Pharmacogenetics – challenges and opportunities ahead

Health & Medicine

Pharmacogenetics, the study of the influence of genetic variation on drug response, and pharmacogenomics, the genome-wide and multifactorial extension of the term (the inclusive code PGx is used from here on), are central to the modern concept of personalized medicine. Although a “ personalized” approach has always been a hallmark of good medical practice, the new aspect is the extensive use of molecular data to tailor drug therapy to the individual patient, in order to maximize therapeutic benefit and to minimize adverse events. PGx developed as an academic discipline over the past six decades, during which a significant amount of astounding examples for pharmacologically relevant genotype-phenotype relationships have been worked out. Basic principles were established, technologies developed, and dozens of genes characterized that have to do with absorption, distribution, metabolism, and excretion (ADME) of drugs, but also receptors and other drug targets.

Only during the past decade first serious attempts have been made to translate this knowledge into clinical practice. Rather suddenly, it became clear that translation is everything but easy. The reasons for these problems are manifold. It will require deeper scientific advances in various directions but also concerted medical, regulatory and social actions to realize the opportunities of PGx for better medical treatment.

PGx is nurtured by two major streams of research, a basic one that aims to discover genetic variation and to understand biological genotype–phenotype correlations, and a clinically oriented one that builds up on basic knowledge to investigate genetic factors in relation to drug response phenotypes and to apply novel diagnostic tools to translate this into clinical care. Modern

technology has revolutionized the speed and output of molecular discovery, providing us with new armament for research. Undoubtedly this will open up great opportunities. However, great challenges must be met in order to realize this potential for basic and clinical PGx.

Challenges in Basic Research

In basic PGx we would like to understand how genetic variation contributes to biological phenotypic variation. Over 300 ADME genes and even more drug target genes have been identified in the human genome [1] . Only few of these have so far been systematically investigated, but even for the well characterized CYP, UGT, or some drug transporter genes, our knowledge is often fragmentary regarding both genetic and phenotypic variation. The current large-scale endeavors like the 1000-genomes project will uncover the existing genetic variation in all our genes across various racial groups within a few years. However the major task will be to find out what these myriads of SNPs and structural variants have to do with our health and variable response to drugs. Genetic alterations can influence gene expression in far more intricate ways than commonly thought, and multiple effects on various levels may turn out to be the rule rather than the exception. To elucidate at least the major functional variants of each gene is precondition for developing diagnostic tools, select relevant variants for pharmacogenetic studies, and correctly interpret associations. Challenges here include improvement of *in silico* prediction tools and *in vitro* test systems, which often lead to controversial unreproducible data, but also development of large collaborative biobanks with extensive medical sample

information available to researchers on request to study genotype–phenotype relationships.

Much of the genetic heritability appears to be hidden in multigenic and multifactorial complex traits. Important genes such as CYP1A2 or CYP3A4 and probably the majority of all genes may lack predictive variants. Yet twin studies as well as recent genome-wide association studies (GWAS) suggest a high proportion of genetic contribution to quantitative (e. g., expression, enzyme activity) phenotypes, which implies the existence of multiple *trans*- and other complex types of interactions. It is currently unclear which strategies could be most successful to tackle these problems. Pathway-oriented approaches are appealing because they are hypothesis-driven. However their limitation is the lack of knowledge about biological gene networks. GWA allows hypothesis-free identification of *cis*- and *trans*- genetic determinants and can in principle capture the entire heritability of almost any phenotype. Current limitations concern incomplete and inappropriate SNP-coverage (lack of causative mutations, difficulties with pseudogenes, etc.) as well as appropriate statistical methods for elucidating the “ hidden heritability” behind the most significant associations that survive multiple testing correction.

Nevertheless, the novel technologies already and undoubtedly will continue to fuel basic research with big challenges, as it will become very important to functionally validate a plethora of new findings and hypotheses.

A helpful hand to contribute to enhanced understanding of complex biological networks should be expected from systems biology modeling

approaches. Although still in its infancy regarding eukaryotes and higher animal biology, there is no doubt that more mechanistic and quantitative models of biological networks will be required to better understand the role of individual genes and their variants in the context of health, disease, and treatment. The challenge here is to develop, together with systems biologists, modeling frameworks for bottom-up and top–down approaches that are adapted to the special requirements and characteristics of PGx research. These include particularly difficult experimental settings (human hepatocytes, tissue collections, clinical studies including healthy volunteers and patients) as well as theoretical challenges, e. g., how to integrate interindividual and population variation into system biology concepts.

