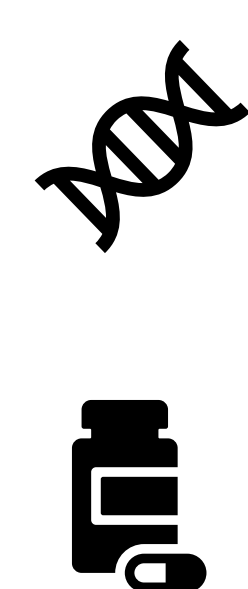


Abstract



Patients with neurodegenerative diseases have insufficient treatments to manage the debilitating and prolonged symptoms of their diseases, therefore, there are no curative options. Here we used our PPI model, PathFX, to assess the connections between approved drugs and neurodegenerative disease pathways to better understand potential treatment strategies. We identified 8 neurodegenerative phenotypes in the PathFX database and found network associations with 5 of them among approved drugs in DrugBank. Our analysis revealed 2,142 drug-phenotype relationships involving 1,113 unique drugs. Supporting literature validated pathways identified by PathFX, including a genetic association between Bridging Integrator 1 (BIN1) and Alzheimer's disease.

Our results indicate robust connectivity between druggable targets and neurodegenerative disease pathways, showing potential for treatment strategies. Furthermore, our analysis demonstrated high gene similarity across neurodegenerative diseases.

PathFX

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

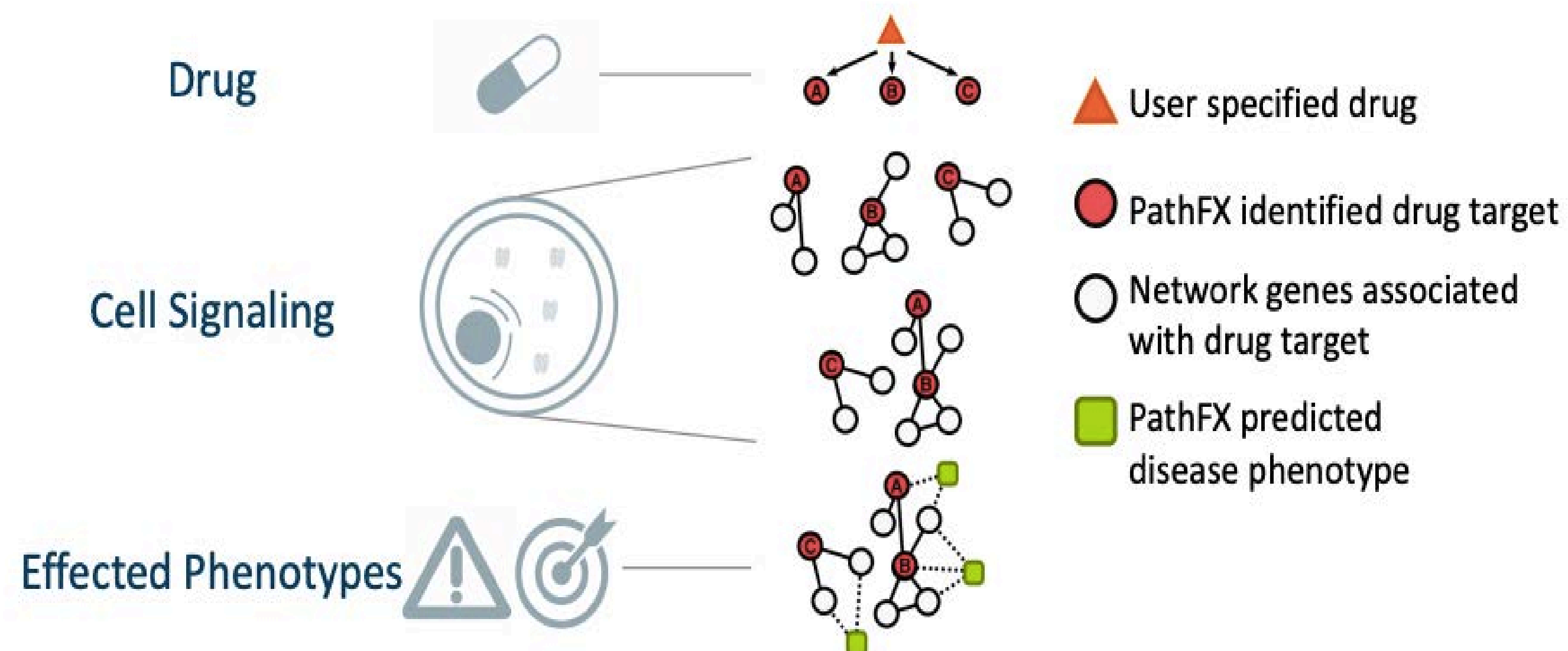
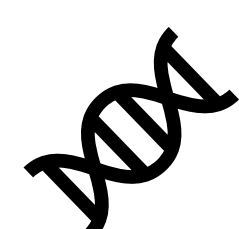


