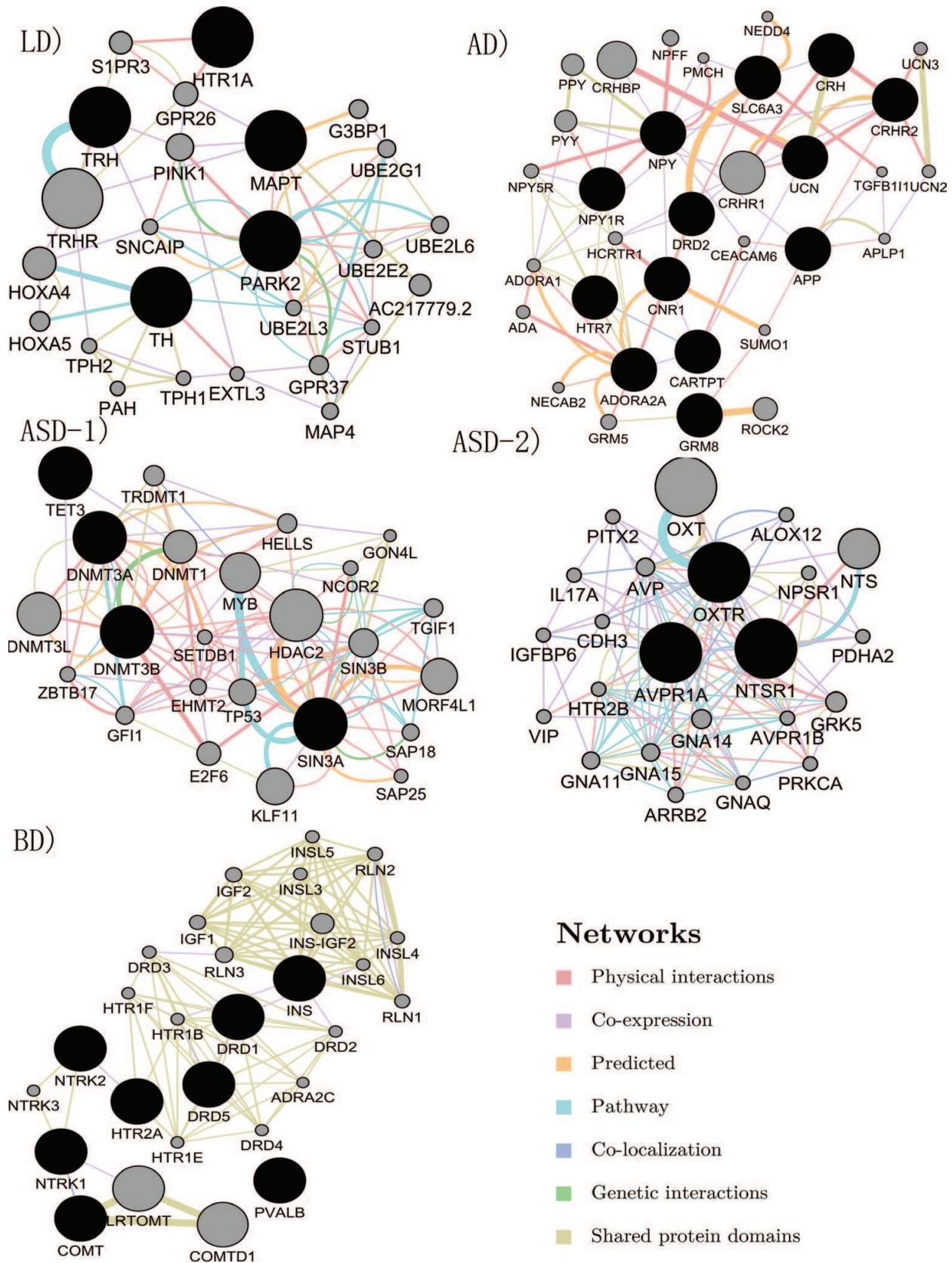


Figure 2. Networks for the genes in the PPI MCODE molecular modules for LD, ASD, AD and BD.

Term	Count	P value	FDR	Genes
BP				
Synaptic signalling	44	2.29E-27	4.33E-24	DRD1, CPLX2, CCL2, CPLX1, SLC6A1, DRD3, GABRB2, GRIK2, DRD2, SLC6A3, SLC6A4, DRD4, GRIK5, OXTR, TAC1, DTNBP1, AKT1, SYP, PLCL2, GAD2, HRH1, GRIN2B, APOE, GRIN2D, CNR1, SYN2, CAMK2B, GAD1, DLG1, GABRD, NOS1, NRXN1, NTSR1, LAMA2, GRM3, GRM2, GSK3A, HTR7, GSK3B, NTRK1, HTR6, RELN, NRGN, HTR2A
Anterograde Trans-synaptic signalling	44	2.29E-27	4.33E-24	DRD1, CPLX2, CCL2, CPLX1, SLC6A1, DRD3, GABRB2, GRIK2, DRD2, SLC6A3, SLC6A4, DRD4, GRIK5, OXTR, TAC1, DTNBP1, AKT1, SYP, PLCL2, GAD2, HRH1, GRIN2B, APOE, GRIN2D, CNR1, SYN2, CAMK2B, GAD1, DLG1, GABRD, NOS1, NRXN1, NTSR1, LAMA2, GRM3, GRM2, GSK3A, HTR7, GSK3B, NTRK1, HTR6, RELN, NRGN, HTR2A
Trans-synaptic signalling	44	2.29E-27	4.33E-24	DRD1, CPLX2, CCL2, CPLX1, SLC6A1, DRD3, GABRB2, GRIK2, DRD2, SLC6A3, SLC6A4, DRD4, GRIK5, OXTR, TAC1, DTNBP1, AKT1, SYP, PLCL2, GAD2, HRH1, GRIN2B, APOE, GRIN2D, CNR1, SYN2, CAMK2B, GAD1, DLG1, GABRD, NOS1, NRXN1, NTSR1, LAMA2, GRM3, GRM2, GSK3A, HTR7, GSK3B, NTRK1, HTR6, RELN, NRGN, HTR2A
Chemical synaptic transmission	44	2.29E-27	4.33E-24	DRD1, CPLX2, CCL2, CPLX1, SLC6A1, DRD3, GABRB2, GRIK2, DRD2, SLC6A3, SLC6A4, DRD4, GRIK5, OXTR, TAC1, DTNBP1, AKT1, SYP, PLCL2, GAD2, HRH1, GRIN2B, APOE, GRIN2D, CNR1, SYN2, CAMK2B, GAD1, DLG1, GABRD, NOS1, NRXN1, NTSR1, LAMA2, GRM3, GRM2, GSK3A, HTR7, GSK3B, NTRK1, HTR6, RELN, NRGN, HTR2A
Cell-cell signalling	62	3.34E-26	6.31E-23	SLC6A1, FAM3D, GRIK2, GABRB2, SLC6A3, SLC6A4, GRIK5, VIPR2, LGR4, AKT1, SYP, BDNF, GRIN2B, APOE, GRIN2D, IL1B, PLCB1, HCAR2, DISC1, DLG1, AVP, MAGI2, NRXN1, NTSR1, GRM3, GRM2, HTR7, HTR6, RELN, NRGN, FGFR1, DRD1, CPLX2, CCL2, CPLX1, TNF, DRD3, HLA-DRB1, DRD2, DRD4, OXTR, TAC1, DTNBP1, PLCL2, HRH1, GAD2, CNR1, SYN2, CAMK2B, VPS35, GAD1, GABRD, DIXDC1, IL6, NOS1, NTF3, LAMA2, LRP1, GSK3A, NTRK1, GSK3B, HTR2A
Modulation of synaptic transmission	31	6.10E-24	1.15E-20	CPLX2, DRD1, CCL2, DRD3, SLC6A1, GRIK2, DRD2, DRD4, SLC6A4, GRIK5, TAC1, OXTR, DTNBP1, SYP, PLCL2, HRH1, APOE, CNR1, CAMK2B, NOS1, NTF3, NRXN1, NTSR1, LAMA2, GRM3, GRM2, GSK3B, NTRK1, RELN, NRGN, HTR2A
Regulation of cell communication	72	2.46E-17	4.64E-14	SLC6A1, FAM3D, GRIK2, SLC6A4, GRIK5, LGR4, SYP, AKT1, BDNF, PAK2, APOE, IL1B, PLCB1, NRG1, HCAR2, DISC1, ALS2CL, DLG1, AVP, MAGI2, PIK3CB, TP53, NRXN1, IL6R, NTSR1, GRM3, GRM2, HTR6, RELN, NRGN, ADAMTS3, FGFR1, DRD1, CPLX2, CCL2, TNF, DRD3, HLA-DRB1, DRD2, DRD4, COL3A1, PML, TAC1, OXTR, NPRL2, DTNBP1, PLCL2, HRH1, RGS12, RB1CC1, CNR1, CAMK2B, VPS35, THBS1, CHD4, DIXDC1, IL6, NOS1, NTF3, PHB, RTN4R, CHI3L1, KDR, LAMA2, LRP1, GSK3A, NTRK1, RGS4, GSK3B, MTOR, RGS9, HTR2A

