Metabolic And Genetic Explorations in Refractory Schizophrenia Project:

Assessing the utility of pharmacogenomic (PGx) testing in a cohort with treatment-resistant schizophrenia (SCZ) or schizoaffective disorder (SZAD)

Hilary Williams*, BSc[1]; Natasha Verzosa*, BSc[1]; Reza Rafizadeh, BSPharm, RPh[2]; Ankita Narang, PhD[3]; Prescilla Carrion, MSc, CGC, CCGC[1]; Ric Procyshyn, PhD[1,4]; Randall White, MD, FRCPC[1]; Guillaume Poirier-Morency, BSc[1,5]; Sanja Rogic, PhD[1,5]; Andrew J. Mungall, PhD[6]; William Honer, MD, FRCPC[1,4]; Paul Pavlidis, PhD[1,5,7]; Robert Stowe MD, FRCPC, UCNS[1,9,7]; Chad Bousman, PhD[3].
*shared first

[1]Department of Psychiatry, University of British Columbia (UBC). [2]Faculty of Pharmaceutical Sciences, UBC. [3]Department of Medical Genetics, Psychiatry, and Physiology and Pharmacology, University of Calgary. [4]BC Mental Health & Substance Use Services (PHSA). [5]Michael Smith Labs, UBC. [6]Canada's Michael Smith Genome Sciences Centre, BC Cancer. [7]Djavad Mowafaghian Centre for Brain Health. [9]Department of Neurology, UBC.

BACKGROUND

The **UBC MAGERS (Metabolic Explorations in Refractory Schizophrenia)** Study is an intensive pilot, multimodal –omics and psychiatric genetic counselling research project conducted in 50 participants with severe and treatment-resistant schizophrenia or schizoaffective disorder hospitalized in the tertiary provincial BC Psychosis Program Unit at UBC Hospital. We assessed the relative frequency of poor (PM), intermediate (IM), rapid (RM), and ultrarapid (UM) metabolizers at the drug metabolizing cytochrome P450 (CYP) enzymes most clinically relevant to commonly used psychiatric medications: CYP2D6, CYP2C19, and CYP2C9, in our cohort.

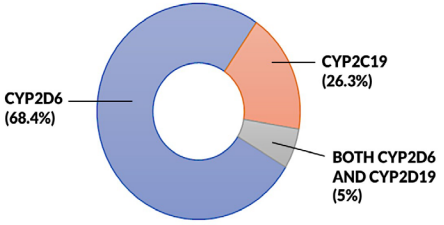
METHODS

1. Detailed medication histories were obtained from interviews, review of medical records, and Pharmanet.
2. Whole genome sequencing (WGS) was performed for 25 participants in the BC Genome Sciences Centre and analyzed in UBC's Michael Smith Laboratories.
3. Actionable PGx variants were extracted using Stargazer in the Psychiatric Pharmacogenomics Lab at the University of Calgary.
4. PGx reports were generated using Sequence2Script Pro software, which integrates inferred medication phenocopies with genotypes, and makes recommendations based on stringent evidence-based guidelines from several databases (CPIC, DPWG, FDA) and resources (PharmVar, PharmGKB, Flockhart Table).
5. Surveys assessing the clinical utility of PGx will be distributed to participants, family members, and treating physicians.

RESULTS

- Mean admission and discharge total PANSS scores were 90.2 and 68.2, respectively.
- 11 participants (44%) had at least one PGx guided recommendation.
- Of the 136 current medications that participants were taking, 19 (14%) had a recommendation: 13 pertained to CYP2D6, 5 to CYP2C19, and 1 to both CYP2D6 and CYP2C19.

CYP2D6 accounted for the majority of PGx recommendations



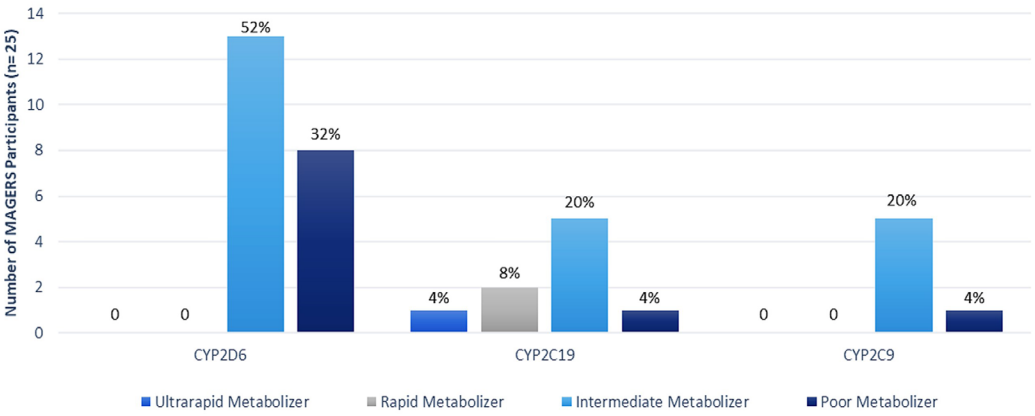


Figure 1. Frequency of poor, intermediate, rapid, and ultrarapid metabolizers at CYP enzymes in a cohort with treatment-resistant schizophrenia or schizoaffective disorder (n=25)

