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Pharmacogenetics and ethical considerations: why care?

Some aspects of pharmacogenetics are likely to have a potentially profound impact on medical practice, research and society. Several studies have examined the ethical, legal and social aspects of pharmacogenomics. However, the debate on ethical and regulatory issues is still mostly scientific and the public debate is missing. It is also possible that the issues studied and reported to date may not be of greatest importance to the public. L Marx-Stoling suggests that the ethics of pharmacogenomics is still a rather new field that needs further investigation as pharmacogenomics moves toward clinical utility. He explains why both scientists and the public should care about both pharmacogenetics and ethical aspects of the field.

Impact of b2-adrenoreceptor gene variants on cardiac cavity size and systolic function in idiopathic dilated cardiomyopathy

Through a multitude of cardiac effects, including apoptosis and necrosis, persistent b-adrenoreceptor (b-AR) activation determines progressive heart failure. Although there is substantial evidence to implicate the b1-adrenoreceptor (b1-AR) subtype in evolving cardiac dysfunction, the role of the b2-AR is uncertain. In heart failure, the Arg16Gly and Gln27Glu polymorphisms of the b2-adrenoreceptor (b2-AR) gene are associated with exercise-capacity, clinical outcomes and response to b-AR blocker therapy. D Badenhorst and co-workers assessed whether these b2-AR genotypes determined LV dimensions and pump function independent of b-AR blockers. They also evaluated the relationship between these polymorphisms and LV dimensions and systolic function in patients with idiopathic dilated cardiomyopathy (IDC) before and 6 months after receiving medical therapy other than b-AR blockers.

Diuretic–gene interaction and the risk of myocardial infarction and stroke

Antihypertensive therapy has been associated with a 35–40% reduction in stroke incidence, and a 20–25% reduction in myocardial infraction in clinical trials. Even though there are effective antihypertensive drugs, it can be difficult to find the most appropriate pharmacological treatment for an individual patient. Two genes that might influence the response to low-ceiling diuretics are the alpha-adducin (ADD1) and G protein b3-subunit (GNB3) gene. The human ADD1 460W-allele can be considered as a candidate allele for hypertension, because it may affect blood pressure by increasing renal tubular reabsorption of sodium through the activation of Naþ, Kþ-ATPase (adenosine triphosphatase). GNB3 is also a candidate because it mediates signal transduction across cell membrane. In this study, H Schelleman and co-workers examined whether the risk of myocardial infarction or stroke in hypertensive patients treated with low-ceiling diuretics is modified by the ADD1 G460W or GNB3 rs2301339 polymorphism.

Molecular therapy in the microRNA era

Non-coding RNAs are genes that are able to function as RNA transcripts. MicroRNAs (miRNAs) are part of the group of non-coding RNAs that can block mRNA translation and affect mRNA stability. In the human genome, recent estimates point to at least several thousand miRNAs. Although several important steps of miRNA biogenesis have been recently identified, the exact mechanisms by which specific miRNAs act still remains largely unclear. However several reports have implicated miRNAs in post-transcriptional regulation of proteins with diverse roles, from cell proliferation and differentiation to fat metabolism. Recently, miRNA-deregulated expression has been extensively described in a variety of diseases, especially cancer. In this article T Wurdinger and FF Costa review important aspects of miRNA function in normal and pathological states, and discuss new modalities of epigenetic intervention strategies that could be used to amend defects in miRNA/mRNA interactions.

Association of the mu-opioid receptor gene with smoking cessation

Although the relationship between candidate genes and cigarette smoking has been widely studied, and despite a large number of association studies, a recent meta-analysis concluded that the findings were equivocal. Using a pharmacogenetic approach to the study of smoking cessation treatment, MR Munafò and co-workers examined the potential role of the mu-opioid receptor, which is expressed in multiple brain regions and mediates feelings of reward, analgesia and withdrawal. This receptor is also the primary site of action for highly addictive opiates such as morphine, and studies have shown that non-opiate drugs such as nicotine may also exert their effects by activation of opioid receptors. Furthermore, nicotine stimulates the release of the endogenous peptide b-endorphin, which has a high affinity for the mu-opioid receptor. The Asn40Asp (A118G) polymorphism (rs1799971), found in exon I of the human mu-opioid receptor (OPRM1) gene, has been associated with functional changes in mu-opioid receptors. Therefore, the team investigated the association of the OPRM1 genotype with long-term smoking cessation and change in body mass index following nicotine replacement therapy or placebo in a randomized controlled trial, and were followed up over 8 years.

Pharmacogenetic analysis of paclitaxel transport and metabolism genes in breast cancer

Paclitaxel is commonly used in the treatment of breast cancer. Variability in paclitaxel clearance may contribute to the unpredictability of clinical outcomes. However, to date, the contribution of genetic variation to these inter-individual differences has not been defined clearly. Paclitaxel elimination is regulated by a wide

array of genes involved in metabolism and extracellular transport. Data from liver microsomes demonstrate that CYP2C8 and CYP3A4 are primarily responsible for paclitaxel metabolism. For example, The CY2C8*3 variant allele has been associated with decreased paclitaxel 6 a-hydroxylase activity in human cell lines and human liver microsomes. Functional variants in the CYP3A gene family have been identified that could potentially impact drug metabolism. In this study S Marsh and co-workers assessed polymorphisms in six genes associated with paclitaxel metabolism and transport to determine the contribution of inherited differences to the pharmacokinetics and progression-free survival of breast cancer patients receiving paclitaxel-containing therapy.