Term	Count	P value	FDR	Genes
Regulation of signalling	72	5.99E-17	2.11E-13	SLC6A1, FAM3D, GRIK2, SLC6A4, GRIK5, LGR4, SYP, AKT1, BDNF, PAK2, APOE, IL1B, PLCB1, NRG1, HCAR2, DISC1, ALS2CL, DLG1, AVP, MAGI2, PIK3CB, TP53, NRXN1, IL6R, NTSR1, GRM3, GRM2, HTR6, RELN, NRGN, ADAMTS3, FGFR1, DRD1, CPLX2, CCL2, TNF, DRD3, HLA-DRB1, DRD2, DRD4, COL3A1, PML, TAC1, OXTR, NPRL2, DTNBP1, PLCL2, HRH1, RGS12, RB1CC1, CNR1, CAMK2B, VPS35, THBS1, CHD4, DIXDC1, IL6, NOS1, NTF3, PHB, RTN4R, CHI3L1, KDR, LAMA2, LRP1, GSK3A, NTRK1, RGS4, GSK3B, MTOR, RGS9, HTR2A
Single-organism behaviour	27	1.71E-15	3.14E-12	DRD1, DRD3, SLC6A1, DRD2, GRIK2, DRD4, SLC6A4, TAC1, OXTR, COMT, HRH1, GRIN2B, GRIN2D, CNR1, IL1B, THBS1, PLCB1, AVP, IL6, NOS1, NRXN1, NTSR1, NTRK1, RELN, MTOR, NRGN, HTR2A
Positive regulation of cell communication	48	9.61E-15	1.82E-11	FGFR1, DRD1, CCL2, TNF, DRD3, HLA-DRB1, GRIK2, DRD2, DRD4, COL3A1, PML, OXTR, TAC1, DTNBP1, LGR4, AKT1, BDNF, PAK2, RB1CC1, IL1B, VPS35, NRG1, PLCB1, THBS1, HCAR2, DISC1, DIXDC1, IL6, NOS1, NTF3, PIK3CB, PHB, TP53, CHI3L1, IL6R, NRXN1, NTSR1, KDR, LAMA2, GSK3A, NTRK1, GSK3B, HTR6, RELN, NRGN, MTOR, ADAMTS3, HTR2A
Positive regulation of signalling	48	1.10E-14	2.08E-11	FGFR1, DRD1, CCL2, TNF, DRD3, HLA-DRB1, GRIK2, DRD2, DRD4, COL3A1, PML, OXTR, TAC1, DTNBP1, LGR4, AKT1, BDNF, PAK2, RB1CC1, IL1B, VPS35, NRG1, PLCB1, THBS1, HCAR2, DISC1, DIXDC1, IL6, NOS1, NTF3, PIK3CB, PHB, TP53, CHI3L1, IL6R, NRXN1, NTSR1, KDR, LAMA2, GSK3A, NTRK1, GSK3B, HTR6, RELN, NRGN, MTOR, ADAMTS3, HTR2A
Learning or memory	21	1.10E-14	2.08E-11	DRD1, DRD3, SLC6A1, DRD2, DRD4, SLC6A4, TAC1, OXTR, COMT, NRXN1, NTSR1, HRH1, GRIN2B, CNR1, NTRK1, IL1B, RELN, NRGN, MTOR, PLCB1, HTR2A
Behaviour	30	1.11E-14	2.10E-11	DRD1, DRD3, SLC6A1, DRD2, GRIK2, SLC6A3, DRD4, SLC6A4, TAC1, OXTR, COMT, HRH1, GRIN2B, GRIN2D, CNR1, IL1B, THBS1, PLCB1, NRG1, IL6, AVP, NOS1, TP53, NRXN1, NTSR1, NTRK1, RELN, MTOR, NRGN, HTR2A
Cognition	22	1.22E-14	2.31E-11	DRD1, DRD3, SLC6A1, DRD2, DRD4, SLC6A4, TAC1, OXTR, COMT, NRXN1, NTSR1, DGCR2, HRH1, GRIN2B, CNR1, NTRK1, IL1B, RELN, NRGN, MTOR, PLCB1, HTR2A
Neuron-neuron synaptic transmission	16	1.33E-14	2.52E-11	DRD1, DRD3, SLC6A1, DRD2, GRIK2, GABRB2, SLC6A3, DRD4, SLC6A4, GRIK5, TAC1, OXTR, NRXN1, NTRK1, RELN, HTR2A
Response to alkaloid	18	1.48E-14	2.79E-11	IL6, AVP, DRD1, TNF, NOS1, SLC6A1, ND4, DRD3, DRD2, SLC6A3, DRD4, TAC1, OXTR, CNR1, NTRK1, IL1B, MTOR, HTR2A
Positive regulation of synaptic transmission	16	8.02E-14	1.52E-10	DRD1, CCL2, NOS1, DRD2, GRIK2, DRD4, TAC1, OXTR, NRXN1, NTSR1, DTNBP1, LAMA2, NTRK1, GSK3B, RELN, NRGN
Regulation of phosphate metabolic process	47	2.16E-13	4.07E-10	FGFR1, DRD1, CCL2, NRG3, TNF, ADCY7, DRD3, GRIK2, DRD2, DRD4, PML, NPRL2, VIPR2, DTNBP1, PLCL2, AKT1, HRH1, PAK2, APOE, RB1CC1, IL1B, NRG1, PLCB1, THBS1, DLG1, IL6, AVP, MAGI2, NOS1, NTF3, PIK3CB, PHB, TP53, RTN4R, CHI3L1, IL6R, NTSR1, KDR, GRM3, GRM2, GSK3A, RGS4, NTRK1, GSK3B, RELN, MTOR, HTR2A

