Chip-Based Genotyping: Translation of Pharmacogenetic Research to Clinical Practice

The observation of interindividual differences in drug tolerance is perhaps as old as pharmacotherapy itself. Since the 1950s several monogenetic traits have been described that explain differences in drug response or drug toxicity in population subsets (1). These early discoveries have evolved into our current understanding of pharmacogenetics as a complex trait. Therapy selection guided by gene test, however, has still not made the transition into clinical practice. In the current issue of Clinical Chemistry, Daly et al. (2) present a dedicated single-microarray assay, or gene chip, for comprehensive genotyping of potentially thousands of variants in genes involved in drug metabolism, excretion, and transport.

These expanded capabilities are necessary because of the complexity of drug disposition. Single polymorphisms alone do not adequately predict drug disposition because multiple routes of metabolism or transport may compensate for deficiencies in a single pathway (3). For example, the anticancer drug irinotecan is not only metabolized by UGT1A1 but is also a substrate for transporter molecules coded by ABCB1, ABCC2, ABCCG2, and SLCO1B1 (4). Comprehensive genotyping based on gene chips allows large-scale studies on the utility of validated and exploratory biomarkers. The pharmacogenetic gene chip developed by Daly et al. (2) covers the 7 valid genomic biomarkers of drug disposition listed by the US Food and Drug Administration (FDA) and thus is an efficient tool for the evaluation of patient variability (5). Also included in this multiplex assay are a further 162 exploratory biomarkers that are currently the subject of ongoing research. Interactions between drugs and transporters are of increasing interest in drug development and drug therapy, and this gene chip may be particularly useful in exploratory analysis in the field of drug transporters. Although evidence does not yet support a clear association between ABCB1 genotype and clinical drug response or toxicity, the gene chip could promote further studies in this field. Of particular potential for future research are organic acid transporters, such as SLCO1B1 or SLC22A1 (6).

This gene chip covers relevant context-specific valid biomarkers and thus could be successfully applied in clinical practice. Our current approaches to pharmacogenetics should parallel those of disease genetics, in which there is a shift toward the recognition of the complex interactions between genes and environmental factors in common diseases (7). Historically, pharmacogenetic investigations have focused on genetic polymorphisms that affect a small number of drugs in a big way, with TPMT as a prime example (8,9). For certain drugs such as antidepressants and antipsychotics, the CYP2D6 and CYP2C19 pathways are of particular importance. These can be comprehensively genotyped with a commercial gene chip (10).

In its current format the diagnostic gene chip as described by Daly et al. (2) has some limitations. Small indels (such as UGT1A1*28) and copy number variations (11) with high relevance for CYP2D6 genotyping cannot be detected. Therefore this chip cannot fully support the gene dose concept for the prediction of CYP2D6 metabolic activity (12). For the reliable detection of such gene duplications an additional specific PCR step upfront has been successfully applied with a different chip (10). Except for these shortcomings the overall accuracy demonstrated for this gene chip assay [Fig. 1 in Daly et al. (2)] is impressive and fully sufficient for routine genotyping, although the detection of rare alleles is not yet fully optimized.

Physicians in clinical practice will intuitively agree that the pretreatment identification of individuals with a low probability of drug response and a high probability of adverse drug reactions would be a significant advantage for individualization of pharmacotherapy. In particular, differences specific to ethnicity can substantially contribute to interindividual variability of drug disposition. Often cited is the 2005 exclusive FDA approval for African-Americans of an antihypertensive medication with isosorbide dinitrate and hydralazine hydrochloride (13). Pharmacogenetic-based prescribing could be facilitated by a pharmacogenetic patient card that would remain with the patient and contain a record of results from a once-in-a-lifetime test with a broad initial screen by using the described gene chip. With the accumulation of further evidence, such information could be used at some later time to find the safest effective drug and dosage for an individual. To take this further, the study of genetic influences on pharmacodynamics due to polymorphisms in drug targets must also be considered. Examples are beta-2 adrenergic receptors or VKORC1 polymorphisms (1). Drug targets are currently not included in the described chip, although such inclusion would be technically feasible.