Genetic susceptibility to Tardive dyskinesia in chronic schizophrenia subjects: V. association of CYP1A2 1545 C4T polymorphism

Tardive dyskinesia (TD) is an iatrogenic disorder developing in a subset of schizophrenia patients chronically treated with typical antipsychotic drugs. Several genes from dopaminergic, serotonergic and oxidative stress pathways have been investigated for their possible contribution to susceptibility to TD. However, only the DRD3 ser9gly polymorphism has been consistently implicated in the genesis of TD. CYP1A2 is involved in the metabolism of atypical antipsychotic drugs such as clozapine and olanzapine. Therfore, AK Tiwari and co-workers analyzed polymorphisms/variations in the cytochrome P450 1A2 gene (CYP1A2;15q22-qter; MIM #124060), which is involved in the metabolism of atypical antipsychotics such as clozapine and olanzapine. And we further investigated whether the CYP1A2 1545 C4T polymorphism has any role to play in susceptibility to TD and schizophrenia.

IMPDH1 promoter mutations in a patient exhibiting azathioprine resistance

Around 9% of inflammatory bowel disease patients are resistant to azathioprine, which is an immunosuppressant that undergoes complex metabolism. Patients are considered to fit the definition of thiopurine resistance if the ratio between the products of the metabolized drug, 6-MMPR and 6-TGN, are in concentrations within red blood cells of more than 30:1. In most cases azathioprine resistance has been attributed to ultrahigh thiopurine *S*-methyltransferase (EC 2.1.1.67) activity. As the incidence of thiopurine resistance is far greater than the apparent incidence of ultra-high thiopurine *S*-methyltransferase activity, RL Roberts and co-workers hypothesized that these patients carried mutations within another purine metabolizing enzyme, inosine-50-monophosphate dehydrogenase (IMPDH). To test this theory they screened 20 azathioprine-resistant patients for variations in the two IMPDH genes (IMPDH1 and IMPDH2), using dHPLC and DNA sequencing.

The association between HTR2C polymorphisms and obesity in psychiatric patients using antipsychotics: a cross-sectional study

The use of antipsychotics is associated with an increased risk of obesity. Psychiatric patients consider weight gain as one of the most disturbing adverse events, and it is an important reason for non-compliance and for switching drugs in daily psychiatric practice. The mechanism behind antipsychotic-induced weight gain is not entirely clear. The high inter-individual variability suggests that genetic make-up is a modulating factor. One of the potential genetic determinants of antipsychotic-induced weight gain and obesity is the genetic variation in the serotonin 2C (5-HT2C) receptor encoded by the HTR2C gene. In this study H Mulder and co-workers conducted a cross-sectional study to see whether polymorphisms in the HTR2C gene were associated with obesity (body mass index 430 kg m^{-2}) in patients using antipsychotics.

Clozapine-induced agranulocytosis in schizophrenic Caucasians: confirming clues for associations with human leukocyte class I and II antigens

Clozapine is thought to be the most efficacious atypical antipsychotic agent in patients with treatment-resistant schizophrenia. But this benefit is reduced by an incidence of nearly 1% of patients who develop agranulocytosis. Clozapine-induced agranulocytosis (CA) is still among the least understood adverse drug reactions in psychopharmacology. It has been hypothesized that simple toxic and immunologic pathways are in general important for developing agranulocytosis. Although support for a genetically based hypothesis is provided by findings indicating CA as an idiosyncratic drug reaction, by a 21-fold higher rate of this drug adverse reaction among Finnish people compared with other ethnic backgrounds, and by a case report of concordant manifestation of CA in monozygotic schizophrenic twins. Furthermore, some reports have postulated human leukocyte antigen class I and II associations with adverse drug reactions. In this study, M Dettling and co-workers performed human leukocyte antigen genotyping and compared allele frequencies in a sample of 42 non-Jewish Caucasian schizophrenic patients with CA and 75 non-Jewish Caucasian schizophrenic patients treated with clozapine without developing agranulocytosis.

Intra-ethnic differences in genetic variants of the UGT-glucuronosyltransferase 1A1 gene in Chinese populations

UGT1A1 is the major UGT1 gene product that catalyzes the glucuronidation of bilirubin. Mutations in the UGT1A1 gene would decrease the enzymatic activity and are responsible for hyperbilirubinemia. UGT1A1 is also involved in the glucuronidation of many drugs, such as the anticancer drug irinotecan, and causes severe adverse reactions. Remarkable inter-individual variations in the pharmacokinetics of irinotecan, especially irinotecan-induced toxicity, have been reported. Global studies of polymorphisms in UGT1A have shown alleles and genotypes to be unequally distributed among different ethnic human populations across the world. In this study, A Zang and co-workers examined the intra-ethnic difference in allele, and haplotype frequencies of polymorphisms in UGT1A1 was examined in three Chinese ethnic populations.