ACCSCIENCE PUBLISHING

Gene & Protein in Disease

ORIGINAL RESEARCH ARTICLE

Pre-addiction phenotype is associated with dopaminergic dysfunction: Evidence from 88.8 million genome-wide association study-based samples

Supplementary File

Tables S1. Summary of primary *in silico*, deep *in silico*, and deep meta-analyses utilized

Level	Database	Website	Software (version)	References
PGx	VAA	https://www.pharmgkb.org/	PharmGKB	1
PPIs	STRING model	https://string-db.org/	STRING (12.0)	2
GRNs	GMIs	https://ccb-compute.cs.uni-saarland.de/mirtargetlink2	miRTargetLink (2.0)	3
EA	Pathway analysis	https://maayanlab.cloud/Enrichr/	Enrichr	4
	GO	https://maayanlab.cloud/Enrichr/	Enrichr	5
	DDA	https://maayanlab.cloud/Enrichr/	Enrichr	5
MA	CEO	https://metascape.org/gp/index.html#/main/step1	Metascape	6

Abbreviations: CEO: Cell expression omnibus; DDA: Diseases drugs assessment; EA: Enrichment analysis; GMIs: Gene-miRNA interactions; GO: Gene ontology; GRNs: Gene regulatory networks; MA: Modular analysis; PGx: Pharmacogenomics; PPIs: Protein-protein interactions; VAA: Variant annotation archive.

Table S2. GWAS-based data included in the study

Phenotype	Trait/genes	Ontology ID	Studies (*n*)	Association (*n*)	Samples (*n*)
Opioid	Opioid dependence	EFO_0005611	17	299	456348
	Opioid use disorder	EFO_0010702	19	108	1,008,514
	Opioid use measurement	EFO_0009937	21	7	336,342
	Opioid overdose severity measurement	EFO_0010140	1	6	3,477
	Response to opioid	EFO_0008541	9	73	8,068
	Opioid-binding protein/cell adhesion molecule measurement	EFO_0020618	5	6	13,643
Pain	Pain	EFO_0003843	276	590	3,392,261
	Chronic pain	HP_0012532	18	171	1,231,927
	Neuropathic pain	EFO_0005762	5	30	451,941
	Multisite chronic pain	EFO_0010100	4	141	387649
	Pain measurement	EFO_0010639	60	12	70,760
	Chronic widespread pain	EFO_0010099	3	15	3,273
	Chronic post-operative pain measurement	EFO_0010640	1	2	303
	Response to opioid	EFO_0008541	9	73	7,226
	Headache disorder	EFO_0009550	53	686	1,401,467
Aging	Aging	GO_0007568	48	313	209,693
	Longevity	EFO_0004300	58	678	1,555,377
	Healthspan	EFO_0009762	4	37	96,314
	Parental longevity	EFO_0007796	31	442	1,518,632
Apoptosis	39 genes	NA	731	863	76,635,166
Total	-	-	1,373	4,552	88,788,381

Note: NA denotes "not applicable."

Table S3. Deep *in silico* pathway enrichment analysis of 27 refined genes

Index	Name	*p*-value	q-value	OR
Reactome	Dopamine receptor (R-HSA-390651)	1.32E-11	2.18E-09	3473.39
Reactome	Neurotransmitter clearance (R-HSA-112311)	5.50E-10	4.56E-08	578.75
KEGG	Dopaminergic synapse	3.70E-10	4.73E-08	55.57
KEGG	Neuroactive ligand-receptor interaction	1.10E-08	7.05E-07	24.83
KEGG	Tyrosine metabolism	1.51E-07	0.000006425	108.38
Reactome	Class A/1 (rhodopsin-like receptors) (R-HSA-373076)	1.96E-07	0.000009661	21.5
Reactome	Amine ligand-binding receptors (R-HSA-375280)	2.33E-07	0.000009661	96.31
KEGG	Cocaine addiction	5.35E-07	0.00001713	77.02
Reactome	Transmission across chemical synapses (R-HSA-112315)	7.77E-07	0.00002578	23.49
Reactome	GPCR ligand binding (R-HSA-500792)	1.88E-06	0.00005211	15.15
Reactome	Neuronal system (R-HSA-112316)	1.04E-05	0.0002476	14.73
Reactome	Interleukin-4 and interleukin-13 signaling (R-HSA-6785807)	1.24E-05	0.0002565	33.55
KEGG	Parkinson disease	1.85E-05	0.0004746	18.38
Reactome	Signaling via GPCR (R-HSA-372790)	2.72E-05	0.0005009	9.9
KEGG	Alcoholism	0.000108	0.001981	18.91
KEGG	Amphetamine addiction	0.000108	0.001981	37.7
KEGG	Complement and coagulation cascades	0.000201	0.002964	30.32
KEGG	Colorectal cancer	0.000208	0.002964	29.95
KEGG	Morphine addiction	0.000246	0.003152	28.25
Reactome	Signal transduction (R-HSA-162582)	0.000191	0.003176	4.91

Notes: The q-value refers to the adjusted *p*-value; OR refers to the odds ratio.

