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Regulatory view on PGx education

From the ISP to the FDA, the need for education to enable moving pharmacogenomics out of the lab and into the clinic is gaining momentum. In this News and Commentary article, Frueh *et al* (pp 218–220) comment on the particular importance of this kind of education in a regulatory context. The authors explain the ways in which regulatory agencies can facilitate the intelligent use of pharmacogenomics, emphasizing the need to provide adequate information to physicians, reviewers and patients.

ISP recommendations for deans of education

In order to discuss the incorporation of pharmacogenomics into medical schools' curricula, a 'Pharmacogenomics Education Forum' was held during the third annual meeting of the International Society of Pharmacogenomics. Based on focused discussions and correspondence, the participants agreed upon a Background Statement, Recommendations and Call to Action for Deans of Education at medical, pharmaceutical and health schools worldwide. The resulting document, the present consensus article by Gurwitz *et al* (pp 221–225), is intended to aid the implementation of personalized medicine into core medical education and practice.

Pyrimidine antagonist pharmacogenetics

Pyrimidine antagonists inhibit the normal processes of DNA and/or RNA synthesis; for this reason, they are widely used in cancer therapy. Extensive metabolism is required for conversion of pyrimidine prodrugs into active compounds. However, interindividual variation can affect the extent of activation, which in turn affects the efficacy of chemotherapy treatment. Maring *et al* (pp 226–243) review current pharmacogenetic data on proteins implicated in the response to pyrimidine antagonists, with the aim of identifying potential genetic factors predictive of toxicity and treatment outcome. The authors further discuss the impact of germline polymorphisms, tumor-specific somatic mutations, and protein expression levels on the pharmacology and pathways of these drugs.

Signaling properties of C23S SNP

In the coding region of the serotonin 2C (5-HT_{2C}) receptor, a cysteine to serine change has been identified at the 23rd amino acid (C23S). This C23S polymorphism has been associated with many disease states. This association of genetic variation with disease implies that the C23S SNP may have a functional consequence on the protein, thus increasing the probability of disease. Whereas a previous study suggested that the C23S SNP in the 5-HT_{2C} receptor was functional, Fentress *et al* (pp 244–254) report results demonstrating the converse. Using multiple stable and transient cell lines, the authors present compelling data from three mammalian cell types documenting no functional consequence of the C23S polymorphism on the 5-HT_{2C} receptor in nonedited INI or edited VSV isoforms.

N-acetyltransferase transgenics

Arylamine *N*-acetyltransferases (NATs) are polymorphic drug-metabolizing enzymes that figure in both the detoxification and the activation of aryl compounds. In this paper, Cao *et al* (pp 255–261) provide analysis of 10 transgenic mouse lines containing either the human *NAT1* or *NAT2* transgene. Despite some lines displaying high copy numbers of the transgene, the authors find negligible or no increases in enzymatic activity in a variety of tissues. These results support previous work showing that it is difficult to raise NAT levels using transgenes, and further indicate that the failure to achieve high expression of either of the transgenes suggests overexpression of NAT genes may have harmful effects on development.

Individualizing warfarin therapy

Warfarin—the most widely prescribed anticoagulant for thromboembolic therapy—is regarded as difficult to handle because of its high interindividual variation in drug response. Hemorrhage during warfarin therapy is one of the leading causes of drug-related death in many Western countries. To explore the genetic story behind this variation, Wadelius *et al* (pp 262–270) evaluate the possible association of SNPs in the *VCORC1* and *GGCX* genes with warfarin dose in a group of 201 patients treated clinically with this anticoagulant. When combined with data obtained previously for *CYP2C9* genotype and other variables, a multiple model was constructed that explained 56% of the warfarin dose variation (and 57.4% when *GGCX* is taken into account).

*CYP2A6*1B* and amount of smoking

Nicotine is mainly inactivated to cotinine in humans, and CYP2A6 mediates about 90% of this conversion. In this study, Gambier *et al* (pp 271–275) investigate the influence of polymorphisms of *CYP2A6* on amount of smoking. Of the numerous allelic variants that have been identified to cause changes in enzyme activity, the *CYP2A6*1B* allele is particularly interesting—subjects who possess this allele oxidize nicotine to cotinine faster than subjects with the *CYP2A6*1A* allele. Moreover, the number of cigarettes smoked per day was much higher in subjects homozygous for *CYP2A6*1B*. While no significant difference in smoking status was observed according to *CYP2A6* genotype, the data do suggest that *CYP2A6*1B* is associated with the number of cigarettes smoked daily.

