nature publishing group

COMMENTARIES

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The Phenotype Standardization Project: Improving Pharmacogenetic Studies of Serious Adverse Drug Reactions

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The ability to predict the risk for serious drug-induced adverse reactions first requires a large patient database for characterization and validation of genetic markers. The Phenotype Standardization Project (PSP) was initiated to standardize phenotypic definitions, thereby facilitating much-needed recruitment without sacrificing the reliability of patient classification. Three phenotypes have been considered in this initial phase: drug-induced liver injury, drug-induced skin injury, and drug-induced torsade de pointes.

Overview and rationale

There is increasing appreciation that genomic variants can be used to successfully predict individual drug response, in terms of both efficacy and toxicity. The mechanisms most often recognized thus far center on genes responsible for a drug's metabolism and/or transport and/or on genes responsible for a compound's mechanism of action. The increasing use of genome-wide association scans, and, in the near future, of whole-genome sequencing technologies, is also likely to identify variants in genes that have not previously been considered to be involved in either the disposition or mode of action of a drug, thereby providing novel insights into the pathways involved in drug response.

Adverse drug reactions (ADRs) are common, but fortunately most are mild or moderate in intensity; however, some ADRs are serious and may have lasting or fatal effects.[1-3] Some ADRs are extensions of a drug's desired pharmacological effects, whereas others are the result of off-target effects, often in patients with individual metabolic or immunological variations that defy conventional modes of prediction.[2,4] Many off-target serious ADRs occur at a low incidence—accounting for only 1 in 3,000 hospitalizations—and are statistically unlikely to emerge until after a drug has not only achieved regulatory approval but has also been used in a sufficiently large pool of patients.[1] Indeed, the recognition of serious ADRs early in the evaluation of a new drug candidate makes regulatory approval difficult.

A genetic approach to improving drug safety

Many serious ADRs occur unpredictably and sometimes phenocopy genetic disease, suggesting a genetic contribution to risk. The completion of the Human Genome Project and the advent of whole-genome mapping techniques have allowed researchers to begin to characterize the genetic components underlying serious ADRs.[4] The identification and validation of these genetic markers will enable the screening of patients at risk for serious ADRs and, in some cases, the tailoring of treatment regimens accordingly. The realization of this goal, however, requires a large and sufficiently diverse patient database and development of screening tests with sufficient sensitivity, specificity, and predictive value. [5]

Accurate and standardized phenotyping is the vital initial step. For example, given the relatively rare incidence of these serious ADRs, only small numbers of well-phenotyped patients can be identified from a single center, necessitating the pooling of samples from multiple centers, often from different countries. A standardized phenotype then becomes crucial for accurate pooling of data. Without a sufficiently large patient database, it would not be possible to identify genetic factors of modest effect or by ethnicity. Another critical point is that phenotypic misclassification may dilute or even mask a significant association with a gene locus or provide a false-positive association.

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doi:10.1038/clpt.2011.30

The International Serious Adverse Event Consortium (iSAEC; http://www.saeconsortium.org), in collaboration with other stakeholders, initiated the PSP. The initial goal of the project is to develop standardized phenotypic definitions for three types of ADRs: drug-induced liver injury (DILI), drug-induced skin injury (DISI), and drug-induced torsade de pointes (DITdP). Although the PSP was created to address the need for sufficient patient cohorts to study the genomic basis of specific drug-related adverse reactions and ultimately to identify individual at-risk patients *a priori*, important secondary goals include (i) ensuring epidemiologically correct patient classification to help clinicians, industry, and regulators in identifying the clinical burden of different types of adverse reactions and (ii) providing potential insight into novel pathways that would contribute to safer drug development. Ultimately, it may be possible to firm up individual patient diagnoses so that appropriate care can be provided to reduce morbidity and mortality. Furthermore, although spontaneous adverse-event reporting systems represent an important form of pharmacovigilance, the quality and reliability of such reports are variable. Therefore, the implementation of standardized phenotypes for ADR reporting systems in many jurisdictions not only would make classification easier but would also facilitate targeted follow-up in cases for which there is inadequate information.

