Pharmacogenomic Discovery Approaches: Will the Real Genes Please Stand Up?
Richard A. Walgren, Melissa A. Meucci, and Howard L. McLeod

ABSTRACT

Genetic inheritance plays a significant role in the interindividual variability of drug response. The field of pharmacogenomics seeks to identify genetic factors that influence drug response, including both those that are inherited and those that arise within tumors, and use this information to improve drug therapy. Candidate gene approaches have led to clinical tests for toxicity avoidance (eg, TPMT, UGT1A1) and efficacy prediction (eg, epidermal growth factor receptor-activating mutations). However, the “right” genes are not known for most anticancer drugs. Strategies for uncovering pharmacogenomic associations vary widely from monogenic candidate gene approaches to polygenic genome-wide approaches. This review will place in context clinically relevant pharmacogenomic discovery approaches, including the relative strengths and weaknesses and the challenges inherent with achieving the goal of individualized therapy.

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INTRODUCTION

The therapeutic repertoire of oncology has developed to the point that there are now several active drugs available for the treatment of most common malignancies. However, this has highlighted the fact that one of the most difficult issues faced in clinical practice is deciding which dose of which drug is the best for an individual patient. The existing knowledge of the safety and efficacy of chemotherapeutic agents is determined from in vitro assays, animal in vivo studies, and human population studies. Despite the increasing complexity of this rigorous, multi-tiered approach, administration of the same dose of a given anticancer drug to a population of patients can be expected to have a varied effect on any given individual in that population with regard to both treatment outcome, ranging from success to failure, and treatment-associated toxicity, ranging from no effect to a lethal event. Factors that contribute to this interindividual variability include the patient’s age, sex, diet, comorbid conditions, and performance status, but it is increasingly apparent that a significant portion of interindividual variability is a result of genetic variations in the biology of an individual’s neoplasia and genetic differences that affect pharmacokinetics and pharmacodynamics.

The concept that genetic inheritance contributes to individual variation in drug response is not new, and there are many examples of pharmacogenetic traits influencing the pharmacokinetics of drugs (eg, variation in N-acetyltransferase activity, thiopurine S-methyltransferase activity, and the activity of cytochrome P450 isoforms). In addition, a number of genetic polymorphisms in drug targets that result in altered pharmacodynamics have been identified. For example, mutations in EGFR alter the response to gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, and polymorphisms in the promoter of the thymidylate synthase gene result in a diminished responsiveness to preoperative fluorouracil-based chemoradiotherapy therapy. What is new is the availability of...
candidate gene strategies

Pharmacogenomics approaches can be broadly separated into two categories, those that are based on candidate genes or those that are genome wide. There are of course advantages and disadvantages to each. The candidate gene approach employs a priori knowledge of pathology and pharmacology to identify genes for which expression may impact therapeutic response. Candidate genes are frequently selected on the basis of signaling and metabolic pathways. This approach typically narrows the field of biologic targets to a list of five to 100 candidate genes that are deemed to have a stronger potential chance of affecting therapeutic outcome. Examination of this number of genes is more manageable, but it remains costly and labor intensive. Therefore, lists of candidate genes are often credentialed or further ranked so that stronger candidates can be tested first. Candidate gene approaches offer the advantage of a potential cost savings if the initial gene list proves sufficient to explain the observed interindividual variation. In addition, the smaller number of starting genes reduces the risk of false-positive findings that could occur in a genome-wide approach, but at the risk of excluding other genes that may be important.

therapeutic agent mechanism of action studies

The mechanism of action of many chemotherapeutic agents is already known; at least in part. Thus, for each of these agents, a list of candidate genes is already available by culling the literature. Because every gene has some level of polymorphism, determining which polymorphisms are relevant for predicting patient response to chemotherapy is challenging but not unrealistic. The prediction of cancer treatment outcome based on gene polymorphisms is becoming possible for a number of chemotherapeutic agents and classes, including the topoisomerase I inhibitor irinotecan.