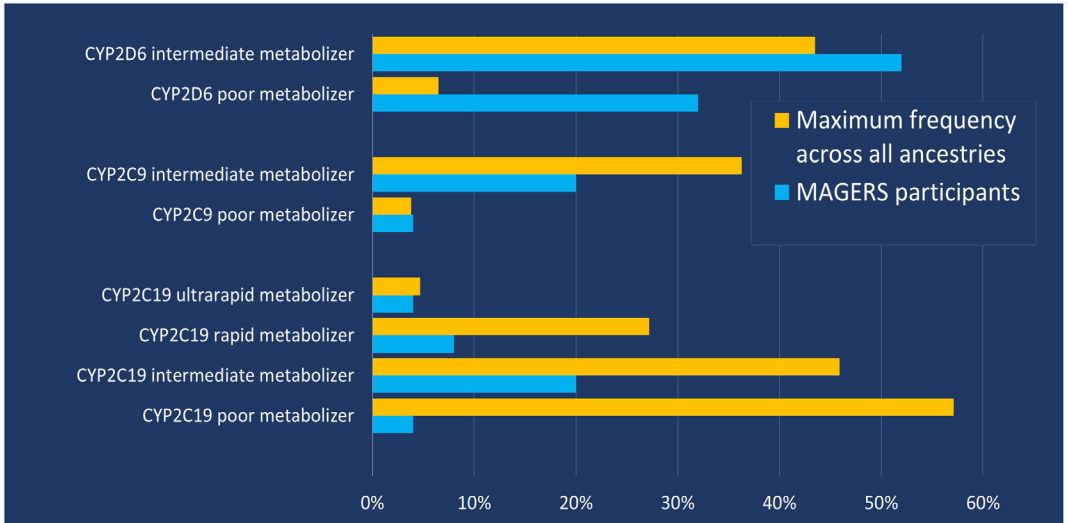


Figure 2. Estimated CYP2D6, CYP2C9, and CYP2C19 maximum phenotype frequencies across all ancestries[1] compared to treatment-resistant schizophrenia or schizoaffective disorder MAGERS cohort (n=25) that consisted of 68% of participants of European/North American ancestry, 12% of East Asian/Chinese ancestry, 12% of Indigenous ancestry, and 12% of African ancestry. The MAGERS cohort had a significantly higher frequency of CYP2D6 PMs compared to the general population (z-score=6.3, p=0.0001).

Case Example – P2

- A 29-year-old male developed psychosis associated with prominent visual hallucinations at age 18. An extensive workup for organic conditions was nondiagnostic.
- His presentation was initially schizoaffective, evolving into continuous schizophrenia.
- Risperidone was tolerated at 1 mg but was discontinued at 4 mg q.d. due to side effects, and he developed 50 msecs of QTc prolongation on 6 mg of haloperidol.
- He was a slow metabolizer (*4/*4) at CYP2D6; DPWG guidelines recommend reducing dosage of both drugs by 50%. He developed fulminant hepatitis on 300 mg q.d. of clozapine level (2413, TR 300-2100 nmol/L), after a very early positive response. Clozapine is metabolized primarily by CYP1A2 (not covered by Sequence2Script), but CYP2D6 may play a significant role in some individuals.
- Poor metabolizer status (*28/*28) at UGT1A1 confirmed clinical suspicion of Gilbert's syndrome as the cause of his intermittent unconjugated hyperbilirubinemia.

CONCLUSIONS

- At CYP2D6, 32% of the participants were PMs in our cohort, compared to an estimated population incidence of 0.4-6.5%[1]. Our preliminary results suggest PGx should be routinely considered in individuals with treatment-resistant psychosis, or who have a history of adverse reactions to multiple psychotropic medications.

LIMITATIONS

- Results were not confirmed in a clinical laboratory; however, we previously reported 98.1% concordance between Stargazer and PharmacoScan, a commercial PGx-optimized array.
- Integration of phenoconversion data relies on assumptions that inducers and inhibitors modify phenotypes similarly to genotypes.
- Our sample size is small (25 more participants have been phenotyped and will undergo whole genome sequencing and PGx analysis later this year).

REFERENCES

1. Bousman, C. A., Bengesser, S. A., Aitchison, K. J., Amare, A. T., Aschauer, H., Baune, B. T., ... & Müller, D. J. (2021). Review and consensus on pharmacogenomic testing in psychiatry. *Pharmacopsychiatry*, *54*(01), 5-17.
2. Narang, A., Lacaze, P., Ronaldson, K. J., McNeil, J. J., Jayaram, M., Thomas, N., ... & Bousman, C. A. (2022). Whole-genome sequencing analysis of clozapine-induced myocarditis. *The Pharmacogenomics Journal*, 1-7.

ACKNOWLEDGMENTS

We thank the UBC Institute of Mental Health, BC Schizophrenia Society Foundation, James Family Foundation, BC Neuropsychiatry Program ERIN Research and Innovation in Neuropsychiatry Funds, and VGH and UBC Hospital Foundation for their financial support, and our research participants for their generous participation.