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PSY-PGx

A UK biobank analysis of pharmacogenetics CYP2C19 and CYP2D6 and clinical outcome in mood disorder patients

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Introduction

- Pharmacogenetics (PGx) investigates how genetic variation influences drug metabolism, with the potential to improve psychiatric treatment outcomes by minimizing adverse effects and enhancing therapeutic benefit [1, 2]. Despite the availability of dosing guidelines for many psychopharmaceuticals, the integration of PGx into clinical psychiatric care remains limited, and treatment efficacy is often suboptimal [3].
- To address this gap, the **European Union-funded PSY-PGx project** was launched in 2021 as the first large-scale, non-commercial, international initiative to implement pharmacogenetics in psychiatry [4]. Its overarching aim is to optimize care, reduce personal suffering, and alleviate the societal and financial burden of psychiatric disorders. A key objective is the development of an algorithm to guide medication selection and dosing at the individual patient level.
- As part of this effort, data from the **UK Biobank (UKB)** is being analyzed. The UKB is a population-based cohort of over 500,000 participants, containing extensive genetic, lifestyle, and health data. Within PSY-PGx, a subsample of **11,437 patients with mood disorders** (major depressive disorder and bipolar disorder) is under investigation. Linked primary care records provide medication histories, while additional demographic and clinical data allow for a comprehensive exploration of treatment response.

Targets

Two primary targets have been developed to assess treatment effectiveness:

- **Subjective treatment** benefit, derived from participants' self-reported response to the question: *"Has this medication helped you feel better?"*
- **Consistent medication use**, defined as ≥12 weeks of continuous intake, serving as a proxy for both tolerability and clinical efficacy.

CYP2C19	Count	%	CYP2D6	Count	%
Poor	317	2.8%	Poor	731	6.5%
Intermediate	3,024	26.5%	Intermediate	4494	40%
Normal	7,497	65.7%	Normal	5504	48.9%
Ultrarapid	526	4.6%	Ultrarapid	154	1.4%
Unknown	40	0.35%	Unknown	367	3.2%
Total	11,404	100%	Total	11,250	100%

Table 1: Phenotype distrubution in the cohort

Methods

To predict these outcomes, a **machine learning model** is currently being developed based on demographic, clinical, psychiatric, and genetic features, including variation in **CYP2C19** and **CYP2D6**, two key pharmacogenes. Logistic regression and random forest classifiers will be applied, incorporating both main effects and interaction terms to capture potential gene–environment interplay.
Two classification approaches will be employed: logistic regression and random forest. The feature set included:

- Demographics: age, sex, socioeconomic status (Townsend index)
- Clinical variables: psychiatric history, number of psychiatric hospitalizations
- Symptom scores (questionnaires): PHQ-4, PHQ-9
- Genetic predictors: CYP2C19 and CYP2D6 genotypes

Next to these classifications, second order terms will be added to capture any gene-environment interactions.

Drug Type	Drug Name	Count	%
ANTIPSYCHOTIC	aripiprazole	24	0.47
ANTIPSYCHOTIC	clozapine	6	0
ANTIPSYCHOTIC	risperidone	60	1
NDRI	bupropion	34	1
NaSSA	mirtazapine	322	6
SNRI	duloxetine	107	2
SNRI	venlafaxine	244	5
SSRI	citalopram	1997	39
SSRI	escitalopram	60	1
SSRI	fluoxetine	1526	30
SSRI	fluvoxamine	8	0
SSRI	sertraline	715	14
TCA	nortriptyline	47	1
	TOTAL	*5150*	

Gene	# Patients taking highlighted drugs
CYP2C19	4758
CYP2D6	4539

Table 2: Distrubtion of medication and genotyping in cohort

Preliminary findings

Preliminary findings show that random forest models performed best in predicting self-reported benefit, particularly for citalopram (weighted F1 score: 0.723), while logistic regression achieved more balanced results across classes. Interestingly, non-genetic predictors such as socioeconomic status, psychiatric symptom severity, and demographic variables carried more predictive weight than pharmacogenetic factors alone. Moreover, complex interactions emerged between CYP2C19/CYP2D6 and clinical variables, including evidence of antagonistic gene–gene effects.

Despite methodological challenges such as class imbalance, both outcome definitions yielded comparable model performance and highlighted overlapping predictors, suggesting they capture related aspects of treatment response.

The **next steps** involve expanding analyses to include all SSRI users in the UK Biobank, exploring diagnostically homogeneous subgroups, and incorporating additional pharmacogenes beyond CYP2C19 and CYP2D6. By integrating genetic with demographic and clinical data, this research contributes to the development of predictive models that may one day support **personalized prescribing strategies** in psychiatry, paving the way for more effective, individualized care.

1. R. van Westrhenen, K. Aitchison, M. Ingelman-Sundberg, M. Jukic. Pharmacogenomics of antidepressants and antipsychotic treatment: how far have we got and where are we going? Frontiers in psychiatry 2020;11(94): doi: 10.3389/fpsyt.2020.00094
2. Kleine Schaars, K., & van Westrhenen, R. (2023). Pharmacogenomics and the Management of Mood Disorders-A Review. *Journal of personalized medicine*, *13*(7), 1183. https://doi.org/10.3390/jpm13071183
3. M. Nijenhuis, J. Brouwer, B. Soree, HJ. Guchelaar, J. Swen, R. van Schaik, J. van der Weide, G. Rongen, AM. Buunk, N. de Boer-Veger, E. Houwink, R. van Westrhenen, B. Wilffert, V. Deneer, and Hans Mulder. Dutch Pharmacogenetics Working Group (DPWG) Guideline for the Gene-Drug Interaction between CYP2C19 and CYP2D6 and SSRIs Eur J of Human Gen 2021 /doi.org/10.1038/s41431-021-01004-7
4. R. van Westrhenen, AH. Young AH, U. Heilbronner, JM., M. Ingelman-Sundberg, M. Jukic, J Kaprio, MJH Kas, R. Moldovan, MM. Nöthen, A. Philipsen, N. Shomron, E. Van der Eycken, E. Vieta, TG Schulze, and The PSY-PGx Consortium, PSY-PGx: a new intervention for the implementation of pharmacogenetics in psychiatry. **World Psychiatry 2025;24(1):141-142**

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