Term	Count	P value	FDR	Genes
Regulation of phosphorus metabolic process	47	2.20E-13	4.16E-10	FGFR1, DRD1, CCL2, NRG3, TNF, ADCY7, DRD3, GRIK2, DRD2, DRD4, PML, NPRL2, VIPR2, DTNBP1, PLCL2, AKT1, HRH1, PAK2, APOE, RB1CC1, IL1B, NRG1, PLCB1, THBS1, DLG1, IL6, AVP, MAGI2, NOS1, NTF3, PIK3CB, PHB, TP53, RTN4R, CHI3L1, IL6R, NTSR1, KDR, GRM3, GRM2, GSK3A, RGS4, NTRK1, GSK3B, RELN, MTOR, HTR2A
Regulation of transport	49	8.08E-13	1.53E-09	FGFR1, DRD1, CPLX2, CCL2, CPLX1, TNF, SLC6A1, DRD3, HLA-DRB1, FAM3D, DRD2, DRD4, GRIK5, PML, OXTR, TAC1, COMT, EDEM2, DTNBP1, LGR4, AKT1, APOE, CNR1, PDE4B, IL1B, CAMK2B, VPS35, NRG1, THBS1, HCAR2, DLG1, IL6, AVP, MAGI2, NOS1, NTF3, PIK3CB, MAOB, TP53, AHI1, NRXN1, NTSR1, PCM1, LRP1, GSK3A, GSK3B, RELN, MTOR, HTR2A
CC				
Neuron projection	48	3.23E-21	4.54E-18	DRD1, CPLX2, CCL2, CPLX1, SLC6A1, GRIK2, DRD2, SLC6A3, SLC6A4, DRD4, GRIK5, TAC1, COMT, DTNBP1, HNRNPA3, SYP, GAD2, MTHFR, RGS12, GRIN2B, PVALB, APOE, CNR1, PDE4B, CAMK2B, NRG1, DISC1, DLG1, AVP, NOS1, MAGI2, RTN4R, NRXN1, NTSR1, LAMA2, GRM3, GRM2, LRP1, HTR7, NTRK1, GSK3B, HTR6, RELN, NRGN, MTOR, TPH1, KPNA1, HTR2A
Synapse	40	6.12E-19	8.61E-16	CPLX2, DRD1, CCL2, CPLX1, GABRB2, GRIK2, DRD2, SLC6A3, DRD4, SLC6A4, GRIK5, COMT, DTNBP1, AKT1, SYP, GAD2, MTHFR, RGS12, GRIN2B, PVALB, GRIN2D, PDE4B, SYN2, CAMK2B, NRG1, GAD1, DISC1, DLG1, GABRD, NOS1, MAGI2, GABRA6, NRXN1, NTSR1, LAMA2, GRM3, GRM2, GSK3A, GSK3B, NRGN
Synapse part	36	1.32E-18	1.86E-15	CPLX2, DRD1, CPLX1, GABRB2, DRD2, GRIK2, SLC6A3, DRD4, SLC6A4, GRIK5, COMT, DTNBP1, SYP, AKT1, GAD2, GRIN2B, PVALB, GRIN2D, PDE4B, SYN2, CAMK2B, GAD1, DISC1, DLG1, GABRD, NOS1, MAGI2, GABRA6, NRXN1, NTSR1, LAMA2, GRM3, GRM2, GSK3A, GSK3B, NRGN
Neuron part	51	3.07E-18	4.33E-15	SLC6A1, GRIK2, SLC6A3, SLC6A4, GRIK5, SYP, GRIN2B, PVALB, APOE, PDE4B, NRG1, DISC1, DLG1, AVP, MAGI2, NRXN1, NTSR1, GRM3, GRM2, HTR7, HTR6, RELN, NRGN, TPH1, KPNA1, CPLX2, DRD1, CPLX1, CCL2, DRD2, DRD4, TAC1, COMT, DTNBP1, HNRNPA3, GAD2, MTHFR, RGS12, CNR1, SYN2, CAMK2B, GAD1, NOS1, RTN4R, LAMA2, LRP1, NTRK1, GSK3B, RGS9, MTOR, HTR2A
Dendrite	32	1.49E-17	2.10E-14	CPLX2, DRD1, CCL2, CPLX1, GRIK2, DRD2, DRD4, GRIK5, COMT, DTNBP1, RGS12, APOE, PDE4B, CAMK2B, NRG1, AVP, NOS1, MAGI2, NTSR1, LAMA2, GRM3, GRM2, LRP1, GSK3B, NTRK1, HTR7, HTR6, RELN, NRGN, MTOR, KPNA1, HTR2A
Somatodendritic compartment	37	2.66E-17	3.74E-14	DRD1, CPLX2, CCL2, CPLX1, GRIK2, DRD2, SLC6A3, DRD4, GRIK5, TAC1, COMT, DTNBP1, RGS12, PVALB, APOE, PDE4B, CAMK2B, NRG1, AVP, NOS1, MAGI2, RTN4R, NRXN1, NTSR1, LAMA2, GRM3, GRM2, LRP1, HTR7, GSK3B, NTRK1, HTR6, RELN, NRGN, MTOR, KPNA1, HTR2A

Term	Count	P value	FDR	Genes
Axon	29	7.56E-16	1.10E-12	CPLX2, DRD1, CCL2, CPLX1, SLC6A1, DRD2, GRIK2, SLC6A3, DRD4, GRIK5, TAC1, COMT, DTNBP1, SYP, GAD2, PVALB, CNR1, NRG1, DISC1, DLG1, RTN4R, NRXN1, NTSR1, GRM3, GRM2, GSK3B, NTRK1, NRGN, HTR2A
Postsynapse	25	4.28E-14	6.02E-11	GABRD, DRD1, NOS1, MAGI2, GABRB2, GRIK2, DRD2, GABRA6, DRD4, GRIK5, COMT, NTSR1, DTNBP1, AKT1, LAMA2, GRM3, GRIN2B, GSK3A, GRIN2D, GSK3B, PDE4B, CAMK2B, NRGN, DISC1, DLG1
Cell body	26	2.58E-11	3.63E-08	CPLX2, DRD1, CPLX1, CCL2, DRD2, GRIK2, SLC6A3, DRD4, GRIK5, TAC1, COMT, RGS12, PVALB, APOE, CAMK2B, NRG1, DISC1, RTN4R, NRXN1, NTSR1, LRP1, NTRK1, GSK3B, MTOR, NRGN, HTR2A
Presynapse	20	2.97E-11	4.19E-08	CPLX2, CPLX1, DRD2, GRIK2, SLC6A3, DRD4, SLC6A4, GRIK5, NRXN1, NTSR1, DTNBP1, SYP, GAD2, GRM3, GRM2, PVALB, PDE4B, SYN2, GAD1, DISC1
Intrinsic component of plasma membrane	45	1.08E-10	1.52E-07	FGFR1, DRD1, NRG3, TNF, SLC6A1, DRD3, HLA-DRB1, GABRB2, GRIK2, DRD2, PLXNA2, SLC6A3, SLC6A4, DRD4, GRIK5, OXTR, VIPR2, LGR4, HRH1, GRIN2B, GRIN2D, CNR1, NRG1, DLG1, GABRD, IL6, GABRA6, PHB, MET, NTNG1, RTN4R, IL6R, NRXN1, NTSR1, TSPAN18, KDR, GRM3, GRM2, LRP1, SLC26A7, HTR7, NTRK1, HTR6, CP, HTR2A
Integral component of plasma membrane	43	4.17E-10	5.87E-07	FGFR1, DRD1, TNF, NRG3, SLC6A1, HLA-DRB1, DRD3, GABRB2, GRIK2, DRD2, PLXNA2, SLC6A3, SLC6A4, DRD4, GRIK5, OXTR, VIPR2, LGR4, HRH1, GRIN2B, GRIN2D, CNR1, NRG1, DLG1, GABRD, IL6, GABRA6, PHB, MET, RTN4R, IL6R, NRXN1, NTSR1, TSPAN18, KDR, GRM3, GRM2, LRP1, SLC26A7, HTR7, NTRK1, HTR6, HTR2A
Neuronal cell body	23	4.45E-10	6.27E-07	DRD1, CPLX2, CCL2, CPLX1, GRIK2, DRD2, SLC6A3, DRD4, GRIK5, RTN4R, TAC1, NRXN1, NTSR1, LRP1, RGS12, PVALB, APOE, GSK3B, NTRK1, CAMK2B, NRGN, MTOR, HTR2A
Axon part	16	4.61E-09	6.49E-06	DRD1, CPLX2, CCL2, CPLX1, DRD2, GRIK2, DRD4, RTN4R, GRIK5, NRXN1, NTSR1, DTNBP1, SYP, PVALB, NRG1, DLG1
Dendritic spine	12	2.08E-08	2.93E-05	LAMA2, DRD1, GRM3, NOS1, DRD2, GSK3B, PDE4B, DRD4, COMT, NRGN, NTSR1, DTNBP1
Neuron spine	12	2.46E-08	3.47E-05	LAMA2, DRD1, GRM3, NOS1, DRD2, GSK3B, PDE4B, DRD4, COMT, NRGN, NTSR1, DTNBP1
Synaptic membrane	16	4.23E-08	5.96E-05	GABRD, GRIK2, GABRB2, GABRA6, GRIK5, NRXN1, COMT, DTNBP1, SYP, GRM3, GAD2, GRM2, GRIN2B, GRIN2D, DISC1, DLG1
Excitatory synapse	13	8.32E-08	1.17E-04	SYP, GRM3, MAGI2, NOS1, DRD2, GRIK2, PDE4B, GRIK5, CAMK2B, NRGN, DTNBP1, DISC1, DLG1
Plasma membrane region	28	1.94E-07	2.73E-04	DRD1, DRD2, GRIK2, GABRB2, SLC6A3, GRIK5, OXTR, COMT, DTNBP1, SYP, GAD2, GRIN2B, GRIN2D, NRG1, DISC1, DLG1, GABRD, NOS1, GABRA6, MET, GIF, NRXN1, IL6R, GRM3, GRM2, SLC26A7, RGS9, HTR2A

