

Table S1. ADMET properties of the most prominent PFAS compounds ((ADMETlab (2.0); <https://admetlab3.scbdd.com>); accessed on 11 August 2024)

Property	PFOS	PFOA	PFHxS	PFNA	PFDA	PFUnDA
Molecular Weight (MW)	499.94	413.97	399.94	463.97	513.97	563.96
Volume	294.953	252.882	236.09	282.313	311.744	341.175
Density	1.695	1.637	1.694	1.643	1.649	1.653
logS	-1.894	-1.643	-1.316	-2.033	-2.357	-2.576
logP	1.817	2.061	1.476	2.427	2.708	2.864
logD7.4	1.302	1.797	1.175	2.026	2.192	2.282
pKa (Acid)	2.965	3.93	2.844	4.119	4.262	4.371
pKa (Base)	3.098	4.509	3.207	4.822	4.901	4.669
Melting point	99.0	60.285	89.35	69.404	77.843	86.142
Boiling point	248.721	185.511	233.389	200.342	213.097	222.185
Lipinski Rule	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted
Pfizer Rule	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted
GSK Rule	Rejected	Rejected	Accepted	Rejected	Rejected	Rejected
GoldenTriangle	Accepted	Accepted	Accepted	Accepted	Rejected	Rejected
PAINS	0	0	0	0	0	0
Alarm_NMR Rule	1	0	1	0	0	0
BMS Rule	0	0	0	0	1	1
Chelating Rule	0	0	0	0	0	0
PAMPA	+++	+++	+++	+++	+++	+++
Pgp inhibitor	+++	++	+++	+++	+++	+++
Pgp substrate	---	---	---	---	---	---
HIA	+++	---	+++	---	---	---
F20%	--	---	-	---	---	---
F30%	+++	---	+++	---	---	---
F50%	++	---	+	---	---	---
PPB	99.2%	99.1%	98.9%	99.1%	99.2%	99.3%
VDss	-0.007	-0.139	-0.099	-0.091	-0.044	-0.0
BBB	---	---	---	---	---	---
Fu	0.5%	0.6%	0.7%	0.5%	0.5%	0.4%
OATP1B1 inhibitor	---	---	---	---	---	---
OATP1B3 inhibitor	+++	++	+	+++	+++	+++
BCRP inhibitor	+++	+	+++	++	+++	+++
MRP1 inhibitor	+++	+++	+++	+++	+++	+++
BSEP inhibitor	+++	+++	++	+++	+++	+++
CYP1A2 inhibitor	---	---	---	---	---	---
CYP1A2 substrate	+++	+++	+++	+++	+++	+++
CYP2C19 inhibitor	---	+	---	++	+++	+++
CYP2C19 substrate	---	---	---	---	---	---
CYP2C9 inhibitor	+++	+	---	+++	+++	+++
CYP2C9 substrate	---	---	---	---	---	---
CYP2D6 inhibitor	---	---	---	---	---	---
CYP2D6 substrate	---	---	---	---	---	---
CYP3A4 inhibitor	---	---	---	---	---	---
CYP3A4 substrate	+++	+++	++	+++	+++	+++
CYP2B6 inhibitor	---	---	---	---	---	---
CYP2B6 substrate	---	---	---	---	---	---
CYP2C8 inhibitor	+++	+++	+++	+++	+++	+++
HLM Stability	---	---	---	---	---	---
CLplasma	2.412	1.91	2.473	1.869	1.837	1.799
T1/2	1.417	1.738	1.444	1.719	1.716	1.724
Acute Aquatic Toxicity Rule	1	2	1	2	2	2

