Drug-Phenotype Associations and Pathway Genes in Neurodegenerative Diseases: Insights from PathFX Analysis

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Abstract

Current Challenges: Neurodegenerative diseases like Alzheimer's and Parkinson's are difficult to treat due to their complex pathology and the absence of curative treatments.

- Hypothesis: Investigating pathway genes that link drugs to phenotypes could uncover new therapeutic effects.
- Previous Findings: This method has successfully predicted rare drug-drug interactions in earlier studies.
- Present Study: We applied PathFX to explore drug-phenotype associations across six major neurological and neurodegenerative disease categories.
- Scale of Data: The analysis identified 1,010 pathway genes that connect 1,255 drugs to 19 phenotypes.
- Results & Implications: Despite generally low similarity among genes within pathways, various neurodegenerative disease categories share a significant number of biological pathways, presenting opportunities for drug repurposing and side-effect studies. A core set of genes was consistently implicated across the biological pathways of these diseases. Furthermore, analyses of GO enrichment and ATC codes have uncovered both shared and unique biological processes and targeted organs across these conditions.

PathFX

A Protein-Protein Interaction Network Method for Predicting Drug Downstream Effects

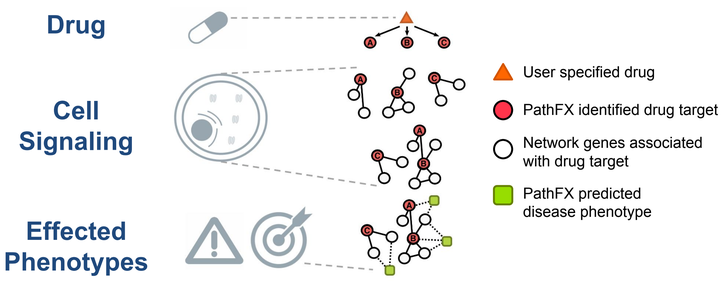
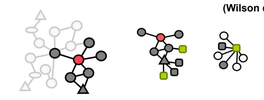


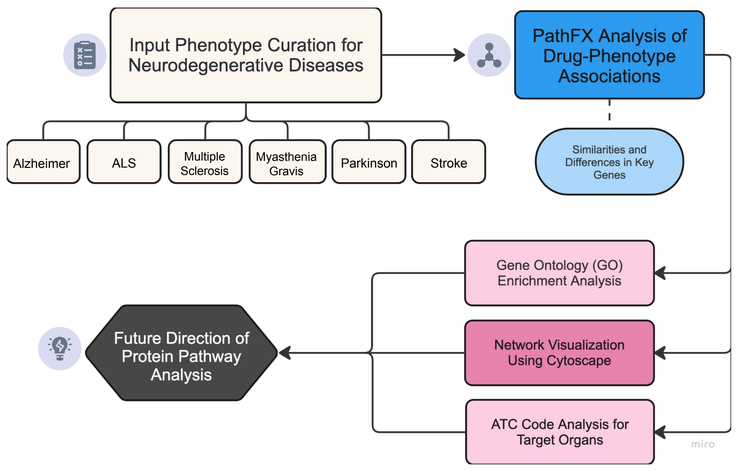
Fig. 1. PathFX algorithms.
(**Wilson** et al, PLoS Comp Bio, 2018; **Wilson** et al, Bioinformatics, 2019)



$$S_{\mathrm{MI}} = \frac{K_p \times S_p(n) + K_m \times S_m(c\nu) + K_t \times S_t(c\nu)}{K_p + K_m + K_t}$$

Predicted phenotype	Predicted phenotype CUI	Benjamini-Hochberg corrected p-value	Pathway genes associated with predicted phenotype	Number of pathway genes associated with predicted phenotype	Total number of genes associated with the phenotype
Diabetes mellitus type 2	C0011860	2.81E-05	PPARGC1A,PRKAG1,PRKAA1, STK11,SLC22A2,PRKAA2,PRKAG2,SLC47A1,SLC22A1,PRKAG3,PRKAB1,PRKAB2	12	1972
Diabetes Mellitus, Type 1	C0011849	4.35E-05	PPARGC1A,PRKAG1,PRKAA1, STK11,SLC22A2,PRKAA2,PRKAG2,SLC47A1,SLC22A1,PRKAG3,PRKAB1,PRKAB2	12	2081

