Need AC, Motulsky AG, Goldstein DB
Priorities and standards in pharmacogenetic research
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Wilkinson GR
Drug metabolism and variability among patients in drug response
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Pharmacogenetics: The State of the Art and How to Proceed

Pharmacogenetics, as the study of germline and somatic predictors of drug response, is almost 50 years old now [1], but, what is the state of the art today, and how to proceed? Need et al., in their recent Perspective's article in *Nature Genetics*, stress the challenge posed by the complexity of drug responses, as these are influenced by multiple genetic as well as epigenetic factors. Setting standards now is a condition necessary for progress both in basic and clinical research, and, as the authors state 'the potential for clinical relevance creates an obligation to raise the standard for pharmacogenetic research as a high priority.'

Prediction, and thereby reduction of adverse drug reactions (ADRs) is the first priority in the clinical area. The article contains a comprehensive table of 34 drugs that, because of ADRs, have been withdrawn from major markets since 1990. However, in many cases no genetic variants related to their withdrawal have been implicated.

Improving the efficacy of pharmacotherapy is the next important issue and the development and application of pharmacogenetic diagnostics will be crucial. These diagnostics can be based on phenotypes or genotypes, and comparative studies will be needed to establish the clinical utility of either approach. The actual definition of drug response to a given drug is therefore of crucial importance. In cancer therapy there is an urgent need for applying somatic pharmacogenetics aiming at the adjustment of therapy to the tumor genotype.

Pharmacogenetic studies would benefit substantially from pharmacogenetic data collected during drug development if these would be submitted as part of the drug approval process. In order to promote this, the Food and Drug Administration issued guidelines for the industry on voluntary pharmacogenomic data submissions in March 2005 (<http://www.fda.gov/cber/gdlns/pharmdntasub.htm>).

Currently, pharmacogenetics is at the stage of translational research, between basic research and clinical application and, as the authors conclude, there is an important role to play for physician-scientists.

Wilkinson, in his article on 'Drug Metabolism and Variability among Patients in Drug Response', also focuses on ADRs, taking, however, drug interactions as a starting point. Cytochrome P-450 enzymes (CYPs) play a key role in the metabolism of drugs and chemicals from the diet and the environment. Inhibition or induction of CYP3A4, the major P-450 enzyme through drug interactions, may have enormous clinical consequences, in particular in the form of ADRs. For example, blood concentrations of cyclosporine may almost double by the regular intake by patients of normal quantities of grapefruit juice. These CYP3A4 effects are independent from the individual genotype. For other CYP enzymes, in particular CYP2D6, CYP2C19, and CYP2C9, common polymorphisms are clinically relevant, as they determine the metabolizer type of an individual. Knowledge about drug interactions and scientific evidence for the clinical consequences of CYP polymorphisms have been available for many years. However, as stated by Wilkinson, there have not yet been clinical trials showing that knowledge of a patient's genotype before prescribing either increases drug efficacy, prevents ADRs, or lowers the costs of therapy. For the time being, according to Wilkinson, the individual patient is best served by an alert physician.

Comment

Both articles comment on the state of the art in pharmacogenetics, with a strong focus on clinical utility, although in very different ways. Need et al. show the wider perspective and try to give a framework for further development, assuming an obligation that arises from the needs in clinical practice. The efforts should be directed towards identifying causal variants that affect drug response through meticulous analysis of phenotype-genotype correlations, applying clear definitions of drug response in clinical practice for given drugs and diseases. The authors hope that involvement of physician scientists in this research will facilitate the translation of basic science into clinical practice. No time frames are mentioned, the proposed priorities and standards appear realistic, and the commitment of the authors to establish clinical utility of pharmacogenetics is convincing.

Wilkinson, by explaining the major mechanism of drug metabolism, draws the attention to the problem that a large part of ADRs are caused by interactions and do not depend on individual genotypes. For another considerable part of ADRs, often related to drug dosage, genetic polymorphisms are causative. Nevertheless, Wilkinson sees no crucial medical need for genotyping, and as the incorporation of new scientific information may take on average 17 years [2], patients should better rely on alert and well-informed physicians.

However, the reality of alarmingly high rates of irreversible, severe and sometimes fatal ADRs [3] confronts us with the fact that many practicing physicians are either not alert, lack the appropriate knowledge, or both. The latter is a strong argument for incorporating basic pharmacogenetics in the medical curriculum [4]. Even if physicians' general knowledge of genetics may be deficient [5] we should not give up seeking for improvement.

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International Rice Genome Sequencing Project
The map-based sequence of the rice genome
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Ninety-Five Percent of Rice Genome Sequenced

Rice (*Oryza sativa* L.) is one of the most important food crops worldwide and feeds over half of the global population. It has important synthetic¹ relationships with the other cereal species and is a model plant for the grasses. In 1998 the International Rice Genome Sequencing Project (IRGSP) started to sequence the genome of rice. It sequenced the temperate rice variety *O. sativa* L. subspecies *japonica* which is cultivated mainly in Japan, Korea and the USA. In *Nature* the authors presented a map-based, finished quality sequence that covers 95% of the 389-Mb genome. A total of 37,544 non-transposable-element-related protein-coding genes were identified.

The authors refer to other researchers who estimate that the world's rice production must increase by 30% over the next 20 years to meet projected demands from population increase and economic development. Rice grown on the most productive irrigated land has achieved nearly maximum production with current strains. Environmental degradation (including pollution, increase in night-time temperature due to global warming), reductions in suitable arable land, water, labour and energy-dependent fertilizer provide additional constraints.

In their publication the authors state that their findings will help to maximize rice productivity and quality by a combination of biotechnology and improved conventional breeding. Comparing genome organization, genes and intergenic regions between cereal species will permit identification of regions that are highly conserved or rapidly evolving. Such regions are expected to yield crucial insights into genome evolution, speciation and domestication.

Comments

The publication in *Nature* of the IRGSP has great value for the community. This genetic study provided a high potential to meet the world's growing demand on food. The authors state that the finished sequence of the rice genome can help to optimize rice production. With biotechnological and conventional breeding, new variations of rice can be developed which have higher yields and can grow in harsher conditions like extreme drought. Moreover, the disclosure of the rice genome can optimize community health by increasing the nutritional value of rice. For example, rice varieties that contain more vitamins can be developed.

On the 10th of August, 2005, the BBC News quoted Rod Wing from the University of Arizona who is a participant in the IRGSP. He said the map-based sequence had led to the identification of genes that confer important traits such as yield and demand for light during growth [1]. Although expectations run high, I would like to emphasize that we should not pitch our expectations too high. Much of the rice genome was known in 2002, and Robin Buell of the Institute for Genome Research already spoke of a milestone in rice research [2]. Many genes are located but the function of most of the genes needs to be unravelled further. In 2002 Robin Buell used the same terms for their results as in this *Nature* publication [1].

This is reminiscent of the fuss which was caused by the HUGO (Human Genome Project) project in 2003. The finished human genome sequence was said to have a great impact on health and the understanding of our genes. Today we see that these promises have only been partially fulfilled. Genes appear to be more complex than expected. And besides, rice is estimated to have 10,000–15,000 more genes than humans. By sequencing genomes, the mystery of life has not yet been revealed.

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- 2 http://www.tigr.org/news/pr_12_18_02.shtml.

¹ Genetic loci that lie in the same order on the same chromosome in different species.