Table S4. Gene ontology assessments through three major processes for 27 candidate genes

Index	Name	*p*-value	q-value	OR
GO Biological Process 2023	Dopamine metabolic process (GO:0042417)	8.93E-14	6.42E-11	438.68
GO Biological Process 2023	Catecholamine metabolic process (GO:0006584)	3.87E-12	1.39E-09	567.19
GO Biological Process 2023	Negative regulation of protein secretion (GO:0050709)	1.69E-09	4.05E-07	133.28
GO Biological Process 2023	Response to ethanol (GO:0045471)	7.95E-09	1.43E-06	247.94
GO Cellular Component 2023	Neuron projection (GO:0043005)	2.83E-08	1.81E-06	17.72
GO Cellular Component 2023	Dendrite (GO:0030425)	5.33E-08	1.81E-06	26.23
GO Biological Process 2023	Prepulse inhibition (GO:0060134)	2.19E-08	3.15E-06	1248.19
GO Biological Process 2023	Negative regulation of protein transport (GO:0051224)	3.27E-08	3.92E-06	165.23
GO Biological Process 2023	Response to cocaine (GO:0042220)	4.38E-08	4.49E-06	832.08
GO Biological Process 2023	Regulation of dopamine uptake involved in synaptic transmission (GO:0051584)	7.65E-08	6.88E-06	624.03
GO Biological Process 2023	Regulation of postsynaptic membrane potential (GO:0060078)	1.34E-07	1.07E-05	111.88
GO Biological Process 2023	Arachidonate transport (GO:1903963)	1.83E-07	1.1E-05	415.98
GO Molecular Function 2023	Postsynaptic neurotransmitter receptor activity (GO:0098960)	2.1E-06	0.000189	155.91
GO Molecular Function 2023	Protease binding (GO:0002020)	2.28E-05	0.001027	28.53
GO Cellular Component 2023	Mitochondrial outer membrane (GO:0005741)	4.79E-05	0.001085	23.46
GO Cellular Component 2023	Organelle outer membrane (GO:0031968)	7.59E-05	0.00129	20.75
GO Cellular Component 2023	Collagen-containing extracellular matrix (GO:0062023)	0.000126	0.00172	12.11
GO Cellular Component 2023	Axon (GO:0030424)	0.000156	0.001772	17.11
GO Molecular Function 2023	Monoamine transmembrane transporter activity (GO:0008504)	9.58E-05	0.002874	177.46
GO Molecular Function 2023	Sodium chloride symporter activity (GO:0015378)	0.000136	0.003052	145.18
GO Molecular Function 2023	G-protein-coupled receptor activity (GO:0004930)	0.000334	0.006004	13.95
GO Cellular Component 2023	Non-motile cilium (GO:0097730)	0.000746	0.006771	56.99
GO Cellular Component 2023	Melanosome (GO:0042470)	0.000797	0.006771	55.02
GO Cellular Component 2023	Ciliary membrane (GO:0060170)	0.001197	0.009047	44.3
GO Molecular Function 2023	Protein homodimerization activity (GO:0042803)	0.001725	0.02228	6.68
GO Molecular Function 2023	Cytokine activity (GO:0005125)	0.001733	0.02228	14.14
GO Molecular Function 2023	Channel activity (GO:0015267)	0.002232	0.02318	31.88
GO Molecular Function 2023	Serine-type endopeptidase inhibitor activity (GO:0004867)	0.002318	0.02318	31.25
GO Cellular Component 2023	Platelet alpha granule lumen (GO:0031093)	0.003569	0.02427	24.89
GO Molecular Function 2023	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, another compound as one donor, and incorporation of one atom of oxygen (GO:0016716)	0.006732	0.0346	192.01

Notes: The q-value refers to the adjusted *p*-value; OR refers to the odds ratio.

