# Using PathFX to Find Novel Drug Pathways to Treat Schizophrenia, Bipolar Disorder, and Major Depressive Disorder/Unipolar Depression

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## Abstract

Schizophrenia (SCZ), Bipolar Disorder (BPD), Major Depressive Disorder (MDD)/Unipolar Disorder (UD) are commonly comorbid diseases, though they are often treated individually. Combination treatments increase the chance of adverse reactions, begetting the need for single-drugs or lower variation of drugs to treat comorbid conditions. Many, including ourselves have used protein-protein interaction (PPI) network models to model drug effects. We used our PPI method, PathFX, to identify drugs with associations to multiple psychiatric diseases and identified shared proteins in these predictions. We discovered several shared proteins GNB1, POMC, SSTR5, APP, OXT, GRM5, HCRT, NPY, CHRM3, and SST and literature support for their connection to disease.
Previous literature has found POMC, GRM5, SST, PDYN, CNR2, and NPY to be associated with these phenotypes. By assessing shared pathways we predicted several single-drug options for comorbid psychiatric treatments, but we require further assessment to validate these predictions as treatments.

## Motivation

- Many psychiatric disorders express with polygenicity
- Patients with the same disease often have alterations in distinct genes
- Due to the complex nature of these traits, one way to understand them is via pathway analysis
- PathFX can be applied to find novel treatments of these diseases

## Introduction

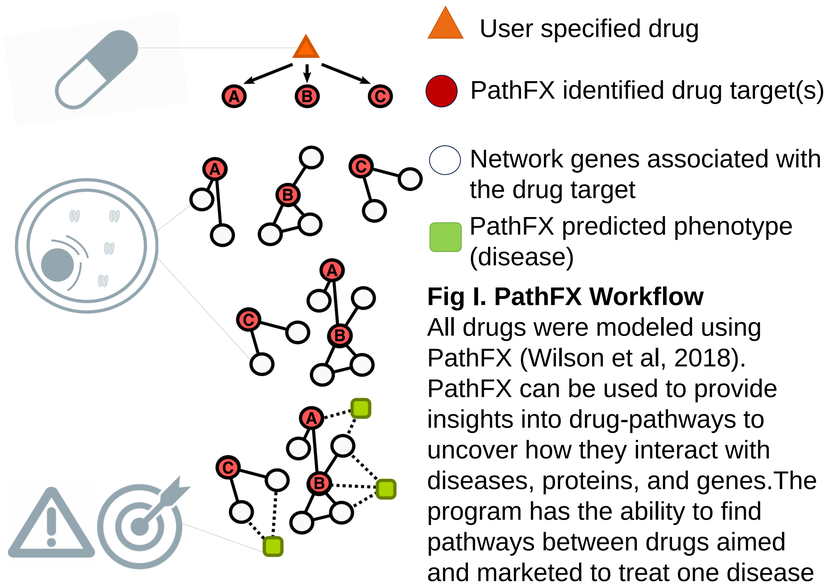


**Fig I. PathFX Workflow**
All drugs were modeled using PathFX (Wilson et al, 2018). PathFX can be used to provide insights into drug-pathways to uncover how they interact with diseases, proteins, and genes.The program has the ability to find pathways between drugs aimed and marketed to treat one disease and others.

## Method

1. Generate PathFX networks for all approved drugs
2. Assessment of PathFX predictions for four psychiatric diseases
3. Analysis of most common pathway genes across and within diseases
4. Literature review of PathFX predictions

## Results

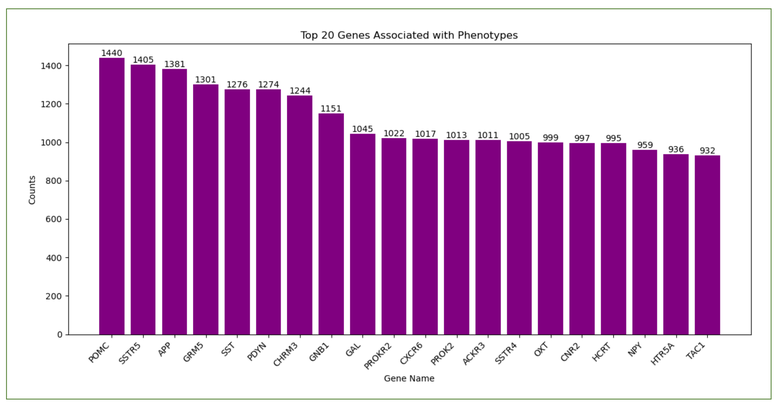


**Figure II:** Bar graph counting the times a protein occurs in a drug pathway for BPD, UD/MDD, or SCZ. 634 unique proteins were found to associate with at least one drug pathway.