Further challenges in basic research concern a variety of additional influential factors that need to be addressed more systematically. Genetic variation is only one side of the coin: we need to know the influence of numerous non-genetic end environmental factors, including sex, age, diet, lifestyle, and our intestinal microflora, to name just a few influential factors for PGx. Furthermore, epigenetic changes, in contrast to the static nature of DNA sequence variants, can influence expression patterns in a time-, environment- and tissue-dependent manner. Circadian rhythms markedly change gene expression patterns of many ADME genes thereby affecting pharmacokinetics and drug response in a time-dependent manner. Exploration of these phenomena and their genetic determinants has just begun, especially in humans. A huge scale of molecular data sets will become available on all these aspects. However, the practical, conceptual,

and computational problems of integrating these data is yet another significant challenge before their full opportunities can be exploited.

Challenges in Clinical Research

As it comes to clinical translation, PGx is faced with big hopes and high expectations by everybody involved: patients who demand effective treatment free of adverse effects; physicians in need of guidance for selecting the most appropriate drug and the right dose for the patient; health care providers who have to find ways to improve medical care while reducing cost at the same time; regulatory agencies who need proof of concept to issue guidelines and laws, and also drug developers who are in fear of losing their costly drug candidates due to unforeseen toxicity in late stages of development.

More than 200 drug labels in the US, corresponding to about 10% of drugs approved by the FDA, contain pharmacogenetic information, still a relatively small figure. But it shows that a significant number of relationships between genetic markers and pharmacokinetic or drug response phenotypes are potentially relevant. However, only very few of them are currently used for individualized treatment, e. g., trastuzumab for HER2 overexpressing breast cancer and some other anticancer agents, and more recently HLA-B*5701 testing to avoid abacavir hypersensitivity 2 . Data proving that genotyping can successfully guide treatment decisions is still largely lacking or controversial, even for well-investigated examples such as TPMT and thiopurines, CYP2C19, and proton pump inhibitors, CYP2D6 and tamoxifen, or CYP2B6 and efavirenz. In addition to well-designed and large enough

prospective studies, development of more advanced algorithms that can take additional genetic predictors and confounding factors into account and deliver quantitative test-data which can be better compared among different studies and with other routinely applied clinical tests (which are often not better regarding their test parameters compared to PGx tests) could help to demonstrate clinical utility.

In addition to these realistic examples, a big challenge in clinical research will be to fill up the PGx pipeline with further successful demonstrations of clinical significance, in order to sustain the development of reliable and cheap enough tests for routine application by the industry, and to continue to motivate other players from industry, health care systems, and regulators to come (or stay) on board and further develop clinical translation.

So, how to fill up the pipeline? Common problems are that pronounced pharmacokinetic effects observed do not affect clinical endpoints, as is the case, for example, for several CNS drugs metabolized by pharmacogenetic enzymes like CYP2D6 or CYP2C19. In addition, reports of clinical significance are often difficult to validate. Better definition of clinical phenotypes and endpoints, and development of standards for clinical PGx studies regarding power, consideration of confounding factors, and test statistics may be required to demonstrate clinical utility in such cases.

Beyond the classical PGx targets, entirely novel discoveries can be made by the GWA technology, which has been firmly established within the past 5 years by showing that highly significant genetic determinants for various phenotypes can be reproducibly identified 3 . Several recent studies on

pharmacological drug response phenotypes (e. g., IL28B and response to hepatitis C interferon-alpha and ribavirin, HLA-B*5701, and drug-induced liver injury due to flucloxacillin, IL15 and risk of minimal residual disease in childhood acute lymphoblastic leukemia) now suggest that GWA could be highly successful also in the PGx context, because associations found in well-designed studies are of immediate clinical significance. Nevertheless, there are several challenges, in part already mentioned above. Particular limitations for pharmacogenetic GWA studies include small sample sizes due to rare adverse drug reactions and the difficulty of replication, lack of rare or even less common (<5%) variants on the microarrays, and heterogeneity of drug response phenotype. There are however solutions to these problems already in sight: establishment of multinational consortia, as currently being pursued in several areas, and of national health care system programs to systematically collect and document drug response phenotypes will help to overcome sample size limitations at least partially; analysis of rare variants will be possible by next generation sequencing or by the advent of the “ personal genome” at reasonable cost; better definition of drug response phenotype could be possible by collecting additional high-density metabolomic or proteomic data. In addition, the multifactorial nature of drug response phenotypes will require novel strategies to detect complex genetic influences from multiple minor impact genes, entire pathways, or gene–gene and gene–environment interactions, a hot topic area already.

Frontiers in Pharmacogenetics is an open-access platform for the publication of research papers that address any of the above mentioned topics. We welcome submission of manuscripts that report new scientific discoveries of

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Footnotes

1. ^ http://www. pharmgkb. org/
2. ^ http://www. fda. gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378. htm
3. ^ http://www. genome. gov/gwastudies/