Review

The Impact of Pharmacogenomics Research on Drug Development

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Summary: Over the last two decades, identification of polymorphisms that influence human diseases has begun to have an impact on the provision of medical care. The promise of genetics lies in its ability to provide insight into an individual’s susceptibility to disease, the likely nature of the disease and the most appropriate therapy. For much of its history, pharmacogenomics (PGx) has been limited to relatively simple phenotypes such as plasma drug levels. Progress in genetic technologies has broadened the scope of exploratory PGx and its implementation into safety and efficacy studies, impacting a broad spectrum of drug discovery and development activities. Recent PGx data show the ability of this approach to generate information that can be applied to target selection, dose selection, efficacy determination and safety issues. This in turn will lead to significant opportunities to influence the approaches to drug discovery, clinical development and the probability of success. In particular, adverse drug reactions are critical issues for pharmaceutical companies and for the patients who will benefit from these new medicines. In this review, we outline current progress in PGx, using examples to highlight the influence of polymorphisms, and discuss contemporary challenges for both researchers and clinicians.

Keywords: drug discovery; drug development; pharmacokinetics; pharmacodynamics; efficacy; safety; pharmacogenomics; pharmacogenetics; GWAS; SNPs

Introduction

In the 21st century, emerging genome sciences and technologies are shifting the paradigm of drug discovery research and the development process, and are improving the strategies of medical care for patients. The differences in response to medications are often greater amongst members of a population than they are within the same person or between monozygotic twins. The existence of large population differences with small intra-patient variability is consistent with the idea of genetic inheritance as a determinant of drug response.

The Human Genome and International HapMap projects1,2 have opened the door for a new generation of diagnostic tools aimed at identifying and characterizing human diversity. In particular, they have provided a large resource of single nucleotide polymorphisms (SNPs) that explains much of the variation between different individuals and different ethnic groups. Accumulating evidence strongly suggests that genetic polymorphisms in drug metabolizing enzymes, transporters, receptors, and other drug targets (e.g., toxicity targets) are contributing to inter-individual differences in the efficacy and toxicity of many medications.

Currently PGx broadly refers to the study of variations of DNA and RNA characteristics as related to drug response (see ICH E15 Guideline3). For much of its history, pharmacogenomics (PGx) has focused on studying the relationship between DNA variants—especially in the genes coding for the body’s drug absorption, metabolism and excretion system and pharmacokinetic profile. Pharmacokinetics refers to the analysis of how drug molecules are made available in the blood stream, transported to the relevant target organ and subsequently metabolized and excreted. The effects of the drug molecule at its molecular target and the subsequent signaling or metabolic events that determine any therapeutic effect are facets of the drug’s pharmacodynamics.

There are many practical reasons why pharmacokinetics has been the first drug response phenotype to be explored:
concentration measurements of the drug and its metabolites in body fluids such as plasma or urine are easily and accurately measured, the number of genes involved is somewhat limited and the magnitude of the genetic variation and its penetrance is generally high. Analysis of more complex phenotypes, such as the pharmacodynamic properties of a drug or the basis for idiosyncratic toxicity not related to abnormal plasma levels, has only recently become possible as such studies required significantly more complex genetic analysis that was beyond the reach of earlier technologies. However, key technological improvements, in particular the ability to carry out genome-wide association analysis, have been pivotal in the implementation of a wide range of pharmacogenetic efficacy and safety studies.

Although these technological developments are now capable of generating large datasets, this has created new problems in data management and compensation for multiple testing that requires modified statistical analysis techniques. In addition, the application of new data mining and pattern recognition methodologies has been advancing genetics technology and broadening the scope of PGx exploration. The implementation of PGx in efficacy and safety studies has impacted a broad spectrum of drug exploration. The implementation of PGx in efficacy and safety studies has impacted a broad spectrum of drug discovery and development activities. Figure 1 shows a framework for the application of the PGx process at various stages throughout discovery including target and candidate selection, clinical development, drug approval and life cycle management (LCM).