Irinotecan is used in the treatment of various solid tumors, and has US Food and Drug Administration approval for the treatment of advanced colorectal cancer. Irinotecan is a prodrug, which is converted by carboxylesterase to its active metabolite, SN-38. Clearance of SN-38 is via hepatic glucuronidation by UDP-glucuronosyltransferase 1A1 (UGT1A1), resulting in the polar and inactive SN-38 glucuronide and is followed by excretion in the bile and urine. Diarrhea and leukopenia are the dose-limiting toxicities of irinotecan and are associated with increased drug response so that the health of patients can be improved. The subsequent discussion will move past the current examples of applied genomics to review clinically relevant pharmacogenomic discovery approaches, in an attempt to begin addressing how these lofty goals can be reached.
levels of SN-38.21 The clinical pharmacogenetics of irinotecan treatment has mainly focused on polymorphic glucuronidation of SN-38 by UGT1A1. UGT1A1 expression is highly variable, with up to a 50-fold interpatient variability in the rate of SN-38 glucuronidation.22-24 In the general population the UGT1A1 promoter region contains between five and eight TA nucleotide repeats. A six-repeat allele is the most common, and an inverse relationship exists between the number of repeats and the expression of UGT1A1. The presence of seven repeats, instead of the wild-type number of six, results in the variant allele UGT1A1*28. The UGT1A1*28 allele is associated with a reduced UGT1A1 expression, and leads to reduced SN-38 glucuronidation. SN-38 glucuronidation in liver microsomes from individuals homozygous for six repeats was 3.85-fold higher than that observed in microsomes from individuals homozygous for seven repeats (UGT1A1*7 homozygotes).25

Clinical results demonstrate that the UGT1A1*28 allele leads to significantly increased amounts of the active metabolite SN-38, and an increased chance of developing diarrhea and leukopenia during irinotecan therapy.25,26 In a small pilot study of 20 patients with solid tumors treated by irinotecan, severe toxicity was observed only in UGT1A1*28 heterozygotes (one patient with grade 4 diarrhea) and UGT1A1*28 homozygotes (one patient with grade 3 diarrhea and grade 4 neutropenia, and one patient with grade 3 neutropenia).25 This study also showed that the UGT1A1 promoter genotype was significantly correlated with absolute neutrophil count at nadir. In a retrospective study of 118 cancer patients treated with irinotecan, 26 patients experienced severe diarrhea (grade 3 or worse) or neutropenia (grade 4) and 12 of these patients were found to have at least one UGT1A1*28 allele. Four (57%) of the seven patients in the study who were found to be homozygous for UGT1A1*28 experienced severe toxicity, as did eight (44%) of the 18 patients in the study who were heterozygous for UGT1A1*28. Among the 92 patients without toxicity, only 3% were UGT1A1*28 homozygotes and 11% were UGT1A1*28 heterozygotes.26 These studies provided the first clear demonstration that determination of UGT1A1 genotypes may be clinically important for the prediction of irinotecan toxicity, and laid the groundwork for the prospective study by Innocenti et al27 in which irinotecan was administered at a dose of 350 mg/m² over 90 minutes to 63 patients. UGT1A1 genotype and haplotype were then correlated with SN-38 pharmacology and incidence of severe toxicity. Three of the six patients identified as homozygous for UGT1A1*28 were among the six patients who experienced grade 4 neutropenia. The remaining three patients who experienced grade 4 neutropenia were identified as heterozygous for the seven-repeat allele. Patients with the 7/7 genotype (UGT1A1*28 homozygous) had a 9.3-fold-greater risk of grade 4 neutropenia compared with the patients with a 6/6 or 6/7 genotype. This study was the first prospective trial with sufficient statistical power to demonstrate that patients with a UGT1A1*28 allele are at higher risk of grade 4 neutropenia.

Collectively, these data suggest that the determination of the UGT1A1 genotypes may be clinically useful for predicting severe toxicity to irinotecan. By excluding patients who are homozygous for the UGT1A1*28 genotype from receiving the standard dose of irinotecan, the incidence of grade 4 neutropenia would have been cut in approximately half in the study by Innocenti et al, and the incidence would drop still further if all patients with a UGT1A1*28 allele were excluded. These data have also now been reviewed by the US Food and Drug Administration and data on UGT1A1 pharmacogenetics are being added to the irinotecan package insert.

