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Pharmacogenetic approaches to rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects up to 1% of the general population. Therapeutic strategies and agents do exist, and disease-modifying anti-rheumatic drugs (DMARDs) are widely accepted as effective. However, the outcome of treatment with DMARDs is known to vary among RA patients. Taniguchi and Kamatani (pp 350–353) review several studies on the relationship between genetic polymorphisms and the efficacy of some DMARDs, suggesting that pharmacogenetics may be applicable to the treatment of RA.

Pharmacogenomics in prescribing information

One promise of pharmacogenomics is the application of genotype-guided therapy to maximize the likelihood of drug benefit, while minimizing the likelihood of harmful effects. As such, pharmacogenomics-based approaches to patient care might improve pharmacotherapy through more rational drug choices. Zineh *et al* (pp 354–358) investigate this possibility by way of a systematic analysis of pharmacogenomics data currently available in drug package inserts. Though they found much relating to drug pharmacokinetics, package inserts generally did not contain sufficient information to guide treatment based on genetic data.

PGRN Fourth Scientific Meeting

Now in its fifth year, the Pharmacogenetics Research Network and Knowledge Base (PGRN) is a nationwide research effort sponsored by the National Institutes of Health. The program aims to elucidate relationships between genetic variation and interindividual differences in drug response, thereby identifying new links between genotype and phenotype. In their Meeting Report, Long and Davis (pp 359–361) present notable research updates from the fourth annual open scientific meeting of the PGRN, held on March 8, 2004 in Los Angeles.

CYP3A5 polymorphism in clinical trials

A growing number of publications report varying degrees of importance that cytochrome

P450 3A5 (CYP3A5) plays in human drug metabolism. Foti *et al* (pp 362–364) suggest that the majority of these studies have missed a major aspect of the polymorphism: population selection. That is, many of these studies have only compared CYP3A5 nonexpressors with people who are heterozygous CYP3A5 expressors. The authors stress that future association studies would be improved by including a statistically significant number of persons who are homozygous CYP3A5 expressors.

Chronic lithium treatment of B-lymphoblasts

Mounting evidence suggests that intracellular calcium (Ca²⁺) dynamics are disrupted in bipolar disorder. Andreopoulos *et al* (pp 365–373) demonstrate that long-term lithium treatment of B-lymphoblast cell lines from bipolar-1 disorder patients significantly decreased levels of TRPC-3 immunoreactive protein. The authors suggest that downregulation of TRPC3 may be an important mechanism by which lithium ameliorates pathophysiological Ca²⁺ disturbances as observed in bipolar disorder.

Linkage disequilibrium (LD) mapping of pharmacogenetic effects

Whole genome LD screening using single-nucleotide polymorphisms (SNPs) is a practical reality, but there is much debate regarding the number of SNPs necessary to construct a map powerful enough to perform genome-wide association studies. Using data from a large phase III clinical trial of tranilast, Xu *et al* (pp 374–378) illustrate that a genome-wide LD scan of 100 000–200 000 SNPs can be sufficient to identify a pharmacogenetic association with a drug-induced adverse event.

Clozapine upregulates striatal nexin

For the treatment of schizophrenia, dopamine-D2 receptor antagonists, such as haloperidol, are relatively successful at managing psychotic features of the disease, but are often insufficient in treating positive symptoms. Clozapine, however, has been shown to reduce both types of schizophrenic symptoms, while also causing fewer extrapyramidal side effects. In this paper, Chong *et al* (pp 379–387) use differential display polymerase chain reaction (ddPCR) to

clarify the drug's mechanism of action at the genetic level, thereby identifying novel gene sequences regulated by chronic clozapine treatment.

Modulation of nicotinic receptors by zinc and fluoxetine

Zinc and nicotinic acetylcholine receptors (nAChRs) appear to be associated with major depression. Some antidepressants, including fluoxetine, antagonize nAChRs. Colunga *et al* (pp 388–393) thus examine the interactions of fluoxetine and zinc ions on nicotinic neuronal and muscle acetylcholine receptors. They find that, at low concentrations, zinc potentiates and fluoxetine inhibits the action of ACh on both neuronal and muscle nAChRs; while fluoxetine greatly reduces, or even abolishes, the potentiating action of zinc. These results may do much to determine the etiology and treatment of major depression.

SNPs of the NK1 receptor

Neurokinin receptors in the central nervous system are involved in the neural circuitry of anxiety, depression and emesis. Knowledge of this role has led to the development of nonpeptidic NK1 receptor antagonists as therapeutic agents, which have demonstrated efficacy in treating chemotherapy-induced emesis and depression. Sequence polymorphisms in genes can potentially influence drug efficacy and are an important consideration in the drug development process. With these issues in mind, Randolph *et al* (pp 394–402) characterize receptor affinity and kinetics, calcium response and receptor internalization of a Y192 variant of the NK1 receptor gene.

CYP2C9 in Mexican-Americans

Despite the fact that Hispanics constitute one of the largest groups in the world, there is a paucity of pharmacogenetic studies in this group. Llerena *et al* (pp 403–406) rectify this lack, by analyzing the CYP2C9 polymorphism in a Mexican-American compared with a Spanish population. The authors find that the frequency of CYP2C9 alleles in this population is compatible with the genomic assembly of the constitutive ethnic origin of this group, and reiterate the need of further pharmacogenetic studies to optimize the recommended drug dosages for Mexican-Americans.