Genotoxic Carcinogenicity Mutagenicity Rule	1	0	1	0	0	0
NonGenotoxic Carcinogenicity Rule	0	0	0	0	0	0
Skin Sensitization Rule	0	0	0	0	0	0
Aquatic Toxicity Rule	0	0	0	0	0	0
NonBiodegradable	1	1	1	1	1	1
SureChEMBL Rule	4	3	4	3	3	3
FAF-Drugs4 Rule	1	0	1	0	0	0
hERG Blockers	+	---	---	---	---	---
hERG Blockers (10um)	--	---	--	---	---	---
DILI	---	---	---	---	---	---
AMES Toxicity	--	--	--	--	--	--
Rat Oral Acute Toxicity	-	-	-	-	-	-
FDAMDD	-	--	-	--	--	--
Skin Sensitization	+	++	+	++	++	++
Carcinogenicity	-	-	-	-	-	-
Eye Corrosion	+++	+++	+++	+++	+++	+++
Eye Irritation	+++	+++	+++	+++	+++	+++
Respiratory	++	++	++	++	++	++
Human Hepatotoxicity	+	+	+	+	+	+
Drug-induced Nephrotoxicity	++	++	+	++	++	++
Drug-induced Neurotoxicity	--	--	--	--	---	---
Ototoxicity	+	-	-	-	+	+
Hematotoxicity	-	-	-	-	-	-
Genotoxicity	+++	+++	+++	+++	+++	+++
RPMI-8226 Immunitoxicity	---	---	---	---	---	---
A549 Cytotoxicity	---	---	---	---	---	---
Hek293 Cytotoxicity	---	---	---	---	---	---
BCF	3.178	2.621	2.996	2.726	2.83	2.931
IGC50	4.039	3.881	3.928	3.958	4.034	4.101
LC50DM	6.341	5.384	6.045	5.555	5.7	5.812
LC50FM	5.744	4.797	5.465	4.962	5.108	5.236
NR-AhR	---	---	---	---	---	---
NR-AR	--	---	--	---	---	---
NR-AR-LBD	---	---	---	---	---	---
NR-Aromatase	---	---	---	---	---	---
NR-ER	-	---	-	---	---	---
NR-ER-LBD	-	---	-	---	---	---
NR-PPAR-gamma	---	---	---	---	---	---
SR-ARE	-	+++	-	+++	+++	+++
SR-ATAD5	---	---	---	---	---	---
SR-HSE	-	--	-	--	--	--
SR-MMP	-	+	-	+	+	+
SR-p53	+	+++	-	+++	+++	+++

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity); Per- and polyfluoroalkyl substances (PFAS); Perfluorodecanoic acid (PFDA); Perfluorohexane sulfonic acid (PFHxS); Perfluorooctanoic acid (PFOA); Perfluorooctane sulfonate (PFOS); Perfluorononanoic acid (PFNA); Perfluoroundecanoic acid (PFUnDA). +++; ---: Represents a high or strong effect. ++; --: Indicates a moderate or medium effect. +; -: Suggests a low or weak effect.

Table S2. List of 40 mutual genes associated with exposure to the six examined PFAS compounds: Perfluorooctane sulfonate (PFOS), Perfluorooctanoic acid (PFOA), Perfluorohexane sulfonate (PFHxS), Perfluorononanoic acid (PFNA), Perfluorodecanoic acid (PFDA), and Perfluoroundecanoic acid (PFUnDA) (Comparative Toxicogenomics Database (CTD; <https://ctdbase.org>; accessed on 15 August 2024)).