The evidence for an association between activating mutations in EGFR and response to EGFR tyrosine kinase inhibitors has been reviewed recently in the Journal.19,28,29 However, the data to date merit brief comment because they are illustrative of the nuances of somatic pharmacogenomics. The initial reports from very small case-control studies demonstrated a near-perfect relationship between somatic mutations in the EGFR kinase domain and response to gefitinib or erlotinib.14,15 However, larger case series (or cohort) studies have shown that the mutations in this region are able to predict 70% to 85% of the responding patients, but also miss predicting for an important number of responses. This should not be surprising because there are very few examples in cancer biology/genomics in which one step in a multistep process can explain the complete story. Further data are emerging for EGFR gene copy number, germline haplotype, and EGFR heterodimeric partners, each with the potential to provide more complete, or at least more convenient, prediction of tumor response. This work needs to be encouraged to completion, as understanding the “rules” for predicting response to EGFR kinase inhibitors will lead us to more intelligent strategies for optimizing use of the emerging number of targeted therapies.

**GENOME-WIDE STRATEGIES**

Whole-genome approaches allow the experiment, rather than the investigators, to identify genes that play a significant role in a phenotype. A significant strength of these strategies is the ability to screen in a manner that can reveal not only genes that could be anticipated to be involved, but also genes that may not, at first, be expected to play a significant role, potentially adding new insight into pathophysiology or pharmacology. There are a number of challenges faced in developing genome-wide strategies, including controlling for the influence of the environment on a trait, gaining access to relevant populations, and...
in conducting linkage analysis to discover genes that are associated with drug effect.34,35

In an attempt to provide a novel model for the discovery of genes influencing chemotherapy drugs, Watters et al35 described an ex vivo familial genetics strategy in which CEPH pedigrees were used to quantify the impact of genetic variation on cytotoxicity for docetaxel and fluorouracil. With this system, the authors were able to demonstrate that the cytotoxicity to the chemotherapy agents was heritable. Narrow sense heritability estimates for docetaxel, varying by dose, ranged from 0.21 to 0.70, whereas the heritability estimates for fluorouracil ranged from 0.26 to 0.65. Thus the heritability of cytotoxicity observed in this system is similar to or greater than that of several common phenotypes such as plasma triglyceride levels (0.19 to 0.55), body mass index (0.32 to 0.59), and asthma (0.06 to 0.52).36 The observed CEPH population mean IC50 for both docetaxel and fluorouracil was similar to IC50 values observed across the NCI60 panel of human tumor cell lines (http://dtp.nci.nih.gov). In addition, docetaxel- and fluorouracil-induced cell death is mediated by caspase-3 cleavage, similar to that observed in tumor cells.37,38 These data are encouraging for the use of CEPH pedigrees as a discovery tool.

Regions likely to contain the genes important for the observed differences in response to docetaxel and fluorouracil were identified using a genome-wide linkage analysis. The effects of docetaxel were mapped to chromosomes 5q11-21 and 9q13-q22. The effects of fluorouracil were mapped to chromosome 9q13-q22. By narrowing the region of interest, an unbiased candidate gene list can be formed. High-resolution SNP genotype data are available for a subset of CEPH individuals, through the efforts of the International Haplotype Map Project (www.hapmap.org). These data are helping to fine map the region and narrow the candidate gene list. Further studies are underway to determine the specifically involved genes within the mapped quantitative trait loci (QTL) regions, but this method has narrowed the search for the causative genes from the entire genome to a significantly smaller, and more manageable subset.