The Pharmacogenomics Journal (2004) 4, 137

www.nature.com/tpj

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Pharmacogenetics in breast cancer treatment

Preliminary pharmacogenetic data strongly suggest an important role for the use of germline genetic information in individualized treatment and prevention of breast cancer. Early results indicate that patterns of gene expression determined on primary tumors may predict sensitivity or resistance to common breast cancer treatments. Stearns *et al* (pages 143–153) provide a comprehensive review of recent developments in cancer genetics research, while also presenting specific genes implicated in drug metabolism and response.

Genetics of β-adrenoceptors and hypertension

Essential hypertension (EH) is a polygenic, multifactorial disease characterized by high blood pressure (BP) without known cause. Beta adrenergic receptors (βARs) are involved in several patho-physiological functions, including BP, and as such are implicated in EH therapy using β-blockers. Filigheddu *et al* (pages 154–160) investigate the association of six genetic polymorphisms of βARs and their G-proteins with EH and analyze antihypertensive response to β-blocker therapy according to genotype. In addition to confirming an association between the R16G polymorphism of the β2AR with EH, the authors also suggest that gender may play a major role in etiology of EH and its treatment.

Pharmacogenetics and bipolar disorder

Pharmacogenetic studies are becoming an increasingly popular method of investigation into the mechanisms of drug response for many psychiatric diseases. Bipolar disorder (BD), or manic depression, is a major psychiatric condition that requires prophylactic and episodic treatment. Existing pharmacologic agents are known to effect significant variability in therapeutic response and side-effect profiles in BD patient populations. Mamdani *et al* (pages 161–170) review recent pharmacogenetic strategies to increase phenotype homogeneity and to identify genetic factors that may mediate response to treatment with lithium and antidepressants.

Pharmacogenomic perspectives of HCV infection

Chronic hepatitis C virus (HCV) infection is recognized as one of the major causes of liver cirrhosis and hapatocellular carcinoma worldwide. Pharmacologic treatment exists, but many patients do not respond to or tolerate the typical full-dose combination therapy. Previous pharmacogenetic analyses suggest that differential response to HCV therapy may be related to promoter and regulatory sequence variations in the human genome. Tang and Kraslow (pages 171–174) review the literature regarding genomic studies and response to HCV therapy and provide perspective on the necessity and direction of future research.

Pharmacogenomics using eukaryotic model systems

A single-nucleotide polymorphism (SNP) in a human gene can drastically affect the activity of the expressed protein, and thereby affect an individual's response to drug therapy. For the purpose of assessing the impact of SNPs on gene function, typical transgenic 'knockout' animal models are inadequate. Brabant *et al* (pages 175–183) present a novel approach for introducing an SNP of choice into virtually any gene through the use of modified single-stranded oligonucleotides (MSSOs). Using a dual-targeting protocol wherein two different MSSOs are designed to edit two different bases in the same cell, the authors created SNPs in a human gene contained in a yeast artificial chromosome.

OPRM1 gene and response to nicotine replacement therapy

Nicotine replacement therapies (NRTs) have proven effective treatments for tobacco dependence, though there is substantial variability in response and relapse rates among smokers. To suggest factors that may be useful to individualize treatment strategies, Lerman *et al* (pages 184–192) examine the role of the functional mu-opiod receptor (OPRM1) gene in response to alternate forms of NRT, including transdermal nicotine (TN) and nicotine nasal spray (NS). Whereas TN provides a gradual and stable delivery of nicotine, NS delivery results in lower and variable nicotine levels. The authors find that smokers carrying the OPRM1 Asp40Asp variant, which increases the binding affinity of beta-endorphin with the mu-opioid receptor, were more likely to have a favorable response to TN.

Gene expression profiling of peripheral blood

Peripheral blood analysis promises to be an important tool for assessing gene expression in various stages of disease, drug response, and therapy. However, gene expression patterns in peripheral blood cells depend largely on temporal and interindividual variations. Debey *et al* (pages 193–207) conduct a thorough study of this problem by examining methods of cell isolation techniques at various temperatures, followed by cDNA microarray analysis of gene expression. The authors observe that a number of genes were downregulated in the process of cell isolation, particularly those associated with metabolism and cell cycle. They conclude that, for large clinical studies, it is crucial to maximally reduce the time to RNA isolation.