Methods



Results

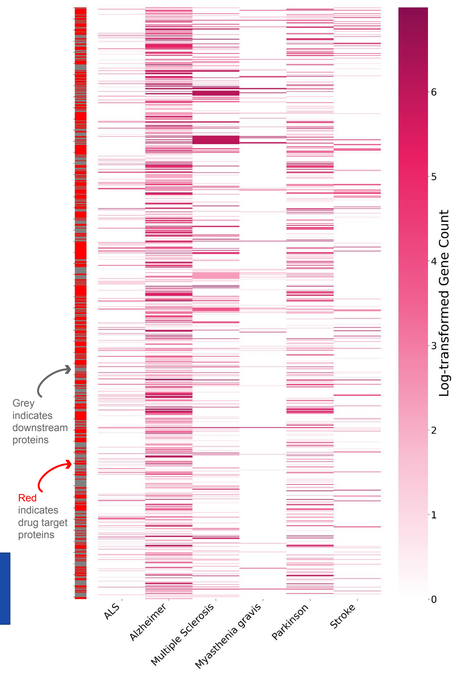


Fig. 2. Heatmap of pathway genes across disease categories. Alzheimer's Disease, Parkinson's Disease, and multiple sclerosis exhibit a broader range of overlapping genes than ALS and Stroke.

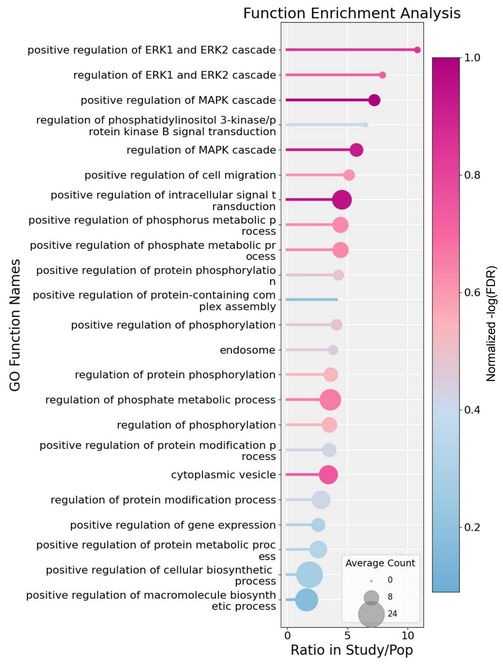


Fig. 3. Function enrichment analysis based on gene ontology. An example of GO terms that appear in the enrichment results across all categories, detailing their study counts and relative significance. While some of these terms are associated with neural diseases, many are predominantly linked to cancers and immune system disorders.

Balanced Genes for Future Control Experiments

Eg.	GeneName	NumDrugPathAssocs	NumAppInCluster	NumAppOutOfCluster
	APP	2353	297	374

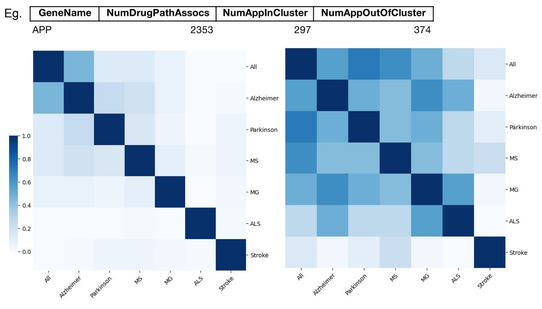


Fig. 4 & 5. Jaccard similarity of balanced gene sets & enriched GO terms. Balanced gene sets across disease categories show low similarity, while low-level GO terms show higher similarity for all but stroke, pointing to shared biological pathways in drug networks.

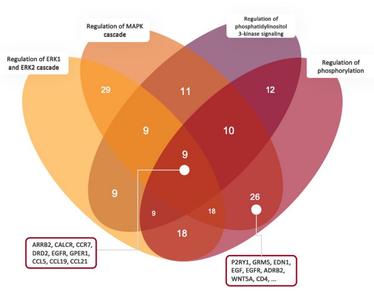


Fig. 6. This Venn diagram illustrates the overlap among gene sets associated with various GO terms. The overlapped genes are then found for all low-level category-shared GO terms.

Gene name	Description	Ratio of approved in vs. out cluster	# associated GO terms	Drug target protein	Literature evidence
CCL5	RANTES, chemokines	0.747 (287 vs. 384)	315	Heparin disaccharide i-s, not approved	Associated with AD, PD, MS, and ALS
APP	Amyloid beta precursor protein	0.794 (297 vs. 374)	353	Phenserine, approved for AD	Associated with AD, PD, and MS
GPER1	G protein-coupled estrogen receptor 1	0.833 (305 vs. 366)	335	MK-0354, studied with atherosclerosis	Associated with AD, PD, and stroke

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Tab. 1. Summary of genes associated with a balanced number of approved drugs both in and out of clusters, which are also widely linked to enriched GO terms and supported by extensive literature evidence for neurodegenerative diseases. It demonstrates our method for identifying key genes of interest for pathway visualization.

