Wilson`s disease: pathogenesis, genetic and epigenetic factors

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Wilson's disease is an autosomal recessive genetic disease caused by mutations affecting the *ATP7B* gene with consequent accumulation of copper in the liver and in the brain. ATP7B transporter is involved with both copper biliary excretion and trafficking within the hepatocytes. Missense and nonsense mutations are the most frequent and, in general, absence of ATP7Base activity has been correlated with earlier and more severe clinical presentation. The most common mutation in patients of European descent is the missense H1069Q, possibly associated with neurological presentation according to some studies. However, studies attempting to link phenotype and genotype in Wilson's disease have not shown convincing results. This could be related to the high prevalence of compound heterozygotes but other genes may be contributing to the pathogenesis and disease severity. Environmental and nutrition factors could affect the phenotype of Wilson's disease. In particular, animal models have shown a possible involvement of epigenetic mechanisms of gene expression regulation in the disease onset and progression. Copper accumulation is associated with inhibition of the expression and activity of the enzyme S-adenosylhomocysteine hydrolase (SAHH) which is the bi-directional enzyme responsible for the synthesis of homocysteine. When SAHH is inhibited, the resulting accumulation of its substrates, SAH, is associated with inhibition of DNA methylation reactions with consequent effects on methylation status. In conclusion, Wilson's disease is a complex disease with challenging pathogenic mechanisms that most likely involve the interaction between genetic, metabolic, and environmental factors.