GENE SYMBOL	GENE NAME
<i>A2M</i>	alpha-2-macroglobulin
<i>ABCA1</i>	ATP binding cassette subfamily A member 1
<i>ACOT2</i>	acyl-CoA thioesterase 2
<i>ALB</i>	albumin
<i>ANGPTL4</i>	angiopoietin like 4
<i>APOA2</i>	apolipoprotein A2
<i>CPT1A</i>	carnitine palmitoyltransferase 1A
<i>CYP7A1</i>	cytochrome P450 family 7 subfamily A member 1
<i>DDIT3</i>	DNA damage inducible transcript 3
<i>EHHADH</i>	enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase
<i>ESR1</i>	estrogen receptor 1
<i>FABP1</i>	fatty acid binding protein 1
<i>FAS</i>	Fas cell surface death receptor
<i>FASN</i>	fatty acid synthase
<i>GSTM3</i>	glutathione S-transferase mu 3
<i>HADHA</i>	hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha
<i>HGF</i>	hepatocyte growth factor
<i>HMGCR</i>	3-hydroxy-3-methylglutaryl-CoA reductase
<i>HMGCS1</i>	3-hydroxy-3-methylglutaryl-CoA synthase 1
<i>HMGCS2</i>	3-hydroxy-3-methylglutaryl-CoA synthase 2
<i>HMOX1</i>	heme oxygenase 1
<i>IL6</i>	interleukin 6
<i>MBL2</i>	mannose binding lectin 2
<i>NFE2L2</i>	NFE2 like bZIP transcription factor 2
<i>NR1I2</i>	nuclear receptor subfamily 1 group I member 2
<i>PCK2</i>	phosphoenolpyruvate carboxykinase 2, mitochondrial
<i>PDK4</i>	pyruvate dehydrogenase kinase 4
<i>PLIN2</i>	perilipin 2
<i>POR</i>	cytochrome p450 oxidoreductase
<i>PPARA</i>	peroxisome proliferator activated receptor alpha
<i>PPARG</i>	peroxisome proliferator activated receptor gamma
<i>PTPN11</i>	protein tyrosine phosphatase non-receptor type 11
<i>SERPIND1</i>	serpin family D member 1
<i>SOD1</i>	superoxide dismutase 1
<i>SULT2A1</i>	sulfotransferase family 2A member 1
<i>TTR</i>	transthyretin
<i>TXNIP</i>	thioredoxin interacting protein

Centrality analysis was conducted on the GeneMania network using CytoNCA (available at <https://apps.cytoscape.org/apps/cytonca>; accessed on 5 November 2024). The table presents the centrality metrics, highlighting key genes based on degree, betweenness, and closeness centrality measures. These results provide insight into the potential roles of genes within the network structure and their importance in biological processes.

Table S3. Centrality Analysis Results for the GeneMania Network, sorted by degree. Top scores for each centrality measure (degree, betweenness, closeness) are highlighted in orange CytoNCA (available at <https://apps.cytoscape.org/apps/cytonca>; accessed on 5 November 2024).

GENE NAME	DEGREE	CLOSENESS	BETWEENNESS
<i>FABP1</i>	32.00	0.67	63.46
<i>EHHADH</i>	30.00	0.68	61.06
<i>APOA2</i>	28.00	0.67	65.36
<i>PPARA</i>	27.00	0.64	52.58
<i>PCK2</i>	24.00	0.71	111.04
<i>MBL2</i>	23.00	0.62	25.86
<i>HMGCS2</i>	20.00	0.61	17.27
<i>PLIN2</i>	19.00	0.63	75.18
<i>PPARG</i>	18.00	0.60	26.98
<i>SULT2A1</i>	18.00	0.60	19.81
<i>SERPIND1</i>	18.00	0.60	17.04
<i>HMGCS1</i>	18.00	0.59	28.96
<i>TTR</i>	17.00	0.59	14.94
<i>SOD1</i>	16.00	0.62	52.49
<i>POR</i>	16.00	0.62	44.04
<i>ALB</i>	16.00	0.55	10.06
<i>ANGPTL4</i>	15.00	0.57	38.72
<i>NR1I2</i>	14.00	0.59	35.98
<i>HGF</i>	13.00	0.59	31.24
<i>CYP7A1</i>	13.00	0.57	33.40
<i>ESR1</i>	13.00	0.56	8.44
<i>FAS</i>	12.00	0.59	42.74
<i>HMOX1</i>	12.00	0.54	26.04
<i>PDK4</i>	11.00	0.56	31.42
<i>HADHA</i>	11.00	0.56	6.76
<i>HMGCR</i>	11.00	0.55	12.50
<i>CPT1A</i>	9.00	0.52	2.76
<i>A2M</i>	8.00	0.55	26.40
<i>PTPN11</i>	8.00	0.49	17.86
<i>ABCA1</i>	7.00	0.51	1.55
<i>ACOT2</i>	6.00	0.51	1.33
<i>GSTM3</i>	5.00	0.52	7.32
<i>DDIT3</i>	5.00	0.49	2.24