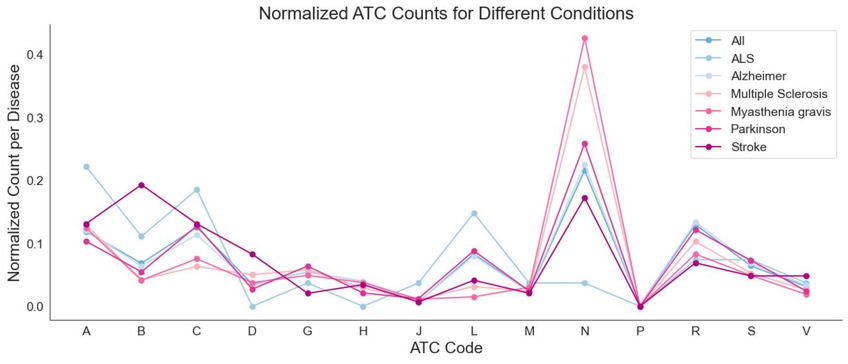

Fig. 7. ATC code analysis reveal that predicted drugs target multiple organs at different counts.
Each letter corresponds to a target organ: A is Alimentary Tract and Metabolism, B is Blood Forming Organs, N is Nervous System, etc. Different categories follow the similar trends except for ALS and stroke.

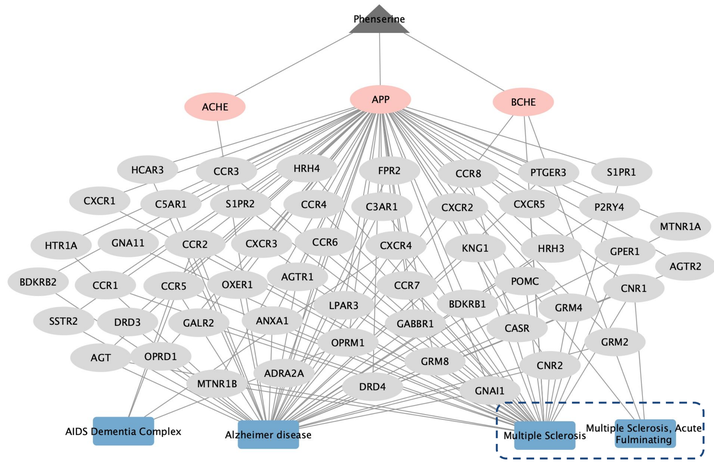

Fig. 8. Pathway visualization of Phenserine. Phenserine, approved for Alzheimer's Disease, targets APP, a gene that we identified to have high potential for implicating multiple phenotype pathways, making it suitable for drug repurposing. The network also suggests relevance to multiple sclerosis and dementia.

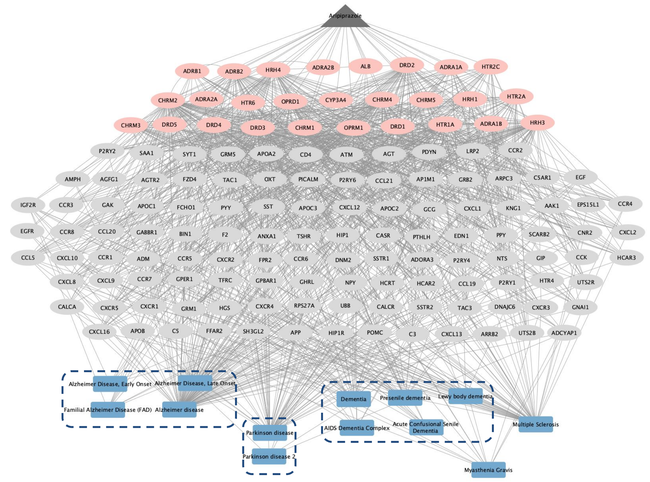

Fig. 9. Pathway visualization of Aripiprazole. Aripiprazole has networks with the highest overlap with the gene lists we identified that are widely associated with significant GO terms and have balanced number of in and out of cluster drugs. It is primarily used for treating bipolar disorders and major depression, has networks with the highest overlap with gene lists associated with significant GO terms. Its network also suggests potential relevance to Alzheimer's, Parkinson's, dementia, multiple sclerosis, and myasthenia gravis.

Conclusion

In our study using PathFX to map drug-phenotype pathways for six primary neurodegenerative disease categories, here are the main findings:

- Despite low gene set similarities, the shared biological processes in low-level GO terms across these categories, which may not be primarily neuro-related, underscore significant potential for the development of multipurpose drugs.
- ATC code analysis showed that while most drug categories target nervous system organs, ALS rarely targets the nervous system and stroke predominantly targets the blood system.
- High similarities across gene sets, GO terms, and ATC counts were observed in Alzheimer's Disease, Parkinson's Disease, and Multiple Sclerosis, contrasted with lower similarities in ALS and Stroke.
- Focusing on genes associated with enriched functions, our cytoscape visualizations identified potential targets for drug repurposing, advancing our understanding of mechanistic pathways in neurodegenerative diseases and supporting strategic drug redirection for multiple therapeutic uses.

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