**PGx Exploratory Study for Target Selection & Toxicity Prediction**

In the past 3 years, genome-wide association studies (GWAS) assaying hundreds of thousands of SNPs in thousands of individuals have reproducibly identified hundreds of associations of common genetic variants with over 80 diseases and traits. The rapid increase in the number of GWAS provides an unprecedented opportunity to examine the potential impact of common genetic variants on complex diseases by systematically cataloging and summarizing key characteristics of the observed associations and the trait/disease associated SNPs (TASs) underlying them. By characterizing the function of interesting TASs or the causative variants further and indentifying potential modifiers of SNP trait associations, this integrated knowledge database provides a great opportunity for target selection. Recently, the development of therapeutic products that depend on the use of a diagnostic test to meet their labeled safety and effectiveness claims has become more common. For example, such a test can identify appropriate subpopulations for treatment or identify populations who should not receive a particular treatment because of an increased risk of a serious side effect. These technologies are making it increasingly possible to individualize, or personalize, medical therapy by identifying patients who are most likely to respond, or who are at lower or higher risk of a particular side effect. The United States (US) Food and Drug Administration (FDA) encourages the development of therapeutic products that depend on the use of an approved or cleared “In Vitro Diagnostics (IVD)” companion diagnostic device and has now finalized the draft guidance “In Vitro Companion Diagnostic Devices” in order to meet this requirement, a PGx exploratory study enables selection of the target early. Thus, creating a molecular profiling of targets and identifying the biological pathways and pharmacodynamic molecular markers are thought to be key approaches to reducing phases II and III attrition.

**PGx for Early Clinical Development**

In clinical development, efficacy PGx should be viewed as distinct from safety PGx: the former is useful for patient segmentation whereas the latter is highly specific for each individual. However, in some areas, such as cancer therapies, efficacy PGx might be used more specifically to select patients to avoid adverse treatment effects in those in whom there is little chance of efficacy. Early efficacy PGx (in phases I and II) can also lay the foundations for identifying patients who require a different dosage regime—either higher to achieve efficacy or lower due to early safety signals.

PGx can be applied either retrospectively or prospectively as shown in Figure 2. As a PGx strategy, GWAS could be applied to identify a candidate gene or genomic biomarker during clinical development, drug approval and LCM management. Retrospectively, PGx looks back over results of clinical trials using genotype data such as the Illumina VeraCode ADME Core Panel in the case of Adsorption, Distribution, Metabolism and Excretion (ADME), related genes (184 markers of 34 genes) or Omni1-Quad, OmniExpress, and Omni2.5-Quad for GWAS, to generate insights into issues such as the pharmacokinetic or pharmacodynamic properties of the drug’s, efficacy and
adverse events. Prospective PGx allows proactive identification and confirmation of patient subgroups (e.g., disease subtypes or poor metabolizers) that are predictive of either positive or negative responses to a drug. If such data were available before or between phase Ia and Ib trials, this would significantly shorten and simplify phase III and increase the probability of success.8 Furthermore, the ability to prospectively identify subgroups of patients responding differently to compounds during early phase II development could permit the progression of multiple compounds for the same therapeutic area with patients being stratified to the compound by genotype.9 The application of PGx to study pharmacokinetics is nonetheless a strong focus of attention at present, but drug regulatory authorities are actively exploring PGx tools to further understand drug exposure (and, in particular, toxicity), utilize this information more widely in selecting drug doses for development and make this information available to physicians. For example, the FDA has released the draft guidance, “Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies,”10 which is intended to assist the pharmaceutical industry and other investigators engaged in new drug development in evaluating how variations in the human genome could affect the clinical pharmacology and clinical responses of drugs. The guidance also provides recommendations on when genomic information should be considered in order to address questions arising during early drug development, and in some cases, during regulatory review. Additionally, the guidance now recommends the routine collection of DNA samples in all clinical studies during development, enabling retrospective analysis to be performed evaluating potential relationships that were unknown prior to trial initiation or discovered during a later phase of development. This kind of information has previously been limited only to the post marketing phase primarily since PGx relationships had generally been discovered later in development. The European Medicines Agency (EMA) have also released a guidance and a draft concept paper11,12 to address the influence of pharmacogenetics on drug pharmacokinetics, encompassing considerations and requirements for the design and conduct of investigations during drug development. In particular, guidance is given regarding the types of studies required and includes specific design considerations and recommendations for different phases of drug development to ensure satisfactory efficacy and safety in pharmacogenetic subpopulations. On January 20, 2011, ICH guideline E16,13 “Genomic biomarkers related to drug response: context, structure and format of qualification submissions,” was finalized in Japan. The objective of the guideline is to create an integrated recommended structure for biomarker qualification and application that will foster consistency of applications across regions and facilitate discussions with and among regulatory authorities. It is also expected that the proposed document format will facilitate incorporation of genomic biomarker data into specific product-related applications. Genomic biomarker qualification can take place at any time during drug or biotechnology product development, ranging from discovery through post-approval.

