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Genetic Polymorphism of NAT2 and CYP2E1 and Anti-tuberculosis Drug-induced Hepatotoxicity in Korean Patients with Pulmonary Tuberculosis

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Background: Antituberculosis drug-induced hepatitis attributed to isoniazid is one of the most prevalent drug-induced liver injuries. Isoniazid is metabolized by hepatic N-acetyltransferase (NAT) and cytochrome P450 2E1 (CYP2E1) to form hepatotoxins. The aim of this study was to evaluate whether the polymorphism of the NAT2 and/or CYP2E1 gene is associated with antituberculosis drug-induced hepatitis in Korean patients.

Methods: A total of 132 tuberculosis patients who received antituberculosis treatment including isoniazid, rifampicin, pyrazinamide and ethambutol were followed retrospectively. Their NAT2 and CYP2E1 genotypes were determined using a polymerase chain reaction with sequencing or restriction fragment length polymorphism methods.

Results: Eighteen (13.6%) patients were diagnosed to have antituberculosis drug-induced hepatitis. For the NAT2 gene, slow acetylators had a higher risk of hepatotoxicity than rapid acetylators (36.8% vs. 9.7%, P=0.005) and there was a 3.8 greater probability of hepatotoxicity for slow acetylators than for rapid acetylators. For the CYP2E1 gene, RsaI polymorphism in 5' untranslated region and a polymorphic repetitive sequence at the CYP2E1 5'-flaking region were analyzed and no significant association between any CYP2E1 genotype and antituberculosis drug-induced hepatitis.

Conclusions: In conclusion, slow-acetylator status of NAT2 is a significant susceptibility risk factor for antituberculosis drug-induced hepatitis and the genotyping of NAT2 gene may be a useful predictive tool for predicting antituberculosis drug-induced hepatitis.