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Short communication

Impact of PD variation on response to commonly prescribed CNS medications in 3,000 individuals

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Introduction

Interindividual variability in response and tolerability to central nervous system (CNS) medications remains a major challenge in neuropsychiatric care (Bousman et al., 2023). Pharmacogenomic variation may contribute to this variability through both pharmacokinetic pathways, which influence drug exposure, and pharmacodynamic pathways, which may influence drug response at the level of drug targets, receptors, transporters and downstream neurobiological mechanisms. While pharmacokinetic gene-drug pairs have clearer implementation frameworks for several CNS medications, the clinical interpretation of pharmacodynamic variants is generally more heterogeneous and often depends on the strength of the underlying evidence (Tesfamicael et al., 2024; Zhang et al., 2024). Therefore, descriptive analyses of pharmacodynamic variant distributions may help characterize the potential relevance and limitations of CNS-focused pharmacogenomic panels in real-world populations.

Aim

To assess the distribution of pharmacodynamic (PD) variants associated with treatment response across commonly prescribed central nervous system (CNS) medications in a cohort of 3,000 individuals, using a CNS-focused pharmacogenomics panel.

Materials and methods

Pharmacogenetic data from 3,000 individuals in a Greek psychiatric cohort were analyzed using anonymized genotype-only profiles generated with a CNS-focused pharmacogenomics panel.

The analysis focused primarily on pharmacodynamic (PD) variants, defined as variants in genes involved in CNS drug targets and downstream neurobiological pathways. Key PD genes analyzed included FKBP5, ANKK1, DRD2, DRD3, SCN1A and GRIK1. Variant–drug associations were mapped to commonly prescribed CNS medications using the ClinPGx knowledge base. The evaluated medications included antidepressants, antipsychotics, and antiepileptic/mood-stabilizing agents.

Analyses included: (i) the proportion of individuals carrying at least one response-associated PD variant for each CNS medication; (ii) the distribution of decreased-response genotype annotations across the cohort; and (iii) the cumulative number of CNS medications per individual with at least one decreased response-associated PD variant. Data processing and descriptive statistical analyses were conducted using R.

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As no prescription data, treatment outcomes or clinical response measures were available, findings were interpreted as genotype-based response associations rather than direct measures of treatment efficacy or clinical outcomes.

Results and discussion

Drug-level analysis showed that genotypes linked to decreased response were common across the evaluated, commonly prescribed CNS medications. The highest frequencies were observed for risperidone and duloxetine, with 97.3% and 94.2% of individuals carrying at least one relevant genotype, respectively. The lowest frequency was observed for aripiprazole but still included 69.7% of individuals. Overall, 99.93% of individuals carried at least one genotype linked to decreased response for at least one CNS medication, although the number of medications affected varied across individuals.

Cumulative burden analysis showed that most individuals carried genotypes linked to decreased response for multiple CNS medications. Overall, 91.3% of the cohort carried such genotypes for ≥10 medications, while 7.7% carried them for 1–3 medications and 0.9% for 4–6 medications. Only two individuals (0.07%) had no genotype linked to decreased response across the evaluated medications.

Overall, these findings indicate that response-associated pharmacodynamic variants are widespread across commonly prescribed CNS medications. The convergence of multiple pharmacodynamic pathways involved in CNS drug response highlights the complex genetic architecture underlying variability in neuropsychiatric treatment response. A drug-centered pharmacogenomic framework incorporating PD variation may provide a more integrated understanding of interindividual variability in treatment response and contribute to improved characterization of CNS pharmacotherapy response profiles.

Conclusion

This study suggests that pharmacogenomic PD variation may contribute to interindividual variability in CNS medication response across a large cohort. Mapping ClinPGx-defined response-associated variants to CNS medications reveals widespread and heterogeneous pharmacogenomic associations relevant to commonly prescribed neuropsychiatric therapies. These findings support the potential value of drug-centered pharmacogenomic approaches in neuropsychiatric medicine and highlight the prospective role of pharmacogenomic profiling in advancing personalized treatment strategies. Nevertheless, further research integrating pharmacogenomic, prescribing and clinical outcome data is needed to better understand these associations and their potential clinical implications.

References

Bousman, C.A. et al., 2023. The emergence, implementation, and future growth of pharmacogenomics in psychiatry: A narrative review. Psychological Medicine 53(16), 7983–7993. https://doi.org/10.1017/S0033291723002817

Tesfamicael, K.G. et al., 2024. Efficacy and safety of pharmacogenomic-guided antidepressant prescribing in patients with depression: An umbrella review and updated meta-analysis. Frontiers in Psychiatry 15, Article 1276410. https://doi.org/10.3389/fpsyt.2024.1276410

Zhang, Y. et al., 2024. The association of FKBP5 gene polymorphism with genetic susceptibility to depression and response to antidepressant treatment: A systematic review. BMC Psychiatry 24, Article 271. https://doi.org/10.1186/s12888-024-05717-z