<i>NFE2L2</i>	5.00	0.47	4.49
<i>IL6</i>	5.00	0.47	3.44
<i>TXNIP</i>	5.00	0.43	1.40
<i>FASN</i>	4.00	0.49	5.85

The following tables contain extracted ToppGene enrichment results (molecular functions, biological processes, pathways and diseases) for the following key genes:

Genes upregulated by PFAS: *EHHADH*, *APOA2*, *FABP1*, *PPARA*, *PCK2*, and *PLIN2*.

Table S4. ToppGene enrichment results (molecular functions, biological processes, pathways and diseases) for genes upregulated by per- and polyfluoroalkyl substances (PFAS): *EHHADH*, *APOA2*, *FABP1*, *PPARA*, *PCK2*, and *PLIN2* (ToppGene Suite portal ((<https://toppgene.cchmc.org>; accessed on 5 November 2024))

1: GO: Molecular Function [[Display Chart](#)] 6 input genes in category / 121 annotations before applied cutoff / 19912 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0051978	lysophospholipid:sodium symporter activity		6.026E-4	1.943E-2	1.045E-1	7.291E-2	<u>1</u>	<u>2</u>
2	GO:0004611	phosphoenolpyruvate carboxykinase activity		6.026E-4	1.943E-2	1.045E-1	7.291E-2	<u>1</u>	<u>2</u>
3	GO:0004613	phosphoenolpyruvate carboxykinase (GTP) activity		6.026E-4	1.943E-2	1.045E-1	7.291E-2	<u>1</u>	<u>2</u>
4	GO:0016509	long-chain-3-hydroxyacyl-CoA dehydrogenase activity		9.038E-4	1.943E-2	1.045E-1	1.094E-1	<u>1</u>	<u>3</u>
5	GO:0070653	high-density lipoprotein particle receptor binding		9.038E-4	1.943E-2	1.045E-1	1.094E-1	<u>1</u>	<u>3</u>

Show 45 more annotations

2: GO: Biological Process [[Display Chart](#)] 6 input genes in category / 642 annotations before applied cutoff / 20649 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0044242	cellular lipid catabolic process		1.706E-9	1.096E-6	7.715E-6	1.096E-6	<u>5</u>	<u>257</u>
2	GO:0016042	lipid catabolic process		1.332E-8	3.451E-6	2.430E-5	8.550E-6	<u>5</u>	<u>387</u>
3	GO:0009062	fatty acid catabolic process		1.613E-8	3.451E-6	2.430E-5	1.035E-5	<u>4</u>	<u>120</u>
4	GO:0072329	monocarboxylic acid catabolic process		3.968E-8	6.368E-6	4.485E-5	2.547E-5	<u>4</u>	<u>150</u>
5	GO:0050996	positive regulation of lipid catabolic process		1.341E-7	1.722E-5	1.213E-4	8.612E-5	<u>3</u>	<u>40</u>

Show 45 more annotations

3: GO: Cellular Component [[Display Chart](#)] 6 input genes in category / 34 annotations before applied cutoff / 20915 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0031907	microbody lumen		1.087E-4	1.848E-3	7.610E-3	3.696E-3	<u>2</u>	<u>57</u>
2	GO:0005782	peroxisomal matrix		1.087E-4	1.848E-3	7.610E-3	3.696E-3	<u>2</u>	<u>57</u>