Expression profiling in rat models of alcoholism

Analyzing gene expression patterns in genetic models of alcoholism may uncover unknown susceptibility genes, and point to novel targets for drug development. Monoaminergic genes involved in brain reward pathways and serotonergic genes involved in impulse control and anxiety traits have been suggested to confer genetic susceptibility for alcoholism. Using oligonucleotide DNA microarrays to compare gene expression profiles in the forebrains of alcohol accepting (AA) and alcohol non-accepting (ANA) rats, Arlinde *et al* (pages 208–218) reveal 48 differentially expressed genes between the two lines. The authors suggest that this functional genomics approach may represent a viable tool in the search for novel targets for pharmacological treatment of alcoholism.

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Pharmacogenomics in Japan

International cooperation is critical for progress in the related fields of pharmacogenomics, pharmacogenetics, and pharmacokinetics. Yet contrary to this truism, information from Asia appears to be lacking in the global scientific discourse. To remedy this, Tamaoki and colleagues (pp 288–290) provide an overview of current pharmacogenomic research and policy initiatives in Japan.

Polymorphism in dopamine-related genes

Idiopathic Parkinson's disease (IPD) is a progressive neurodegenerative disorder for which no restorative or neuroprotective therapy is available. Approximately 15–20% of patients with the disease do not respond to treatment with levodopa, while those who do respond often develop adverse fluctuations in motor response. In this review, Gilgun-Sherki *et al* (pp 291–306) summarize the polymorphism-association studies on IPD performed to date, with emphasis on the influence of polymorphisms in dopamine-related genes on the efficacy of levodopa.

Gemcitabine pharmacologic pathway SNPs

Gemcitabine is a deoxycytidine analog that has demonstrated anticancer activity in several solid tumors, including pancreatic, lung and breast cancers. In clinical practice, however, gemcitabine has shown considerable variability in efficacy and toxicity. As there are currently no tools for prospective identification of patients at risk for untoward events, Fukunaga *et al* (pp 307–314) set themselves the task of identifying a series of genetic polymorphisms potentially relevant for gemcitabine pharmacokinetics and pharmacodynamics. Their study provides an important initial step toward the identification of markers capable of predicting variability in gemcitabine response.

Functional mapping of drug response

Differential drug response, or pharmacodynamics, is likely to be a complex trait controlled by the influence of multiple genes and various biochemical, developmental and environmental factors. In order to identify specific genes affecting variation in pharmacological response, genetic mapping has proven to be a powerful tool for detecting specific quantitative trait loci (QTL) based on polymorphic markers. In this article, Gong *et al* (pp 315–321) present a novel statistical model for genetic mapping of QTLs, which facilitates the simultaneous analysis of multiple components of drug response.

Venlafaxine enhances hippocampal resilience

Previous studies have demonstrated that prolonged stress negatively alters hippocampal plasticity, while antidepressant treatment can increase neurogenesis in the hippocampus. Taking this as a point of departure, Xu *et al* (pp 322–331) investigate cellular and molecular changes in the hippocampi of rats subjected to repeated stress (RS), as well as the poststress effects of chronic administration of an antidepressant drug, venlafaxine. The authors found that RS supressed hippocampal cell proliferation, decreased BDNF levels, and increased levels of copper/zinc superoxide dismutase (Cu/Zn-SOD) and the number of Cu/ZN-SOD immunostained interneurons. In animals treated with venlafaxine, these striking neural changes returned to control levels.

Rivastigmine in APOE ε4 carriers and noncarriers

Over the past decade, several risk factors have been associated with Alzheimer's disease (AD), including genetic background. At the moment, the only successful pharmacological treatment of cognitive impairment in AD has been cholinesterase inhibitors, such as rivastigmine. The strongest genetic association in patients with late-onset AD is with apolipoprotein E (APOE) gene polymorphisms, particularly the ε4 allele. Although the specific mechanisms governing APOE isoform-specific effects in AD are not fully understood, an interaction between APOE ε4 and cholinesterase genotypes has been proposed. Farlow *et al* (pp 332–335) investigate this link with a retrospective analysis of two double-blind, placebo-controlled studies aimed to evaluate the efficacy of rivastigmine on cognitive outcomes in patients with or without the APOE ε4 allele.