Figure 1. A schematic of PathFX –

- (1) input a drug
- (2) PathFX identifies the primary drug targets
- (3) and predicts phenotypes



Methods

Generate PathFX networks for all approved drugs

Assessment of PathFX predictions for eight neurodegenerative diseases

Analysis of most common pathway genes across and within diseases

Literature review of PathFX predictions

Results

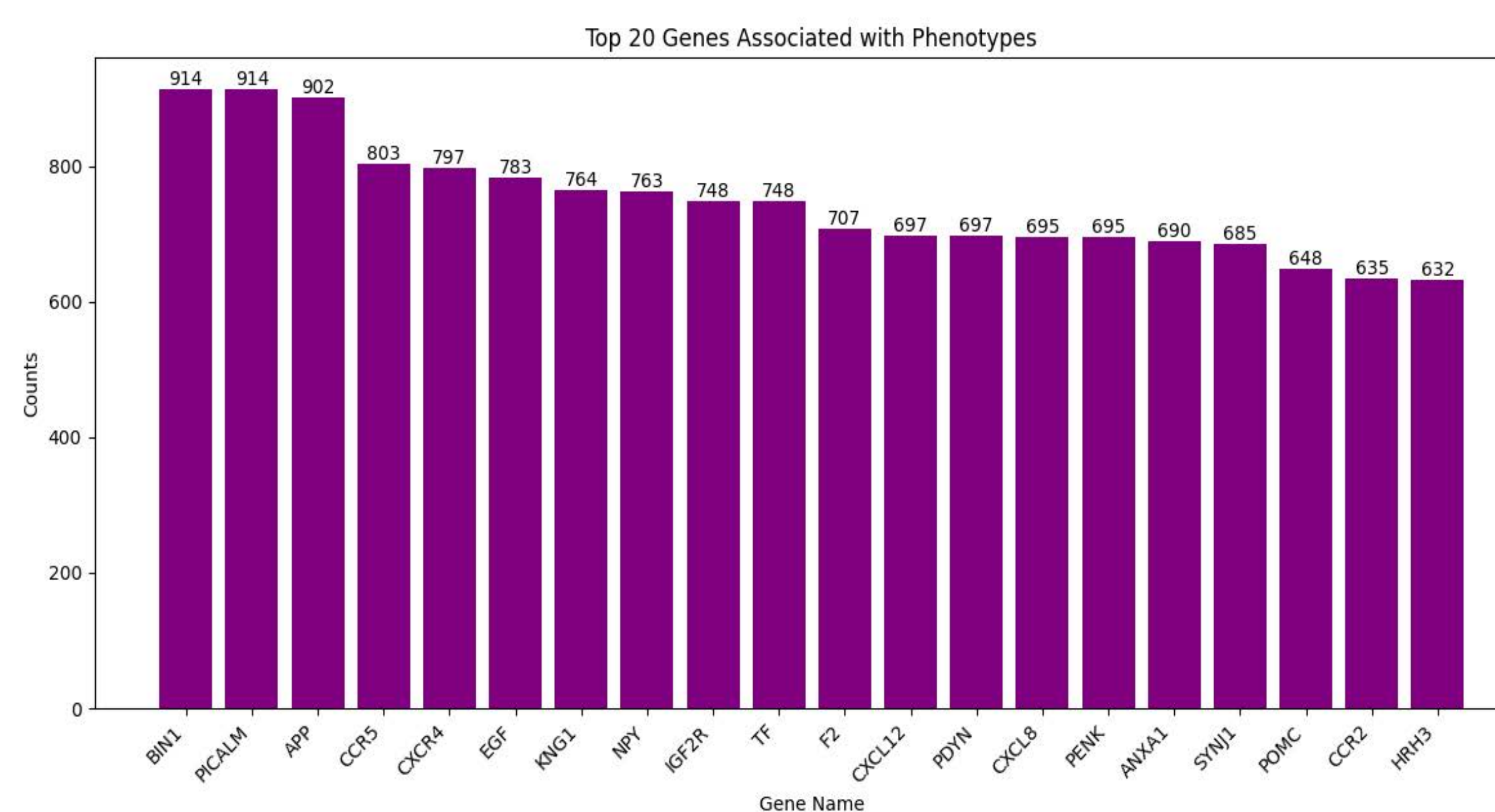


Figure 2. The bar graph illustrates the top genes associated with drug-phenotype predictions from PathFX: Alzheimer's Disease "AD" (1010 drugs), Parkinson's Disease "PD" (422 drugs), Dementia "DEM" (256 drugs), Familiar Alzheimer's Disease "FAD" (452 drugs).