3	GO:0005777	peroxisome		9.308E-4	7.912E-3	3.258E-2	3.165E-2	<u>2</u>	<u>167</u>
4	GO:0042579	microbody		9.308E-4	7.912E-3	3.258E-2	3.165E-2	<u>2</u>	<u>167</u>
5	GO:0034366	spherical high-density lipoprotein particle		2.579E-3	1.670E-2	6.877E-2	8.770E-2	<u>1</u>	<u>9</u>

Show 9 more annotations

4: Pathway [\[Display Chart\]](#) 6 input genes in category / 214 annotations before applied cutoff / 13850 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	M39553	WP PPAR SIGNALING PATHWAY	WikiPathways	1.360E-11	1.509E-9	8.970E-9	2.911E-9	<u>5</u>	<u>67</u>
2	M13088	KEGG PPAR SIGNALING PATHWAY	KEGG Legacy Pathways	1.583E-11	1.509E-9	8.970E-9	3.387E-9	<u>5</u>	<u>69</u>
3	MM15995	WP PPAR SIGNALING PATHWAY	WikiPathways	2.115E-11	1.509E-9	8.970E-9	4.526E-9	<u>5</u>	<u>73</u>
4	M39547	WP PPAR ALPHA PATHWAY	WikiPathways	1.460E-10	7.809E-9	4.643E-8	3.124E-8	<u>4</u>	<u>26</u>
5	M2404	BIOCARTA PPARA PATHWAY	BioCarta Pathways	2.635E-9	1.128E-7	6.706E-7	5.639E-7	<u>4</u>	<u>52</u>

Show 45 more annotations

5: Disease [\[Display Chart\]](#) 6 input genes in category / 238 annotations before applied cutoff / 29490 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	C0022672	Acute Kidney Tubular Necrosis	DisGeNET Curated	2.069E-7	4.925E-5	2.981E-4	4.925E-5	<u>2</u>	<u>4</u>
2	C0022661	Kidney Failure, Chronic	DisGeNET Curated	3.875E-5	3.459E-3	2.093E-2	9.223E-3	<u>2</u>	<u>48</u>
3	C0015695	Fatty Liver	DisGeNET Curated	1.310E-4	3.459E-3	2.093E-2	3.119E-2	<u>2</u>	<u>88</u>
4	C2711227	Steatohepatitis	DisGeNET Curated	1.310E-4	3.459E-3	2.093E-2	3.119E-2	<u>2</u>	<u>88</u>
5	DOID:9427 (implicated via orthology)	hypertensive encephalopathy (implicated via orthology)	AllianceGenome	2.035E-4	3.459E-3	2.093E-2	4.842E-2	<u>1</u>	<u>1</u>

Show 45 more annotations

Genes downregulated by PFAS: *MBL2*, *SULT2A1*, *FABP1*, *PPARA* (downregulated by PFDA and/or PFUnDa)

Table S5. ToppGene enrichment results (molecular functions, biological processes, pathways and diseases) for genes downregulated by per- and polyfluoroalkyl substances (PFAS): *MBL2*, *SULT2A1*, *FABP1*, *PPARA* (downregulated by perfluorodecanoic acid (PFDA) and/or perfluoroundecanoic acid (PFUnDa)) ToppGene Suite portal ((<https://toppgene.cchmc.org>; accessed on 5 November 2024))

1: GO: Molecular Function [\[Display Chart\]](#) 4 input genes in category / 93 annotations before applied cutoff / 19912 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0033876	glycochenodeoxycholate sulfotransferase activity		2.009E-4	1.401E-2	7.166E-2	1.868E-2	<u>1</u>	<u>1</u>
2	GO:0051978	lysophospholipid:sodium symporter activity		4.017E-4	1.401E-2	7.166E-2	3.736E-2	<u>1</u>	<u>2</u>
3	GO:0008289	lipid binding		5.097E-4	1.401E-2	7.166E-2	4.740E-2	<u>3</u>	<u>1016</u>
4	GO:0047704	bile-salt sulfotransferase activity		6.026E-4	1.401E-2	7.166E-2	5.604E-2	<u>1</u>	<u>3</u>
5	GO:0004027	alcohol sulfotransferase activity		8.034E-4	1.494E-2	7.643E-2	7.471E-2	<u>1</u>	<u>4</u>