**Comparative Studies of Ex Vivo Tissues**

Tumor specimens are obtained routinely for many types of cancer at the time of initial diagnosis and staging. Pathologic evaluation of these samples and assessment of local or metastatic spread form the basis of current staging systems. However, even with the most rigorous initial evaluations, individuals within a particular staging group will not behave identically. For example, even after definitive surgical treatment approximately one quarter of individuals with Dukes’ B colorectal cancer will die from recurrent disease and using current prognostic techniques it is unclear if adjuvant chemotherapy is of benefit.39,40

**Pharmacogenomic Discovery Approaches**

In vitro cell-based assays allow for the rigorous testing of samples while minimizing the influence of environmental conditions. Traditional familial genetics methods in chemotherapy studies are thwarted because of the rarity of simultaneous occurrence of a specific tumor type among family members and the inability to administer chemotherapy agents to healthy, normal volunteer subjects. The identification of a need for cell-line based assays which would enable family-based linkage analysis and tests for association led to the development of the Centre d’Etude du Polymorphisme Humain (CEPH) pedigree cell lines.30 CEPH pedigrees are Epstein-Barr virus-transformed lymphoblastoid cell lines that include cell lines derived from individuals in a number of multigenerational families. The CEPH multigenerational families are easily accessible and microsatellite and SNP genotype data are widely and freely available.31-33 Recent studies have highlighted the use of phenotype generation in these pedigrees as a means of obtaining adequate sample sizes. Not the least of the challenges is that genome-wide strategies can be cost prohibitive. To reduce costs, these strategies can be performed at reduced resolutions, such as selecting functionally interesting single nucleotide polymorphisms (SNPs) or haplotype-tagging SNPs to represent a gene. Examining thousands of genes can also be anticipated to generate large numbers of false positives, a factor that will not be attenuated by a reduction in genotyping costs. Three distinct genome-wide strategies have been used to achieve a more optimal selection of candidate genes for predictive oncology: in vitro discovery approaches, comparative studies of ex vivo tissues, and murine in vivo comparative studies (Fig 2).

**In Vitro Discovery Approaches**

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**Fig 2.** Genome-wide pharmacogenomic discovery approaches. Three distinct genome-wide strategies have been used to achieve a more optimal selection of candidate genes for predictive oncology: in vitro discovery approaches, comparative studies of ex vivo tissues, and murine in vivo comparative studies.
Recognizing the complexity of disease progression, Wang et al\textsuperscript{41} employed a DNA microarray–based gene expression profiling strategy to systematically search in a combinatorial manner for molecular markers of cancer classification and outcome prediction in patients with Dukes’ B colon cancer. This effort generated a gene expression–based algorithm with a 23-gene signature that was able to identify patients among a homogeneously classified Dukes’ B group who had an increased probability of recurrence. Validation of the signature in independent patients (Fig 3) demonstrated a performance accuracy of 78%, correctly identifying 13 of 18 relapse patients and 15 of 18 disease-free patients, with an odds ratio of 13 for recurrence (95% CI, 2.6 to 65; $P = .003$).

Similar studies of the simultaneous analysis of large numbers of genes in other cancers (eg, breast,\textsuperscript{42} lung,\textsuperscript{43} and lymphoma\textsuperscript{44}) suggest that this approach may develop into a powerful clinical tool that will greatly complement current staging methods. In addition to serving as a diagnostic tool, the sets of genes that are identified in these approaches may help to direct novel research into the biology of treatment failures, recurrences, and metastasis. This utility is further illustrated by several exciting pharmacologic observations involving childhood acute lymphocytic leukemia (ALL).

Although pediatric ALL is considered curable, approximately one fifth of patients will experience a treatment failure, and little is known about the genetic basis of this resistance. Two recent studies have assessed the genome-wide expression patterns in pediatric patients diagnosed with ALL in an attempt to identify genes that influence the response to treatment. In the first study, Holleman et al\textsuperscript{45} examined leukemia cells from 173 newly diagnosed ALL patients for sensitivity in vitro to prednisolone, vincristine, asparaginase, and daunorubicin, and gene expression in samples was assayed using 14,500 probe sets to identify differentially expressed genes in drug-sensitive and drug-resistant ALL. Using this technique, the authors were able to identify sets of differentially expressed genes in B-lineage ALL that were sensitive or resistant to the four chemotherapeutic agents. A combined gene-expression score of resistance to all four agents was significantly related to treatment outcome ($P = .027$) and was confirmed in an independent cohort of 98 patients ($P = .003$). Interestingly, of the 124 differentially expressed genes identified, only three had been previously associated with resistance to any of the four agents investigated.