Consensus process

The PSP, which is headed by one of us (M.P.), collaborates with the Wellcome Trust and the US Food and Drug Administration. Each of the three ADR Expert Working Groups (DILI, DISI, and DITdP) held meetings and teleconferences pertaining to their phenotypic areas before a meeting was organized at the Wellcome Trust Hinxton Campus in Hinxton, UK, on 16 March 2010. Each Expert Working Group was composed of individuals with varied backgrounds, representing specialists in the relevant field, electronic medical database managers, regulatory agencies, and researchers. The opinions presented in the three articles produced by the groups are based on a consensus process involving expert opinions and published literature. We have not undertaken standardization approaches, for example, those utilizing a Delphi exercise.

The goal of each Expert Working Group was to identify the phenotypic requirements that would allow accurate identification of patients with a given serious ADR and to develop a corresponding clinical classification algorithm to assist in the recruitment of such cases. In addition, participants provided recommendations for key elements to include in the patient record (for use as covariates in a genomic analysis, for example) and the prioritization of patient sample collection.

Participants considered the recruitment of patients using multiple methods, noting their various limitations. Clearly the most accurate methodology is to recruit patients at the time they are experiencing the reaction (i.e., in the acute state). However, this approach alone is not practical and will prolong case recruitment not only because of the relatively uncommon incidence of severe ADRs but also because of the lack of proper infrastructure for recruitment in resource-poor settings. Therefore, we also considered that there may be novel methodologies for identifying and recruiting patients with serious ADRs, for example, using electronic medical records. A patient identified through electronic medical records as having an ADR and who can have the phenotype verified using standardized criteria should be recruited. However, the challenge will be in identifying these patients in the first place, given that the coding used in different databases may vary in terms of sensitivity, specificity, and accuracy. In addition, diagnostic criteria that might be sought in prospective studies may be absent in a retrospective approach, in that documentation of the nature of the reaction in case notes is often incomplete. In such circumstances, a pragmatic approach may be required so that valuable patients are not lost from studies, while at the same time ensuring that researchers do not overcompensate to such a degree that it leads to overinclusion, patient heterogeneity, and, in the end, the inability to identify any genetic associations.

In conclusion, we have undertaken phenotype standardization for three serious forms of ADRs affecting the skin, liver, and heart, which collectively cause significant morbidity and mortality and have been responsible for the withdrawal of drugs from the market. The first two of these standardized phenotypes are described in this issue of the Journal, and the other one will be published in a subsequent issue.[6,7] The PSP will continuously review and reevaluate these standardized phenotypes in response to new clinical or molecular findings and is committed to outlining standardized phenotypes for other types of drug-induced adverse reactions as well. Once available, the adoption of common phenotypic criteria is likely to benefit future research efforts, whether conducted by academic institutions, pharmaceutical companies, or regulatory bodies, with the ultimate aim of creating a robust—and ultimately predictive—pharmacogenomic database that is relevant for all ethnicities.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

1. Pirmohamed, M. *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* **329**, 15–19 (2004).
2. Riedl, M.A. & Casillas, A.M. Adverse drug reactions: types and treatment options. *Am. Fam. Physician* **68**, 1781–1790 (2003).
3. Wester, K., Jonsson, A.K., Spigset, O., Druid, H. & Hagg, S. Incidence of fatal adverse drug reactions: a population based study. *Br. J. Clin. Pharmacol.* **65**, 573–579 (2008).
4. Pirmohamed, M. Pharmacogenetics of idiosyncratic adverse drug reactions. *Handb. Exp. Pharmacol.* **196**, 477–491 (2010).
5. Hughes, A.R., Brothers, C.H., Mosteller, M., Spreen, W.R. & Burns, D.K. Genetic association studies to detect adverse drug reactions: abacavir hypersensitivity as an example. *Pharmacogenomics* **10**, 225–233 (2009).
6. Pirmohamed, M. *et al.* Phenotype standardization for immune-mediated drug-induced skin injury. *Clin. Pharmacol. Ther.* **89**, 896–901 (2011).
7. Aithal, G.P. *et al.* Case definition and phenotype standardization in drug-induced liver injury. *Clin. Pharmacol. Ther.* **89**, 806–815 (2011).