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In Drug Development, Systems Pharmacology is used to Predict Medication Safety

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Abstract

In medication research and development, as well as regulatory evaluation, a better biomarker-based assessment of drug safety is required. Identifying drug safety biomarkers such as genes, proteins, miRNA, and single-nucleotide polymorphisms, on the other hand, remains a significant difficulty. We may now investigate drug activities at the organ and organismal levels thanks to breakthroughs in 'omics' and computational tools such as genomics, transcriptomics, metabolomics, proteomics, systems biology, network biology, and systems pharmacology. To aid biomarker-based drug safety evaluation for drug discovery and development, as well as to inform better regulatory decisions, computational and experimental systems pharmacology methodologies could be used. The current state and progress of systems pharmacology methods to the development of prediction models for drug safety evaluation biomarkers.

Keywords: Systems Pharmacology, Drug safety, Biomarker-based

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Introduction

In many cases over the last decade, the traditional drug discovery and development paradigm of "one gene, one drug, and one disease" has been called into question, and the idea of polypharmacology, or network pharmacology, was developed for medications that operate on numerous targets rather than just one. Drug toxicity or side effects can be caused by a variety of mechanisms, including unintended consequences of target engagement (e.g., COX-2 inhibitors reduce prostaglandin production but not platelet thromboxane), promiscuity of the drug target causing (e.g., tyrosine kinase inhibitors cause cardio toxicity) [1], or nonspecific interactions of reactive metabolites (e.g., as seen with acetaminophen-induced liver damage). To ensure the greatest level of drug safety profiles, drug safety assessment is a rigorous process that encompasses several preclinical investigations and clinical evaluations. Deciphering the interactome between medications and genes, which includes drug–protein interactions, drug–miRNA links, drug–SNPs (single-nucleotide polymorphisms) correlations, and so on, is a vital step in improving drug toxicity assessment and enabling precision medicine. Nonclinical drug toxicity has traditionally been studied in vitro utilising cellular assays, cell culture, and tissue culture models to evaluate molecular, cellular, tissue, and even organ effects. Animal models also provide important information at the organism level that cannot be replicated in vitro. Many efforts are being made to enhance existing methods with high-throughput screening and new technology in the hopes of eventually replacing animal testing. Experimental drug toxicity testing is currently exceedingly expensive and time-consuming, especially for medications that will be given on a long-term basis [2].

There are still certain obstacles to overcome, such as extrapolating results from adult human research to effects on youngsters or pregnant women. As a result, it's critical to create new methodologies, such as the ones listed above, as well as computational tools for drug toxicity evaluations, to replace current in vitro and in vivo experimental experiments. Computational approaches like quantitative structure–activity relationship (QSAR) models, for example, are widely used in medication safety and toxicity risk assessment. However, due to the complicated pharmacological activities in humans and other biological species, QSAR approaches have several drawbacks. Recent breakthroughs in 'omics' technologies, such as genomics, transcriptomics, metabolomics, proteomics, systems biology, toxicology, and pharmacology, have enabled us to examine drug activities at the systems level. The pharmacological application of systems biology is known as systems pharmacology. It combines traditional pharmacology and 'omics' data by doing quantitative investigations of large-scale biological networks involving drug–gene, drug–protein, drug–miRNA, and drug–SNP interactions or connections at the molecular, cellular, organ, and organismal levels. Systems pharmacology is an interdisciplinary research field

that requires a wide range of skills, including biology, chemistry, computer science, engineering, mathematics, and physics, and employs high-context, high-dimensional 'omics' data to systematically characterise drug actions at the system level. The application of biomarker-based drug safety assessment in drug discovery and development, as well as regulatory evaluation, is made possible by systems pharmacology [3]. For example, drug–target interactions, chemical–miRNA connections, drug side effects, and drug repositioning have all been predicted using systems pharmacology-based techniques. Drugs typically target proteins for efficacy, which could also be the mechanism through which they cause undesired side effects. Kuhn et al. have published a large-scale study that systematically characterises proteins involved in pharmacological adverse effects. Using a statistical framework, they combined phenotypic data collected during clinical trials with known drug–target interactions to identify overrepresented protein side effect combinations [4].

Conclusion

Next-generation sequencing (NGS) allows for the quick detection of both common and unusual genomic variations. For the application of customised pharmacotherapy, the discovery of variations that contribute to therapeutic medication response or side effects is critical. Despite predicted technological obstacles, short-read based NGS has already been demonstrated to be successful in pharmacogenes with high sequence homology, adjacent pseudogenes, and complicated structure. However, little is known about the efficacy of such panels in detecting copy number variation (CNV) in the highly polymorphic cytochrome P450 (CYP) 2D6 gene or identifying the UDP glucuronosyl transferase (UGT) 1A1*28 promoter (TA)7 TAA repeat polymorphism. PGxSeq, a targeted exome panel for pharmacogenes relevant to drug disposition and response, was created and validated.

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