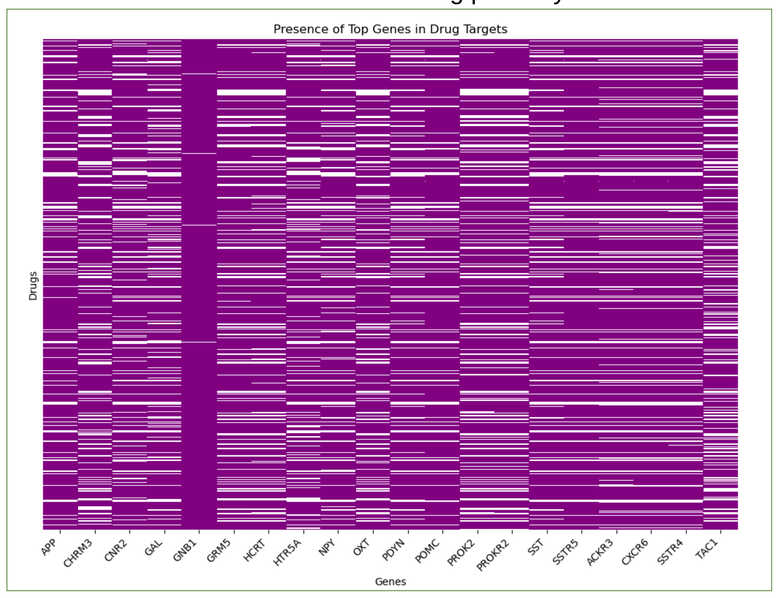


**Figure III:** 757 (rows) unique drugs plotted against the top 20 genes (columns) and if they are (purple) or are not in the drug's association (white). These are an extract of 2245 drug-phenotype associations from PathFX of which 606 drugs were associated with BPD, 416 with SCZ, 740 with UD, and 586 with MDD.

## Results

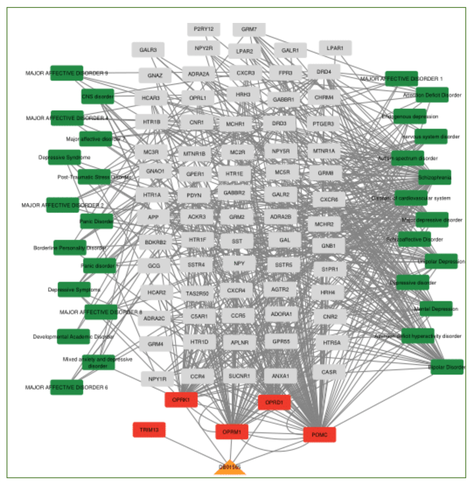

**Figure IV:** Network diagram for dihydromorphine (DB01565, orange triangle), and its' drug targets (red rounded rectangle), phenotypes with associated diseases (green round rectangles), and downstream proteins (grey round rectangles). Dihydromorphine is an analgesic primarily used for moderate to severe pain relief and in this instance associated with all four phenotypes.

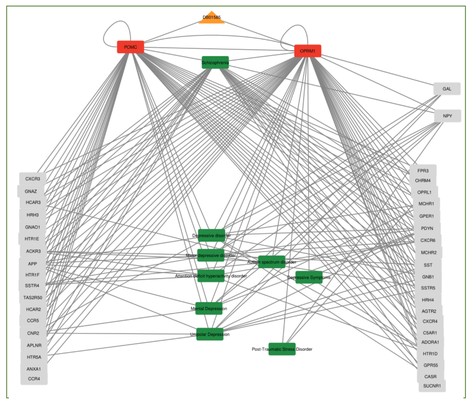

**Figure V:** Dihydromorphine network filtered through OPRM1 and related psychiatric disorders. Psychiatric disorders shown express polygenicity. Distinct pathways can be discerned between dihydromorphine, drug targets, associated phenotypes, and downstream proteins.

## Conclusion

- Network analysis via PathFX has revealed common genes and proteins for SCZ, BPD, and MDD/UD.
- Novel drugs to treat these disorders has been found (e.g., dihydromorphine).
- Further experimental tests and analyses are required to understand these pathways and how they could then be applied to treating patients.

## References

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Wilson JL, Wong M, Chalke A, Stepanov N, Petkovic D, Altman RB. PathFXweb: a web application for identifying drug safety and efficacy phenotypes. Bioinformatics. 2019 Nov 1;35(21):4504-4506. doi: 10.1093/bioinformatics/btz419. PMID: 31114840; PMCID: PMC6821302.

## Acknowledgements

Special thanks to Dr. Jennifer L. Wilson, the Lab for Understanding Network Effects at UCLA, the UCLA Department of Bioengineering, and the UCLA Bruins-In-Genomics (B.I.G.) Summer Program. This project was funded by NIH: NIDCR Grant Number R25DE030117.