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Pharmacogenomics of drug disposition: integrated understanding of gene-environmental interaction

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Individual variation in drug response is a major problem of clinical practice and of a development. These variations can range from therapeutic failure to adverse or even fatal effects of drugs in some patients. The incidence of serious and fatal adverse drug reactions (ADRs) has been reported to be 6.7% and 0.32% of hospitalized patients in USA, respectively.

The risk for therapeutic failure or toxicity of a drug in an individual patient is determined by the interaction of genes and environment. Environmental factors include drug-drug interactions, patient's age, weight, renal and liver dysfunction, or other disease factors or clinical variables such as smoking and alcohol consumption. Many of these environmental factors have long been considered in determining the individualized dose regimen in conventional pharmacotherapeutics. However, inherited individual variability of drug responses has been left as a so-called "idiosyncrasy" that are not predictable by physicians. Recently, the rapid development of pharmacogenetics/pharmacogenomics provide us extensive information regarding on the genetic background on the wide inter-individual variation of drug responses, which is expected to lead to the era of personalized pharmacotherapy. Pharmacogenetics is a science that is interesting to the inherited variants of genes related to pharmacokinetics (drug metabolizing enzymes, drug transporters etc.) and pharmacodynamics (receptor, ion channel, target enzyme etc.), which are associated to the susceptibility of an individual to the higher risk of ADR or therapeutic failure.

The alteration of drug metabolizing enzymes and drug transporters are major factors that cause the individual variation of concentrations of their substrate drugs in plasma or action site, which resulted to

the therapeutic failure or toxic side effects in the individual patient whose genotypes are atypical compared to the general population. The genetic alternation of drug receptors also causes the unexpected serious adverse drug reactions or insufficient therapeutic efficacy. Additional data on the gene expression profiles in relation to the drug response are also expected to be a good approach to predict the personalized pharmacotherapy of a disease which therapy is influenced by multiple genes. At the moment a few scientists already apply pharmacogenetic/pharmacogenomic data to the pharmacotherapy of patients though it is limited to a few pharmacotherapeutic fields.

In the clinical situation, it is very frequent to take several different drugs that are mutually interacting, which seems to alter the effect of genetic polymorphisms of metabolizing enzymes and drug transporters on the disposition of substrate therapeutic drugs. The mild to moderate effect of genetic polymorphism of CYP2D6 allelic variant on the disposition of a therapeutic drug may be clinically significant if an inhibitor of the enzyme catalyzing the same substrate drug is co-administered. The genotype-phenotype correlation may be different among different ethnic populations who take different kind of foods that influence on the enzyme activity of metabolizing enzymes or drug transporters. Therefore, gene-environmental factors should be considered together to predict the disposition pharmacogenetics of an individual patient. The lecture will discuss issues of gene-environmental interactions in the prediction of personalized pharmacotherapy.