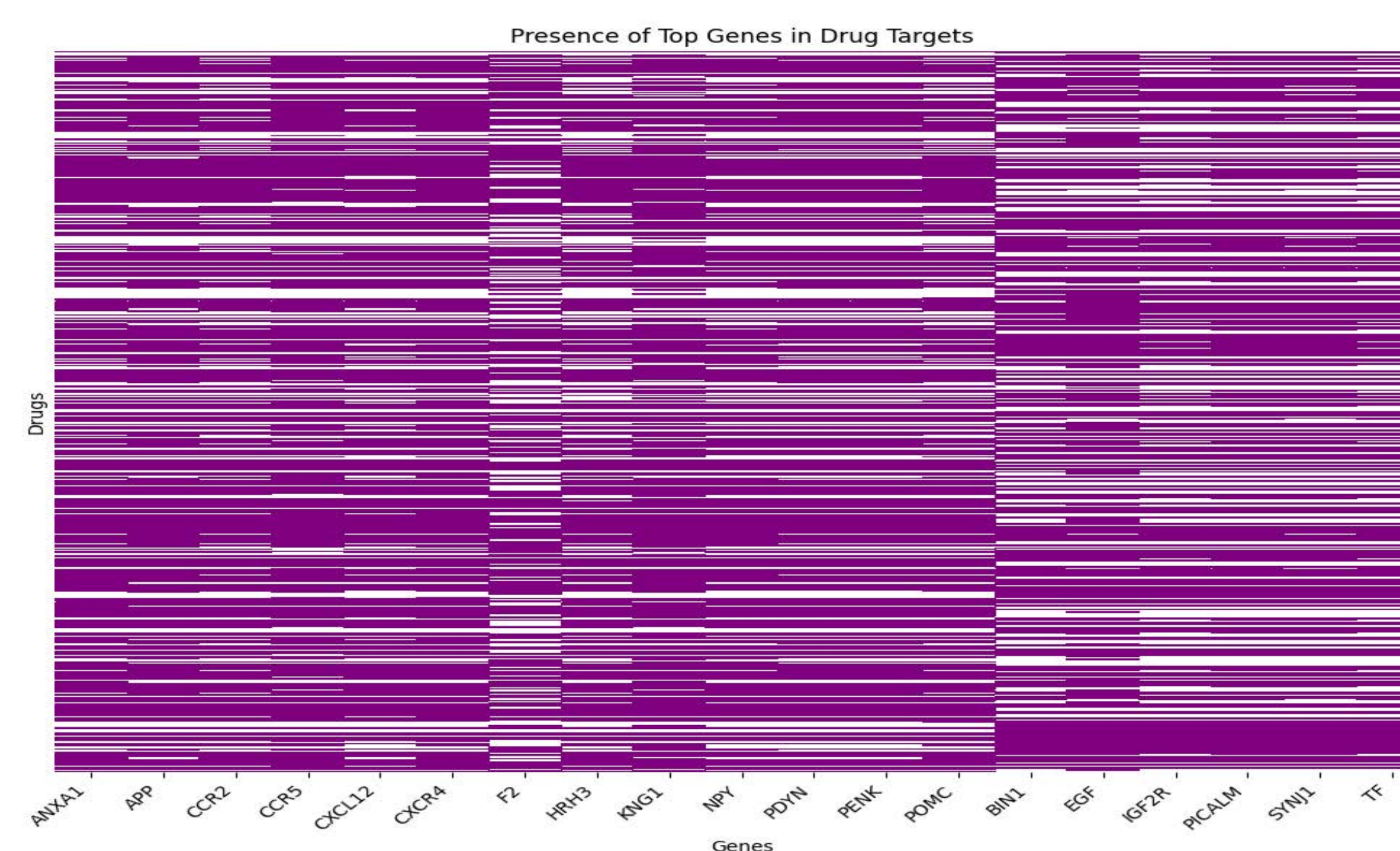


Figure 3. The heat map shows each drug (rows) and the top genes (columns) to which they are associated. This data is generated from 2142 total drug-phenotype relationships discovered from PathFX.