Term	Count	P value	FDR	Genes
Axon terminus	11	2.90E-07	4.08E-04	SYP, DRD1, CPLX2, CPLX1, CCL2, PVALB, DRD2, GRIK2, DRD4, GRIK5, NTSR1
MF				
Signal transducer activity	46	2.55E-11	3.79E-08	FGFR1, DRD1, NRG3, DRD3, HLA-DRB1, GABRB2, GRIK2, DRD2, PLXNA2, ADGRF4, DRD4, GRIK5, OXTR, NR3C1, VIPR2, LGR4, PLCL2, TAAR6, HRH1, RGS12, GRIN2B, PAK2, GRIN2D, CNR1, PLCB1, NRG1, HCAR2, GABRD, AVP, MAGI2, IL2RA, GABRA6, MET, RTN4R, IL6R, NRXN1, NTSR1, KDR, GPR153, GRM3, GRM2, HTR7, NTRK1, HTR6, RGS9, HTR2A
Neurotransmitter receptor activity	12	8.07E-10	1.20E-06	DRD1, GRIN2B, DRD3, DRD2, GRIK2, HTR7, GRIN2D, GABRA6, HTR6, DRD4, GRIK5, HTR2A
Transmembrane receptor activity	37	2.01E-09	2.98E-06	FGFR1, DRD1, HLA-DRB1, DRD3, GABRB2, GRIK2, PLXNA2, DRD2, ADGRF4, DRD4, GRIK5, OXTR, VIPR2, LGR4, TAAR6, HRH1, GRIN2B, GRIN2D, CNR1, HCAR2, DLG1, GABRD, IL2RA, GABRA6, MET, RTN4R, IL6R, NRXN1, NTSR1, KDR, GPR153, GRM3, GRM2, NTRK1, HTR7, HTR6, HTR2A
Transmembrane signalling receptor activity	36	2.61E-09	3.87E-06	FGFR1, DRD1, HLA-DRB1, DRD3, GABRB2, GRIK2, PLXNA2, DRD2, ADGRF4, DRD4, GRIK5, OXTR, VIPR2, LGR4, HRH1, TAAR6, GRIN2B, GRIN2D, CNR1, HCAR2, GABRD, IL2RA, GABRA6, MET, RTN4R, IL6R, NRXN1, NTSR1, KDR, GPR153, GRM3, GRM2, NTRK1, HTR7, HTR6, HTR2A
Signalling receptor activity	37	5.46E-09	8.09E-06	FGFR1, DRD1, HLA-DRB1, DRD3, GABRB2, GRIK2, PLXNA2, DRD2, ADGRF4, DRD4, GRIK5, OXTR, NR3C1, VIPR2, LGR4, HRH1, TAAR6, GRIN2B, GRIN2D, CNR1, HCAR2, GABRD, IL2RA, GABRA6, MET, RTN4R, IL6R, NRXN1, NTSR1, KDR, GPR153, GRM3, GRM2, NTRK1, HTR7, HTR6, HTR2A
Molecular transducer activity	39	4.31E-08	6.38E-05	FGFR1, DRD1, HLA-DRB1, DRD3, GABRB2, GRIK2, PLXNA2, DRD2, ADGRF4, DRD4, GRIK5, OXTR, NR3C1, VIPR2, LGR4, TAAR6, HRH1, GRIN2B, GRIN2D, CNR1, HCAR2, DLG1, GABRD, IL2RA, GABRA6, MET, RTN4R, IL6R, NRXN1, NTSR1, KDR, GPR153, GRM3, LRP1, GRM2, NTRK1, HTR7, HTR6, HTR2A
Receptor activity	39	4.31E-08	6.38E-05	FGFR1, DRD1, HLA-DRB1, DRD3, GABRB2, GRIK2, PLXNA2, DRD2, ADGRF4, DRD4, GRIK5, OXTR, NR3C1, VIPR2, LGR4, TAAR6, HRH1, GRIN2B, GRIN2D, CNR1, HCAR2, DLG1, GABRD, IL2RA, GABRA6, MET, RTN4R, IL6R, NRXN1, NTSR1, KDR, GPR153, GRM3, LRP1, GRM2, NTRK1, HTR7, HTR6, HTR2A
Receptor binding	34	4.69E-07	6.95E-04	CCL2, NRG3, TNF, FAM3D, DRD3, DRD2, SLC6A3, COL3A1, TAC1, PLCL2, BDNF, APOE, TRAK1, IL1B, VPS35, DAO, NRG1, THBS1, DLG1, IL6, AVP, MAGI2, NTF3, PHB, TP53, IL6R, NRXN1, KDR, NRIP1, LAMA2, LAMA1, LRP1, NTRK1, RELN
Dopamine binding	5	1.93E-06	2.85E-03	DRD1, DRD3, DRD2, SLC6A3, DRD4
Glutamate receptor activity	6	3.67E-06	5.44E-03	GRM3, GRM2, GRIN2B, GRIK2, GRIN2D, GRIK5

Term	Count	P value	FDR	Genes
Drug binding	9	8.84E-06	1.31E-02	DRD1, IL2RA, DRD3, DRD2, SLC6A3, CNR1, SLC6A4, DRD4, HTR2A
Catecholamine binding	5	1.03E-05	1.52E-02	DRD1, DRD3, DRD2, SLC6A3, DRD4
Dopamine neurotransmitter receptor activity	4	2.39E-05	3.54E-02	DRD1, DRD3, DRD2, DRD4

Table 5. GO analysis for the genes related to schizophrenia.

