The Pharmacogenomics Journal (2007) 7, 221

www.nature.com/tpj

The Pharmacogenomics Journal (2007) **7,** 221. doi:10.1038/sj.tpj.6500475

Candidate genes for alcoholism

Convergent functional genomics aims to unravel the genetics of complex neuropsychiatric disorders. This approach integrates gene expression data from a relevant animal model with human genetic linkage data, as well as human tissue gene expression data and biological data as a more confident way to find high-probability genes. ZA Rodd *et al*. describe a comprehensive translational approach for identifying candidate genes for alcoholism. The analysis of three rat animal models and their response to treatment with alcohol was used alongside a comprehensive analysis of microarray gene expression data from five key brain regions. They found that alcohol had many effects on multiple systems. Some of the pathways identified suggested avenues for pharmacotherapy of alcoholism with existing agents, such as angiotensin-converting enzyme inhibitors, but other new pathways were also found. The authors conclude that the overall picture showed that physical and physiological robustness may permit alcohol-preferring individuals to withstand the adverse effects of alcohol.

Metabolism of codeine and CYP2D6 activity

Codeine is a widely used analgesic drug, and the *O*-demethylation of codeine into morphine is mediated by the genetically polymorphic enzyme cytochrome P4502D6. The CYP2D6 gene duplication leads to ultra-rapid metabolism if the duplicated genes are fully active and if the duplication is combined with another active CYP2D6 allele. The impact of this genotype on pharmacokinetic parameters of codeine and opioid side effects has never been systematically studied. Kirchheiner *et al*. analyzed the pharmacokinetic differences of codeine between a group of ultra-fast metabolizers carrying the CYP2D6 gene duplication and extensive metabolizers carrying the wild-type allele. Significant differences were found between both groups in plasma and urine concentrations. And 91% (10 of 11) of the ultra-fast metabolizers felt sedation compared with 50% (6 of 12) of the extensive metabolizers. The authors conclude that it might be useful for physicians to know the CYP2D6 duplication genotype of their patients before administering codeine.

DRD2 *Taq*I-B polymorphism and smoking abstinence and withdrawal

Nicotine enhances dopamine activity and the role of this and other factors in the dopaminergic pathway are thought to be of interest in identifying risk factors. Many genes are considered to be involved in the regulation of the dopamine system and the DRD2 gene is one of the most frequently studied in addictive disorders. Robinson *et al*. studied the relationship of the DRD2 *Taq*I-A and -B polymorphisms with abstinence and withdrawal collected from diary data of 116 smokers using nicotine patches plus either venlafaxine or placebo. Smokers homozygous for the *Taq*I-B2 allele had progressively better results with withdrawal symptoms compared with smokers with the *Taq*I-B1 allele who showed little change.

Mechanism behind antipsychotic-induced weight gain

Weight gain occurs in up to 50% of patients under chronic administration of antipsychotics. The atypical antipsychotics clozapine and olazapine are associated with this side effect and it has been considered that central and peripheral AP target receptors could be potentially involved. Theisen *et al*. used radioligand-binding assays to investigate the potential involvement of several central and peripheral receptors in antipsychotic-induced weight gain. They suggested that the binding profiles of atypical (clozapine, olanzapine) and typical (haloperidol) antipsychotics may cause differences in weight gain. The drugs had negligible affinity for the range of tested receptors except for the melanin-concentrating hormone receptor. And overall the team could not identify a novel binding site of cloazapine and olanzapine that could contribute to induced weight gain.

Novel polymorphism associated with lower serum testosterone in Caucasian men

Male androgens testosterone and DHT are strongly associated with the development and progress of prostate cancer. Identification of genetic variation in the androgen-metabolizing enzymes is of great interest as they may influence the risk of prostate cancer. Jackobson *et al*. have identified five novel polymorphisms in the AKR1C3 gene, which is highly expressed in the prostate gland and plays a major role in the formation and metabolism of androgens. One polymorphism A>G substitution in exon 2 that conferred a Glu77Gly changed occurred in 4.8% of Caucasians, but was absent in Orientals. The testosterone level was lower in subjects with the Gly77 allele.