Show 34 more annotations

2: GO: Biological Process [\[Display Chart\]](#) 4 input genes in category / 511 annotations before applied cutoff / 20649 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0072329	monocarboxylic acid catabolic process		1.495E-6	5.605E-4	3.820E-3	7.639E-4	<u>3</u>	<u>150</u>
2	GO:0032000	positive regulation of fatty acid beta-oxidation		2.194E-6	5.605E-4	3.820E-3	1.121E-3	<u>2</u>	<u>13</u>
3	GO:0046321	positive regulation of fatty acid oxidation		7.111E-6	8.409E-4	5.731E-3	3.634E-3	<u>2</u>	<u>23</u>
4	GO:0031998	regulation of fatty acid beta-oxidation		9.133E-6	8.409E-4	5.731E-3	4.667E-3	<u>2</u>	<u>26</u>
5	GO:0046395	carboxylic acid catabolic process		9.874E-6	8.409E-4	5.731E-3	5.046E-3	<u>3</u>	<u>281</u>

Show 45 more annotations

3: Pathway [\[Display Chart\]](#) 4 input genes in category / 128 annotations before applied cutoff / 13850 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	M27316	REACTOME REGULATION OF LIPID METABOLISM BY PPARALPHA	Reactome Pathways	2.397E-6	3.068E-4	1.667E-3	3.068E-4	<u>3</u>	<u>118</u>
2	MM15034	REACTOME REGULATION OF LIPID METABOLISM BY PPARALPHA	Reactome Pathways	9.557E-6	6.117E-4	3.323E-3	1.223E-3	<u>2</u>	<u>18</u>

3	M39547	WP PPAR ALPHA PATHWAY	WikiPathways	2.029E-5	8.655E-4	4.703E-3	2.597E-3	<u>2</u>	<u>26</u>
4	M39428	WP NUCLEAR RECEPTORS META PATHWAY	WikiPathways	4.540E-5	1.453E-3	7.893E-3	5.811E-3	<u>3</u>	<u>314</u>
5	M2404	BIOCARTA PPARA PATHWAY	BioCarta Pathways	8.256E-5	1.900E-3	1.032E-2	1.057E-2	<u>2</u>	<u>52</u>

Show 45 more annotations

4: Disease [[Display Chart](#)] 4 input genes in category / 302 annotations before applied cutoff / 29490 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	C0022672	Acute Kidney Tubular Necrosis	DisGeNET Curated	8.279E-8	2.500E-5	1.572E-4	2.500E-5	<u>2</u>	<u>4</u>
2	C0022661	Kidney Failure, Chronic	DisGeNET Curated	1.553E-5	2.048E-3	1.288E-2	4.691E-3	<u>2</u>	<u>48</u>
3	DOID:1485 (is marker for)	cystic fibrosis (is marker for)	AllianceGenome	2.602E-5	2.048E-3	1.288E-2	7.859E-3	<u>2</u>	<u>62</u>
4	DOID:10652 (is implicated in)	Alzheimer's disease (is implicated in)	AllianceGenome	1.168E-4	2.048E-3	1.288E-2	3.528E-2	<u>2</u>	<u>131</u>
5	C3280586	Mannose-Binding Protein Deficiency	DisGeNET Curated	1.356E-4	2.048E-3	1.288E-2	4.096E-2	<u>1</u>	<u>1</u>