In a second study from the same group, Lugthart et al\textsuperscript{46} reported results from studies which used a similar genome-wide differential expression approach to identify 45 genes which contribute to cross resistance to prednisolone, vincristine, asparaginase, and daunorubicin in ALL. This list included genes involved in nucleic acid metabolism, transcription, nucleic acid processing, and DNA repair. Of the genes associated with multidrug resistance, only 16 of the genes overlapped with the genes that the group had previously found to be associated with single-agent resistance. Expression of the 45 multidrug resistance genes was found to identify a subset of patients with poorer treatment outcome in two independent patient cohorts. Collectively these two studies have used genome-wide approaches to provide novel insights into the biology of treatment resistance, illuminating novel potential therapeutic targets. Additionally, they have provided tools to identify patients predisposed to treatment failure, which may help to redirect early intervention with chemotherapy. The sheer number of genes involved in identifying and segregating this polygenetic phenotype is also staggering evidence for the power of genome-wide approaches. The reduction of multigenic clusters into dichotomus (or at least a small number) groups will then allow for meaningful analysis in an attainable sample size, as has been reported recently.\textsuperscript{47,48}

**Murine In Vivo Comparative Studies**

Interindividual variation in drug response is a complex trait, and it is safe to assume that for most drugs, multiple genes contribute, with varying degrees, to any given phenotype. Thus, for technical, economic, and ethical reasons pharmacogenic studies in humans have been limited to a small number of candidate genes that are expected to have a relatively large influence on drug response. In contrast, there are a number of features that favor the use of well-characterized laboratory animals with validated similarities in pathophysiology and anatomy, such as the
mouse. Use of a murine system allows control of diet and other environmental factors such that observed phenotypic differences between groups are most likely of a genetic origin. Whole-genome association studies analyze the differences in the frequency of genetic variants between two groups of unrelated subjects (ie, case and control groups) in comparison with phenotypic differences. With a murine approach it is possible to create rather large family pedigrees by cross breeding populations from distinct well-defined inbred mouse strains. The short generation time of the mouse yields statistical strength in numbers while the more than 20 generations of inbreeding has served to reduce genetic complexity by segregating and fixing genetic factors.

In an attempt to identify genes that influence bleomycin-dependent susceptibility to pulmonary fibrosis, Haston et al. applied a genome-wide screening approach to compare phenotypically extreme mice derived from susceptible (C57BL/6J(B6)) and resistant (C3Hf/Kam) strains. Two loci were identified as having highly significant linkage, one on chromosome 17 and the other on chromosome 11, and were named bleomycin-induced pulmonary fibrosis 1 and 2 (Blmpf1 and Blmpf2). The Blmpf1 loci accounted for approximately 20% of the observed phenotypic variation in both men and women while Blmpf2 accounted for approximately 9% of the phenotypic variation in men only. The existence and sex specificity of Blmpf2 was confirmed in a chromosome substitution strain, and the presence of Blmpf2 was associated with a reduction in pulmonary fibrosis. Although the precision of the mapping did not allow identification of single associated gene for each region, the authors were able to narrow the linkage region for Blmpf1 to a 2.7-cM region between markers D17Mit175 and D17Mit148 within the major histocompatibility complex. Further studies will be needed to examine the influence of the candidate genes from these loci on the bleomycin-induced phenotypic response.

As an alternative to generating and characterizing cross-bred populations many groups have begun to identify and catalog genetic variations across the genomes of recognized inbred strains. Lists of inbred strains and their known phenotypic characteristics are accessible on the Internet (http://informatics.jax.org; Mouse Genome Informatics) along with detailed murine genealogies. This collection of information has the potential to rapidly detail how the strains are related and could serve to speed up QTL mapping by focusing efforts on genomic intervals that have been previously shown to differ between strains. Studies in murine models will never completely recapitulate the pharmacogenomic relationships in humans, but these studies may provide sufficient insights to better select candidate markers for clinical evaluations.

