Systems pharmacology-based identification of pharmacogenomic determinants of adverse drug reactions using human iPSC-derived cell lines

J. G. Coen van Hasselt[1,2] and Ravi Iyengar[1]

Abstract

Few pharmacogenomic predictors of adverse drug reactions (ADRs) are currently available. Pharmacogenomic ADR studies are challenged by the multifactorial nature of ADRs and by insufficient sample sizes. Identification of pharmacogenomic predictors for personalized prediction of ADR risk may be enabled by development of large-scale libraries of patient-derived induced pluripotent stem cells. Using such libraries, ADR-related transcriptomic signatures can be mapped to the pharmacokinetics and pharmacodynamics of drugs, and correlated with clinical datasets and genomic profiles of individuals. Integration of these different data using computational quantitative systems pharmacology models based on machine learning-based algorithms can enable systematic mechanism-based characterization of ADRs. Establishing large scale cell line libraries, and databases and development of algorithms will lead to a knowledge-base that can be used to predict ADR risk in individual patients and for new drug candidates.

Addresses

[1] Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[2] Division of Pharmacology, Leiden University, Leiden, The Netherlands

Corresponding author: Iyengar, Ravi (ravi.iyengar@mssm.edu)

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Introduction

Precision medicine approaches to personalize treatment decisions using molecular profiling technologies are rapidly developing. Significant successes have been achieved in the field of cancer therapy. However, for prediction of adverse drug reactions (ADRs), much less progress has been made. Adverse drug reactions represent a significant challenge in devising therapeutic strategies. One study identified that 7.5% of hospital admissions were associated to ADRs [1], illustrating their major clinical impact on patient care. Several major classes of ADRs remain poorly characterized, and poorly predictable. Examples include peripheral neuropathies, non-arrhythmic cardiac toxicity, skin toxicities (e.g. hand-foot syndrome, rashes), and drug-induced liver injury. Moreover, even when predictive preclinical- or clinical ADR models exist, these models are typically useful for only a subset of patients. A systematic approach may be crucial to increasing our ability to predict ADRs.

The majority of preclinical drug safety studies are conducted to assess major organ toxicities such as cardiac arrhythmogenic potential. These assessments are based on experiments using established cell lines or animal models. Such studies cannot address the crucial role of human inter-individual variation associated with risk of ADR occurrence and severity. Given that attrition of drug candidates due to safety reasons remains high [2], better characterization of human variability of ADRs during preclinical studies is needed.

The value of pharmacogenomic approaches to identify patient-associated genetic ADR predictors is significant and widely recognized [3]. For instance, patients with particular genetic variants of the thiopurine-S-methyltransferase gene may experience severe hematological toxicity if receiving thiopurines due impaired metabolism of the active compound. Similarly, patients with particular genetic variants of the dihydropyrimidine dehydrogenase gene may experience drug accumulation and potential toxicities after receiving standard dosing with fluoropyrimidines due to deficiency of the dihydropyrimidine dehydrogenase enzyme [4]. In spite of these examples, overall, the numbers of unique clinically impactful pharmacogenomic predictors are few.

Here we describe the pharmacological basis and determinants of ADRs and the challenges we face in identifying genomic determinants for ADRs. We then outline how a computational systems pharmacology based approach based on integrating experiments with human induced pluripotent stem cell (hiPSC) derived cell types, genomic and transcriptomic profiling, and clinical data to systematically characterize the genomic

basis of ADRs could be used to predict ADR risk in individuals.