Term	Count	P value	Genes
KEGG			
Neuroactive ligand-receptor interaction	23	2.33E-08	GABRD, DRD1, DRD3, GABRB2, GRIK2, DRD2, GABRA6, DRD4, GRIK5, OXTR, NR3C1, NTSR1, VIPR2, HRH1, GRM3, TAAR6, GRM2, GRIN2B, GRIN2D, CNR1, HTR7, HTR6, HTR2A
Cocaine addiction	10	2.35E-05	DRD1, GRM3, BDNF, GRM2, GRIN2B, DRD2, SLC6A3, GRIN2D, MAOB, RGS9
Dopaminergic synapse	13	2.28E-04	DRD1, DRD3, DRD2, SLC6A3, MAOB, DRD4, COMT, AKT1, GRIN2B, GSK3A, GSK3B, CAMK2B, PLCB1
cAMP signalling pathway	14	4.17E-03	DRD1, ADCY7, PIK3CB, DRD2, OXTR, VIPR2, AKT1, BDNF, GRIN2B, GRIN2D, PDE4B, HTR6, CAMK2B, HCAR2
Calcium signalling pathway	12	4.66E-02	DRD1, HRH1, NOS1, ADCY7, HTR7, GRIN2D, HTR6, OXTR, CAMK2B, NTSR1, PLCB1, HTR2A
WikiPathways			
Monoamine GPCRs	8	3.30E-05	HTR6, HRH1, HTR7, HTR2A, DRD1, DRD2, DRD3, DRD4
Circadian rhythm-related genes	15	9.90E-05	NTRK1, GSK3B, TPH1, PML, SLC6A4, IL6, HTR7, NRIP1, AVP, DRD1, DRD2, TP53, DRD3, LGR4, DRD4
SIDS susceptibility pathways	12	8.30E-04	IL6, TPH1, VIPR2, BDNF, IL1B, HTR2A, AVP, TAC1, NR3C1, TNF, IL6R, SLC6A4
Spinal cord injury	10	9.54E-04	RTN4R, IL6, BDNF, IL1B, PLXNA2, CCL2, NOS1, TP53, TNF, RTN4
Alzheimer's disease	10	9.54E-04	GSK3B, LRP1, IL1B, APOE, NOS1, PLCB1, TP53, TNF, GRIN2B, GRIN2D
Vitamin B12 metabolism	7	9.54E-04	IL6, GIF, IL1B, MTHFR, CCL2, APOE, TNF
Monoamine transport	6	8.30E-04	IL1B, NOS1, SLC6A1, TNF, SLC6A3, SLC6A4
Hypothetical network for drug addiction	6	8.30E-04	CAMK2B, DRD1, DRD2, GRIN2B, DRD4, GRIN2D
Reactome			
Transmission across chemical synapses	17	7.71E-07	CAMK2B, GABRB2, GABRA6, GRIK5, GAD1, GAD2, GRIK2, SLC6A1, COMT, ADCY7, GRIN2B, SYN2, CPLX1, SLC6A3, GRIN2D, DLG1, PLCB1

Term	Count	P value	Genes
Amine ligand-binding receptors	9	2.36E-06	HTR6, HRH1, HTR7, TAAR6, HTR2A, DRD1, DRD2, DRD3, DRD4
Neuronal system	17	3.63E-05	CAMK2B, GABRB2, GABRA6, GRIK5, GAD1, GAD2, GRIK2, SLC6A1, COMT, ADCY7, GRIN2B, SYN2, CPLX1, SLC6A3, GRIN2D, DLG1, PLCB1
Signalling by GPCR	35	2.07E-04	CAMK2B, OXTR, VIPR2, PIK3CB, HTR2A, PHB, ADCY7, HCAR2, RGS4, GRM3, GRM2, HTR6, HRH1, HTR7, CNR1, PDE4B, AKT1, CCL2, DRD1, TAC1, DRD2, RGS9, DRD3, DRD4, NTSR1, TAAR6, NRG1, GRIN2B, GRIN2D, NRG3, IL2RA, RGS12, AVP, PLCB1, FGFR1
Signal Transduction	53	2.07E-04	GSK3B, GSK3A, OXTR, VIPR2, TRRAP, HTR2A, PIK3CB, NR3C1, TNF, GRM3, RGS4, GRM2, HTR6, HTR7, KDR, PDE4B, AKT1, VPS35, IL6R, RGS9, TAAR6, NRG1, NRG3, AVP, PLCB1, TP53, CAMK2B, LRP1, PHB, ADCY7, THBS1, RTN4, HCAR2, HRH1, CNR1, CCL2, APOE, DRD1, DRD2, TAC1, DRD3, PAK2, DRD4, NTSR1, NTRK1, GRIN2B, MTOR, GRIN2D, IL6, IL2RA, RGS12, LGR4, FGFR1
Class A/1 (Rhodopsin-like receptors)	16	2.07E-04	OXTR, TAAR6, HTR2A, HCAR2, HTR6, HRH1, HTR7, CNR1, CCL2, AVP, DRD1, DRD2, TAC1, DRD3, NTSR1, DRD4
GPCR ligand binding	18	6.14E-04	OXTR, TAAR6, HTR2A, HCAR2, GRM3, GRM2, HTR6, HRH1, HTR7, CNR1, CCL2, DRD1, AVP, DRD2, TAC1, DRD3, DRD4, NTSR1
Signalling by PDGF	15	1.72E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, THBS1, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
Downstream signalling of activated FGFR4	14	1.72E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
Downstream signalling of activated FGFR3	14	1.72E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
Signalling by FGFR4	14	1.72E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
Downstream signalling of activated FGFR2	14	1.72E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
Signalling by FGFR3	14	1.72E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
Downstream signalling of activated FGFR1	14	1.72E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
NGF signalling via TRKA from the plasma membrane	15	1.72E-03	NTRK1, CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
Signalling by FGFR1	14	1.80E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
DAP12 signalling	14	2.09E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1
Downstream signal transduction	14	2.00E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1

Term	Count	P value	Genes
Neurotransmitter receptor ainding and downstream transmission in the postsynaptic cell	10	7.83E-04	CAMK2B, GABRB2, DLG1, GABRA6, GRIK5, GRIK2, PLCB1, ADCY7, GRIN2B, GRIN2D
Signalling by EGFR	14	2.51E-03	CAMK2B, GSK3B, GSK3A, NRG1, PHB, PIK3CB, ADCY7, GRIN2B, MTOR, GRIN2D, NRG3, IL2RA, AKT1, FGFR1

Table 6. Pathway analysis for the genes related to schizophrenia.

PAFAH1B2, VLDLR, MAP1B and SNCA might interact with BPA because of their involvement in the same pathway with RELN [40]. LRTOMT and COMTD1 might also be the candidate interacted genes with BPA because of their shared protein domains. In module 4, 10 genes are involved. Co-expression and physical interactions are the main interaction modes for these genes. HCRTR1, ZDHHC23, CLIC6 and MUC20 are the possible candidate genes influenced by BPA mainly because of their physical and genetic interactions. In module 5, TSPAN18, NKAPL and ZKSCAN4 were connected by physical interactions, co-expression, co-localization and shared protein domains. NKAP, ZSCAN9, ZSCAN16-related genes could also be the candidate interacted genes of BPA because of the shared protein domains or co-expression.