CHALLENGES FOR THE FUTURE OF PHARMACOGENOMICS DISCOVERY

It is the goal for patients to be treated as individuals, with a plan of care that recognizes each patient’s specific needs. So it is of little surprise that there is enthusiasm for the promises of pharmacogenomics. Unfortunately, the days of genetically individualized care remain in the future. To date, relatively few pharmacogenomic findings have made the transition from a research finding to clinical practice. For many existing drugs, the impact of genetic polymorphism seems relatively small; thus, there is less impetus to push for adoption of pharmacogenetic screening of most drugs. In part, this is because the current drug development process favors the selection of drugs with reduced interindividual variability. However, as knowledge of the potential targets uncovered in the human genome increases, a time may come when fewer drugs are able to achieve this goal. It is also easy to imagine that there are a number of drug candidates that would make very good, novel drugs except that it is not currently possible to differentiate between the limited target population in which these agents would be successful and the particular subpopulation that would experience significant adverse effects. Given these relationships, it is no surprise that the field of oncology has been so accepting of pharmacogenomics. Indeed, small changes as a result of pharmacogenetic factors could have potentially great effects in a field that deals with drugs that have a narrow therapeutic index and where small changes in clinical outcomes represent great improvements. Significant challenges remain for the translation of pharmacogenomic research and they should influence the design and implementation of pharmacogenomic discovery approaches. Included among these is the perennial challenge of cost, but also included are the availability of subjects for clinical trials, and the difficulties in developing clinically suitable genomic tests.

The use of candidate gene approaches has been favored because of the ability to scale the search to the available funds (eg, if funds are short, shorten the list of candidate genes). The candidate gene approach has highlighted the value of pharmacogenomics, but it is an inefficient method of discovery and is unlikely by itself to provide sufficient information to allow custom tailoring of drug therapy in a timely fashion. The true strength of the candidate gene approach is as a second-line screening and validation method. Genomic discovery approaches are likely to generate large numbers of candidate genes. Unfortunately, until the level of resolution of these methods is enhanced, the positive associations found by such methods will include regions of genes and not individual genes. Therefore, candidate gene approaches will play a vital role in credentialing and validating these implicated genes.
Genome-wide discovery approaches offer the promise of delivering previously unknown associations as well as identifying potential multigenic associations. Yet, these benefits are constrained and numbers are a principle challenge (eg, number of genes, cost, and number of patients). The sheer number of genes examined and the variability within those genes challenge statistical methods. It is possible to reduce this variability by reducing the resolution of the genomic evaluation or by reducing the genomic variability, as is done in murine approaches. Although these modifications have the added benefit of also reducing sequencing costs, they do pose new problems. For example, rather than implicating a single gene for each positive association, the use of a reduced-resolution approach results in the identification of multiple candidate genes for each positive association whether it is a true positive or a false positive. This in effect, delays rather than reduces sequencing costs. Low-resolution approaches also have an inherent risk of missing associations and will create a need to develop and support techniques for efficient, higher-resolution rescreening.

Clinical trials that include pharmacogenomic discovery approaches will require large numbers of patients to meet power calculation demands. These studies will require large collaborative efforts among academic and nonacademic medical centers, regulatory bodies, and pharmaceutical firms. It is also necessary to convince physicians and patients that any potential trial will offer more benefit than a more traditional one that is just delivering previously unknown associations as well as identifying potential multigenic associations. The future of cancer pharmacogenomics lies in whole-genome approaches that promise to better characterize patient populations and better predict prognosis and drug response. The discovery approaches discussed in this review illustrate the strong scientific basis for the use of genomic information in cancer therapy and suggest avenues for unlocking the promises it may hold. However, advances in and refinements to pharmacogenomic discovery approaches will be necessary to reduce cost, streamline data analysis, increase efficiency, broaden application of this technology, and facilitate translation into the clinic.

**Authors’ Disclosures of Potential Conflicts of Interest**

The authors indicated no potential conflicts of interest.