Show 45 more annotations

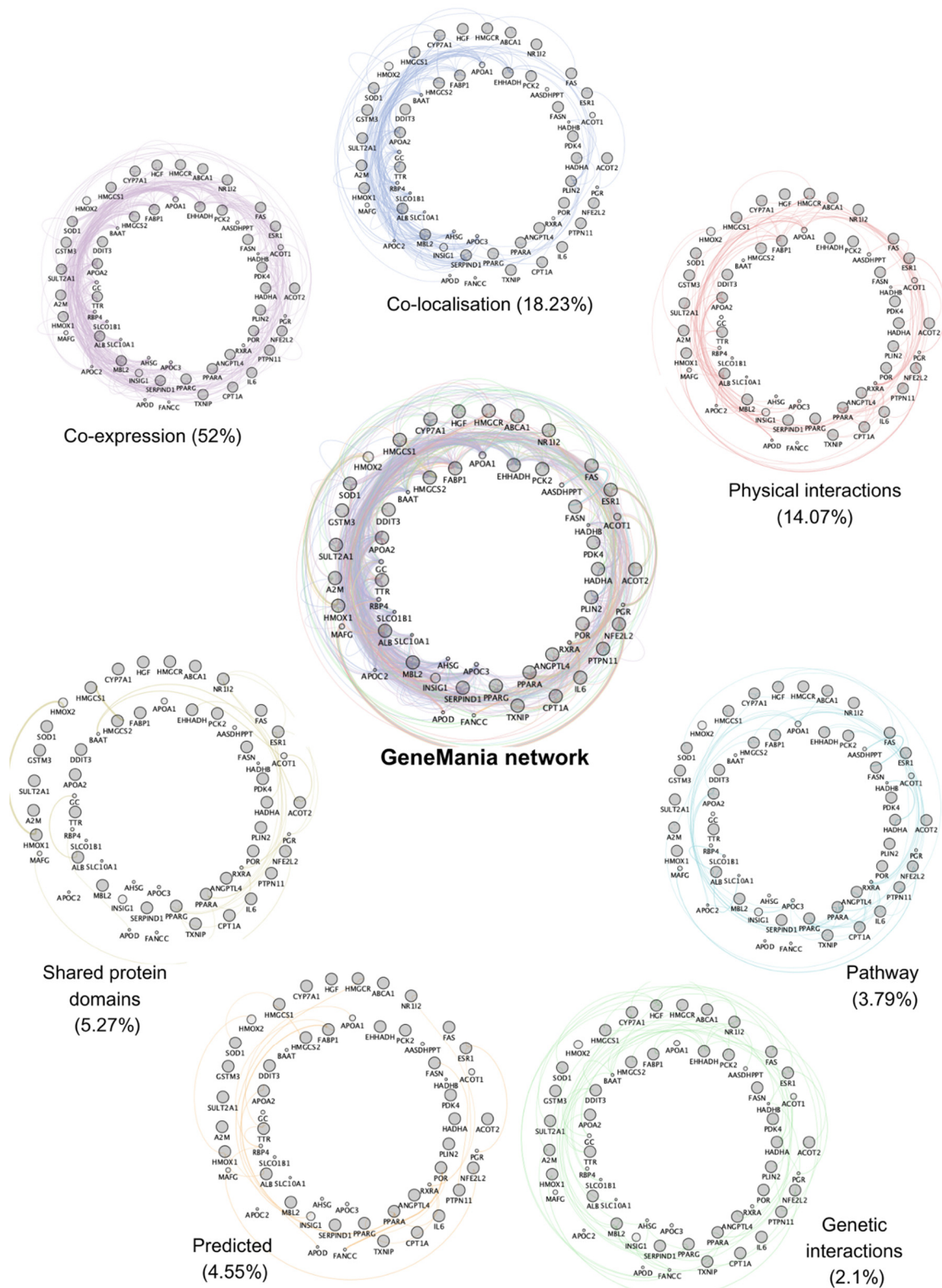


Figure S1. GeneMania network in circular layout: combined and interaction-specific views (GeneMANIA (<https://genemania.org>; accessed on 5 November 2024))