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Direct sequencing of mutations in the copper-transporting P-type adenosine triphosphate (*ATP7B*) gene for diagnosis and pathogenesis of Wilson's disease

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ABSTRACT. Copper-transporting P-type adenosine triphosphatase (*ATP7B*) has been identified as the pathogenic gene in hepatolenticular degeneration, or Wilson's disease (WD). The aim of this study was to explore the correlation between genetic mutations and the clinical profile of WD, and to discuss the value of mutation examination in its diagnosis for providing a scientific basis for the development of a method to examine genetic mutations. Sixty-eight Chinese Han patients with WD and 20 controls were included in this study. The *ATP7B* gene in DNA extracted from patient blood samples was amplified by PCR and sequenced. These sequences were compared against corresponding gene sequences obtained from healthy controls to statistically analyze the genetic mutations. Five of the nineteen mutations in *ATP7B*

were newly detected mutations; moreover, 8 of these mutations were polymorphic (2 were newly identified). The Arg778Leu and Pro992Leu mutations in exons 8 and 13 were detected at the highest mutation frequencies of 25.74 and 16.91%, respectively. The frequencies of all other mutations were below 5%. However, the clinical manifestations of WD did not differ significantly in patients with the Arg778Leu and Pro992Leu mutations. Therefore, these mutations were considered as hotspot mutations in Chinese WD patients. However, we observed no significant correlation between these genetic types and the clinical symptoms of WD. The correlation between the mutation genotype and disease phenotype remains to be elucidated. In conclusion, the highly sensitive and specific direct DNA sequencing method can be used to screen for the causative genes of WD.

Key words: Genetic mutation; ATP7B; Wilson's disease; Impaired copper metabolism