Although prescribing practices have not yet been significantly altered, the rapid development of techniques in the area of genome analysis has facilitated identification and provided predictive tools to improve drug response and reduce the number of adverse drug reactions. Some of these are now integrated by the FDA and the European Medicines Agency into drug label inserts; currently there are more than 74 items with specific PGx information included in the FDA’s list.14

PGx for ADRs

i) Challenges of the PGx approach for ADRs in the industry: Adverse drug reactions (ADRs) are a major clinical problem.15 Once a molecule is in clinical development, patient safety is the main concern. There are two important places in the development pipeline where PGx studies can contribute towards safety. The first occurs during early clinical trials in which indications of a potential ADR can occur. Observations of AEs can present considerable risks to a development program. However, these risks can be effectively managed during clinical trials to allow “Go/No Go” development decisions to be made in a timely manner, cutting the dead time between the steps in the progression of a drug through the pipeline. For example, if reversible changes in liver function tests are seen in a small subset of patients in a phase II study, it can be difficult to assess the importance of this. Many valuable and effective medicines have a small impact on liver function but, on the other hand, a number of medicines have failed either in late development or after launch due to a subset of patients who exhibit these liver function changes and subsequently develop severe liver failure. If high-risk patients could be identified before starting the drug (e.g., with inexpensive genetic screening), the overall safety of a medicine in the clinical trial would increase considerably and the abrupt
abandonment of drugs at later stages of development could be avoided. The second application of safety PGx is expected in post-launch phase (phase IV) when AEs begin to be observed only after tens of thousands of patients have had exposure to the drug. This is the most critical time for new safety concerns to arise, and the high costs becomes a burden.

In clinical development, significant numbers of samples are available from phase III studies and these datasets provide significant information on the power of genetic data to identify PGx signals and provide insights into other aspects of experimental design. However, greater statistical power can be obtained by increasing the number of controls, while keeping the number of cases constant. An epidemiological control from an unrelated population can be as effective as the matched controls from phase III studies.

Indeed, some major US and European pharmaceutical companies already have their own databases of Caucasian control DNA. By comparing the genotypes of those patients suffering an ADR with the genotypes of a large number of control subjects, it is possible to identify which gene variants are implicated in contributing to the ADR. One of the successful examples, lumiracoxib, is a selective cyclooxygenase-2 inhibitor used to treat acute pain and osteoarthritis, was withdrawn in 2005 because of DILI (drug-induced liver injury) cases. Retrospective genetic analyses revealed that HLA-DQ allelic variants could predict elevated transferase (ALT, AST) levels. The research revealed the association of the HLA-DQA1*0102 allele with patients bearing the highest transferase levels in 100% sensitivity, with an additional negative predictive value of 99%. Novartis has now submitted an application to the EMA for the use of lumiracoxib in genetically selected populations.

The following table presents a summary of the established genetic ADR risk factors:

### Table 1. Examples of established genetic ADR risk factors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reaction</th>
<th>Prevalence</th>
<th>Risk allele</th>
<th>Genetic risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel³⁷,³⁸</td>
<td>Cardiovascular events</td>
<td>0.13</td>
<td>CYP2C19*2/3/4/5</td>
<td>0.03</td>
</tr>
<tr>
<td>Geltinib³⁹</td>
<td>Diarrhea</td>
<td>0.28</td>
<td>ABCG2 Q141K</td>
<td>0.07</td>
</tr>
<tr>
<td>Isoniazid³⁰</td>
<td>Hepatotoxicity</td>
<td>0.15</td>
<td>CYP2E1 &amp; NAT2</td>
<td>0.133</td>
</tr>
<tr>
<td>Co-amoxiclav³⁸</td>
<td>Hepatotoxicity</td>
<td>&lt;0.001</td>
<td>HLA-DRB1*1501</td>
<td>0.2</td>
</tr>
<tr>
<td>Irinotecan³⁹,⁴⁰</td>
<td>Neutropenia</td>
<td>0.2</td>
<td>UGT1A1*28</td>
<td>0.32</td>
</tr>
<tr>
<td>Ticlopidine³¹</td>
<td>Hepatotoxicity (cholestatic)</td>
<td>&lt;0.001</td>
<td>HLA-A*3303</td>
<td>0.14</td>
</tr>
<tr>
<td>Tranilast³²</td>
<td>Hyperbilirubinemia</td>
<td>0.12</td>
<td>UGT1A1*28</td>
<td>0.3</td>
</tr>
<tr>
<td>Fluoxacillin³³</td>
<td>Hepatotoxicity</td>
<td>&lt;0.001</td>
<td>HLA-B*5701</td>
<td>0.04</td>
</tr>
<tr>
<td>Allopurinol³⁴</td>
<td>Severe cutaneous reaction</td>
<td>&lt;0.001</td>
<td>HLA-B*5801</td>
<td>0.15</td>
</tr>
<tr>
<td>Abacavir³⁵</td>
<td>Hypersensitivity reaction</td>
<td>0.08</td>
<td>HLA-B*5701</td>
<td>0.04</td>
</tr>
<tr>
<td>Carbamazepine³⁶</td>
<td>Stevens-Johnson</td>
<td>&lt;0.001</td>
<td>HLA-B*1502</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Allele frequency of the ADR susceptibility variant in the analyzed population.

