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Exploring Common Mechanisms of Adverse Drug Reactions and Disease Phenotypes

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Abstract

Adverse drug reactions (ADRs) are a major concern in clinical healthcare, significantly affecting patient safety and drug development. ADRs are ranked as the second primary reason for drug withdrawals and the fourth leading cause of mortality in the US [1]. The need for a deeper understanding of ADR mechanisms is crucial for improving drug safety profiles in drug design and repurposing, and in making informed healthcare decisions as they can reveal the complexity of in-vivo human phenotypic responses [2]. By understanding the underlying mechanisms of ADRs, we can gain insight into a drug's mechanism of action, which can assist in identifying new drug targets, predicting new therapeutic indications, and advancing personalized medicine.

In this study, we introduce a novel network-based method for exploring the mechanisms underlying ADRs at a molecular level. For this purpose, we construct a comprehensive knowledge graph of 17,010 nodes across six node types (drugs, diseases, genes, proteins, disease phenotypes (DPs), and ADRs) and 159,556 edges across seven edge types (drug–ADR, drug–protein, diseases–gene, disease–DP, gene–protein, protein–protein, ADR–DP). We hypothesize that phenotypically similar ADRs and DPs might result from targeting the same biological mechanisms and pathways. By considering such similarities, our method investigates the commonalities regarding their impact on the protein-protein interaction network and robustly identifies protein sets associated with the underlying biological mechanisms. Applying our proposed method on ADRs from the SIDER database (version 4) [3], we identified the mechanism of action for 67 ADRs (e.g., ventricular arrhythmia, hyperchloremia, vasculitis). To evaluate the relevance and novelty of the identified proteins, we performed pathway enrichment analysis and a

literature search. While our findings align with prior knowledge, we also unveiled novel associations that have not been previously reported.

We further demonstrate how our method can be used for drug repurposing, suggesting candidate drugs for eight different phenotypes, including ventricular fibrillation, precocious puberty, and peptic ulcers. These drugs were selected based on multiple criteria. Moreover, among the drugs suggested by our method, some of them are currently being investigated in clinical trials [4] for each phenotype.

Keywords

Adverse drug reaction, disease phenotype, network-based analysis, network diffusion, drug repurposing.

References

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