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Tackling gastric cancer with PGx

The statistics for advanced gastric cancer are grim: the survival expectancy is less than one year and is second in cancer-related mortalities worldwide. From oral fluoropyrimidines to platinum derivatives to topoisomerase I inhibitors, Toffoli *et al.* (pp 76–80) highlight the gamut of drug treatments and research to date on the genetic polymorphisms affecting therapy response. Studies on 5-fluorouracil and platinum derivatives indicate that similarities in treatment sensitivity exist between gastric cancer and other tumors. Continued examination of other cancer treatments may provide viable and translatable therapy options for gastric cancer.

Cutting down on cigarettes

Smoking tobacco is the leading cause of preventable death in the world and accounts for 5 million deaths per year. Although most smokers possess a desire to quit, very few succeed. Research shows when smokers start the habit and whether they can quit may depend on their genes. Ho and Tyndale (pp 81–98) document the various known polymorphisms that may play a role in smoking behavior and summarize the results of genome-wide linkage and candidate gene association studies. Most variants are found in genes encoding dopamine receptors, dopamine transporters, serotonin transporters and cholinergic receptors.

Careful dosage of warfarin

Warfarin poses a particularly difficult therapeutic challenge, owing to the fine line between an effective dose and a dose that causes severe and sometimes fatal hemorrhage. At least 30 genes are involved in warfarin's anticoagulatory effect, and the two major genetic spotlights are *CYP2C9* and *VKORC1*. These two genes and others explain the widely varying doses across patients, where one out of every three individuals is dosed outside the standard therapeutic range. In their review, Wadelius and Pirmohamed (pp 99–111) declare that the ability to accurately assess warfarin dose continues to improve with new studies, but a large prospective study of variations in warfarin response would be the next ideal step.

Inducing CHD risk via α-adducin

Previous literature has shown that the α-adducin gene may be linked to hypertension and may interact with diuretics. The Genetics of Hypertension-Associated Treatment study investigates a possible interaction between the α-adducin Gly460Trp polymorphism and different antihypertensive drugs to determine an influence on coronary heart disease (CHD) risk and other cardiovascular disease outcomes. Davis *et al.* (pp 112–122) conclude that the Gly460Trp genotype does not significantly influence CHD risk for males on antihypertensive treatment but reveal that for females, the Trp allele confers an increased CHD risk when chlorthalidone is prescribed, as compared to amlodipine or lisinopril. The paper additionally illuminates the strengths and limitations of its study design in the context of other published studies.

New target for bipolar disorder

With 0.5–1.5% of the world population suffering from bipolar disorder (BD), finding new therapeutic targets for this prevalent disease is in high demand. Borsotto *et al.* (pp 123–132) reveal the KCNQ2 potassium channel as a possible new target by demonstrating that its splice variants contribute to neuronal hyperexcitability, a characteristic of the manic and hypomanic phases of BD. KCNQ2 also interacts with the brain-specific PP2A-B_γ regulatory subunit of a protein encoded by *PPP2R2C*, whose single nucleotide polymorphisms have been associated with BD. Although susceptibility loci for BD have been previously identified, very few studies until now have illuminated the molecular pathways responsible for BD.

SULT: variants predict function?

The ability to predict the functional consequences of gene variation in drug-metabolizing enzymes is a principal goal in gauging individual therapy response. Involved in the bioprocessing of steroid hormones, neurotransmitters and drugs, the human cytosolic sulfotransferase (SULT) gene family constitutes a range of such enzymes. Through employing gene resequencing, functional genomics, amino-acid characterization and crystal structure analysis, Hildebrandt *et al.* (pp 133–143) examine the possibility of using SULT variant allozymes to predict alterations in protein function. The paper investigates both synonymous and nonsynonymous polymorphisms, and also draws comparisons to similar research on variants of membrane transporter genes.

Population studies of *NAT2* diversity

N-acetyltransferase 2 (*NAT2*) polymorphisms affect the pharmacokinetics of antituberculosis drugs and AIDS antibiotics. These polymorphisms give rise to three identifiable acetylator phenotypes: slow, intermediate and fast. Examining several native American populations, Fuselli *et al.* (pp 144–152) report three high-frequency *NAT2* variants, and compare diversity indices with other major geographic regions. While native American intrapopulation diversity of *NAT2* is similar or higher than that of other regions, the overall distribution of acetylator phenotypes across the populations is homogeneous, suggesting that pharmacological therapy need not accommodate specific populations.