*Genetic effect is the estimate of the genotypic risk ratio for those homozygous for the susceptible genotype compared to the low-risk homozygote.
However, in the real world, all patients who take a new medicine are not under direct observation, nor are sufficient rapid and reliable reporting surveillance procedures available. In fact, the reporting process for AEs is based on selective self-reported, physician-reported or attorney-reported cases. If the rate of such an AE is actually very low, in the range of 1 out of every 10,000 patients, then a very large cohort of treated patients would be needed.

ii) Introduction of JPDSC activity in Japan: To solve the issue, a nonprofit organization, the International Serious Adverse Event Consortium (iSAEC), was founded in 2007, which is comprised of leading pharmaceutical companies, the Wellcome Trust, and academic institutions, with scientific and strategic input from the FDA and other international regulatory bodies. The mission of the iSAEC is to identify DNA variants useful in predicting the risk of drug-related serious adverse events (SAEs) through international collaboration. However, there was no Japanese involvement because the domestic pharmaceutical companies in Japan have only just started to collect DNA samples during clinical trials. In addition, another important consideration is that the overwhelming majority of GWAS and other genetic studies have been limited to European ancestry populations, whereas genetic variation is greatest in populations of recent African ancestry, and studies in non-Europeans have yielded intriguing new variants. Recently simulation studies showed that the inclusion of different proportions of individuals from different regions of Japan into case and control groups can lead to an inflated rate of false-positive results when the sample sizes are large. Therefore, to elucidate the causes of ADRs seen among the Japanese, a control DNA database of a Japanese population is urgently needed. Since the construction of such a database addresses a common issue facing drug companies in Japan, a group of Japanese pharmaceutical companies have thus established the Japanese PGx Data Science Consortium (JPDSC). JPDSC was established on Feb 20, 2009, with six leading pharmaceutical companies in Japan. The charter companies, Astellas, Otsuka, Daiichi Sankyo, Taisho, Takeda, and Mitsubishi Tanabe Pharmaceuticals, have worked jointly to build a Japanese control DNA database to identify the risks of drug-related SAEs and to improve the efficacy of drugs through a PGx approach. In the first phase, 1,000 control samples have been genotyped with the Illumina 1M bead array. To confirm the hypothesis and usefulness of epidemiological control, 119 Sevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) cases, collected by NIH (National Institute of Health Science) according to spontaneous reports from Japanese pharmaceutical companies, were analyzed with quality-checked data of 991 population controls. A pilot exploratory GWAS study

Genomic location

Fig. 3. Genome-wide association results for all SNPs (n = 863,137) included in the analysis (−log_{10} p values graphed by genomic location)
The analysis result of 119 SJS cases with 991 Japanese population controls.

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demonstrated that a large number of SNPs on chromosome 6 are associated with SJS/TEN (Fig. 3). Most of these significant SNPs are located in extended MHC regions. This result suggested the usefulness of using race-specific population control for ADRs. Currently 2,000 new control samples from over 10 different regions of Japan have been collected; these are age matched to the Japanese population distribution. To complete the Japanese epidemiologic population control database, genotyping with the Illumina 2.5 M bead array and refined HLA regions is currently under progress.

Conclusions

The current activities given here show the potential of PGx to influence both discovery and development of new medicines and their use. The methods for genomic analyses are developed and wait to be fully integrated into both drug development and clinical practice. SNP arrays covering 5 million SNPs will soon become a reality, and the cost for whole-genome sequencing is rapidly decreasing, with companies now offering such services for as little as a few thousand US dollars. The amount of data generated in a whole-genome sequencing approach is huge, but in general, still only genetic information specifically related to the drug treatment would be relevant and be approved by ethic committees in Japan.

The development of PGx and related technologies applicable to the “personalization” of medicines is proceeding at such a pace that it is not a matter of “if” these technologies impact on medicine prescription, but “when”—and to what extent. Although these transformations will make better use of resources, both by healthcare providers and pharmaceutical companies, it is the lives of patients that will see the most significant differences resulting from these developments. Overall, we can look forward to an exciting future in this area.

Acknowledgments: The authors wish to thank the members of JPDSC and NIH.

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