Pharmacogenetic information can be valuable in beginning the process of identifying patients with abnormal metabolism, then individual dosage can be adapted based on this information. For this purpose, approved dosage guidelines based on pharmacogenetic evidence are needed. So far, only very preliminary and limited guidelines are available. Pharmacogenetics has now come to a point where prospective outcome data and pharmacoeconomic analyses must prove the value of an intriguing concept (14,15).

Pharmacogenetic testing for dosage individualization is of particular interest for drugs with a narrow therapeutic range. The complexity of genetic interactions, the effects of disease, and other environmental factors complicate the interpretation of pharmacogenetic results. For example, much effort has been focused on CYP3A4 because of its dominant role in drug elimination. The ~10-fold variation
in CYP3A4 mediated clearance, however, cannot convinc-
ingly be attributed to genetic variation and is primarily
related to environmental and disease factors (15). Moni-
toring of serum or blood drug concentrations and/or
drug effects during treatment is then necessary to achieve
ranges considered safe and efficient according to outcome
studies and observational data.

After many years of intense pharmacogenetic research,
perhaps it is ironic that thus far the only valid biomarker
for which testing is required before drug prescription is a
protein. Overexpression of Her2/neu is used to select
patients with breast cancer appropriate for drug therapy
with trastuzumab (5). With this beginning, the broad field
of pharmacogenomics enters a challenging future with the
use of high-throughput genomic analysis technologies
(1). Pharmacogenomics may help to define subgroups of
patients who will benefit from targeted therapy. The
integration of pharmacogenomics and proteomics may
enhance opportunities to discover powerful new biomar-
kers for optimizing therapy.

The gene chip described by Daly et al. (2) may be
helpful in prospective drug outcome studies to generate
more evidence on genetic markers that influence drug
transport and disposition. Provided that the associated costs
will be reimbursed, the availability of such data, along
with acceptance among healthcare professionals and pub-
lic awareness, could pave the way toward comprehensive
pharmacogenetic genotyping in clinical practice.

References

4. Kim TW, Innocenti F. Insights, challenges and future directions in irinoge-
netics. Ther Drug Monit 2007 (in press).
5. Food and Drug Administration (FDA). Table of valid genomic biomarkers in
the context of approved drug labels. http://www.fda.gov/cder/genomics/
6. Kerb R. Implications of genetic polymorphisms in drug transporters for pharma-
7. Schmitt VD, Campbell DA, Sehgal S, Anderson WH, Burns DK, Middleton LT,
8. Evans WE. Thiopurine S-methyltransferase: a genetic polymorphism that
affects a small number of drugs in a big way. Pharmacogenomics 2002;12:
421–3.
9. Schütz E, von Ahsen N, Oellerich M. Genotyping of eight thiopurine methyl-
transferase mutations: three-color multiplexing, “Two-Color/Shared” an-
chor, and fluorescence-quenching hybridization probe assays based on
37.
et al. AmpliChip CYP450 GeneChip: a new gene chip that allows rapid and
Allele-specific change of concentration and functional gene dose for the
prediction of steady-state serum concentrations of amitriptyline and nortri-
pyline in CYP2C19 and CYP2D6 extensive and intermediate metabolizers.
13. Lee SS. The ethical implications of stratifying by race in pharmacogenomics.
14. Dervieux T, Bala MV. Overview of the pharmacoeconomics of pharma-
科genetics. Pharmacogenomics 2006;7:1175–84.
15. Andersson T, Flockhart DA, Goldstein DB, Huang SM, Kroetz DL, Milos PM,
et al. Drug-metabolizing enzymes: evidence for clinical utility of pharma-

Nicolas von Ahsen*
Michael Oellerich

Department of Clinical Chemistry
University of Göttingen
Göttingen, Germany

* Address correspondence to this author at: Georg-August University, Department Clinical Chemistry, Robert-Koch-Str. 40, 37099 Göttingen, Germany. Fax 49-551-39-8551; e-mail nahsen@gwdg.de.

DOI: 10.1373/clinchem.2007.088005