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Treat arthritis by knowing your genes

Up to one-third of patients suffering from rheumatic disease may not respond at all to the most potent type of treatment. Ferraccioli *et al.* (pp 2–9) review the key genetic hotspots that dictate disease susceptibility, severity and efficacy of treatment. Most notably, the shared epitope (SE) of HLA-DRB1 not only predisposes individuals to rheumatoid arthritis, but is also associated with greater severity. The interleukin (IL)1 gene cluster and the tumor necrosis factor α receptor 2 also confer disease risk. While more research about TNFRII polymorphisms is needed, the future is certain: genotyping patients for the above haplotype and others will become the first step in treating rheumatic disease.

PGx of Alzheimer's disease

Using Alzheimer's disease (AD) as a case in point for complex diseases, Roses *et al.* comprehensively review the state of drug discovery, development and efficacy (pp 10–28). A principal assertion is that the 'one-size-fits-all' paradigm for drug dosage prevents patients from deriving the maximum benefit of medical treatment. The article examines and refreshes the field of pharmacogenetics (PGx) by drawing insightful parallels to pathogenetics and calling for a redefinition of drug response as a kind of classifiable phenotype. Disease genetics and PGx are similar and seamlessly interlinked. For example, differential rosiglitazone response confirms the pathogenetic hypothesis connecting APOE4 and mitochondrial dysfunction to the age of onset, rate of decline and pathology of AD.

Faint hope for failed hearts and lungs

Many ADRB (beta-adrenergic receptor) polymorphisms are associated with clinical disease phenotypes and these gene variants often interact differentially with drug therapy. For example, Gly16 carriers for *ADRB2* are at risk for both higher asthma severity and decreased response to albuterol. A review article by Taylor (pp 29–37) highlights research targeting ADRB variants and discusses the potential implications for drug therapy. Despite the numerous association findings that appear promising when evaluated separately, the overall results still vary significantly across geographic region and population size.

Biological pathways of booze

Alcohol alters the expression of genes related to various pathways, including stress response, ethanol metabolism, gene regulation and cell signaling. Such modifications ultimately lead to the familiar physiological effects of ethanol and can also influence personal alcohol preference and dependence. Through bioinformatic analyses, Uddin and Singh (pp 38–47) identify the key transcription factor (TF) motifs and *cis*-regulatory modules (CRMs) that regulate ethanol-responsive (ER) genes. Among these major TFs are CREB and MTF1, whose activation of the genes *Mt1* and *Mt2* normally contributes to zinc ion homeostasis. Alternatively, changes in these TFs' binding position and orientation causes *Mt1* and *Mt2* to regulate a myriad of other pathways, such as intracellular signaling cascades. These findings represent a preliminary understanding of the biological factors underlying alcohol effects.

Bouncing back from depression

People with depression may respond more markedly to antidepressant drugs if they carry at least one allele of a particular dopamine transporter (*DAT1*) gene polymorphism. Kirchheiner *et al.* (pp 48–55) report a dose-dependent correlation between the 10-repeat allele of a *DAT1* variable number of tandem repeats (VNTR) polymorphism and antidepressant response. Specifically, homozygous carriers experience the greatest decline in depression symptoms, heterozygous carriers gain an intermediate improvement, and individuals homozygous for the nine-repeat allele exhibit the mildest response. The relationship was consistent for incident and recurrent patients, as well as for all types and combinations of depression medication.

Polymorphisms of renal cancer

Membrane transporter proteins that assist in xenobiotic metabolism and detoxification may contribute to varying interindividual disease risk for kidney cancer. Variants of ABCB1 and ABCC2, genes that encode transporter proteins P-gp and MRP2, modulate mRNA and protein expression in renal cancer cells. Haenisch *et al.* (pp 56-65) found lower expression of ABCB1 and ABCC2 in clear-cell renal cell cancer (CCRCC) than in adjacent normal cortex cells on both mRNA and protein levels. Although no associations were found between these transporter genotypes and cancer risk, further research on the decreased expression is needed to define its role in cancer susceptibility and response to chemotherapy.

Trimming the fat: *LPL* influence

Lipoprotein lipase (*LPL*) haplotypes may underlie dyslipidemia, hypertension, insulin resistance and atherosclerosis. The enzyme's major role in lipid metabolism, such as regulating lipid uptake and delivering fatty acids to adipose tissue and muscle, suggests that response to lipid-lowering drugs may vary with *LPL* haplotypes. Using a cohort of post-coronary artery bypass graft patients, Goodarzi *et al.* (pp 66–73) investigate 12 SNPs at the 3′ end of *LPL* and their effects on atherosclerosis progression and HDL-C response to lovastatin. Of the various haplotypes studied, one was found to protect against graft occlusion, while another corresponded to increased risk of atherosclerosis progression. *LPL* variants may influence response to statin therapy through modifying the effect of statins on *LPL* expression rather than altering lipid metabolism directly.