Pharmacokinetic and pharmacodynamic determinants of ADRs

ADRs can be related to either increases in drug exposure (i.e. pharmacokinetics, PK), or, to variability in drug sensitivity (pharmacodynamics, PD). Genetic factors for PK-associated ADRs include genomic variations in drug-metabolizing enzymes that lead to elevated drug or drug metabolite concentrations associated with drug toxicity. Similarly, drug–drug interactions due to competition for drug metabolizing enzymes, or comorbidities such as reduced renal or hepatic function may lead to similar PK-associated ADRs. The majority of pharmacogenomics studies investigating ADRs have been related to PK-associated ADRs. Few genetic determinants of PD-mediated ADRs have been identified, as these determinants can be more diverse and complex in their origin. Examples of PD-associated genetic ADR mechanisms include cutaneous hypersensitivity reactions in patients with the human leukocyte antigen (HLA) A*3101 [5], and *SLCO1B1* gene variants associated with statin-induced myopathies [6]. Comorbidities may also lead to or exacerbate ADRs upon drug exposure, e.g. pre-existing early-stage heart failure may exacerbate cardiotoxicity ADRs. These key factors that contribute to ADRs are summarized in Figure 1. Systematically resolving the determinants of ADRs through their underlying PK- and/or PD-mediated mechanisms will allow us to resolve the different components contributing to inter-individual variability in ADR responses.

Pharmacogenomic studies to identify ADR predictors

ADR-specific pharmacogenomic studies have mostly had the form of candidate gene studies, and to a lesser extent genome-wide association studies (GWAS) [7,8]. The majority of these studies are focused on anti-cancer drugs, and additionally on drugs used for treatment of rheumatoid arthritis, transplantation and epilepsy. These studies predominantly focused on hematological, gastrointestinal, and skin toxicities, whereas a smaller

Figure 1

Schematic representation of key factors that determine clinical adverse drug reactions (ADRs).

number of studies have investigated liver, Musculo-skeletal and peripheral neuropathies. A key limitation of these pharmacogenomic studies is their limited sample size, which when combined with substantial patient heterogeneity related to comedications and comorbidities, result in insufficient statistical power such that we cannot unambiguously identify the genes and their variants involved [7]. Thus, a new paradigm that can allow us to circumvent the hurdles of current ADR pharmacogenomic studies (e.g. sample size limitations, multifactorial causes of ADRs) is needed, and could be transformative in impacting drug safety assessment and patient care. We propose that the combined use of hiPSC-derived cell lines, genomic and transcriptomic profiling, and electronic medical record data, integrated through quantitative systems pharmacology (QSP) modeling could represent a useful approach to enable such a paradigm shift.
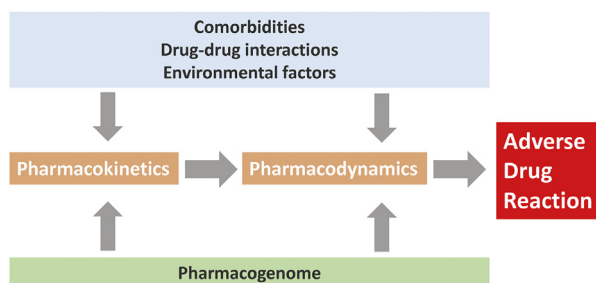
Human iPSC-derived cell lines for ADR characterization

The availability of tissue-specific hiPSC-derived cell types is continuously expanding. hiPSC-derived cell lines from different donors remain transcriptionally associated with their donors [9]. While epigenetic associations with donor age have been shown [10]. Cell types differentiated from hiPSCs are notably difficult to develop into adult phenotypes. Approaches to improve maturation of hiPSC derived cells and tissue types are continuously improving [11]. In spite of these limitations hiPSC-derived cell lines have been shown to be able to recapitulate clinical drug response variability [12—14]. Thus, the potential relevance for hiPSC cell lines in safety pharmacology is substantial. For several poorly predictable ADRs, hiPSC derived cell lines or organoids have become available (Table 1). Particularly, hiPSC cell lines derived from individuals with different levels of ADR severity may be of great relevance [12,14,15]. For instance, commonly used human hepatoma cell lines may offer a better model for hepatotoxicity [16]. Further, organoids, three-dimensional culture platforms and micropatterned surfaces can improve the ability of these in vitro systems to mimic in vivo conditions. Examples include formation of entire kidney structures [17], and studies which show how micropatterned substrates lead to hiPSC-derived hepatocytes with improved properties [18]. For some ADRs that result from more complex interactions between organs, single cell type hiPSC cell lines or organoids may not be sufficient. To this end, multi-compartmental microfluidic platforms that allow interactions between multiple tissues are of great relevance and interest for ADR studies [19,20].

Multi-scale data integration for ADR prediction

We propose that integration of molecular and cell biological data like transcriptomic profiles from hiPSC cell