Pharmacogenomics and Its Applications

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ABSTRACT

Adverse drug reactions (ADRs) in patients cause more than 2 million hospitalizations including 100,000 deaths per year in the United States. In 2002, ADRs accounted for 6.5% of hospital admissions and 0.15% of subsequent deaths in United Kingdom. In order to improve the efficacy and safety and to understand the disposition and clinical consequences of drugs, pharmacogenetics and pharmacogenomics have undertaken studies on the genetic personalization of drug response. This is because many drug responses appear to be genetically determined and the relationship between genotype and drug response may have a valuable diagnostic value. Identification and characterization of a large number of genetic polymorphisms (biomarkers) in drug metabolizing enzymes and drug transporters in an ethnically diverse group of individuals may provide substantial knowledge about the mechanisms of interindividual differences in drug response and improve the management of patient care by determining which patients should avoid a specific drug and which patients should take a modified dose of the drug. This strategy could potentially reduce medical costs and improve the process of drug development.

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor and is frequently used as one of the basic components in highly active antiretroviral therapy for HIV-1 infection in resource-limited countries because of its efficiency and availability as an affordable generic combined pill. However, it often causes cutaneous adverse drug reactions with an approximate incidence of 15-20%. This study aimed to investigate an association between genetic risk factors and NVP-induced skin rash in 80 HIV patients with NVP-induced skin rash and 80 NVP-tolerant patients by means of candidate genes and genome-wide approaches. As well, the study evaluated a replication sample set (80 NVP-rash cases and 142 tolerant patients).

The candidate gene approach revealed a significant association between HLA-B*3505 and NVP-induced skin rash with a p-value of 3.8 x 10^-9 in a combined data set (OR = 21.79, 95% CI = 5.62-84.03). Using the genome-wide approach, the verification of SNP marker loci identified significant associations of 15 polymorphisms in the CCHCR1 gene with an equivalent p-value of 1.2 x 10^-8 in a combined data set (OR = 4.36, 95% CI = 2.58-7.36). Logistic regression analysis also indicated that HLA-B*3505 and CCHCR1 polymorphisms were significantly associated with skin rash with p-values of 0.00155 and 0.0080, respectively. A combination of these novel genetic markers predicts the risk of NVP-induced skin rash with a sensitivity and specificity of 37.8% and 88.4%, respectively.

Our findings supported the importance of this study in identifying common moderate risk alleles in pharmacogenomic studies. As well, the research findings may be useful in the development of a diagnostic test for the prevention of NVP-induced skin rash especially in Thai population.