Table S5. Disease-drug analysis of 27 candidate genes

Index	Name	*p*-value	q-value	OR
DisGeNET	Addictive behavior	2.01E-19	4.13E-16	94.18
DisGeNET	Heroin dependence	3.09E-19	4.13E-16	225.35
DisGeNET	Mental depression	1.73E-18	1.54E-15	50.52
DisGeNET	Gambling, pathological	2.76E-18	1.84E-15	1397.76
DisGeNET	Nicotine dependence	3.96E-18	2.12E-15	120.83
DisGeNET	Nonorganic psychosis	3.49E-17	1.55E-14	76.02
DisGeNET	Psychotic disorders	5.12E-17	1.95E-14	60.08
DisGeNET	Alcohol problem	6.74E-17	2.25E-14	698.71
DisGeNET	Mental disorders	8.31E-17	2.37E-14	57.76
DisGeNET	Depressive disorder	9.58E-17	2.37E-14	38.62
GeDiPNet 2023	Mood disorder	1.13E-12	1.87E-10	44.77
GeDiPNet 2023	Mental depression	1.17E-12	1.87E-10	21.63
GeDiPNet 2023	Bipolar disorder	1.28E-12	1.87E-10	26.19
GeDiPNet 2023	Cognitive disorder	3.45E-11	3.77E-09	138.9
GeDiPNet 2023	Minimal brain dysfunction	7.85E-11	6.86E-09	266.79
GeDiPNet 2023	Schizophrenia	1.03E-09	7.49E-08	13.69
GeDiPNet 2023	Age-related memory disorders	2.82E-09	1.73E-07	119.23
GeDiPNet 2023	Memory disorders	3.17E-09	1.73E-07	116.17
GeDiPNet 2023	Jacksonian seizure	3.88E-09	1.88E-07	59.78
GeDiPNet 2023	Delirium	6.19E-09	2.71E-07	267.02

Notes: The q-value refers to the adjusted *p*-value; OR refers to the odds ratio.

Table S6. Enrichr-KG results for 27 candidate genes

Library	Name	*p*-value	q-value	z-score
DisGeNET	Addictive behavior	2.01E-19	4.13E-16	94.18
DisGeNET	Heroin dependence	3.09E-19	4.13E-16	225.4
DisGeNET	Mental depression	1.73E-18	1.54E-15	50.52
DisGeNET	Gambling, pathological	2.76E-18	1.84E-15	1398
DisGeNET	Nicotine dependence	3.96E-18	2.12E-15	120.8
GO_Biological_Process_2021	Dopamine metabolic process (GO: 0042417)	8.93E-14	7.07E-11	438.7
GO_Biological_Process_2021	Catecholamine metabolic process (GO: 0006584)	9.01E-12	3.56E-09	453.7
Reactome_2022	Dopamine receptor (R-HSA-390651)	1.32E-11	2.18E-09	3473
GO_Biological_Process_2021	Regulation of dopamine uptake involved in synaptic transmission (GO: 0051584)	1.84E-10	4.84E-08	868.2
KEGG_2021_Human	Dopaminergic synapse	3.70E-10	4.73E-08	55.57
Reactome_2022	Neurotransmitter clearance (R-HSA-112311)	5.50E-10	4.56E-08	578.8
GO_Biological_Process_2021	Negative regulation of protein secretion (GO: 0050709)	1.69E-09	3.34E-07	133.3
KEGG_2021_Human	Neuroactive ligand-receptor interaction	1.10E-08	7.05E-07	24.83
GO_Biological_Process_2021	Regulation of protein secretion (GO: 0050708)	1.40E-08	2.22E-06	47.67
KEGG_2021_Human	Tyrosine metabolism	1.51E-07	6.43E-06	108.4
Reactome_2022	Class A/1 (rhodopsin-like receptors) (R-HSA-373076)	1.96E-07	9.66E-06	21.5
Reactome_2022	Amine ligand-binding receptors (R-HSA-375280)	2.33E-07	9.66E-06	96.31
KEGG_2021_Human	Cocaine addiction	5.35E-07	1.71E-05	77.02
Reactome_2022	Transmission across chemical synapses (R-HSA-112315)	7.77E-07	2.58E-05	23.49
KEGG_2021_Human	Parkinson's disease	1.85E-05	0.000475	18.38
TRRUST_Transcription_Factors_2019	NFKB1 human	4.74E-05	0.001809	15.01
TRRUST_Transcription_Factors_2019	ERCC2 human	4.89E-05	0.001809	266.2
TRRUST_Transcription_Factors_2019	POU4F1 mouse	4.89E-05	0.001809	266.2
TRRUST_Transcription_Factors_2019	ABL1 human	7.85E-05	0.002177	199.7
TRRUST_Transcription_Factors_2019	NFKB1 mouse	0.000142	0.003157	17.55

Note: The q-value and z-score refer to the adjusted *p*-value and standard deviation, respectively.

References

1. PharmGKB. Stanford (CA): Stanford University. Available from: https://www.pharmgkb.org/ [Last accessed 2025 Jul 02].
2. Andreadis P, Karagiannis T, Malandris K, *et al.* Semaglutide for type 2 diabetes mellitus: A systematic review and meta-analysis. *Diabetes Obes Metab.* 2018;20(9):2255-2263.
3. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab.* 2017;19(4):524-536.
4. Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
5. Marso SP, Daniels GH, Brown-Frandsen K, *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(4):311-322.
6. Zhou Y, Zhou B, Pache L, *et al.* Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. *Nat Commun.* 2019;10(1):1523.

   doi: 10.1038/s41467-019-09234-6