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Mutation & SNP spectrum of the human ATP7B gene of Korean patients with Wilson Disease and their functional characterization

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Wilson disease (WND), an autosomal recessive disorder of copper transport, is characterized by excessive accumulation of intracellular copper in the liver and extrahepatic tissues because of the impaired biliary copper excretion and disturbed incorporation of copper into the ceruloplasmin. Hepatic cirrhosis and neuronal degeneration are major symptoms in WND.

In this study, efforts have been made to identify novel mutations, to analyze their functional defects and to investigate an allele frequency of each mutation in Korean patients with WND. This study included 120 unrelated Korean patients diagnosed as WND by clinical and biochemical findings. We identified 30 different mutations in 120 unrelated Korean patients. Among these mutations, ten mutations were novel. We characterized molecular defects of the ATP7B gene in only 76.3% of Korean Wilson patients. The p.R778L is the most common mutation with 39.2% of allele frequency. In order to evaluate the functional defects of ATP7B protein caused by novel mutations, we used the yeast complementation assay system and confocal microscopic evaluation for analyzing the localization of mutants after transient expression in mammalian cell system. Five novel amino acid substitutions, p.C656X, p.G891D, p.V1106I, p.T1029I, and p.T1031A were constructed into both the yeast expression and the mammalian expression vectors. According to the functional assay, p.V1106I turned out to be a polymorphism, the others are novel mutations perturbing the ATP7B function. Yeast complementation assay and confocal microscopic evaluation are useful tools for functional study on mutant ATP7B protein.