4.4. Autism spectrum disorders

We found 51 ASD genes that could biinteract with BPA. These genes are partly involved in the BPs such as organism development, system development, synapse organization, behaviour, learning or memory, regulation of synapse structure or activity, multicellular organismal process, nervous system development, membrane potential, cellular process and cell-cell signalling-related processes. Involved CC was synaptic membrane, and MFs included neuro-ligin family protein binding and chromatin binding. The KEGG pathways such as neuroactive ligand-receptor interaction and cocaine addiction were found as Sch. Like ID and LD, MECP2 and associated Rett syndrome (WikiPathways) was also found in ASD. PRC2 methylates histones and DNA, non-integrin membrane-ECM interactions, and gastrin-CREB-signalling pathway via PKC and MAPK were the main pathways found in Reactome.

Two molecular modules were found for ASD (**Figure 2:** ASD-1, ASD-2). In module 1, TET3, SIN3A, DNMT3A and DNMT3B were connected to each other by physical interactions, co-expression, predicted, pathway, co-localization, genetic interactions and shared protein domains. HDAC2 and MORF4L1 might be the candidate genes interacted with BPA because of their predicted interaction with SIN3A [24]. DNMT3L and MYB are another two main genes in this module because of their direct or indirect interactions with other genes. AVPR1A, OXTR and NTSR1 composite the module 2 through physical interactions, co-expression, pathway, co-localization and shared protein domains. OXT and NTS are another two main genes in this module; they share the same pathway with OXTR, NTSR1, AVPR1A and some other genes [40] and, thus, might be influenced by BPA.

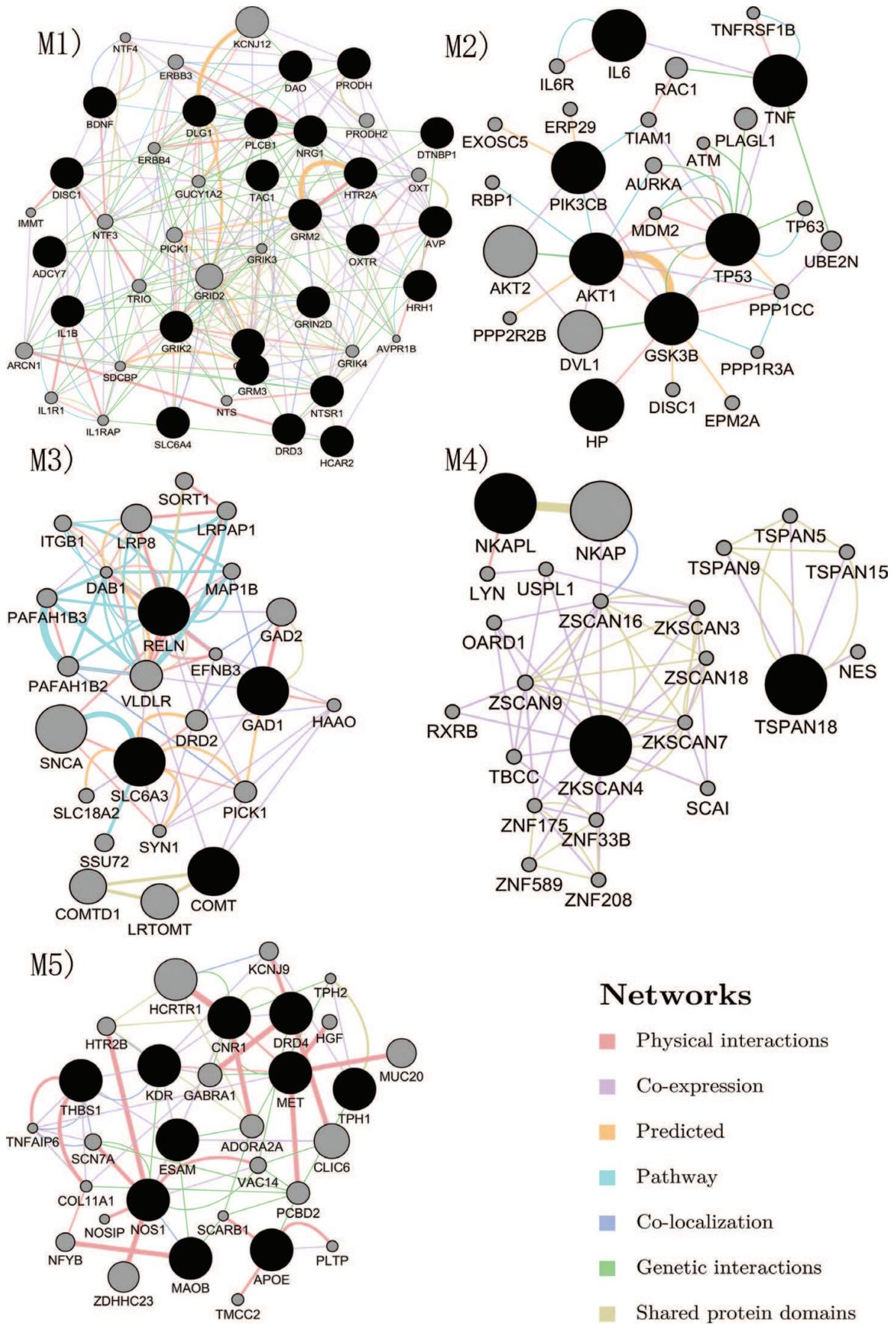


Figure 3. Networks for the genes in the PPI MCODE molecular modules for Sch.

4.5. Anxiety disorders

A total of 34 genes associated with AD were found bi-interacted with BPA. GO analysis for these genes indicated that behaviour, learning or memory, cognition, monoamine transport, chemical synaptic transmission, cell-cell signalling, anterograde trans-synaptic signalling and neurological system process were all significant BPs such as LD, Sch and ASD. Interestingly, blood circulation, circulatory system process and regulation of blood pressure were found significant for AD. Like ID, LD, Sch and ASD, significant CCs included neuron part, neuron projection, somatodendritic compartment, synapse part, axon, synapse, dendrite, cell body, presynapse and neuronal cell body. Significant MFs included receptor binding, neuropeptide hormone activity and G-protein-coupled receptor binding. The significant KEGG pathways were as those found in LD. Neuroactive ligand-receptor interaction, alcoholism, cAMP signalling pathway, serotonergic and dopaminergic synapse, Rap1 signalling pathway and retrograde endocannabinoid signalling are the potential KEGG pathways that might be influenced by BPA in AD. For WikiPathways, monoamine transport was again found related to BPA bi-interacted genes in AD. Other significant pathways included circadian rhythm-related genes, nicotine activity on dopaminergic neurons, corticotropin-releasing, GPCRs, cytosine methylation, myometrial relaxation and contraction pathways and estrogen-signalling pathway. In Reactome pathways, GPCR related, Class A/1, Class B/2, G alpha-related signalling events and peptide ligand-binding receptors were found possibly involved in the BPA-AD interactions.

Only one molecular module was found for AD, in which UCN, ADORA2A, CRH, NPS, CRHR2, NPY, NPY1R, APP, HTR7, CNR1, GRM8, SLC6A3, DRD2 and CARTPT were involved (**Figure 2: AD**). The interaction modes for these genes included predicted, physical interactions, shared protein domains, co-expression and co-localization. The genes in this module are all involved in neuroactive ligand-receptor interaction (KEGG pathway) which is consistent with the Reactome pathways of GPCR signalling and G alpha signalling events.