Results

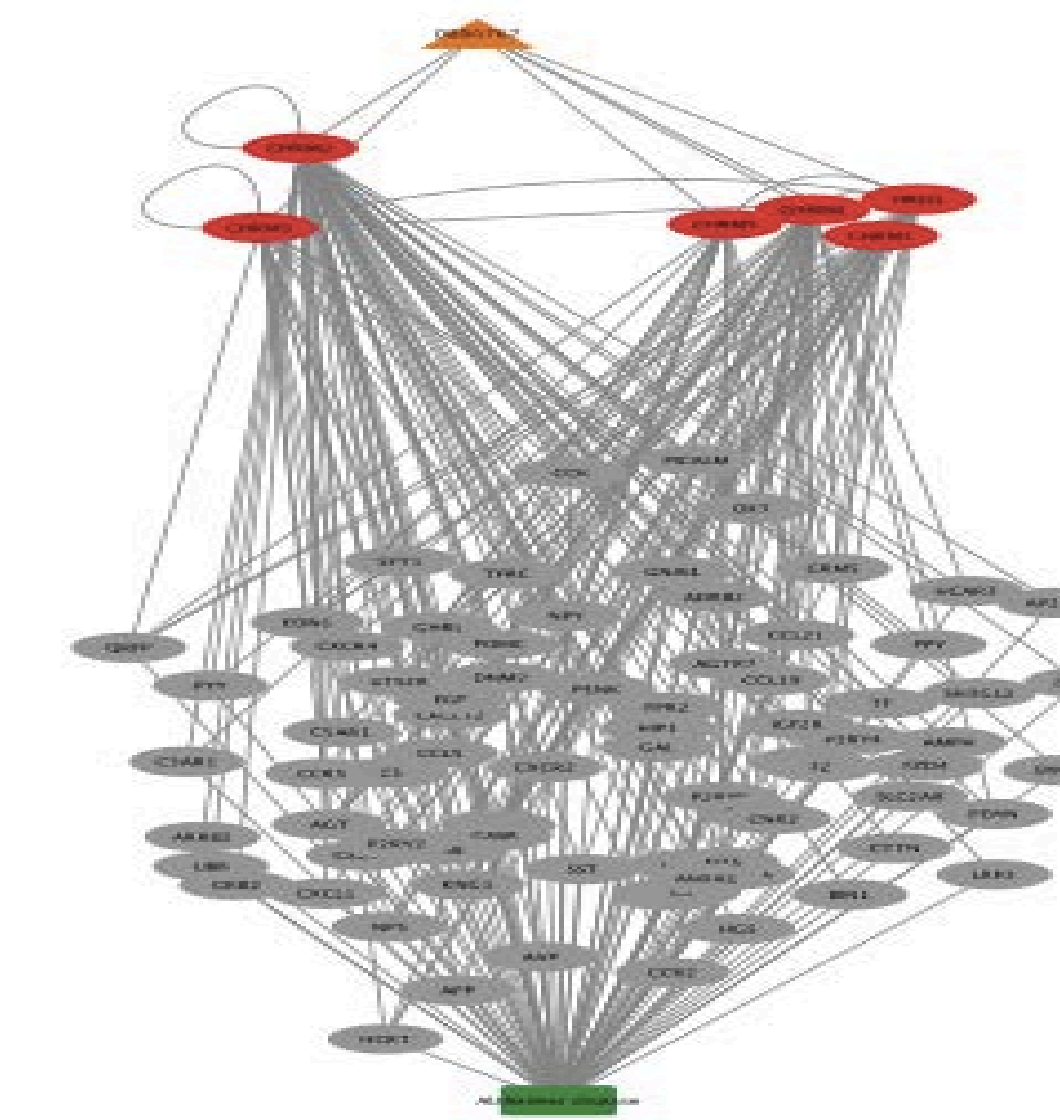


Figure 4. This network diagram shows benzquinamide's (DB00767) association to Alzheimer's disease, but is not, yet, used clinically to treat AD.

Protein coding Gene	Description	Occurred in X networks	Gene Function
BIN1	Bridging Integrator 1	914	Associated with AD, PD, DEM, FAD
PICALM	Phosphatidylinositol Binding Clathrin Assembly Protein	914	Associated with AD, DEM, FAD
APP	Amyloid Beta Precursor Protein	902	Associated with AD, DEM, FAD
CXCR4	C-X-C Motif Chemokine Receptor 4	797	Associated with AD, PD, LBD (type of DEM)
EGF	Epidermal Growth Factor	783	Associated with AD, FAD
KNG1	Kinogen 1	764	Associated with AD, Associated with PD — the cognitive impairment
NPY	Neuropeptide Y	763	Associated with AD, PD, FTD(type of DEM), FAD
IGF2R	Insulin Like Growth Factor 2 Receptor	748	Associated with AD, PD, DEM

Figure 5. Table of literary evidence for the neurodegenerative diseases, using the top common genes.

Conclusion

PathFX can be used to predict associations between drugs and neurodegenerative diseases

- Network analysis revealed common network genes and biological pathway.
- PathFX identified network proteins with several published associations to diseases.
- Further experimental tests and observational studies require to understand patient outcomes to drug exposure.

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