Abstract of Presentation

Presentation Title: Pharmacogenomics-based individualization of drug therapy

Adverse drug reactions (ADRs) are often unpredictable, owing to the fact that responses to drugs vary among different individuals. However, it is believed that applying knowledge of pharmacogenomics/pharmacogenetics in clinical treatment can help to improve prediction of efficacy and/or toxicity of drugs, leading to appropriate therapeutic regimens for individual patients and to contribute to improvement of our medical care. In attempts to identify genetic parameters that predict efficacy or risk of ADRs for various drugs, many investigators have conducted and are conducting association studies by using genetic polymorphisms detected in genes encoding drug-metabolizing enzymes, transporters, receptors, and proteins involved in the drug-signaling pathway. Moreover, in recent years, FDA also recommended genotyping of polymorphisms in drug-related genes prior to drug administration for avoidance of severe ADRs for several drugs, such as irinotecan. Single nucleotide polymorphism (SNP) is the most abundantly-found polymorphism in the human genome, and current improvement in SNP-based genotyping method has made possible our hope to achieve the goal of personalized medicine that aims to provide the right drug at appropriate dose for each individual patient.

The clinical outcomes of breast cancer patients treated with tamoxifen may be influenced by the activity of cytochrome P450 2D6 (CYP2D6) because tamoxifen is metabolized to its active form, endoxifen by CYP2D6. We evaluated association of *CYP2D6*10* allele, which decreased CYP2D6 activity, with clinical efficacy of tamoxifen in patients receiving adjuvant tamoxifen monotherapy after surgical operation on breast cancer. Among 67 patients, those homozygous for the *CYP2D6*10* alleles revealed a significantly shorter recurrence-free survival compared to those homozygous for the wild-type *CYP2D6*1* alleles (P = 0.0031), or compared to *CYP2D6*1/*1 + *1/*10* (P = 0.0010). The present study suggests that the *CYP2D6* genotype should be considered for decision about adjuvant hormonal therapy course of breast cancer patients.

Warfarin is the most commonly-used oral anticoagulant for treating thromboembolism but difficult to use owing to the large inter-individual variability in its dose requirement. We analyzed SNPs in two candidate genes of warfarin sensitivity, *VKORC1* and *CYP2C9* by using DNA samples of 828 Japanese patients treated with warfarin. Then, we classified our patients into three categories based on their genotypes of these SNPs. We named this classification method as the "warfarin-responsive index" and found that the median of daily warfarin dose of patients classified into each of the three warfarin-responsive index groups varied significantly (2.0 mg/day for the index 0 group, 2.5 mg/day for the index 1 group, 3.5 mg/day for the index 2 group; $P = 4.4 \times 10^{-13}$). Our results indicate that a combination of genotypes in *VKORC1* and *CYP2C9* should be applicable to predict the effective and safe dose of warfarin for the Japanese patients. The validation of our prediction system is currently underway by using reagent-chip all-in-one full-automatic SNP analysis systems, leading to establishment of the personalized warfarin treatments.