4.6. Bipolar disorder

A total of 39 genes were found bi-interacted with BPA for BD. The BPs, CCs and MFs were quite the same as AD. Neuroactive ligand-receptor interaction, dopaminergic synapse, calcium-signalling pathway, neurotrophin-signalling pathway, synaptic vesicle cycle, insulin secretion, morphine signalling pathway, MAPK signalling pathway, glutamatergic synapse and serotonergic synapse were found in KEGG pathways. Like LD and Sch, SIDS susceptibility pathways was also found significant for BD. GPCR-related pathways such as monoamine GPCRs in WikiPathways and GPCR ligand binding in Reactome were found to be involved in BPA-BD as in BPA-AD.

One molecular module was found for BD (**Figure 2: BD**), in which D1, NTRK1, DRD5, PVALB, NTRK2, HTR2A, COMT and INS were involved. Shared protein domains, co-localization and co-expression were the main interactions in this module. COMTD1 and LRTOMT might also be influenced by BPA because of their shared protein domains with COMT.

4.7. Other neurodevelopmental disorders

A total of 14 genes were found for bi-interacted BPA in DS. GO analysis indicated cellular oxidant detoxification-related BPs significant for these genes, and the MF of antioxidant activity

was found significant consistently. The pathway analysis showed that KEGG pathway like one carbon pool by folate, and some pathways related to folate, one carbon or water-soluble vitamins metabolism in WikiPathways or Reactome pathways. Detoxification of reactive oxygen species and cellular responses to stress were also found significant in Reactome pathways. Consistent with the results of GO and pathway analyses, PPI interaction showed two different molecular modules, one with SLC19A1, MTR and MTHFR, and the other with SOD1, PRDX2 and PRDX6. It is clear that the module 1 is related to the clustering function of folate and other water-soluble vitamins metabolism, and the module 2 is for the detoxification of reactive oxygen species. Folate pathway has been regarded as involved in the pathogenesis of DS. Simultaneously, BPA exposure has the potential effects on the human phenotypes and altering DNA methylation [49, 50], which could be counteracted by the supplementation of methyl donors such as folate, choline, betaine and vitamin B12 [50]. Detoxification of reactive oxygen species and cellular responses to stress are important to maintain the mitochondrial function, which has been associated with the aetiology of early-onset dementia in patients with DS [51, 52].

For other NDs, less reference count or low inference score was found. But the limited results of GO and pathway analyses showed similar BPs, CCs, MFs and pathways with the above mentioned NDs in some extent.

5. Gene regulation

Transcription factors (TFs) and microRNAs (miRNAs), the largest families of transacting, share a common regulatory logic and represent the most numerous gene regulatory factors in multicellular genomes [53, 54]. The library of ENCODE and ChEA Consensus TFs from ChIP-X in EnrichR (<http://amp.pharm.mssm.edu/Enrichr/> [13, 14]) were used for the possible TFs and related networks. The TargetScan library in EnrichR was used for the possible miRNA interaction. Here we only analysed the genes of ID, LD, Sch, ASD, LD, SMD, BD and SD whose inference score all over 10.

For the TFs, it was only ID, ASD, AD and BD that were found significant TFs (**Table 7**). USF2, MAX, SPI1, SMAD4, POU5F1, PPARA, MYC and RUNX1 were found significant for ID. The regulated genes for each of these TFs are shown in **Table 7**. The direct evidences for the USF2 linked to ID were the regulating role of USF2 on FMR1 of Fragile X mental retardation [55, 56]. SUZ12 was found common in ASD, AD and BD, and REST was found in both ASD and BD. SUZ12, as a component of the polycomb repressive complex, was shown to interact with some of long non-coding RNAs like AK055040 to involve in neural development and brain function [57]. REST is a key TF that represses expression of genes involved in neurogenesis and neuronal function in non-neural and immature neural cell types [58].

Some miRNAs were found in Sch, ASD, AD and BD (**Table 8**). MIR-218 and MIR-485-3p were significant in both Sch and AD. It has been reported that miR-218 is involved in Sch [59], and miR-485-3p is associated with obsessive-compulsive disorder, a type of AD [60]. MIR-380-3p was found significant in both ASD and BD, but no direct evidence in human studies.

Term	Overlap	Adjusted P-value	Combined score	Genes
ID				
USF2	16/965	0.0050	9.01	PECR, FMR1, PMM2, HEXA, PTEN, TRMT1, WDR62, ZBTB40, MED13L, AP4M1, NAGLU, CAPN10, FASN, SC5D, MAN1B1, RALGDS
MAX	27/2073	0.0049	8.74	HDAC4, KDM5A, HEXA, PTEN, ADK, WDR62, TSEN2, ZBTB40, AP4M1, EEF1B2, NAGLU, CASP2, SC5D, RALGDS, PARP1, PMM2, SRD5A3, ELP2, VRK1, TRMT1, TTI2, METTL23, AHI1, POLR3B, FASN, L2HGDH, MAN1B1
SPI1	17/1056	0.0050	8.46	KDM5A, KDM6B, TSEN34, DOCK8, DNMT3A, AP4E1, ELP2, VRK1, ERLIN2, TSEN54, TMCO1, EEF1B2, METTL23, AHI1, POLR3B, CAPN10, PEX6
SMAD4	11/584	0.0152	6.85	INPP4A, PDHX, SETBP1, DOCK8, PAX6, SRGAP3, FRY, MCC, GRIN2B, FGFR2, SHANK2
POU5F1	7/261	0.0167	6.31	EEF1B2, ENTPD1, UBR7, FASN, PAX6, FGFR2, ZBTB40
PPARD	7/285	0.0232	5.83	TMEM135, POLR3B, SLC31A1, PMM2, NF1, TSEN2, TTI2
MYC	18/1515	0.0416	4.47	ACBD6, PARP1, PMM2, SRD5A3, PTEN, ADK, SLC2A1, ELP2, TRMT1, TSEN2, AP4M1, EEF1B2, METTL23, POLR3B, NAGLU, FASN, MAN1B1, RALGDS
RUNX1	16/1294	0.0426	4.46	DOCK8, PTEN, SLC2A1, ELP2, FRY, KIF7, TSEN54, TMCO1, LETM1, NAGLU, DEAF1, CAPN10, NSD1, GNAS, SC5D, RALGDS
ASD				
SUZ12	15/1684	0.0009	10.75	DLX1, RYR2, OXTR, TSHZ3, BDNF, EN2, DIO3, NRXN2, AVPR1A, GRIN2B, DPP6, RELN, LRRTM3, SOX9, NTSR1
TCF3	9/1006	0.0323	5.60	LRRTM3, ITGB3, DNMT3A, DNMT3B, NRXN2, TBL1X, JARID2, FOXP1, SCN1A
REST	10/1280	0.0323	5.38	GABRB3, RYR2, DPP6, RELN, LRRN3, BDNF, NRXN1, DNMT3A, NRXN2, C3ORF58
AD				
SUZ12	13/1684	0.0001	14.64	GABRA2, EOMES, UCN, APP, CHRNA5, OXT, SLC6A4, HTR7, ADORA2A, CNR1, NPY, GRM8, DRD2
BD				
REST	10/1280	0.0073	8.07	POMC, SNAP25, NTRK2, RELN, TRPC3, BDNF, GRIK2, DRD1, CPLX2, DRD5
SUZ12	10/1684	0.0331	5.13	NTNG1, NTRK2, RELN, TENM4, BDNF, GRIK2, TAC1, CPLX2, DRD5, SLC6A4

Table 7. Transcription factors for the BPA-interacted genes involved in the neurodevelopmental disorders.