Valproate, an HDAC inhibitor, inhibits excitotoxicity

Valproic acid (VPA) is used to treat bipolar mood disorder and seizures and is known to inhibit histone deacetylase (HDAC). In this paper, Kanai *et al* (pp 336–344) present the effects of VPA and other HDAC inhibitors on excitoxicity, histone acetylation and GADPH (a gene previously shown to be proapoptotic) in rat cerebellar granule cells in culture. Their results strongly suggest that VPA protects neurons from excitotoxicity through the inhibition of HDAC activity. The authors further suggest that this neuroprotective effect may involve supression of excitotoxicity-induced accumulation of GAPDH protein in the nucleus.

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www.nature.com/tpj

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Genetics of tardive dyskinesia

Tardive dyskinesia (TD) is a potentially irreversible movement disorder following long-term treatment with antipsychotic drugs. For clinical practice, pharmacogenetic assessment of individuals at high risk for adverse effects such as TD would be extremely valuable to minimize the side effects. The paper by Müller *et al* (pages 77–87) summarizes the pharmacogenetic studies on TD and highlights the major findings.

HapMap project and its application

A central goal in the study of human biology is to understand the molecular basis of common disease, and variable sensitivity to drugs and other environmental factors. Research has been greatly enhanced by the wealth of information on new genes and variants currently available as a result of the Human Genome Project. The article by Deloukas and Bentley (pages 88–90) discusses the applications of the HapMap project (launched in October 2002) whose aim is constructing a genome-wide map of linkage disequilibrium and common haplotypes in four populations from Africa, East-Asia and Europe.

CAR/PXR-mediated expression and regulation of Cyp3a41 and 11

Cytochrome *P*450s (CYPs) are a family of heme thiolate proteins responsible for the oxidative metabolism of various clinically active drugs. The phase I metabolism of more than 50% of therapeutic drugs is catalyzed mainly by the CYP3A subfamily. To add to the complexity, CYP3As can also be induced and suppressed by a wide variety of xenobiotics. The study by Anakk *et al* (pages 91–101) defines the role of two known xenobiotic receptors involved in CYP3A regulation, PXR and CAR.

Stress-induced cigarette craving

Cigarette smoking is one of the most preventable causes of morbidity and mortality. Despite the widely recognized risks, about one-third of people continue to smoke worldwide. Findings by Erblich *et al* (pages 102–109) provide strong support for the possibility that dopamine involvement in stress-induced craving well established in animal models also applies to humans, and suggest a potential genetic risk factor for persistent smoking behavior.

Synaptic vesicle proteins (SVP) and antidepressants

SVP play a critical role in neurotransmitter release and neural plasticity, and have been implicated in the pathophysiology of psychiatric disorders such as depression. In order to investigate the effects of antidepressant compounds on SVP-mRNA levels, the expressions of synaptophysin, synaptotagmin, VAMP and synapsin-I have been analyzed in rats. The paper by Rapp *et al* (pages 110–113) demonstrates that synaptophysin, synaptotagmin, synapsin-I and VAMP are drug-responsive genes, and raise the possibility that alterations in the expression of these or other SVP might be important in producing some of the molecular and cellular effects of antidepressants in the limbic system.

Gene expression in learned helplessness rats

In an effort to better understand the molecular and genetic bases underlying the pathophysiology of depressive disorder and to improve the rationale for the design of antidepressant drugs, Nakatani *et al* (pages 114–126) performed DNA microarray analysis using an animal model of depression. The authors screened over 8000 rat genes and expressed sequence tags, and identified 82 distinct transcripts in the frontal cortex and hippocampus that are relevant to 'learned helplessness' and responsive to conventional antidepressants.

Anticancer drug screen and gene expression

Pharmacogenomics requires massive computer exploration on heterogeneous databases. Li and Yuan (pages 127–135) demonstrate how the cell-line gene expression database can be co-mined with the drug sensitivity database to distil an enormous amount of information relevant to the understanding of drug mechanism, the characterization of the physiological roles for proteins of clinical importance, the study of gene networking and the strategic planning in chemotherapy, such as combination of drugs, hormones and cytokines.