Term	Overlap	Adjusted P-value	Combined score	Genes
Sch				
MIR-485-3P	7/155	0.0171	7.68	ADAMTS3, CNR1, NRXN1, MAGI2, GAD2, CPLX2, NR3C1
MIR-218	11/402	0.0171	7.60	KLF12, RELN, HTR7, NRXN1, MAGI2, GRIK2, TAC1, NR3C1, SLC6A1, RTN4, LGR4
ASD				
MIR-380-3P	5/103	0.0008	13.50	MEF2C, LRRTM3, BDNF, NRXN1, IL1RAPL1
MIR-524	8/437	0.0009	12.82	DLX1, MEF2C, LRRTM3, PCDH9, IL1RAPL1, TBL1X, SOX9, FOXP1
MIR-368	3/40	0.0061	9.16	DLX1, MEF2C, BDNF
MIR-302C	5/243	0.0120	7.57	GABRB3, DLX1, PCDH9, TBL1X, FOXP1
MIR-518C	4/149	0.0143	7.07	PCDH9, ITGB3, DNMT3A, NRXN2
MIR-373	4/227	0.0483	5.01	GABRB3, DLG4, EN2, SOX9
MIR-191	2/29	0.0483	4.45	BDNF, FOXP1
AD				
MIR-218	5/402	0.0232	7.15	MECP2, HTR7, MAGI2, GNB1, NPY1R
MIR-498	3/114	0.0232	6.98	MECP2, CRH, PAM
MIR-101	4/257	0.0232	6.83	APP, MAGI2, GNB1, FOS
MIR-141, MIR-200A	4/310	0.0325	6.07	MECP2, CNR1, DIXDC1, DRD2
MIR-485-3P	3/155	0.0336	5.97	CNR1, MAGI2, GNB1
BD				
MIR-494	4/164	0.0251	6.71	SP4, GRIK2, CACNA1C, TAC1
MIR-410	3/93	0.0317	6.41	NTRK2, SP4, NR3C1
MIR-380-3P	3/103	0.0317	6.27	SNAP25, BDNF, SP4

Table 8. miRNA for the BPA bi-interacted genes in neurodevelopmental disorders.

6. Comparable chemicals

The CTD provides a way to group chemicals based upon their biological effects, instead of their physical or structural properties, which provides a novel way to view and classify genes and chemicals and will help advance testable hypotheses about environmental chemical-gene disease networks [61]. Comparable chemicals were curated for the possible sharing with many of the networks common to BPA in neurodevelopmental disorders (**Table 9**). Tetrachlorodibenzodioxin, benzo(a)pyrene, vehicle emissions and dibutyle phthalate, as the common environmental pollutants, were found interacting with 312, 269, 204 and 159 of the 403 BPA bi-interacted genes in the NDs, respectively. Drugs such as valproic acid, acetaminophen,

Chemical	CAS RN	Similarity index	CIGs	CIGs for NDs
Tetrachlorodibenzodioxin	1746-01-6	0.5582	12,047	312
Valproic acid	99-66-1	0.5035	10,936	316
Benzo(a)pyrene	50-32-8	0.4511	9511	269
Acetaminophen	103-90-2	0.4093	8435	247
Aflatoxin B1	1162-65-8	0.3851	8140	252
Cyclosporine	59865-13-3	0.3566	7234	187
Nanotubes, carbon		0.3498	7134	199
Vehicle emissions		0.3458	7156	204
Pirinixic acid	50892-23-4	0.3305	6663	201
Estradiol	50-28-2	0.2930	5864	202
Copper Sulfate	7758-98-7	0.2785	5598	145
(6-(4-(2-Piperidin-1-ylethoxy)phenyl))-3-pyridin-4-ylpyrazolo(1,5-a)pyrimidine		0.2583	5186	186
4-(5-Benzo(1,3)dioxol-5-yl-4-pyridin-2-yl-1H-imidazol-2-yl)benzamide		0.2582	5185	183
Ethinyl estradiol	57-63-6	0.2535	5101	153
Tretinoin	302-79-4	0.2428	4835	193
Tetradecanoylphorbol acetate	16561-29-8	0.2315	4530	146
Atrazine	1912-24-9	0.2293	4559	175
Ammonium chloride	12125-02-9	0.2273	4509	215
Dibutyl phthalate	84-74-2	0.2262	4427	159
Silicon dioxide	7631-86-9	0.2224	4441	157

CIGs: common interacting genes; NDs: neurodevelopmental disorders.

Table 9. Chemicals having comparable sets of interacting genes to bisphenol A.

cyclosporine, pirinixic acid, tretinoin and tetradecanoylphorbol Acetate were found interacted with 316, 269, 247, 187, 201, 193 and 146 of the 403 BPA bi-interacted genes, respectively. Dietary pollutant aflatoxin B1, pesticide atrazine, and occupational exposure like copper sulphate, ammonium chloride and silicon dioxide and even estrogen estradiol could interact with the genes of those BPA bi-interacted within the NDs.

7. Future trends and conclusion

With the existed data libraries (mainly CTD, GO, pathway, TFs and miRNA relate databases), bioinformatics softwares (Cytoscape, MCODE and Genemania) or web-based tools (STRING, GEO, ArrayExpress, David and EnrichR), BPs, CCs, MFs, signal pathways and gene regulation in the BPA-gene-disease networks were presented. These data integration and curation

yielded insight into the actions of BPA and provide a basis for developing hypotheses about the molecular mechanisms underlying the aetiology of the neurodevelopmental disorder ID, LD, Sch, ASD, AD and BD, although most of the other neurodevelopmental disorders showed no enough information to make a conclusion. The nervous system-related CCs such as neuron related, synapse related, dendrite and axon related are common in CC annotation; the commonly found MFs are neurotransmitter receptor binding or activity, signal transducer or receptor binding or activity; and the main commonly involved BPs include synaptic signalling, cognition, learning or memory, behaviour, the development of nervous system and brain, and the regulation of the related BPs. Neuroactive ligand-receptor interaction, dopaminergic, glutamatergic and serotonergic synapse, monoamine transport, synaptic vesicle pathway may involve in the action of BPA in the neurodevelopmental disorders. Simultaneously, the BPA disease may share the common pathways with drug addictions (cocaine addiction, nicotine addiction and alcoholism), or other types of neurological diseases (Alzheimer's disease, Rett syndrome and sudden infant death syndrome). Unique pathways might also contribute to the BPA action in different NDs like one carbon metabolism and detoxification of oxidative stress-related pathways in Down syndrome. Although GO and pathway results indicate some common characteristics, the predicted PPI molecular function clusters are quite different for each ND. In addition, some of the NDs share the same TFs and miRNAs, which indicate these disorders have the similar expression profiles. What needs to be emphasized that the BPA-gene-disease networks might be influenced by some of the comparable chemicals such as environmental pollutants, drugs, dietary pollutants or occupational exposure, which share the same interacted genes with BPA.

The integrated and curated biological processes and pathways shall shed light on the future studies to find the possible BPA interacted or influenced genes. This will contribute to complete the BPA-disease networks, which surely help to screen the potential biomarker of BPA-induced neurodevelopmental diseases. However, it should be noted that most of the evidences were from curation of the cell or animal experiments. Simultaneously, the biinteraction mode for BPA-gene interaction was adopted for the precise network. Therefore, the future study design should consider the human subjects. Given the sample shortage, the peripheral blood instead of the brain tissue should be preferred in the future. This will contribute to the clinical diagnosis or intervention. Finally, our results should be carefully interpreted because the results might be changed with the increasing abundance of the enrichment of BPA bi-interacted genes.

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